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ORIGINAL RESEARCH

Model Prediction of Infection Risk After Glucocorticoid Treatment for Severe Drug-Induced Liver Injury: Globulin is a Core Predictive Factor

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Purpose: Glucocorticoids are frequently administered in cases of severe drug-induced liver injury (DILI) to promote patient recovery and shorten hospitalization duration. However, their use is associated with an increased risk of infection. This study developed a predictive model for infection after glucocorticoid therapy in patients with DILI.

Patients and Methods: We retrospectively analyzed patients with severe DILI treated with glucocorticoids at the Fifth Medical Center of the Chinese People's Liberation Army between 2017 and 2024. We constructed and interpreted eight machine learning models: random forest, support vector machine, generalized linear model, gradient boosting machine, least absolute shrinkage and selection operator, XGBoost, K-nearest neighbor classification, and artificial neural network. Decision curve analysis, calibration curves, receiver operating characteristics (ROC), and Shapley Additive Explanations model scores were used to interpret the optimal model.

Results: Among the eight models, the gradient boosting machine showed the best results (area under the ROC curve: 0.981 and 0.928 for the validation and test sets, respectively) and had the smallest residuals. Decision curve analysis and calibration curves confirmed the model's strong clinical prediction performance. Globulin (GLO) was a key variable in the models, with significantly low levels in infected patients compared with those in the control group ($p < 0.001$). Patients with pre-treatment GLO levels below 20 g/L had a higher infection rate (41.1%), while those with post-treatment GLO levels below 21.5 g/L exhibited an even greater infection rate (82.3%).

Conclusion: Our early warning model for the prediction of infection is valuable for guiding hormonal therapy for severe DILI. Monitoring changes in GLO levels may provide a simple and effective clinical monitoring tool for preventing infection development.

Keywords: drug safety, hepatoprotective, liver damage, patient recovery

Introduction

Drug-induced liver injury (DILI) results from exposure to chemicals, biologics, and proprietary Chinese medicines, making it a major cause of adverse drug reactions.[1] Owing to the onset of an aging population, the rate of medication-exposed individuals has increased significantly, increasing the incidence of DILI. Meta-analysis indicate a steady increase of the overall annual DILI incidence, and the integration of epidemiological data from various countries has identified DILI as a leading cause of acute liver failure worldwide.[1,2] Despite its clinical significance, no specific treatment is currently available.

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The DILI network in the United States (US) reported that 82% of patients with severe DILI, including those who underwent liver transplantation, were treated with glucocorticoids.[3] While some studies suggest that glucocorticoid treatment does not improve the survival rate in severe DILI, our previous study and other research have shown it accelerates bilirubin clearance, improves coagulation mechanism, and may promote patient recovery and potentially improve survival outcomes.[4–6] Yue-Meng Wan et al[7] prospectively compared patients with DILI treated with prednisone to a control group, and found a significantly higher survival rate in the prednisolone-treated group. Although the study did not focus on the infection risk, infections were reported as adverse event in 18% (12/66) of patients in the prednisolone-treated group, which was higher than the 12.5% (3/24) observed in the control group. Consequently, empirical glucocorticoid therapy for severe DILI is commonly used in clinical practice; however, the associated infection risk[6] limits its application. To optimize the therapeutic benefits of glucocorticoids while minimizing adverse events, developing a predictive model for infection risk is imperative.

Machine learning, a branch of artificial intelligence, employs algorithms to learn from data and generate predictive decisions. It has become an essential tool in the medical field, leveraging its capability to handle high-dimensional data and uncover non-linear relationships. These strengths have demonstrated considerable potential in disease diagnosis, drug discovery, and patient care.[8] Several machine learning models are commonly employed in clinical prediction tasks, each with distinct strengths. Random Forest (RF) is an ensemble learning method that constructs multiple decision trees and outputs the mode of their predictions through voting, enhancing robustness and accuracy. Support Vector Machine (SVM) identifies the optimal hyperplane that maximizes the margin between classes, and applies kernel functions to address non-linear separability. Generalized Linear Model (GLM) extends linear regression by using link functions to accommodate non-normal distributed response variables. Lasso Regression applies L1 regularization to linear models, enabling feature selection in high-dimensional datasets by shrinking less important coefficients to zero. k-Nearest Neighbors (KNN) classifies observations based on the majority label among the closest neighbors in the feature space, determined by a distance metric. Artificial Neural Network (ANN) comprises multilayer neural units capable of capturing complex non-linear mappings and interactions. Gradient Boosting Machine (GBM) sequentially fits decision trees to the residuals (gradients) of prior models, effectively learning from errors to refine prediction. XGBoost, an optimized implementation of gradient boosting, incorporates regularization and second-order derivatives, offering superior performance in computational competitions.[9]

In summary, each algorithms exhibits distinct advantages in feature selection, model fitting, and handling data complexities. To evaluate their performance, we selected these eight models for constructing predictive frameworks. By leveraging the strengths of machine learning, we aim to comprehensively analyze the diagnostic efficacy of clinical biomarkers in disease detection.

Combining patient clinical data with advanced modeling tools to create disease prediction models can help clinicians make more personalized and cost-effective management decisions. Given that glucocorticoid therapy for severe DILI may induce infection risk, an early warning system can assist clinicians to adjust glucocorticoid dosages and regimens to prevent infections. This study developed a machine-learning risk prediction model, combined with logistic regression, to assess infection risk following glucocorticoid treatment in patients with severe DILI. Additionally, we identified early warning indicators of infection that can be clinically useful.

Materials and Methods

Compliance with Ethical Requirements

The study protocol was approved by the local ethics committee of our institute (approval number: No. 2015147D) and was performed following the ethical principles of the 1975 Declaration of Helsinki (6th revision, 2008). Informed consent was obtained from the patients or their first relatives if they could not provide informed consent themselves.

Inclusion and Exclusion Criteria

Data were collected from patients with severe DILI who received glucocorticoid therapy at the Fifth Medical Centre of the General Hospital of the People's Liberation Army between January 2017 and December 2024. Overall, 184 patients received

treatment from December 2017 to December 2023. For the testing set, data from a prospectively collected cohort (n = 30) from January to December 2024 were used (Figure 1). Patients were included if they met the diagnostic criteria for DILI based on the Guidelines for the Diagnosis and Treatment of Pharmacological Liver Injury,[1] had a Roussel Uclaf Causality Assessment Method (RUCAM) causality score of ≥ 6, and a DILI severity grading of ≥ 3.[10] Patients with vital organ dysfunction (heart, brain, kidney), immune system diseases, malignant tumors, or incomplete medical records were excluded.

