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Glucocorticoid-Associated Infection Risk in Severe Drug-Induced Liver Injury: A Machine Learning Prediction Model Identifying Globulin as the Key Predictor

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ABSTRACT

Glucocorticoids are widely used in managing severe drug-induced liver injury (DILI) to enhance clinical improvement and reduce the length of hospital stay, yet they may elevate susceptibility to infections. This work aimed to build a model capable of forecasting infection following glucocorticoid administration in individuals with DILI. A retrospective review was carried out on patients diagnosed with severe DILI who received glucocorticoid treatment at the Fifth Medical Center of the Chinese People's Liberation Army from 2017 to 2024. Eight machine-learning approaches were developed and assessed: random forest, support vector machine, generalized linear model, gradient boosting machine, least absolute shrinkage and selection operator, XGBoost, K-nearest neighbor classification, and an artificial neural network. The most effective model was examined using decision curve analysis, calibration plots, ROC curves, and Shapley Additive Explanations.

Of the eight algorithms, the gradient boosting machine yielded the strongest performance, achieving an area under the ROC curve of 0.981 for the validation cohort and 0.928 for the test cohort, along with the lowest residuals. Its clinical utility was further supported by decision curve analysis and calibration plots. Among the predictive features, globulin (GLO) stood out, showing markedly lower concentrations in infected individuals than in non-infected patients ($p < 0.001$). Those whose GLO values before treatment were under 20 g/L demonstrated an infection rate of 41.1%, while individuals with post-treatment GLO below 21.5 g/L had an even higher infection rate of 82.3%. The early-warning model presented here offers practical value for guiding glucocorticoid therapy in severe DILI. Tracking GLO level fluctuations may represent a straightforward and efficient method for identifying patients at increased risk of infection.

Keywords: Drug safety, Hepatoprotective, Liver damage, Patient recovery

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Introduction

Drug-induced liver injury (DILI) arises from exposure to pharmaceuticals, biologics, and various traditional Chinese remedies, making it a major contributor to adverse drug reactions [1]. With aging demographics and more widespread medication use, the number of individuals vulnerable to DILI has risen substantially. Meta-analytic evidence shows a continual rise in yearly DILI incidence, and global epidemiological findings identify DILI as one of the dominant causes of acute liver failure [1, 2]. Despite its importance, no targeted therapeutic option is currently available.

According to data from the United States DILI Network, 82% of patients with severe forms of the condition—including those requiring liver transplantation—received glucocorticoid therapy [3]. Although some reports argue that steroids do not enhance survival in severe DILI, both our earlier work and other investigations indicate they can accelerate bilirubin reduction, improve coagulation parameters, and may assist clinical improvement and potentially survival [4–6]. In a prospective comparison by Yue-Meng Wan *et al*. [7], patients treated with prednisolone exhibited a notably higher survival rate than the control group. While infection was not the main focus, adverse events occurred in 18% (12/66) of prednisolone-treated subjects, compared with 12.5% (3/24)

among controls. As a result, glucocorticoids are frequently used in practice for severe DILI, yet concerns about infection risk [6] continue to restrict their broader use. Therefore, establishing a tool to estimate the likelihood of infection is essential for balancing therapeutic advantages against potential harms.

Machine learning—an area of artificial intelligence—applies computational models that learn from data to make predictions. It has become highly valuable in medical applications due to its capacity to manage complex datasets and detect non-linear associations. These strengths have made it influential in diagnostics, pharmaceutical development, and clinical decision-support [8]. Several machine-learning methods are routinely implemented for clinical forecasting. Random Forest (RF) aggregates outcomes from numerous decision trees, improving stability and predictive accuracy. Support Vector Machine (SVM) determines a separating hyperplane with maximal margin and uses kernel functions for non-linear classification. Generalized Linear Models (GLM) broaden linear regression methods by applying link functions suitable for non-normally distributed responses. Lasso Regression incorporates L1 regularization, allowing both shrinkage and variable selection. k-Nearest Neighbors (KNN) assigns class labels based on the predominant category among the closest points. Artificial Neural Networks (ANN) consist of multiple interconnected layers…

Integrating clinical profiles with computational modeling platforms enables the construction of tools that anticipate disease outcomes, supporting clinicians in making tailored and financially efficient therapeutic decisions. Because glucocorticoids used in severe DILI can elevate susceptibility to infection, a predictive alert system may help clinicians fine-tune dosage and treatment schedules to reduce this complication. In this project, we assembled a machine-learning framework, supplemented by logistic regression, to estimate infection likelihood after glucocorticoid administration in patients with severe DILI. We also pinpointed early clinical markers useful for anticipating infection.

Materials and Methods

Compliance with ethical requirements

This investigation received approval from the institutional ethics board (approval No. 2015147D) and adhered to the ethical standards outlined in the 1975 Declaration of Helsinki (6th revision, 2008). Participants—or, when necessary, their immediate relatives—provided informed consent.

