

A machine learning-based model for assessing the risk of new-onset liver injury following cardiac surgery under cardiopulmonary bypass

Zhuo Zheng

West China Hospital of Sichuan University

Jiawei Luo

West China Hospital of Sichuan University

Liren Yang

West China Hospital of Sichuan University

Yishun Wang

West China Hospital of Sichuan University

Xiaoyan Yang

West China Hospital of Sichuan University

Xiaobo Zhou

The University of Texas Health Science Center at Houston

Yingqiang Guo

West China Hospital of Sichuan University

Lei Du

dulei@scu.edu.cn

West China Hospital of Sichuan University

Article

Keywords: Cardiac Surgery, Cardiopulmonary Bypass, Liver Injury, Predictive Modeling, Postoperative Complications

Posted Date: August 26th, 2024

DOI: <https://doi.org/10.21203/rs.3.rs-4766168/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Objective:

This study aimed to develop and validate a predictive model for assessing the risk of new-onset liver injury following cardiac surgery under cardiopulmonary bypass (CPB), using non-redundant and informative features extracted from electronic health records.

Materials and Methods:

We employed machine learning algorithms including Generalized Additive Model (GAM), Random Forest, XGBoost, LightGBM, and Fully Convolutional Network (FCN) to construct the models using data from 5,364 patients at a large medical center in China, and validated these models with an independent dataset of 1,207 patients from another center. A three-stage feature selection process was used to refine the input variables.

Results:

The GAM model displayed the best performance with good predictive accuracy in both internal and external validations, despite a noticeable performance decline in the external dataset potentially due to differences in feature distributions. The most impactful factors included CPB time, cryo time, and preoperative bilirubin levels.

Conclusion:

The predictive model developed provides a valuable tool for early identification of patients at risk of postoperative liver injury, potentially aiding in preventive treatment planning. However, the model requires further prospective validation and optimization for broader application across different medical centers. The model's robustness against clinical practice variations highlights its potential utility in improving patient safety and reducing healthcare costs.

Key points

Question:

What are the key predictors for new-onset liver injury post-cardiac surgery under cardiopulmonary bypass, and how effectively can a predictive model assess these risks preoperatively?

Findings:

The machine learning models, particularly the Generalized Additive Model (GAM), identified cryo time, CPB time, and preoperative bilirubin levels as significant predictors of postoperative liver injury. The models demonstrated good predictive accuracy, with the GAM model showing the highest performance metrics both internally and externally.

Meaning:

The development of a machine learning-based predictive model offers a valuable clinical tool for early identification of patients at risk for new-onset liver injury post-cardiac surgery. This tool can aid in preventive treatment planning, potentially enhancing patient outcomes and reducing healthcare costs.

Introduction

Millions of patients globally undergo cardiac surgery each year, many utilizing cardiopulmonary bypass (CPB) technology to maintain circulation and oxygenation^[1–4]. While CPB supports bloodless surgical procedures, it may also increase the risk of new-onset liver injury postoperatively, often linked to abnormal increases in liver enzymes such as aspartate transaminase (AST) and alanine transaminase (ALT)^[5–7]. Severe cases can lead to high mortality^[8]. However, the occurrence of liver injury following cardiac surgery is considered a rare postoperative complication, with limited literature available. The incidence of liver failure post-cardiac surgery is about 4%, but up to 10% of patients undergoing CPB may experience some degree of liver injury^[9]. Thus, being able to predict which patients might develop new-onset liver injury after cardiac surgery, and the severity of their risk, could help optimize postoperative care and interventions, especially among those at high risk.

To our knowledge, there is a lack of exploration in predictive models for liver enzyme abnormalities and liver injury post-cardiac surgery under CPB in patients with previously normal liver function. Existing clinical scoring systems and studies primarily focus on tasks like short-term or long-term mortality, length of hospital stay, and acute kidney injury post-cardiac surgery^[10–15]. However, these models are not directly applicable for assessing the risk of liver injury.

Therefore, the aim of this study is to develop a risk assessment tool for new-onset liver injury specific to the context of cardiac surgery under CPB, based on preoperative and intraoperative data directly extracted from patient electronic health records. Through a meticulously designed three-step feature selection scheme, we identified a set of non-redundant, informative risk factors, and subsequently utilized machine learning algorithms to account for the non-linear relationships between these factors and liver injury, creating a personalized postoperative new-onset liver injury risk prediction model. This model was validated in external cohorts from different medical centers. We hypothesize that the model we constructed will produce satisfactory results in predicting the risk of new-onset liver injury following cardiac surgery under CPB.

Materials and Methods

All methods were performed in accordance with the relevant guidelines and regulations.