Sample Collection and Processing

The venous blood of participants was collected in the early morning on an empty stomach. The total bilirubin (TBIL), alanine aminotransferase (ALT), alkaline phosphatase, globulin (GLO), and albumin were determined using dry tubes and prothrombin activity (PTA) using anticoagulant tubes. Samples were collected and stored for 20 min and were centrifuged at 1500 × *g* for 10 min to separate the serum for testing. All tests were performed at the laboratory department by testing technicians. TBIL, ALT, alkaline phosphatase, GLO, and albumin levels were analyzed using the Beckman automatic biochemistry analyzer AU680 and Beckman's supporting reagents, and PTA was measured using the Heath-McConnell CS5100 system and its accompanying reagents in Japan.

Glucocorticoid Dose Calculation and Administration

The study population received various glucocorticoids, including prednisolone, methylprednisolone, and dexamethasone, based on the clinical experience of the attending physicians. To present the glucocorticoid dosage more intuitively, doses were converted to prednisolone dosage according to the anti-inflammatory efficacy.

One approach is steroid step-down therapy, which involves gradually reducing the daily dose over several weeks (methylprednisolone [range 40–80 mg/day] or prednisone [range 60–120 mg/day] for 3–7 days and then phased reduction). The other approach is a steroid pulse therapy conducted for 5–14 days (methylprednisolone [range 30–80 mg/day] or prednisone [range 60–120 mg/day]).

Statistical Analysis

IBM SPSS Statistics 25 was used for the analysis of baseline indicators. The chi-squared test was used to compare categorical variables. Normally distributed data are expressed as mean ± standard deviation and were analyzed

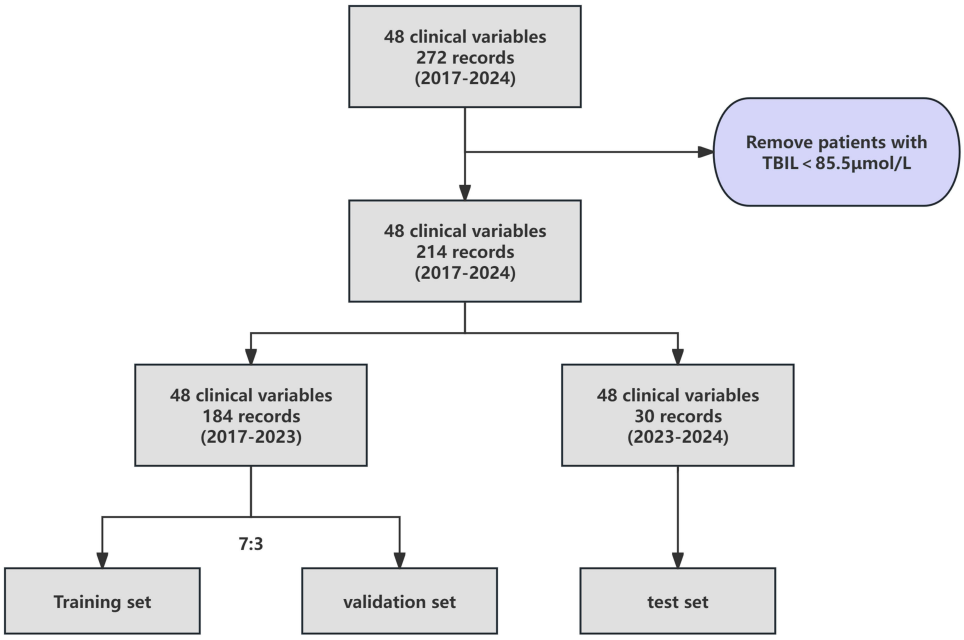

Figure 1 Flow diagram describing the selection of variables.
Abbreviation: TBIL, total bilirubin.

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using a paired *t*-test. Non-normally distributed data were analyzed using the Mann–Whitney *U*-test and are expressed as an interquartile range. Receiver operating characteristic (ROC) curves were plotted using MedCalc 15.2.2 to find cut-off values. Prism 9.01 and Ai 2021 were used for graphing. Differences were considered significant at $p < 0.05$.

Modeling Methods

To identify the most suitable model based on the data and improve the accuracy and applicability of the prediction model, we first established eight machine learning methods: random forest (RF), support vector machine (SVM), generalized linear model (GLM), gradient boosting machine (GBM), least absolute shrinkage and selection operator (LASSO), XGBoost, k-nearest neighbor classification (KNN), and artificial neural network (ANN). Using the DALEX, XGboost, Keras, caret, pacman, randomForest, RMDA, and pROC packages in R (4.0.1), the data were divided into training and validation sets in a 7:3 ratio. The models were trained using the train function in the caret package, and the residual analysis was applied to assess the goodness of fit of the models. The optimal model was selected by being combined with the ROC curve to carry out the precise training.

Among the eight models, we assessed the importance of 48 clinical indicators using the permutation importance approach. This method evaluates the contribution of each variable by randomly permuting its values and observing the subsequent changes in model performance. A significant decline in model performance following permutation indicates that the variable plays a crucial role to the model's predictive capability. The formulas are provided below:

$$\text{Performance original} = \mathrm{f}(\mathrm{X})$$

$$\text{Performance permuted} = \mathrm{f}(\mathrm{X1}, \mathrm{X2}, \ldots, \text{permute}\,(\mathrm{Xj}), \ldots, \mathrm{Xp})$$

$$\text{Importance}(\mathrm{Xj}) = \text{Performance original} - \text{Performance permuted}$$

To refine feature selection for the optimal model, GBM, we applied the Boruta algorithm to identify key variables within the dataset. Boruta operates by generating a set of "shadow features" from the original feature set. It then compares the importance of each original feature to that of the highest-ranking shadow feature. Features are classified as "confirmed" if their importance is significantly greater than that of the highest-ranked shadow feature, while "tentative" denote uncertain importance.