Inclusion and exclusion criteria

Records were obtained from individuals diagnosed with severe DILI who were managed with glucocorticoids at the Fifth Medical Centre of the General Hospital of the People's Liberation Army between January 2017 and December 2024. A total of 184 patients were treated from December 2017 through December 2023. For model testing, a prospective dataset (n = 30) collected from January to December 2024 was used **(Figure 1)**. Entry criteria required meeting the standard diagnostic guidelines for pharmacological liver injury,1 achieving a RUCAM score of ≥ 6, and presenting with severity grade ≥ 3.10. Subjects with major organ failure (cardiac, neurologic, or renal), autoimmune disorders, malignant disease, or missing clinical information were not included.

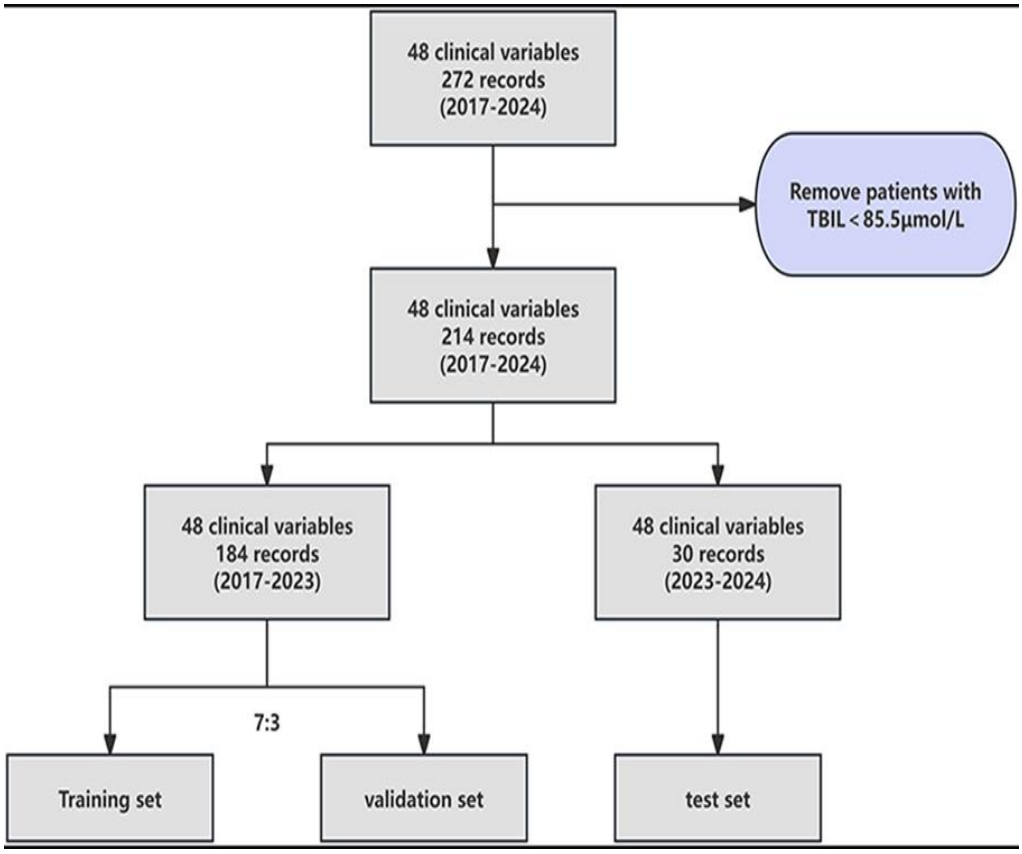


Figure 1. Flowchart showing variable screening.
Abbreviation: TBIL, total bilirubin.

Sample collection and processing

Fasting venous blood was drawn early in the morning. Dry tubes were used for TBIL, ALT, alkaline phosphatase, GLO, and albumin, while anticoagulant tubes were used to assess PTA. Samples rested for 20 minutes, followed by centrifugation at 1500 × g for 10 minutes to isolate serum. All analyses were performed by qualified laboratory personnel. TBIL, ALT, alkaline phosphatase, GLO, and albumin were measured via the Beckman AU680 analyzer with its standard reagents, and PTA was quantified using the Heath-McConnell CS5100 system with its proprietary kits from Japan.

Glucocorticoid dose calculation and administration

Patients received various glucocorticoid agents—prednisolone, methylprednisolone, or dexamethasone—according to clinician judgment. All doses were standardized to prednisolone equivalents based on relative anti-inflammatory activity.

Two main regimens were utilized:

• Step-down therapy, in which medication was tapered over several weeks (methylprednisolone 40–80 mg/day or prednisone 60–120 mg/day for 3–7 days before sequential reduction).

• Pulse therapy, administered for 5–14 days (methylprednisolone 30–80 mg/day or prednisone 60–120 mg/day).