Population and Dataset

This study received ethical approval from the Ethics Committees of the Second Affiliated Hospital of Zhejiang University School of Medicine in Hangzhou (approval number: 096/2017) and West China Hospital of Sichuan University in Chengdu (approval number: 256/2017). Patient data was sourced from two institutions: Sichuan University West China Hospital, which contributed data from 7,102 adult patients who underwent cardiac surgery under cardiopulmonary bypass from January 1, 2011, to June 30, 2017, and Zhejiang University School of Medicine Second Affiliated Hospital, which provided data from 1,419 patients from September 1, 2013, to June 30, 2017. We excluded patients who (1) had pre-existing liver dysfunction, cirrhosis, or met the criteria for liver injury in preoperative laboratory tests; (2) underwent emergency surgeries; (3) died intraoperatively; (4) underwent surgery for aortic dissection; (5) experienced postoperative difficulties in discontinuing CPB; and (6) lacked perioperative data on AST, ALT, or total bilirubin, which are necessary for annotating liver injury. After these exclusions, 5,364 patients from Sichuan University West China Hospital and 1,207 from Zhejiang University School of Medicine Second Affiliated Hospital were included in the study. Data from Sichuan University West China Hospital were randomly divided in an 8:2 ratio into a training set for model development and an internal test set for model validation. Data from Zhejiang University School of Medicine Second Affiliated Hospital were used as an external test set (Fig. 1).

Definition of Liver Injury

Due to differences in the definitions of liver injury between males and females, we have gender-specific criteria for postoperative new-onset liver injury. Liver injury is identified when the maximum postoperative AST or ALT levels exceed three times the upper limit of normal (ULN) or when total bilirubin levels exceed twice the ULN. For males, the ULN for AST or ALT is set at 56 U/L, and for females, it is 45 U/L. The ULN for total bilirubin is set at 17 mg/dL for all individuals.

Data Preprocessing

The predictive factors included in this study encompass demographic data, medical history, preoperative diagnoses, laboratory tests, and intraoperative parameters (**Supplementary Table S1**). The last laboratory test results before surgery were chosen for preoperative data. Data preprocessing involved identifying outliers within reasonable value ranges to correct any erroneous entries in medical records. For missing data, we used multiple imputations by chained equations (MICE) to fill in missing values and mitigate bias in the results analysis. **Supplementary Figure S1** illustrates the patterns of missing data in the internal and external datasets.

Feature Selection Algorithm

In this study, a filtering method was employed for feature selection. The first step involved scoring each variable using machine learning or statistical methods to represent their importance, followed by ranking

them based on these scores. The second step utilized an incremental feature selection (IFS) strategy to choose the optimal set of variables. This strategy involves adding variables incrementally according to their importance, forming various subsets of variables. The first subset contains the top-ranked feature, the second includes the top two features, and so on until all subsets are formed. The algorithm then evaluates the performance of each subset and selects the subset that performs best as the optimal variable subset. In this research, the IFS strategy was combined with logistic regression, Pearson correlation coefficient (PCC), and the statistical significance of variable coefficients based on generalized additive model (GAM) to select the optimal subset of variables.

Liver Injury Risk Assessment Model

In this study, five models were compared: Generalized Additive Model^[16], Random Forest, XGBoost^[17], LightGBM^[18], and Fully Convolutional Network (FCN)^[19]. These algorithms each possess distinct characteristics. The Generalized Additive Model is a statistical model capable of capturing non-linear relationships between variables through smoothing functions, offering flexibility and interpretability. This method is particularly suited for analyzing complex interactions between variables. Random Forest, an ensemble learning method based on decision trees, improves prediction accuracy by averaging predictions across multiple trees and is effective for handling data with complex interactions. XGBoost, a tree-based model, is one of the best performing in its category and optimizes performance through gradient boosting. LightGBM, a gradient boosting framework, utilizes a histogram-based algorithm that allows faster training and more efficient memory usage compared to other tree-based methods. FCN is a multi-layer neural network model that has emerged in recent years, capable of learning non-linear features. All models used the same input variables.

Model Evaluation

In the feature selection phase, models generated by the Incremental Feature Selection (IFS) strategy were evaluated using the area under the receiver operating characteristic curve (AUROC) values under five-fold cross-validation to select the optimal subset of variables. In the model performance evaluation phase, models built with GAM, Random Forest, XGBoost, LightGBM, and FCN were assessed on independent internal and external validation sets using recall, accuracy, precision, F1 score, AUROC, area under the precision-recall curve (AUPRC), ROC curves, and PRC curves to identify the best modeling approach. Bootstrap resampling, set at 200 iterations, was used to estimate 95% confidence intervals for these metrics.