The performance of the models was evaluated by 10-fold cross-validation, and a trained machine model was finally obtained. Thereafter, the trained model was used to form predictions using the validation data. The predicted ROC curve was plotted, and the performance of the model in the classification task was evaluated using the confusion matrix, thereby clarifying the prediction accuracy and misclassification rate of the model, as well as guiding the tuning and improvement of the model. Afterwards, a calibration curve plot was used to assess the degree of difference between the predicted and actual risks. Decision curve analysis (DCA) was performed to evaluate the clinical benefit and utility of the constructed prediction models.

Finally, the best model was tested using the test data, and the Youden index was used to calculate the optimal threshold for the ROC curve. Prediction categories were generated based on the prediction results and optimal thresholds, and the confusion matrix and ROC curves were constructed.

Model Interpretation

The Shapley Additive Explanations (SHAP) model that is derived from the Shapley values in game theory and helps interpret the output of machine learning models was used to provide a numerical value for each feature, indicating the extent to which that feature contributes to the model output. The Shapley value helps to understand the importance of each feature in the prediction model. SHAP is applicable to many types of machine learning models, including linear, tree, and deep learning models. Therefore, this study used the SHAP algorithm, and the Shapley value of each feature was computed using the shapviz package in R (4.0.1).

Results

Patients' Demographic Profile

In total, 242 patients with DILI were treated with glucocorticoids between January 2017 and December 2023. Twenty-three patients with incomplete data for clinical indicators and 35 patients who did not reach the level of severe DILI (TBIL < 85.5 μmol/L) were excluded. Overall, data from 184 patients were analyzed. A total of 48 relevant clinical indicators were finally included (Figure 1). A total of 34 patients developed infections within 3 months after glucocorticoid therapy; of those, 28 (82.3%) had pulmonary infections, two (5.8%) had sepsis, and four (11.7%) had primary peritonitis. Subsequently, from January to December 2024, we included an additional 30 patients to test the models.

Patients were divided into two groups according to whether infection occurred or not. The number of inpatient days and values for GLO, TBIL, aspartate aminotransferase (AST), eosinophil (EO), difference in GLO (GLO1W-GLO), platelets, and other indexes in the baseline data ($p < 0.05$), as well as one-week indexes of GLO, ALT, and PTA ($p < 0.05$), differed between the two groups (Table 1).

Table 1 Comparison of Baseline Indicators

Variable	Infected Group (n = 34)	Non-Infected Group (n = 150)	*p*-value	Infected Group (n = 5)	Non-Infected Group (n = 25)	*p*-value
	Training and Validation Set			Test Set		
Age (yr)	51.00 [34.50, 59.50]	50.00 [37.00, 60.00]	ns	45±9.67	47.32±13.44	ns
Inpatient days	45.00 [25.55, 70.00]	31.00 [21.00, 42.25]	$p < 0.01$	15.00 [7.00, 21.00]	19.00 [12.50, 27.50]	ns
Initial dose of methylprednisolone (mg)	50.00 [40.00, 60.00]	55.00 [40.00, 60.00]	ns	40.00 [40.00, 40.00]	40.00 [40.00, 40.00]	ns
Days with doses > 40 mg	10.00 [6.00, 18.00]	14.00 [4.00, 14.00]	ns	7.00 [7.00, 7.00]	7.00 [7.00, 7.00]	ns
Days with doses > 30 mg	15.00 [7.00, 28.00]	21.00 [7.00, 28.00]	ns	14.00 [14.00, 14.00]	14.00 [14.00, 14.00]	ns
Duration of initial dosage used	6.00 [3.00, 7.00]	7.00 [4.00, 7.00]	ns	7.00 [7.00, 7.00]	7.00 [7.00, 7.00]	ns
Total duration of steroid used	35.00 [28.00, 61.50]	35.00 [21.00, 53.00]	ns	28.00 [28.00, 31.50]	14.00 [10.50, 14.00]	$p < 0.05$
ALB (g/L)	33.00 [28.00, 36.50]	32.50 [29.00, 35.00]	ns	29.00 [27.00, 36.50]	33.00 [30.00, 35.50]	ns
GLO (g/L)	21.30 [18.50, 25.00]	23.20 [20.47, 28.60]	$p < 0.01$	20.60±3.36	25.40±7.26	$p < 0.05$
TBIL (μmol/L)	380.30 [321.65.491.40]	271.00 [183.13, 351.57]	$p < 0.001$	283.76±105.17	300.36±130.95	ns
ALT (U/L)	145.00 [66.50, 338.00]	178.50 [76.00, 424.25]	ns	96.00 [34.00, 382.00]	190.00 [113.50, 292.50]	ns
AST (U/L)	147.00 [74.50, 342.00]	272.00 [98.50, 432.00]	$p < 0.05$	136.00 [53.00, 444.00]	191.00 [111.50, 429.50]	ns
ALP (U/L)	167.00 [135.00, 289.00]	179.50 [133.50, 258.50]	ns	134.00 [112.00, 166.50]	155.00 [114.00, 198.00]	ns
GGT (U/L)	105.00 [56.00, 247.00]	100.50 [58.75, 209.50]	ns	80.00 [61.00, 149.00]	127.00 [59.50, 189.00]	ns
TBA (μmol/L)	195.00 [145.50, 278.00]	217.00 [164.50, 286.25]	ns	296.00 [192.00, 513.00]	209.00 [167.80, 269.00]	ns
GLU (mmol/L)	5.00 [4.25, 7.20]	4.65 [4.20, 5.65]	ns	5.10 [4.05, 5.85]	4.60 [3.85, 6.15]	ns
CRE (μmol/L)	74.00 [61.50, 81.50]	65.00 [56.00.79.25]	ns	56.40±17.85	69.56±21.50	ns
NA (mmol/L)	138.00 [134.50, 139.00]	138.00 [136.00, 140.00]	ns	132.00 [130.00, 138.50]	137.00 [134.00, 138.00]	ns
TC (mmol/L)	2.80 [1.65, 3.95]	3.35 [2.30, 4.52]	ns	2.76 [1.74, 3.34]	3.06 [2.00, 4.80]	ns
INR	1.30 [0.95, 1.50]	1.10 [1.00, 1.40]	ns	1.53 [1.33, 2.14]	1.43 [1.16, 1.82]	ns
PTA (s)	57.00 [47.70, 93.75]	59.50 [57.00, 80.30]	ns	51.10 [19.50, 64.20]	57.00 [41.40, 85.80]	ns
AMMO	39.50 [25.50, 51.55]	34.00 [21.35, 47.47]	ns	37.70 [30.15, 52.00]	40.60 [32.15, 53.85]	ns
AFP (ng/mL)	16.10 [5.30, 133.95]	16.05 [4.30, 64.95]	ns	22.00 [10.51, 150.50]	37.21 [9.37, 159.15]	ns
EO. ($\times 10^9$/L)	0.025 [0.00, 0.10]	0.10 [0.00, 0.20]	$p < 0.01$	0.03 [0.01, 0.08]	0.11 [0.06, 0.29]	$p < 0.05$
NE. ($\times 10^9$/L)	5.10 [3.35, 10.40]	4.30 [3.00, 6.90]	ns	3.45 [2.70, 7.58]	3.29 [2.38, 5.07]	ns
WBC ($\times 10^9$/L)	6.60 [5.25, 12.70]	6.90 [5.20, 9.62]	ns	6.08 [4.60, 6.87]	6.01 [4.03, 6.34]	ns
Difference in GLO (GLO1W-GLO)	5.00 [1.00, 7.95]	1.00 [−2.70, 5.63]	$p < 0.01$	3.00 [2.50, 6.00]	2.00 [0.00, 4.00]	ns
TBIL.1w (μmol/L)	188.10 [106.90, 357.30]	171.65 [90.95, 314.62]	ns	217.00 [113.35, 368.55]	154.80 [109.65, 265.20]	ns
GLO.1w (g/L)	16.00 [15.00, 20.50]	23.00 [20.00, 26.00]	$p < 0.001$	17.00 [12.50, 20.50]	22.00 [20.00, 28.00]	$p < 0.05$
ALT.1w (U/L)	111.00 [88.50, 226.50]	91.00 [50.00, 136.50]	$p < 0.01$	47.00 [42.50, 293.00]	123.00 [70.00, 184.00]	ns
AST.1w (U/L)	122.00 [64.50, 225.50]	90.00 [54.00, 145.75]	ns	74.00 [46.50, 251.00]	69.00 [58.00, 153.50]	ns
ALP.1w (U/L)	166.00 [131.50, 227.50]	165.00 [131.50, 221.75]	ns	101.00 [96.00, 185.00]	130.00 [107.00, 163.50]	ns
GGT.1w (U/L)	122.00 [62.00, 678.00]	119.00 [63.75, 238.00]	ns	79.00 [50.50, 184.00]	113.00 [57.00, 191.00]	ns
CRE.1W (μmol/L)	58.00 [54.00, 73.50]	56.00 [52.00, 71.00]	ns	53.00 [36.00, 66.50]	57.00 [55.50, 78.00]	ns