Statistical analysis

Baseline characteristics were processed in IBM SPSS Statistics 25. Categorical outcomes were assessed using chi-square testing. Data consistent with normal distribution were reported as mean ± standard deviation and compared via paired t-tests. Non-normal variables were presented as interquartile ranges and evaluated with the Mann–Whitney U-test. ROC analyses to determine optimal cut-off points were created with MedCalc 15.2.2. Graphs were generated using Prism 9.01 and Ai 2021. A p-value < 0.05 was treated as statistically meaningful.

Modeling methods

To determine which analytical strategy best matched the dataset and to ensure strong predictive performance, we generated eight distinct machine-learning frameworks: 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). The analysis was conducted in R (4.0.1) using the DALEX, XGboost, Keras, caret, pacman, randomForest, RMDA, and pROC libraries. The dataset was partitioned so that 70% of observations formed the training subset and the remaining 30% served as the validation group. Model fitting relied on caret's *train* routine, while residual-based diagnostics were applied to evaluate overall model adequacy. ROC-oriented assessment guided the choice of the model retained for detailed tuning.

Across all eight algorithms, the contribution of 48 clinical features was examined using a permutation-driven importance technique. In this procedure, each variable is disrupted by random value shuffling, and the resulting change in predictive output is measured. A notable loss in performance after permutation indicates that the variable is fundamentally important for model discrimination. The related formulas appear below:

$$\text{Performance original}=f(X) \quad (1)$$

$$\text{Performance permuted}=f(X1, X2,\ldots,\text{permute}(Xj),\ldots Xp) \quad (2)$$

$$\text{Importance}(Xj)=\text{Performance original}- \text{Performance permuted}) \quad (3)$$

To further narrow down the most informative predictors for the selected GBM model, the Boruta method was employed to screen essential attributes in the dataset. In this approach, a series of "shadow features"—duplicates with randomized values—are produced from the original variables. Each real feature is then evaluated against the top-performing shadow counterpart. Variables that exceed the importance score of the leading shadow feature are labeled "confirmed," whereas those that do not show clear superiority are marked "tentative."

Model performance was assessed through 10-fold cross-validation, after which a finalized machine-learning model was obtained. This trained algorithm was then applied to the validation dataset to generate predictions. An ROC curve based on these predictions was plotted, and classification behavior was examined through a confusion matrix to determine accuracy, error distribution, and areas requiring parameter refinement. A calibration curve was subsequently used to compare predicted versus observed probabilities, and decision curve analysis (DCA) was carried out to determine the practical clinical value of the prediction models.

The highest-performing model was ultimately evaluated with the test dataset. Using the Youden index, the optimal cutoff for the ROC curve was computed. Prediction groups were then defined according to this threshold, and both the confusion matrix and corresponding ROC curves were constructed.

Model interpretation

To understand how individual predictors influenced the output, we applied SHAP (Shapley Additive Explanations), which is grounded in game-theoretic Shapley values. SHAP assigns a numerical contribution score to each feature, clarifying its effect on a model's prediction. The method can be used across linear, tree-based, and neural models. In this study, we calculated Shapley values using the shapviz package in R (4.0.1).

Results and Discussion

Patients' demographic profile

Altogether, 242 individuals with DILI received glucocorticoid therapy between January 2017 and December 2023. Exclusions included 23 patients missing clinical data and 35 who did not meet the severe DILI threshold (TBIL < 85.5 μmol/L). Ultimately, 184 patient records were included. A total of 48 clinical indicators were retained **(Figure 1)**. Among these patients, 34 developed infections within 3 months following glucocorticoid treatment: 28 (82.3%) had pulmonary infections, two (5.8%) developed sepsis, and four (11.7%) had primary peritonitis. An additional 30 patients from January–December 2024 were enrolled for external testing.

Patients were categorized based on infection status. Several baseline measures differed significantly between groups ($p < 0.05$), including hospitalization duration; GLO, TBIL, AST, eosinophil (EO), change in GLO (GLO1W–GLO), platelet count, and other indices. At the one-week mark, GLO, ALT, and PTA values also showed significant differences ($p < 0.05$) **(Table 1)**.