Statistical Methods

Continuous variables following a normal distribution are presented as mean (standard deviation); skewed distributions are presented as median [IQR]; categorical variables are shown as numbers (percentage, %). In the GAM model, continuous numerical variables were transformed nonlinearly using penalized cubic splines. Since new-onset liver injury post-cardiac surgery is a binary prediction task, the model was built using GAM based on logistic regression. The Wald Chi-square test was used to assess the significance of the coefficients for both continuous and categorical variables in the generalized

additive model. This involves evaluating the non-linear relationships modeled by cubic regression splines for continuous variables and the impact of categorical factors on the outcome variable. In comparing internal and external datasets, if the continuous data are normally distributed, analysis is conducted via t-tests; otherwise, the Mann-Whitney U test is used. Categorical variables are presented in frequencies and percentages, and are analyzed through the chi-square test or Fisher's exact test. A two-sided P value < 0.05 is considered statistically significant.

Implementation Details

The GAM model was constructed using the 'mgcv' package in R software, while the machine learning models were built using the 'scikit-learn' package in Python. The calculation of Shapley values for the GAM model was conducted using the 'fastshap' package in R, and for other models, Shapley values were calculated using the 'shap' package in Python. Web-based computational tools were developed using the 'shiny' package in R. Multiple imputations by chained equations were performed using the 'mice' package in R. The versions used were R 4.1.2 and Python 3.7.3.

Results

Datasets and Descriptive Statistics

Figure 1 shows the relationships between each dataset used in this study and provides their sample sizes. Initially, our dataset was divided by different centers; subsequently, we randomly split the internal data into a training set and an internal validation set at an 8:2 ratio. This division resulted in three distinct datasets for our analysis: a training dataset consisting of 4,292 patients, an internal validation dataset with 1,072 patients, and an external validation dataset comprising 1,207 patients. The median age in the internal dataset was 51.00 [45.00, 60.00] years, with 39.5% being male, whereas the external dataset had a median age of 59.00 [51.00, 66.00] years, with 51.0% male. Most patients underwent valve-related surgeries, and the average surgery duration exceeded four hours for both groups. Significant differences were observed between the two datasets in most measured variables, particularly with patients in the external dataset generally exhibiting poorer health conditions. The incidence of new-onset liver injury post-surgery was also higher in the external dataset compared to the internal dataset (Table 1; **Supplementary Table S2**).

Table 1
Baseline characteristics of patients in the internal and external data sets.

	Internal		External		<i>P</i> value
	Overall	Training	Internal validation	External validation	
N	5364	4292	1072	1207	
Demographic Characteristics					
Age (year)	51.00 [45.00, 60.00]	51.00 [45.00, 60.00]	52.00 [45.00, 60.00]	59.00 [51.00, 66.00]	< 0.001
Gender (Male)	2117 (39.5)	1671 (38.9)	446 (41.6)	616 (51.0)	< 0.001
Ethnicity					< 0.001
Han Chinese	5208 (97.1)	4167 (97.1)	1041 (97.1)	1204 (99.8)	
Tibetan	78 (1.5)	61 (1.4)	17 (1.6)	2 (0.2)	
Other	78 (1.5)	64 (1.5)	14 (1.3)	1 (0.1)	
Current smoker	1441 (26.9)	1134 (26.4)	307 (28.6)	364 (30.2)	0.024
Current alcohol	985 (18.4)	774 (18.0)	211 (19.7)	205 (17.0)	0.242
BMI (kg/m ²)	22.68 [20.72, 24.97]	22.72 [20.76, 24.91]	22.66 [20.58, 25.08]	22.39 [20.33, 24.61]	0.001
Intraoperative data					
Cryo time (minute)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	< 0.001
Intraoperative RBC transfusion (U)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	2.00 [0.00, 4.00]	< 0.001
CPB time (minute)	112.00 [87.00, 137.00]	111.00 [87.00, 137.00]	114.00 [89.00, 138.00]	118.00 [87.00, 152.00]	< 0.001
Operation time (hour)	4.80 [4.17, 5.50]	4.75 [4.10, 5.50]	4.90 [4.25, 5.58]	4.00 [3.30, 5.00]	< 0.001