(*Continued*)

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Table 1 (Continued).

Variable	Infected Group (n = 34)	Non-Infected Group (n = 150)	*p*-value	Infected Group (n = 5)	Non-Infected Group (n = 25)	*p*-value
	Training and Validation Set			Test Set		
Na.1W (mmol/L)	138.00 [135.00, 140.00]	138.00 [136.00, 139.00]	ns	137.00 [135.00, 138.50]	138.00 [138.00, 139.5.00]	ns
TBA.1W (μmol/L)	180.00 [113.00, 221.00]	173.00 [130.25, 215.50]	ns	296.00 [210.00, 658.50]	173.00 [140.00, 256.75]	$p < 0.05$
WBC.1w ($\times 10^9$/L)	9.10 [6.30, 10.80]	8.60 [6.67, 11.52]	ns	7.89±3.52	8.34±3.99	ns
GLU.1W (mmol/L)	4.80 [4.00, 5.46]	4.90 [4.20, 5.00]	ns	5.10 [3.75, 6.60]	4.92 [4.05, 5.05]	ns
NE.1W ($\times 10^9$/L)	5.30 [4.30, 8.30]	5.30 [3.52, 5.85]	ns	4.80±3.32	5.11±2.44	ns
EO.1W ($\times 10^9$/L)	0.10 [0.00, 0.11]	0.10 [0.02, 0.12]	ns	0.01 [0.00, 0.15]	0.12 [0.03, 0.16]	ns
PTA.1W (s)	76.20 [52.35, 80.49]	77.20 [69.87, 91.10]	$p < 0.05$	62.20 [52.05, 79.70]	77.22 [64.85, 110.40]	ns
INR.1w	1.10 [1.00, 1.25]	1.00 [0.90, 1.20]	ns	1.51±0.32	1.14±0.22	ns
CHE (U/L)	3668.83±1338.02	4018.48±1447.13	ns	3133±1787.69	4134.88±1469.67	ns
FE (μmol/L)	27.66±11.49	31.09±12.99	ns	26.54±9.81	36.13±14.02	ns
TG (mmol/L)	3.07±1.24	2.98±1.48	ns	1.80±1.22	2.61±1.18	ns
HGB (g/L)	124.42±18.72	122.11±18.80	ns	97.00±25.02	121.32±15.76	ns
PLT ($\times 10^9$/L)	184.52±82.67	234.89±102.295	$p < 0.01$	107.80±50.02	196.28±98.69	$p < 0.05$

Abbreviations: 1W, 1 week; AFP, alpha fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transferase; CHE, choline esterase; CRE, creatinine; EO, eosinophil; FE, ferritin; GLU, glucose; GGT, gamma-glutamyltransferase; GLO, globulin; HGB, haemoglobin; INR, international normalised ratio; Na, serum sodium; NE, neutrophilic granulocyte; PLT, platelet; PTA, coagulation activity; TBA, total bile acid; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

Development of Prediction Models

To identify the most suitable model based on the data and enhance the accuracy and applicability of the prediction model, we first established eight machine learning methods. The ROC values for each model were as follows: RF, 0.978; SVM, 0.933; GLM, 0.839; GBM, 0.981; LASSO, 0.843; XGBoost, 0.973; KNN, 0.736; and NNET, 0.811. Among these, the GBM model performed the best (Figure 2A). We further calculated the residual values for each model, finding that the absolute residual of the GBM model was the smallest (Figure 2B and C). This indicates that the GBM model has the least discrepancy between predicted and observed values and demonstrates the best overall performance. Therefore, we chose the GBM model for the next phase of accurate training and testing.