Table 1. Comparison of Baseline Indicators

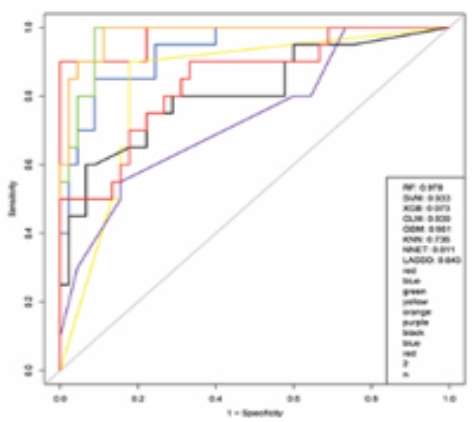
Variable	Training and Validation Set			Test Set		
	Infected (n=34)	Non-Infected (n=150)	p-value	Infected (n=5)	Non-Infected (n=25)	p-value
Age (years)	51.00 [34.50, 59.50]	50.00 [37.00, 60.00]	ns	45 ± 9.67	47.32 ± 13.44	ns
Length of hospital stay (days)	45.00 [25.55, 70.00]	31.00 [21.00, 42.25]	$p < 0.01$	15.00 [7.00, 21.00]	19.00 [12.50, 27.50]	ns
Initial methylprednisolone dose (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 dose > 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 dose > 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 (days)	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 glucocorticoid use (days)	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]	$p < 0.05$
Albumin (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
Globulin (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	$p < 0.05$
Total bilirubin (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
Total bile acids (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
Glucose (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
Creatinine (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
Sodium (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
Total cholesterol (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
Prothrombin activity (PTA, %)	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
Ammonia (AMMO, μmol/L)	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

Eosinophils (EO, ×10⁹/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
Neutrophils (NE, ×10⁹/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
White blood cells (WBC, ×10⁹/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
ΔGLO (1 week post-treatment – baseline)	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 at 1 week (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 at 1 week (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 at 1 week (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 at 1 week (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 at 1 week (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 at 1 week (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
TBA at 1 week (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
Platelet count (PLT, ×10⁹/L)	184.52 ± 82.67	234.89 ± 102.29	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, hemoglobin; INR, international normalized 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 determine which analytical approach aligned best with the dataset and to improve predictive robustness, eight distinct machine-learning algorithms were generated and compared. Their ROC scores were: 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. The GBM algorithm produced the highest ROC value **(Figure 2a)**. Residual analyses were then performed, and the GBM method displayed the lowest absolute residuals **(Figures 2b and 2c)**, indicating the closest alignment between predictions and observed outcomes. Because of this superior performance, GBM was selected for subsequent focused training and evaluation.



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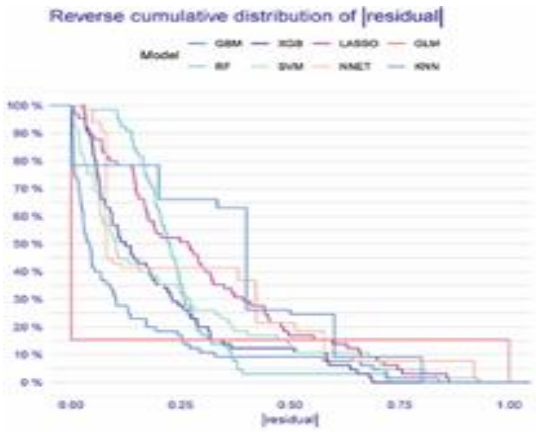