	Internal		External		<i>P</i> value
	Overall	Training	Internal validation	External validation	
Aortic cross-clamp time (minute)	73.00 [55.00, 95.00]	72.00 [55.00, 95.00]	74.00 [56.00, 96.00]	84.00 [59.00, 115.00]	< 0.001
CPB machine blood volume (mL)	600.00 [600.00, 800.00]	600.00 [600.00, 800.00]	600.00 [600.00, 800.00]	500.00 [500.00, 650.00]	< 0.001
NYHA classification					
Ⅰ	77 (1.4)	56 (1.3)	21 (2.0)	71 (5.9)	< 0.001
Ⅱ	1326 (24.7)	1063 (24.8)	263 (24.5)	498 (41.3)	
Ⅲ	3853 (71.8)	3091 (72.0)	762 (71.1)	536 (44.4)	
Ⅳ	108 (2.0)	82 (1.9)	26 (2.4)	102 (8.5)	
ASA physical status					
Ⅰ	96 (1.8)	73 (1.7)	23 (2.1)	166 (13.8)	< 0.001
Ⅱ	4991 (93.0)	3999 (93.2)	992 (92.5)	954 (79.0)	
Ⅲ	277 (5.2)	220 (5.1)	57 (5.3)	87 (7.2)	
Surgery type					
Simple Valve Replacement Surgery	2046 (38.1)	1664 (38.8)	382 (35.6)	529 (43.8)	< 0.001
Complex Valve Replacement Surgery	2761 (51.5)	2195 (51.1)	566 (52.8)	402 (33.3)	< 0.001
CABG	441 (8.2)	334 (7.8)	107 (10.0)	204 (16.9)	< 0.001
Myxoma Resection Surgery	58 (1.1)	50 (1.2)	8 (0.7)	0 (0.0)	0.001
Valve Replacement and CABG	58 (1.1)	49 (1.1)	9 (0.8)	72 (6.0)	< 0.001
Radiofrequency Ablation Surgery	1221 (22.8)	1002 (23.3)	219 (20.4)	133 (11.0)	< 0.001
Thrombus Removal Surgery	606 (11.3)	497 (11.6)	109 (10.2)	58 (4.8)	< 0.001

	Internal		External		<i>P</i> value
	Overall	Training	Internal validation	External validation	
Outcome					
Liver injury	1088 (20.3)	871 (20.3)	217 (20.2)	525 (43.5)	< 0.001

ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; NYHA, New York Heart Association; RBC, red blood cell.

Liver Injury Risk Factor Selection

To identify representative and stable features from the initial pool of potential risk factors, we conducted a three-stage feature selection process for all preoperative and intraoperative characteristics. In the first stage, LR was employed as the base classifier, and each feature's discriminative power was evaluated through five-fold cross-validation. Features were then ranked based on their AUROC. Using incremental feature selection (IFS), 43 relevant indicators were filtered out (Fig. 2a, Supplementary **Table S3**).

In the second stage, we examined the correlations between these 43 features using the Pearson Correlation Coefficient (PCC). If the correlation coefficient between two features exceeded 0.4, the feature with the lower AUROC was removed, retaining the one with the higher AUROC. For example, features like International Normalized Ratio and Partial Thromboplastin Time were excluded due to their correlation with Prothrombin Time surpassing the 0.4 threshold, leaving 32 features to advance to the next stage (Fig. 2b).

The third stage involved constructing a Generalized Additive Model (GAM), incorporating the variables selected from the second stage. All continuous numerical variables were transformed non-linearly using restricted cubic splines, with postoperative liver injury as the dependent variable. Feature selection was based on the statistical significance of variables ($P < 0.05$) (Fig. 2c). The optimal feature subset comprised 8 variables, including age, preoperative status (total bilirubin, prothrombin time, alanine aminotransferase, hypothyroidism), and intraoperative conditions (CPB time, cryo time, intraoperative red blood cell transfusion) (Supplementary **Table S4**).

This three-stage feature selection scheme ensured transparency throughout the process, making the selected features easier to interpret and understand while yielding stable results. The first stage quantified the individual contribution of each feature to new-onset liver injury. In the second stage, we used intuitive and direct PCC to assess redundancy between features. The third stage employed a model-based feature selection scheme to enhance model performance.

Model Performance Evaluation

We input the 8 selected features (age, total bilirubin, prothrombin time, alanine aminotransferase, hypothyroidism, CPB time, cryo time, intraoperative red blood cell transfusion) into five different algorithms: GAM, Random Forest, XGBoost, LightGBM, and FCN, to construct risk assessment models for new-onset liver injury post-cardiac surgery and compared their performance on both internal and external validation sets. Given the potential nonlinear relationships between continuous numerical features and liver injury, we used GAM as a substitute for the classical linear classifier, LR. Evaluation metrics for the five models, including AUROC, AUPRC, accuracy, precision, recall, and F1 score, are recorded in Table 2. As shown in Fig. 2d, the performance of the five algorithms was very similar, with the GAM model slightly outperforming the other four. On the internal validation set, the GAM model predicted new-onset liver injury with an AUROC of 0.74 (0.70, 0.77), an AUPRC of 0.45 (0.37, 0.51), and a Brier score of 0.14. On the external validation set, the GAM model demonstrated consistent and stable performance, with an AUROC of 0.67 (0.64, 0.70) and an AUPRC of 0.61 (0.56, 0.66), and a Brier score of 0.22.

It is noteworthy that when data are straightforward and there is a low degree of linear correlation between variables, the fit of various algorithms tends to be similar. However, in the current dataset, the GAM model exhibited slightly better performance, possibly due to its use in the third stage of feature selection, making it better suited to the results of the current feature selection. This also illustrates that the restricted cubic splines in GAM effectively model the nonlinear relationships between some variables and postoperative liver injury.