Recursion and Consolidation of Key Clinical Indicators

The top 10 variables for each model are summarized in Figure 2D, which revealed that models with high performance (AUC > 0.9) consistently identified GLO-1W as highly important. Figure 3A shows the important variables identified by the GBM model along with their percentages, with GLO-1W ranking the highest. Consequently, we conducted an in-depth analysis of GLO and GLO-1W.

GBM Modeling and Testing Results

Based on the previous screening of the best-performing GBM models in each category, we further performed model optimization and proposed to develop more stable predictive models. We randomly divided the data of 184 patients collected from 2017 to 2023 into a training set and a validation set in a 7:3 ratio. After the training process, we used 10-fold cross-validation to determine the optimal parameters and construct the best model. The results showed that the optimal model had an AUC of 0.997, an ACC of 0.988, a Sen of 0.978, and a Spe of 1 (Figure S1). We then enrolled 30 patients from January to December 2024 as a test set, which included 5 infected patients (lung infection) and 25 non-infected patients (Table 1). The test results showed an AUC of 0.896, an ACC of 0.860, a Sen of 0.920, and a Spe of 0.800 (Figure 3B).

GBM Model Interpretation

We used SHAP for a global interpretation of the GBM model to understand which features have a significant impact on the model's overall decision by analyzing feature importance. Verification was conducted on the previously identified important variable GLO-1W, and the results showed that GLO-1W had the highest contribution (Figure 3D). The lower

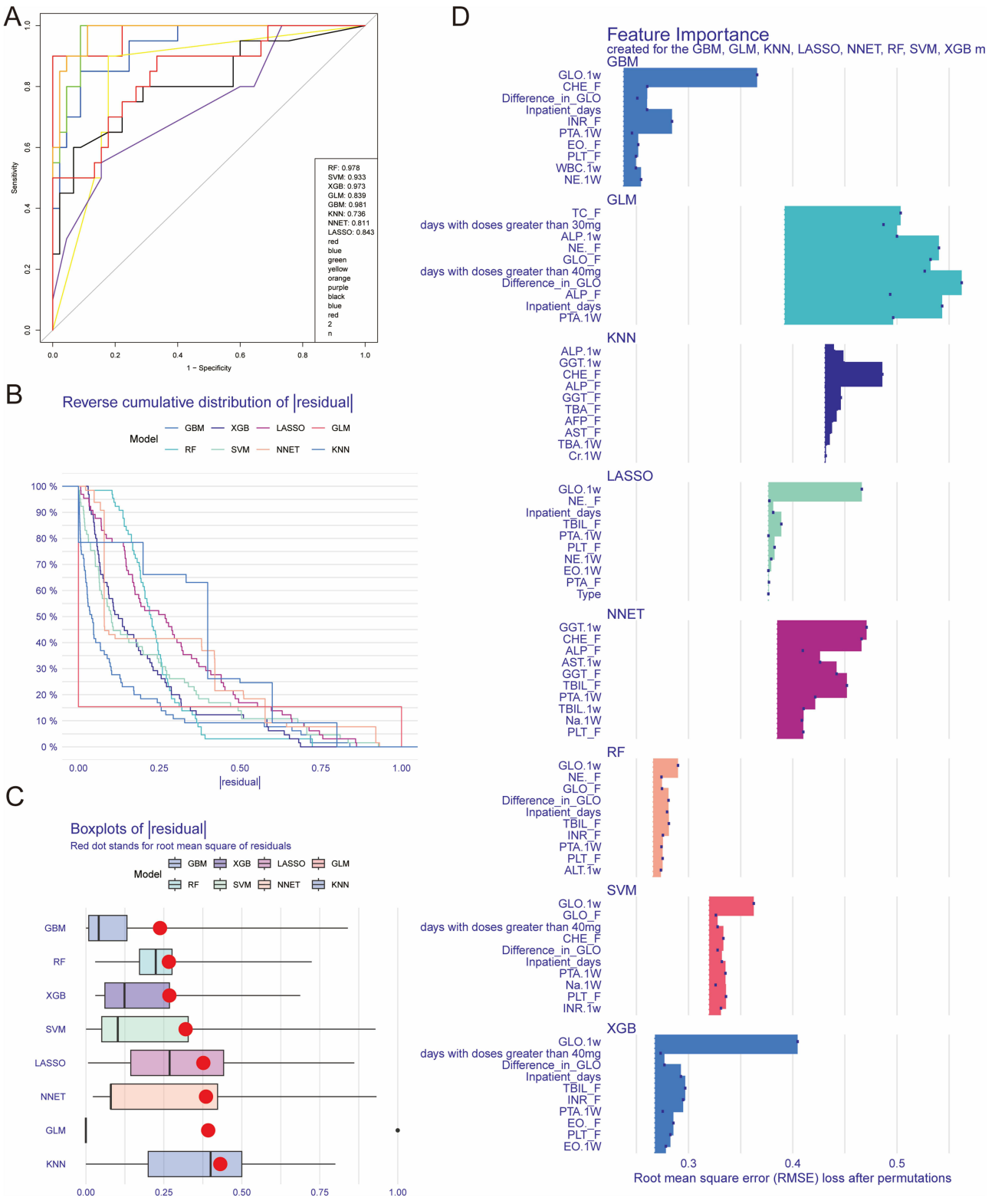

Figure 2 Construction diagram of eight machine learning models. (**A**) ROC curves of the eight models, (**B**) Residual line plots of the eight models, (**C**) Box plots of residual distribution of the eight models, and (**D**) Important feature selection diagram of the eight models.