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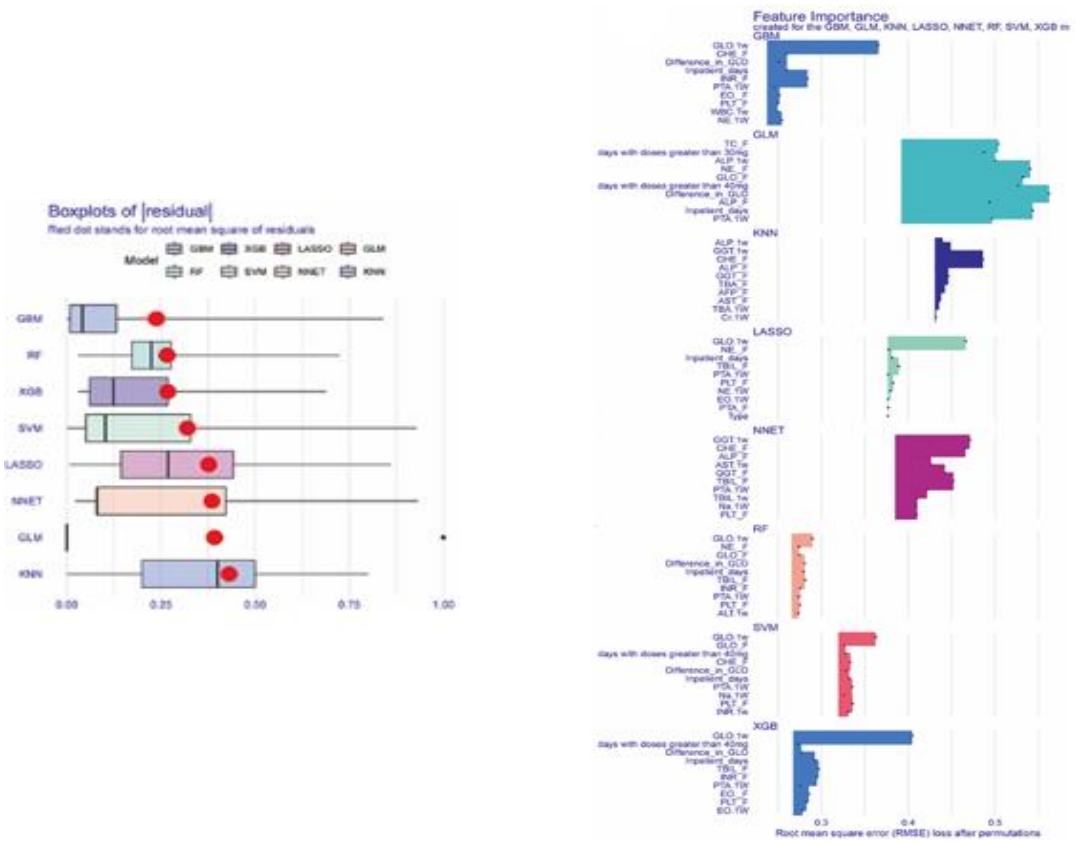
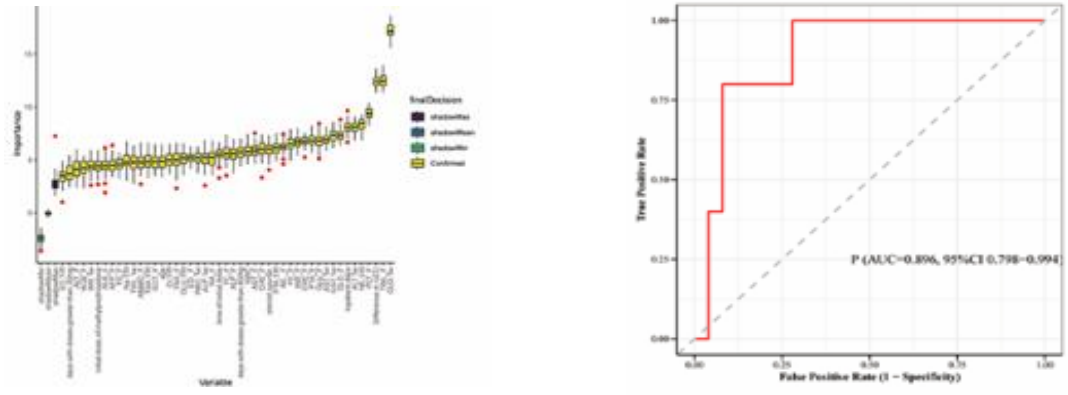


c) d)

Figure 2. Illustration of the eight machine-learning frameworks: (a) ROC comparisons, (b) residual trend lines, (c) residual box distributions, and (d) feature-importance mapping.

Recursion and consolidation of key clinical indicators

Figure 2d lists the top 10 ranked variables for each algorithm, showing that models with an AUC above 0.9 repeatedly emphasized GLO-1W as a major factor. In **Figure 3a**, the GBM model's influential inputs and their proportions are displayed, with GLO-1W emerging as the most dominant contributor. As a result, a targeted investigation of both GLO and GLO-1W was performed.



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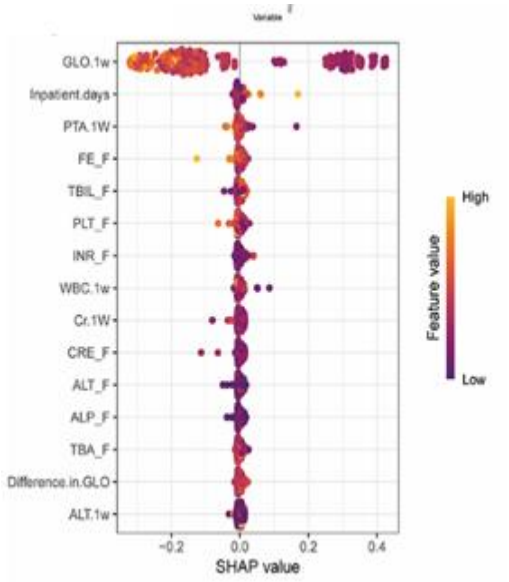

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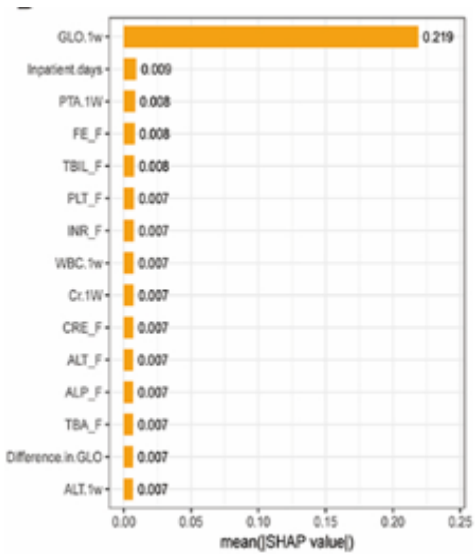