Decision curve analysis indicates that in the internal validation set, when the probability of predicting new-onset liver injury is greater than 0.04 and less than 0.79, this predictive model provides more clinical benefit than the "treat all patients" or "treat no patients" approach. Similarly, in the external validation set, when the threshold probability of predicting new-onset liver injury is greater than 0.38 and less than 0.71, this predictive model offers more clinical benefit than the "treat all patients" or "treat no patients" approach (Supplementary **Figure S2**).

Table 2
Performance Metrics of the Postoperative New-Onset Liver Injury Risk Assessment Model.

Data	Model	AUROC	AUPRC	Accuracy	Recall	Precision	F1
Internal validation	GAM	0.74	0.45	0.68	0.69	0.35	0.47
		(0.70, 0.77)	(0.37, 0.51)	(0.62, 0.76)	(0.55, 0.78)	(0.30, 0.43)	(0.42, 0.52)
	FCN	0.72	0.43	0.63	0.74	0.32	0.45
		(0.68, 0.75)	(0.37, 0.49)	(0.58, 0.75)	(0.55, 0.82)	(0.29, 0.41)	(0.41, 0.49)
	RF	0.70	0.40	0.67	0.61	0.33	0.43
		(0.67, 0.74)	(0.34, 0.47)	(0.60, 0.77)	(0.45, 0.74)	(0.27, 0.45)	(0.38, 0.49)
External validation	GAM	0.67	0.61	0.62	0.68	0.56	0.61
		(0.64, 0.70)	(0.56, 0.66)	(0.61, 0.67)	(0.42, 0.73)	(0.53, 0.67)	(0.51, 0.64)
	FCN	0.66	0.59	0.63	0.57	0.58	0.58
		(0.62, 0.68)	(0.55, 0.63)	(0.59, 0.66)	(0.49, 0.72)	(0.52, 0.63)	(0.54, 0.63)
	RF	0.65	0.59	0.62	0.48	0.58	0.52
		(0.62, 0.68)	(0.55, 0.64)	(0.58, 0.66)	(0.31, 0.74)	(0.50, 0.69)	(0.43, 0.61)
	Lightgbm	0.67	0.60	0.61	0.70	0.54	0.61
		(0.64, 0.69)	(0.56, 0.65)	(0.60, 0.67)	(0.44, 0.81)	(0.52, 0.65)	(0.52, 0.64)
	Xgboost	0.67	0.61	0.63	0.59	0.58	0.58
		(0.63, 0.69)	(0.56, 0.65)	(0.60, 0.67)	(0.46, 0.78)	(0.53, 0.64)	(0.51, 0.65)

Relationship Between Features and Liver Injury

We utilized Shapley Additive Explanations (SHAP) for interpretability analysis. The best-performing GAM model and the similarly effective XGBoost model were selected to compute SHAP values. Figures 3a and 3b show the ranking of feature importance in the training set for the GAM and XGBoost models, respectively. Figures 3c and 3d display SHAP plots representing all samples in the training set based on the GAM and XGBoost models, where color indicates the magnitude of feature values (red for high, blue for low, and purple for values close to the average). The magnitude of values on the x-axis indicates their impact on the model. These factors have a minor influence on the risk of liver injury when they are at or below the average value. However, as these values exceed the average, their impact on the risk of liver injury significantly increases with increasing values. These visuals suggest that there might be nonlinear relationships between continuous features and the occurrence of new-onset postoperative liver injury. Consequently, to further analyze the quantitative relationships between continuous features and the risk of postoperative liver injury, we explored the marginal effects of each continuous feature on the risk of liver injury within the GAM model. Figure 4a displays the restricted natural cubic spline plots for continuous numerical variables and the risk of postoperative liver injury in the GAM model. Additionally, we plotted dependency graphs based on the SHAP values and variable values for the XGBoost model (Fig. 4b). The nonlinear relationships between these continuous features and new-onset postoperative liver injury are generally consistent in both the GAM and XGBoost models. However, in regions with smaller sample sizes, the effects of features in the GAM model exhibit high variance, indicating less reliability in the effect estimates for these areas, such as a sharp increase in the variance of risk estimates for new-onset liver injury in patients over 77 years old. In these continuous variables, preoperative Total Bilirubin (TBil), CPB time, cryo time, preoperative ALT, and intraoperative red blood cell transfusion exhibits a monotonic relationship with the risk of new-onset postoperative liver injury, meaning the risk increases monotonically as the values of these features increase. There may be a U-shaped relationship between preoperative PT and the risk of new-onset postoperative liver injury.