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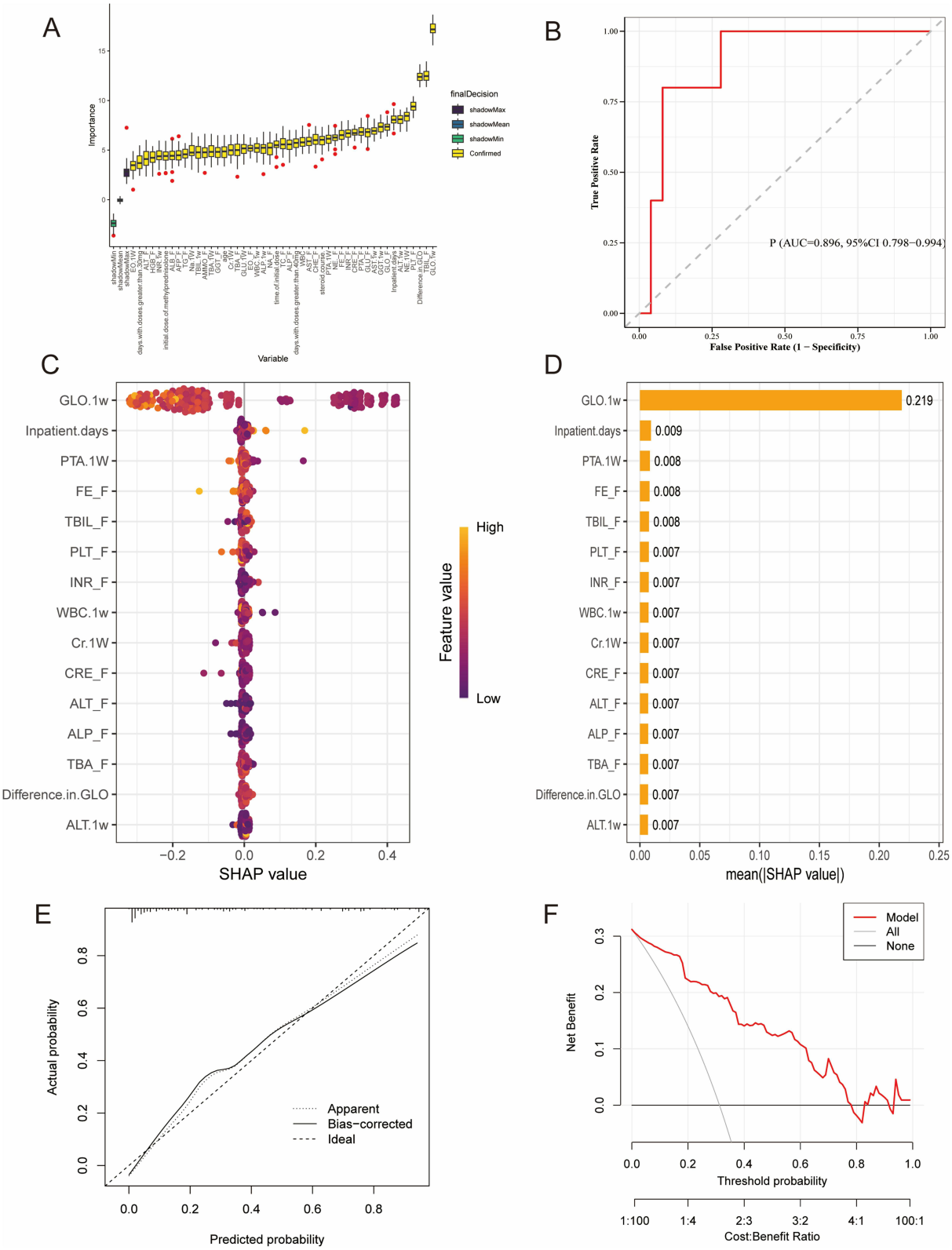

Figure 3 Testing and evaluation of the GBM model. (**A**) Box plot of important feature selection for the GBM model, (**B**) ROC curve of internal testing for the GBM model, (**C**) SHAP validation bee plot for the GBM model, (**D**) SHAP validation bar plot for the GBM model, (**E**) Calibration curve of the GBM model, and (**F**) DCA curve of the GBM model.
Abbreviations: 1W, 1 week; AFP, alpha fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, Aspartate transferase; CHE, choline esterase; Cr, creatinine; CRE, creatinine; EO, eosinophil; FE, ferritin; GLU, glucose; GGT, gamma-glutamyl transferase; GLO, globulin; HGB, hemoglobin; INR, international normalized ratio; NE, neutrophilic granulocyte; PLT, platelet; PTA, coagulation activity; ROC, receiver operating characteristic; TBA, total bile acid; TBIL, total bilirubin; TC, total cholesterol; WBC, white blood cell.

the value of GLO-1W, the higher the SHAP value, which had a greater positive impact on the model (Figure 3C), indicating a higher risk of infection.

GBM Model Evaluation

In addition to the internal tests, the calibration curve and DCA of the model were plotted in this study to further observe the accuracy and clinical value of the model. The calibration curve showed good calibration of the GBM model (Figure 3E). DCA indicated a clear positive net benefit for the GBM model, demonstrating excellent clinical applicability (Figure 3F).

GLO After Glucocorticoid Therapy

The most significant variable identified was GLO-1W; to our knowledge, changes in GLO have not been previously reported. Histograms illustrating GLO changes before and after treatment in both infected and non-infected groups are presented in Figure 4A. We observed a significant decrease in GLO levels after treatment ($P < 0.001$) (Figure 4C), with levels in the infected group being notably lower than those in the non-infected group ($P < 0.001$). Furthermore, within the infected group, GLO levels significantly decreased after one week of glucocorticoid treatment compared to pre-treatment levels ($P < 0.01$). In contrast, the change in GLO levels was not statistically significant in the non-infected group (Figure 4B). The critical GLO values before and after treatment were 20 g/L and 21.5 g/L, respectively. A chi-squared test revealed that the infection rate was higher among individuals with GLO levels below 20 g/L before treatment, with an infection rate of 41.1% ($P = 0.019$). As displayed in Figure 4D, post-treatment GLO levels below 21.5 g/L were associated with an increased likelihood of infection, showing an infection rate of 82.3% ($P = 0.000$).