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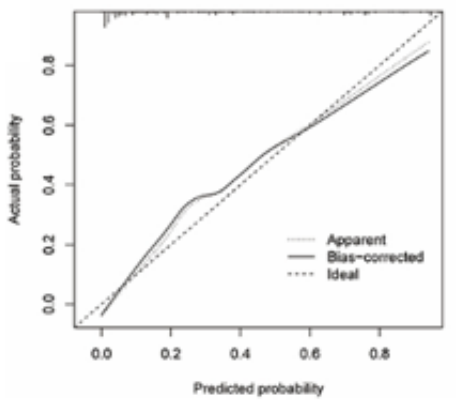

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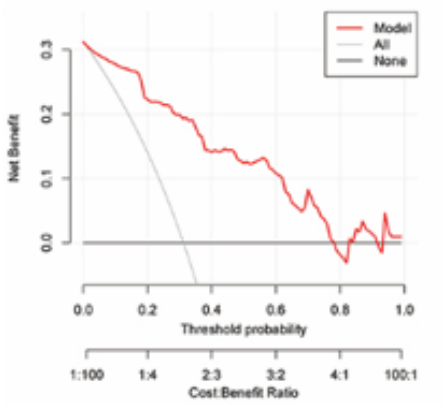


f)

Figure 3. Evaluation of the GBM framework: (a) feature-ranking box plot, (b) ROC curve for internal validation, (c) SHAP bee-swarm verification, (d) SHAP bar analysis, (e) calibration assessment, and (f) decision-curve analysis.

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.

GBM Modeling and testing results

After identifying GBM as the leading algorithm, additional refinement was carried out to construct a more dependable predictive system. A dataset of 184 patients (2017–2023) was randomly partitioned into training and validation groups using a 7:3 ratio. Ten-fold cross-validation was then applied to obtain the best tuning parameters. The optimized model achieved an AUC of 0.997, ACC of 0.988, Sen of 0.978, and Spe of 1. An independent set of 30 patients collected from January to December 2024, containing 5 lung-infection cases and 25 non-infection cases **(Table 1)**, yielded an AUC of 0.896, ACC of 0.860, Sen of 0.920, and Spe of 0.800 **(Figure 3b)**.

GBM model interpretation

SHAP analysis was used to provide global interpretability and to confirm which variables most strongly influenced the GBM model's decisions. GLO-1W, identified earlier as an essential feature, again showed the highest contribution **(Figure 3d)**. Lower GLO-1W values corresponded with greater SHAP outputs,

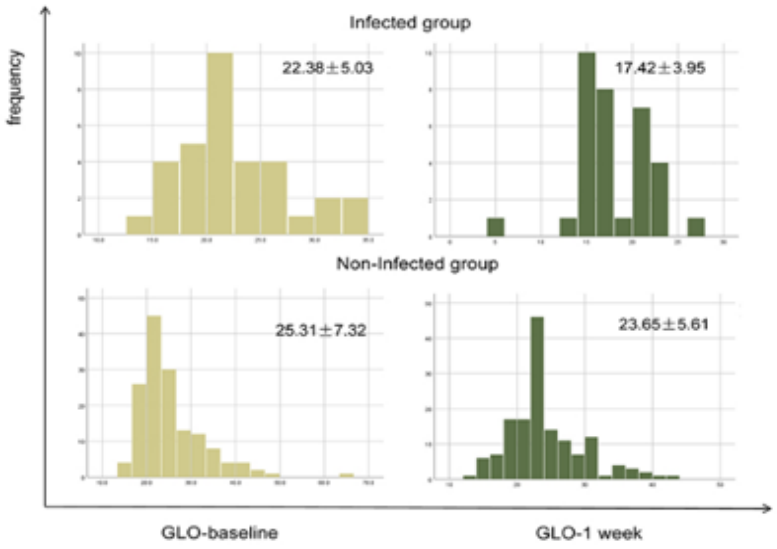
demonstrating a stronger positive effect on infection prediction **(Figure 3c)**, meaning that reduced GLO-1W was linked to higher infection risk.

GBM model evaluation

To further assess predictive reliability and clinical usefulness, calibration and DCA curves were plotted. The calibration assessment indicated close agreement between predicted probabilities and observed results **(Figure 3e)**. The decision-curve analysis revealed a clear positive net benefit, confirming that the GBM model has substantial clinical application value **(Figure 3f)**.

GLO after glucocorticoid therapy

The variable with the greatest influence was GLO-1W; to date, fluctuations in GLO itself have not been formally described. **Figure 4a** displays histograms showing pre- and post-therapy GLO patterns in both infected and non-infected cohorts. A marked reduction in GLO was detected after treatment ($P < 0.001$) **(Figure 4c)**, and values in the infected cohort were significantly lower than those in individuals without infection ($P < 0.001$). Within the infected subgroup, GLO levels dropped substantially after one week of glucocorticoid exposure relative to baseline ($P < 0.01$). Conversely, the non-infected subgroup did not exhibit a statistically meaningful change **(Figure 4b)**. The threshold GLO levels before and after treatment were 20 g/L and 21.5 g/L, respectively. Chi-square analysis indicated that patients with baseline GLO below 20 g/L showed an infection proportion of 41.1% ($P = 0.019$). As illustrated in **Figure 4d**, GLO values under 21.5 g/L following treatment corresponded to an infection rate of 82.3% ($P = 0.000$).