Discussion

In this work, we leveraged machine learning algorithms to design a postoperative new-onset liver injury risk assessment model for patients undergoing cardiac surgery under cardiopulmonary bypass, using a set of selected non-redundant and informative features based on preoperative and intraoperative data. The goal is to identify patients at high risk of postoperative liver injury in advance, thereby assisting physicians in taking preventive treatment measures to reduce the incidence or severity of liver injury. The required input variables for the model are readily available from electronic health records. To our knowledge, this is the first predictive model for postoperative new-onset liver injury among the Chinese population, developed using data from 5,364 patients at a major medical center in China and validated independently with 1,207 patients at another medical center. The model demonstrated good predictive performance in the internal validation set but showed a slight decline in the external validation process. This decline may be attributed to differences in feature distributions between the internal and external data. The patients in the external validation set were notably older, with higher CPB time and

intraoperative red blood cell transfusion, factors that increase the risk of postoperative new-onset liver injury, helping explain the higher incidence rates in the external validation set.

Despite these differences, our model still showed good predictive performance and might be robust against clinical practice variations across different medical centers. However, our model should be prospectively optimized and regularly updated to reflect current practices. During CPB-assisted cardiac surgery, organ blood flow is provided by non-pulsatile flow and relatively lower pressures^[15, 20]. Additionally, the use of anesthetics, antibiotics, and anticoagulants, commonly employed in cardiac surgeries, can impact liver function and may lead to acute liver injury^[21]. The effects on the liver can be exacerbated in individuals with underlying liver conditions or risk factors. Therefore, we found that patients with higher preoperative TBil and ALT levels had a higher incidence of postoperative liver injury. Furthermore, we identified CPB time as a prominent risk factor strongly correlated with new-onset liver injury post-surgery, consistent with previous studies that link CPB to liver ischemia-reperfusion, acute systemic inflammatory response syndrome^[22, 23], and oxidative stress. Artificial cooling during cardiopulmonary bypass is a crucial part of the procedure, used to reduce metabolic demand and protect vital organs, especially the brain and heart^[24, 25]. However, this artificial cooling can exacerbate systemic inflammatory responses, coagulation disorders, and organ dysfunction. Restricted cubic spline plots suggest that even brief periods of cooling can linearly increase the risk of postoperative liver injury as the duration extends. Prolonged cooling may decrease liver blood flow due to vasoconstriction and blood redistribution caused by low temperatures, leading to liver dysfunction or damage due to the liver's high sensitivity to oxygen deprivation^[26, 27].

Intraoperative red blood cell transfusion is also an important risk factor for new-onset postoperative liver injury. Evidence from cardiac surgery research clearly indicates that transfusions are associated with increased morbidity and mortality, and these adverse effects increase in a dose-dependent manner^[28–30]. During the perioperative period, intraoperative red blood cell transfusions are commonly employed to increase hemoglobin levels, enhance tissue oxygen delivery, and improve hypoxia. However, these transfusions can activate immune and inflammatory responses. This is particularly critical in cardiac surgery and cardiopulmonary bypass, where the introduction of bioactive substances from transfused red blood cells may exacerbate organ dysfunction^[31, 32]. Additionally, multiple transfusions increase the risk of adverse reactions due to exposure to different donor immune systems. Furthermore, the U-shaped relationship between prothrombin time and the risk of new-onset liver injury post-surgery underscores the importance of maintaining PT within a normal range to ensure that it is neither prone to clotting nor excessive bleeding^[33–35].

Conclusion

In summary, we established and externally validated a model based entirely on preoperative and intraoperative data easily extracted from electronic health records, which could help facilitate interventions to reduce the incidence or severity of liver injury in high-risk populations after CPB-assisted

cardiac surgeries. With further prospective improvements and validation, our model could support enhancing patient safety and reducing healthcare costs. Notably, our model represents an important step towards developing personalized postoperative liver injury risk assessments. We have provided an online tool based on the developed machine learning model for assessing the risk of new-onset liver injury after cardiac surgery, accessible at https://jiaweihome.shinyapps.io/liver_injury_pred/. This tool allows for the calculation of the risk of postoperative new-onset liver injury based on 8 submitted indicators, thus facilitating the management of personalized postoperative liver injury complications.

Limitations

The representativeness of the sample included in this study is limited, for example, there are fewer samples for patients older than 77 years, which may limit the generalizability of the model. Additionally, some variables related to medical interventions, such as CPB time and cryo time, were included in the model. The distribution of these factors is closely related to geographic location, medical standards, and environment, which may lead to similar performance declines when the model is externally validated in other medical centers. Secondly, as there were no available studies on models for postoperative new-onset liver injury after cardiac surgery for comparison, our analysis was only comparative between different machine learning models. Thirdly, our definition of liver injury relies on ALT, AST, and TBil, which may lack comprehensiveness in evaluating liver function.