Discussion

Mild DILI is manifested by mild abnormalities in liver function, which can mostly be cured by stopping the drugs suspected to cause liver damage. Severe DILI requires hospitalization and active treatment, and some patients even progress to liver failure, which is life-threatening. The main manifestations of severe DILI are hyperbilirubinemia and impaired coagulation mechanisms, and treatment includes discontinuation of liver-injuring drugs, administration of hepatoprotective drugs, application of glucocorticoids, and artificial liver and liver transplantation. Glucocorticoid therapy is often applied to patients with hyperbilirubinemia. Given that the efficacy of glucocorticoids in the treatment of severe DILI is not yet sufficiently established, the risk of adverse effects is high, and current opinions on glucocorticoid therapy in the major guidelines for DILI differ.[1,11–13] However, all guidelines recommend large-sample studies to further demonstrate the pros and cons.

Hou et al[6] collected data from 70 patients with hepatocellular DILI with TBIL ≥ 10 × upper limit of normal, 20 of whom were treated with corticosteroids. They found that the time to recovery of DILI was short in patients treated with corticosteroids. Hu et al[5] retrospectively analyzed 33 patients with TBIL > 243 μmol/L treated with glucocorticoids and confirmed that glucocorticoids can significantly shorten the time used for TBIL recovery. Karkhanis et al[14] retrospectively analyzed 131 patients with drug-induced hepatic failure, 16 of whom were treated with corticosteroids, and found that corticosteroids did not improve overall survival. We found that glucocorticoid treatment of patients with severe DILI (TBIL > 85.5 μmol/L, including non-hepatic and hepatic failure) favored rapid recovery, and although the application of glucocorticoid therapy did not improve the survival of patients with hepatic failure, none of the patients with non-hepatic failure in the group of glucocorticoid therapy application (52 cases) developed hepatic failure and related deaths—similarly for the non-glucocorticoid therapy group (52 cases). Three of the patients died because of hepatic failure; glucocorticoid therapy may reduce the occurrence of hepatic failure, indicating potential clinical value.

To our knowledge, no study has reported an increased risk of infection with glucocorticoid therapy. However, this may mainly be due to the lack of clinical studies with large samples. Theoretically, glucocorticoid therapy inevitably reduces a patient's immunity, increasing the risk of infection and other hormonal adverse effects. Glucocorticoids are inexpensive, and most patients experience rapid recovery after severe DILI application; however, once a serious infection occurs, the loss outweighs the gain, leading clinicians to cease applying glucocorticoids to treat severe DILI.[1,11,13] This underscores the fact that high-level evidence-based medical support favoring glucocorticoids remains lacking. Moreover,

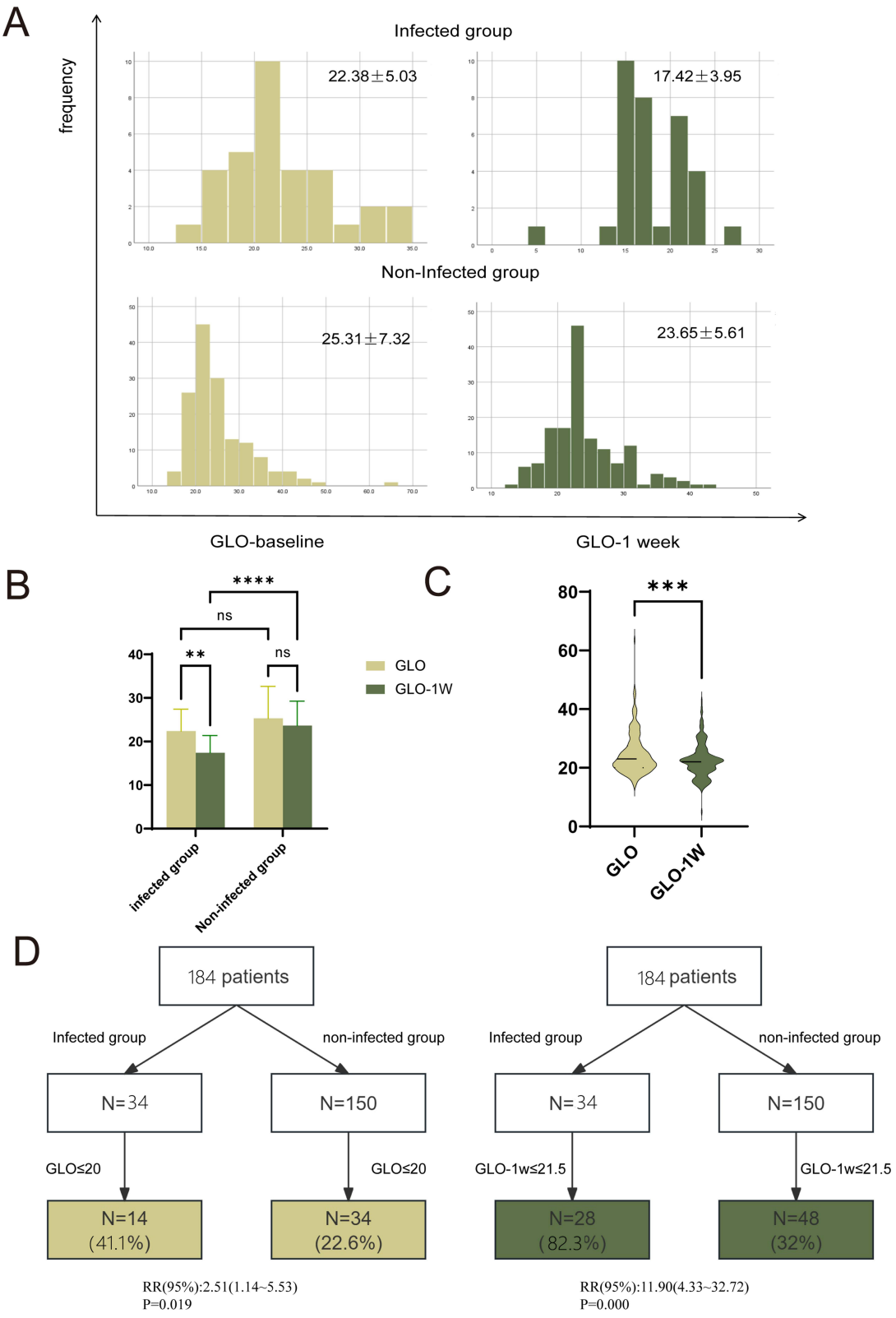

Figure 4 (**A**) Histogram of intergroup distribution of GLO and GLO-1W, (**B**) Graph of changes in GLO levels before and after treatment in infected and non-infected groups, (**C**) Violin plot of GLO levels before and after treatment, and (**D**) Before and after treatment chi-square test stratified plots.
Abbreviations: 1W, 1 week; GLO, globulin.

the use of glucocorticoids for treating severe DILI has been referred to as a "double-edged sword", necessitating careful integration with clinical decision-making. However, there remains a lack of specific, evidence-based guidelines to inform decision-making in this context.