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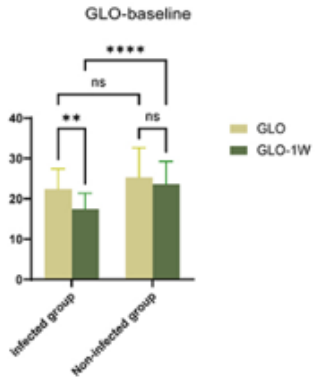

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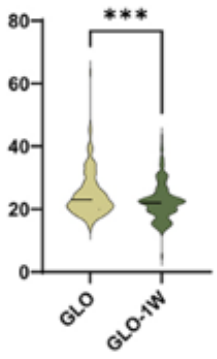

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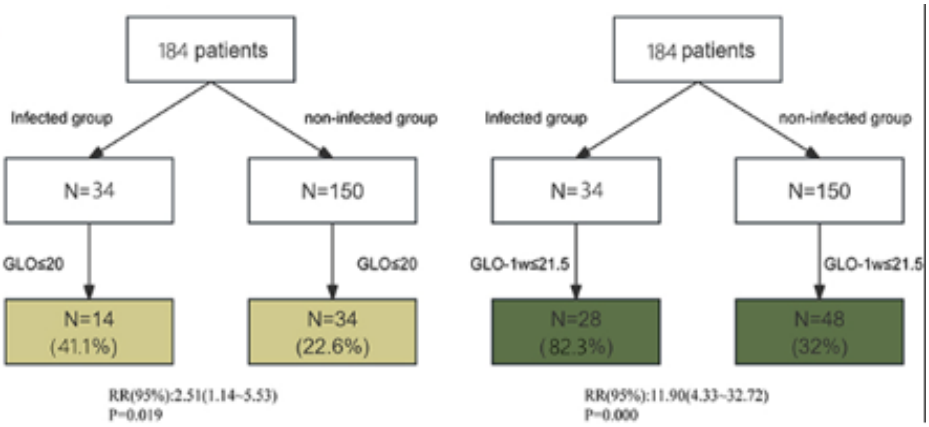

d)

Figure 4. (a) Histogram comparing GLO and GLO-1W across groups, (b) plot showing GLO variation pre- and post-therapy in infected versus non-infected subjects, (c) violin map of GLO before and after treatment, and (d) stratified chi-square charts for both time points.
Abbreviations: 1W, 1 week; GLO, globulin.

Mild DILI typically presents with slight hepatic function disturbances and usually resolves once the offending drug is withdrawn. In contrast, severe DILI requires inpatient care and aggressive management, and a subset of these patients can deteriorate into liver failure, which may be fatal. Hallmark features of severe DILI include elevated bilirubin levels and coagulation dysfunctions. Management strategies encompass stopping hepatotoxic agents, prescribing liver-supportive medications, using glucocorticoids, and, when necessary, providing artificial liver support or pursuing transplantation. Glucocorticoids are frequently used in patients with significant hyperbilirubinemia. Nonetheless, their overall effectiveness in severe DILI is still uncertain, adverse reactions are not uncommon, and major clinical guidelines show inconsistencies regarding glucocorticoid use [1, 9–11]. All available guidance emphasizes the need for large-scale studies to determine their benefits and limitations.

Hou *et al.* [6] examined 70 individuals with hepatocellular DILI and TBIL ≥ 10 × the upper limit of normal, 20 of whom received corticosteroids. Their results indicated that corticosteroid-treated patients improved more quickly. Hu *et al.* [5] retrospectively reviewed 33 patients with TBIL > 243 μmol/L who received glucocorticoids and similarly concluded that bilirubin recovery time was significantly shortened. Karkhanis *et al.* [12] analyzed 131 cases of drug-related hepatic failure, including 16 treated with corticosteroids, and noted no enhancement in overall survival. Our findings show that patients with severe DILI (TBIL > 85.5 μmol/L, encompassing both hepatic and non-hepatic failure) tended to recover more rapidly with glucocorticoid therapy. Although this treatment did not improve survival in those who already had hepatic failure, none of the non-hepatic failure patients receiving glucocorticoids (52 cases) progressed to hepatic failure or died—an outcome mirrored in the group not receiving glucocorticoids (52 cases). Three deaths resulted from hepatic failure in total. Thus, glucocorticoid administration may help prevent the onset of hepatic failure, suggesting potential clinical benefit.