Declarations

Conflict of Interest and Financial Disclosure:

All authors declare that there are no potential conflicts of interest or financial disclosures related to this study within the 36 months prior to this submission.

Funding

This research was funded by the Center of Excellence-International Collaboration Initiative Grant at West China Hospital, Sichuan University (Grant Number: 139170052), as well as the Sichuan Science and Technology Program (Grant Number: 2023YFS0200).

Ethics approval and consent for participate

This study was approved by the Ethics Committees of the Second Affiliated Hospital of Zhejiang University School of Medicine in Hangzhou (096/2017) and West China Hospital of Sichuan University in Chengdu (256/2017). Due to the retrospective nature of the data used in this study, the requirement for informed consent was waived by the Ethics Committee.

Consent for publication

All authors have reviewed the final version of the manuscript and approved its submission.

Competing interests

All authors declare no conflicts of interest in this study

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Due to patient privacy and confidentiality agreements, the data are not publicly available. All data provided will be de-identified to ensure patient confidentiality.

Author contributions

Name: Zhuo Zheng (M.Med)

Contribution: This author participated in designing the analysis plan, extracting research data, interpreting data, writing the manuscript, and approving the final version.

Name: Jiawei Luo (Ph.D)

Contribution: This author participated in designing the analysis plan, performing data analysis, interpreting data, drafting the manuscript, and revising the final version.

Name: Liren Yang (M.Sc)

Contribution: This author assisted with data extraction and analysis, and revised and approved the final manuscript.

Name: Yishun Wang (M.Med)

Contribution: This author assisted with data extraction, drafted the manuscript, and approved the final version.

Name: Xiaoyan Yang (Ph.D)

Contribution: This author assisted in designing the analysis plan, drafting the manuscript, and approving the final version.

Name: Xiaobo Zhou (Ph.D)

Contribution: This author assisted in designing the analysis plan, drafting the manuscript, and approving the final version.

Name: Yingqiang Guo (M.D.)

Contribution: This author assisted in designing the analysis plan, drafting the manuscript, and approving the final version.

Name: Lei Du (M.D.)

Contribution: This author assisted in designing the analysis plan, drafting the manuscript, and approving the final version.

References

1. AYKUT A, ZENGİN E N, DEMİR Z A. Acute Hepatic Injury Following Cardiac Surgery: Retrospective Observational Study [J]. *Journal of Anesthesia/Anestezi Dergisi (JARSS)*, 2023, 31(4).
2. WEISSE A B. Cardiac surgery: a century of progress [J]. *Texas Heart Institute Journal*, 2011, 38(5): 486.
3. IQBAL U, HANIF M, IQBAL N. Effect of cardiopulmonary bypass on liver function in patients undergoing coronary artery bypass grafting [J]. *Biomedica*, 2015, 31(1): 27.
4. ZAKKAR M, GUIDA G, SULEIMAN M, et al. Cardiopulmonary bypass and oxidative stress [J]. *Oxidative Medicine and Cellular Longevity*, 2015, 2015.
5. RAVEENDRAN D, PENNY-DIMRI J C, SEGAL R, et al. The prognostic significance of postoperative hyperbilirubinemia in cardiac surgery: systematic review and meta-analysis [J]. *Journal of Cardiothoracic Surgery*, 2022, 17(1): 129.
6. SABZI F, FARAJI R. Liver function tests following open cardiac surgery [J]. *Journal of cardiovascular and thoracic research*, 2015, 7(2): 49.
7. RAHBARI N N, GARDEN O J, PADBURY R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS) [J]. *Surgery*, 2011, 149(5): 713-24.
8. KIROV H, CALDONAZO T, AUDISIO K, et al. Association of liver dysfunction with outcomes after cardiac surgery—a meta-analysis [J]. *Interactive CardioVascular and Thoracic Surgery*, 2022, 35(6): ivac280.
9. MICHALOPOULOS A, ALIVIZATOS P, GEROULANOS S. Hepatic dysfunction following cardiac surgery: determinants and consequences [J]. *Hepato-gastroenterology*, 1997, 44(15): 779-83.
10. NASHEF S A, ROQUES F, SHARPLES L D, et al. Euroscore ii [J]. *European journal of cardio-thoracic surgery*, 2012, 41(4): 734-45.
11. MIYATA H, TOMOTAKI A, MOTOMURA N, et al. Operative mortality and complication risk model for all major cardiovascular operations in Japan [J]. *The Annals of thoracic surgery*, 2015, 99(1): 130-9.
12. LAPAR D J, LIKOSKY D S, ZHANG M, et al. Development of a risk prediction model and clinical risk score for isolated tricuspid valve surgery [J]. *The Annals of thoracic surgery*, 2018, 106(1): 129-36.
13. SIREGAR S, GROENWOLD R H, DE HEER F, et al. Performance of the original EuroSCORE [J]. *European journal of cardio-thoracic surgery*, 2012, 41(4): 746-54.
14. KWIECINSKI J, DABROWSKI M, NOMBELA-FRANCO L, et al. Machine learning for prediction of all-cause mortality after transcatheter aortic valve implantation [J]. *European Heart Journal-Quality of Care and Clinical Outcomes*, 2023: qcad002.