This study retrospectively included 184 patients with severe DILI treated with glucocorticoids for model training and validation. Subsequently, 30 patients were prospectively included for internal testing. During treatment and follow-up, 34 patients were found to have infections in the training and validation sets, of which three succumbed to death, and five patients were found to have infections in the testing set. The biochemical indices of patients at baseline and after one week of partial treatment were analyzed and it was revealed that the number of inpatient days, and levels of GLO, TBIL, AST, EO, platelets, difference in GLO (GLO1W-GLO), GLO-1W, ALT-1W, and PTA-1W differed between the two groups ($p < 0.05$). Based on the above data, we constructed eight machine learning models and selected the GBM model by comprehensively analyzing their area under the ROC curve and residual values. We further optimized and tuned the parameters of the GBM model using ten-fold cross-validation and tested it with internal data, which showed good performance. The calibration curve and DCA also confirmed the accuracy and clinical benefits of the model. Such models can play an early warning role in managing the emergence of infectious complications during glucocorticoid therapy for severe DILI.

Screened indicators showed that the values of baseline GLO after one week of treatment were strongly correlated with infection and could be used as part of an early warning indicator of infection. The correlation between GLO levels and infection before and after glucocorticoid therapy has not been reported in previous studies, and we report for the first time the value of GLO levels for providing early warning of infection. GLOs are pathophysiologically important in defending against infection. Glucocorticoid therapy can reduce GLO synthesis directly or indirectly by altering the distribution of lymphocyte subpopulations, reducing the immune response,[15] which is one of the reasons infections are prone to occur after glucocorticoid application.

In our study, we found a significant correlation between baseline GLO levels at one week of treatment and the development of infections, an indicator that may provide clinicians with an actionable tool for the prudent use of glucocorticoid therapy. According to this indicator, the dosage and course of treatment of glucocorticoids can be adjusted in time to avoid the occurrence of infection. Conversely, immunoglobulin can be supplemented to prevent and control infection in a timely manner. Such approaches have been applied to some patients in our department and have shown good results. However, since this is a single-center study, the sample size was relatively small. Further multi-center studies with larger sample sizes are warranted to verify our results.

China has a large population base, and a tremendous number and variety of clinical medications. The application of TCM-NM-HP-DS is more common. Currently, the lack of adequate knowledge among non-hepatology medical professionals and the public at large regarding drug safety issues and DILI coupled with the trend of a rising ageing population has led to a considerable increase in the number of drug-exposed individuals, leading to an annual increase in the number of DILI incidences. Glucocorticoid therapy for severe DILI is commonly used in primary care units because it accelerates patient recovery and shortens hospitalization time. Severe infections increase the risk of patient death and considerably increase medical resource consumption, presenting a serious consequence that complicates physicians' use of glucocorticoid therapy for severe DILI. Our early warning model for the occurrence of infections is of significant value in guiding hormonal treatment of severe DILI, as well as monitoring changes in GLO levels, which may provide an actionable means for preventing the occurrence of infections.

To facilitate clinical practical of the model, we have implemented the relevant clinical assessment scales within our hospital. With further data collection, we plan to prepare scientific manuscripts and develop an web-based predictive model for broader patient benefit. However, this study is limited by its single-center sample size; therefore, collaborative multicenter external validation studies are warranted.

Conclusion

Our early warning model for the prediction of infection is valuable for guiding hormonal therapy for severe DILI. Monitoring changes in GLO levels may provide a simple and effective clinical monitoring tool for preventing infection development.

Research in Context

Evidence Before This Study

The annual incidence of Drug-Induced Liver Injury (DILI) has shown a rising trend year by year. Comprehensive epidemiological data from various countries indicate that DILI has become a major cause of acute liver failure globally; however, effective treatment options are currently lacking. We used the keywords "DILI, machine learning, infection, globulin" to search PubMed for articles from the database's inception until March 2025. Currently, most articles on DILI and machine learning focus on strategies to reduce its occurrence and progression, with few addressing treatment-related guidance models post-development.

Added Value of This Study

This study developed a model to predict the risk of infection following hormone therapy-related liver injury and proposed relevant prevention and treatment strategies to guide clinicians in medication use, minimizing the risk of infection for patients. The advantage of our model lies in the novel incorporation of "globulin" as a core observational indicator, which simplifies the decision-making process. Additionally, the model has demonstrated good performance in both calibration and clinical benefits.

Implications of All the Available Evidence

Our predictive model can provide practical guidance for hormone therapy in patients with drug-induced liver injury, helping to mitigate the risk of infection. Monitoring changes in GLO levels may provide an easy-to-use clinical monitoring tool for preventing infection development.

Abbreviations

DILI, drug-induced liver injury; ROC, receiver operating characteristics; RUCAM, Roussel Uclaf Causality Assessment Method; GLO, globulin; TBIL, total bilirubin; ALT, alanine aminotransferase; PTA, prothrombin activity; RF, random forest; SVM, support vector machine; GLM, generalized linear model; GBM, gradient boosting machine; LASSO, least absolute shrinkage and selection operator; KNN, k-nearest neighbor classification; ANN, artificial neural network; DCA, decision curve analysis; SHAP, Shapley Additive Explanations; EO, eosinophil.

Data Sharing Statement

The data generated and/or analyzed during the current study are available with the corresponding authors upon reasonable request.

Ethical Approval and Informed Consent

The Ethics Review Team of the Fifth Medical Center of the Chinese People's Liberation Army General Hospital approved the study protocol (approval number: No.2015147D), and the study was performed in compliance with the ethical principles of the 1975 Declaration of Helsinki (6th revision, 2008). Informed consent was obtained from the patients or their first relatives if they could not provide informed consent themselves.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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