To date, no publications have documented an increased infection risk specifically linked to glucocorticoid treatment for DILI, likely due to the absence of sufficiently large clinical datasets. Mechanistically, however, glucocorticoids weaken immune defenses, inherently predisposing patients to infections and other systemic hormonal side effects. Although the medication is inexpensive and often leads to quick recovery in severe DILI, the consequences of a serious infection can outweigh therapeutic gains, prompting many clinicians to avoid administering glucocorticoids in these scenarios [1, 9, 11]. This highlights the lack of strong, evidence-based support for their use. The characterization of glucocorticoid therapy as a “double-edged sword” remains accurate, underscoring the need for careful clinical judgment. Yet, concrete, data-driven guidance for decision-making in severe DILI is still absent.

This study retrospectively included 184 patients with severe DILI who received glucocorticoid therapy for model training and validation. A separate group of 30 patients was then prospectively enrolled for internal testing. Among those in the training/validation cohorts, 34 individuals developed infections during treatment or follow-up, with three deaths recorded. In the testing cohort, infections were identified in five patients. An assessment of biochemical markers at baseline and at one week of partial treatment revealed significant differences between infected and non-infected groups in inpatient duration; GLO, TBIL, AST, and EO values; platelet count; changes

in GLO (GLO1W–GLO); GLO-1W; ALT-1W; and PTA-1W ($p < 0.05$). Using these variables, eight machine-learning models were created, and the GBM model was selected based on comparative ROC performance and residual analyses. Further parameter tuning was achieved through ten-fold cross-validation, and internal evaluation demonstrated strong predictive capability. Consistency plots and DCA also supported the accuracy and clinical usefulness of the model. This framework offers potential for early detection of infectious complications in patients receiving glucocorticoids for severe DILI.

Analysis of selected indicators showed that baseline GLO values measured after one week of therapy were strongly associated with infection risk and could serve as part of an early alert strategy. Prior literature has not discussed the relationship between GLO variation and infection in the context of glucocorticoid use, and our work is the first to highlight the potential value of GLO as an early infection-related signal. GLO plays a central role in immune defense. Glucocorticoids may lower GLO concentrations directly or indirectly by modifying lymphocyte-subset distribution and dampening immune responsiveness [13], helping to explain the higher susceptibility to infection following glucocorticoid administration.

Our findings indicate a clear association between one-week baseline GLO values and the likelihood of infection, suggesting that this metric may offer clinicians a practical reference for adjusting glucocorticoid dose or duration to prevent infectious complications. Immunoglobulin supplementation could also be considered when necessary to reduce infection risk. Several patients in our institution have already benefited from such an approach. Nevertheless, because this investigation was performed at a single center with a limited number of cases, validation in larger, multi-center cohorts is essential.

Given China's large population and wide spectrum of medication use—including extensive use of TCM-NM-HP-DS—limited public and non-hepatology clinician awareness of DILI and drug-safety issues, combined with an aging demographic, has led to a growing number of drug-exposed individuals and a continued upward trend in DILI cases. Primary care facilities frequently rely on glucocorticoids for severe DILI, as treatment often accelerates recovery and shortens hospitalization. However, severe infections increase mortality and demand extensive medical resources, making clinicians cautious about hormonal therapy. Our infection early-warning model, along with close monitoring of GLO levels, provides a meaningful tool for guiding glucocorticoid administration and supporting prevention strategies.

To support clinical implementation, the model-related assessment scales have already been incorporated into our institutional workflow. As additional data accumulate, we intend to prepare research manuscripts and develop a web-based prediction platform for broader clinical use. Nonetheless, the present study's single-center design remains a limitation, and external verification through collaborative multicenter studies is needed.

Conclusion

The infection early-warning model offers a useful reference for optimizing glucocorticoid use in severe DILI. Tracking GLO fluctuations may serve as a straightforward and effective method for reducing infection risk.

Research in context

Evidence before this study

Reports from recent years show that the yearly rate of Drug-Induced Liver Injury (DILI) continues to rise, and international epidemiological surveys now identify DILI as a prominent contributor to acute liver failure worldwide, with few effective therapies available. A PubMed search covering all entries up to March 2025, using the terms **"**DILI, machine learning, infection, globulin", indicated that the majority of published work focuses on using machine-learning tools to anticipate the onset or progression of DILI. Only a small portion of the literature explores models intended to guide management or treatment outcomes after DILI has occurred.

Added value of this study

This investigation introduces a predictive approach for estimating infection risk in patients experiencing hormone therapy–related liver injury and outlines practical measures to aid clinicians in choosing medications that help lower infection probability. A defining feature of our framework is the incorporation of "globulin" as a principal assessment variable, enabling clearer and more streamlined clinical judgments. The model also showed strong performance in terms of calibration and overall clinical applicability.

Implications of all the available evidence

The model presented here may serve as a useful decision-support tool for hormone-treated individuals with drug-induced liver injury, offering guidance that could decrease infection risk. Tracking fluctuations in GLO levels may provide a straightforward means for clinicians to monitor and prevent emerging infectious complications.

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Conflict of Interest: None

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Ethics Statement: None

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