15. DI TOMASSO N, MONACO F, LANDONI G. Hepatic and renal effects of cardiopulmonary bypass [J]. Best practice & research Clinical anaesthesiology, 2015, 29(2): 151-61.
16. WOOD S N. Generalized additive models: an introduction with R [M]. chapman and hall/CRC, 2017.
17. CHEN T, GUESTRIN C. Xgboost: A scalable tree boosting system; proceedings of the Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining, F, 2016 [C].
18. KE G, MENG Q, FINLEY T, et al. Lightgbm: A highly efficient gradient boosting decision tree [J]. Advances in neural information processing systems, 2017, 30.
19. RUMELHART D E, HINTON G E, WILLIAMS R J. Learning representations by back-propagating errors [J]. nature, 1986, 323(6088): 533-6.
20. CHACON M M, SCHULTE T E. Liver dysfunction in cardiac surgery—what causes it and is there anything we can do? [J]. Journal of Cardiothoracic and Vascular Anesthesia, 2018, 32(4): 1719-21.
21. YAMADA T, OCHIAI R, TAKEDA J, et al. Off-pump coronary artery bypass attenuates transient hepatocellular damage after myocardial revascularization [J]. Journal of cardiothoracic and vascular anesthesia, 2005, 19(5): 603-7.
22. SQUICCIMARRO E, STASI A, LORUSSO R, et al. Narrative review of the systemic inflammatory reaction to cardiac surgery and cardiopulmonary bypass [J]. Artificial organs, 2022, 46(4): 568-77.
23. ALJURE O D, FABBRO M. Cardiopulmonary bypass and inflammation: the hidden enemy [J]. Journal of cardiothoracic and vascular anesthesia, 2019, 33(2): 346-7.
24. ABBASCIANO R G, KOULOIROUDIAS M, CHAD T, et al. Role of hypothermia in adult cardiac surgery patients: a systematic review and meta-analysis [J]. Journal of Cardiothoracic and Vascular Anesthesia, 2022, 36(7): 1883-90.
25. LOMIVOROTOV V V, SHMIREV V A, EFREMOV S M, et al. Hypothermic versus normothermic cardiopulmonary bypass in patients with valvular heart disease [J]. Journal of cardiothoracic and vascular anesthesia, 2014, 28(2): 295-300.
26. KAPLAN M, KARAAGAC A, CAN T, et al. Open heart surgery at patient's own temperature without active cooling; proceedings of the The Heart Surgery Forum, F, 2018 [C].
27. WANG Y-C, HUANG H-H, LIN P-C, et al. Hypothermia is an independent risk factor for prolonged ICU stay in coronary artery bypass surgery: an observational study [J]. Scientific Reports, 2023, 13(1): 4626.
28. MURPHY G J, REEVES B C, ROGERS C A, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery [J]. Circulation, 2007, 116(22): 2544-52.
29. MING Y, LIU J, ZHANG F, et al. Transfusion of red blood cells, fresh frozen plasma, or platelets is associated with mortality and infection after cardiac surgery in a dose-dependent manner [J]. Anesthesia & Analgesia, 2020, 130(2): 488-97.
30. ZHOU L, LIU X, YAN M, et al. Postoperative nadir hemoglobin and adverse outcomes in patients undergoing on-pump cardiac operation [J]. The Annals of thoracic surgery, 2021, 112(3): 708-16.

31. PAPARELLA D, YAU T, YOUNG E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update [J]. European Journal of Cardio-Thoracic Surgery, 2002, 21(2): 232-44.

32. BRONICKI R A, HALL M. Cardiopulmonary bypass-induced inflammatory response: pathophysiology and treatment [J]. Pediatric Critical Care Medicine, 2016, 17(8): S272-S8.

33. DAHLBERG S, SCHÖTT U, KANDER T. The effect of vitamin K on prothrombin time in critically ill patients: an observational registry study [J]. Journal of Intensive Care, 2021, 9: 1-9.

34. MARSHALL S V, NOBLE J, FLORES A S. Prothrombin complex concentrate in liver transplant surgery: correction of therapeutic anticoagulation and the coagulopathy of end-stage liver disease: case series [J]. Frontiers in Pharmacology, 2020, 11: 566433.

35. VASSANASIRI W, RUNGSAKULKIJ N, SURAGUL W, et al. Early postoperative serum aspartate aminotransferase for prediction of post-hepatectomy liver failure [J]. Perioperative Medicine, 2022, 11(1): 51.

Figures

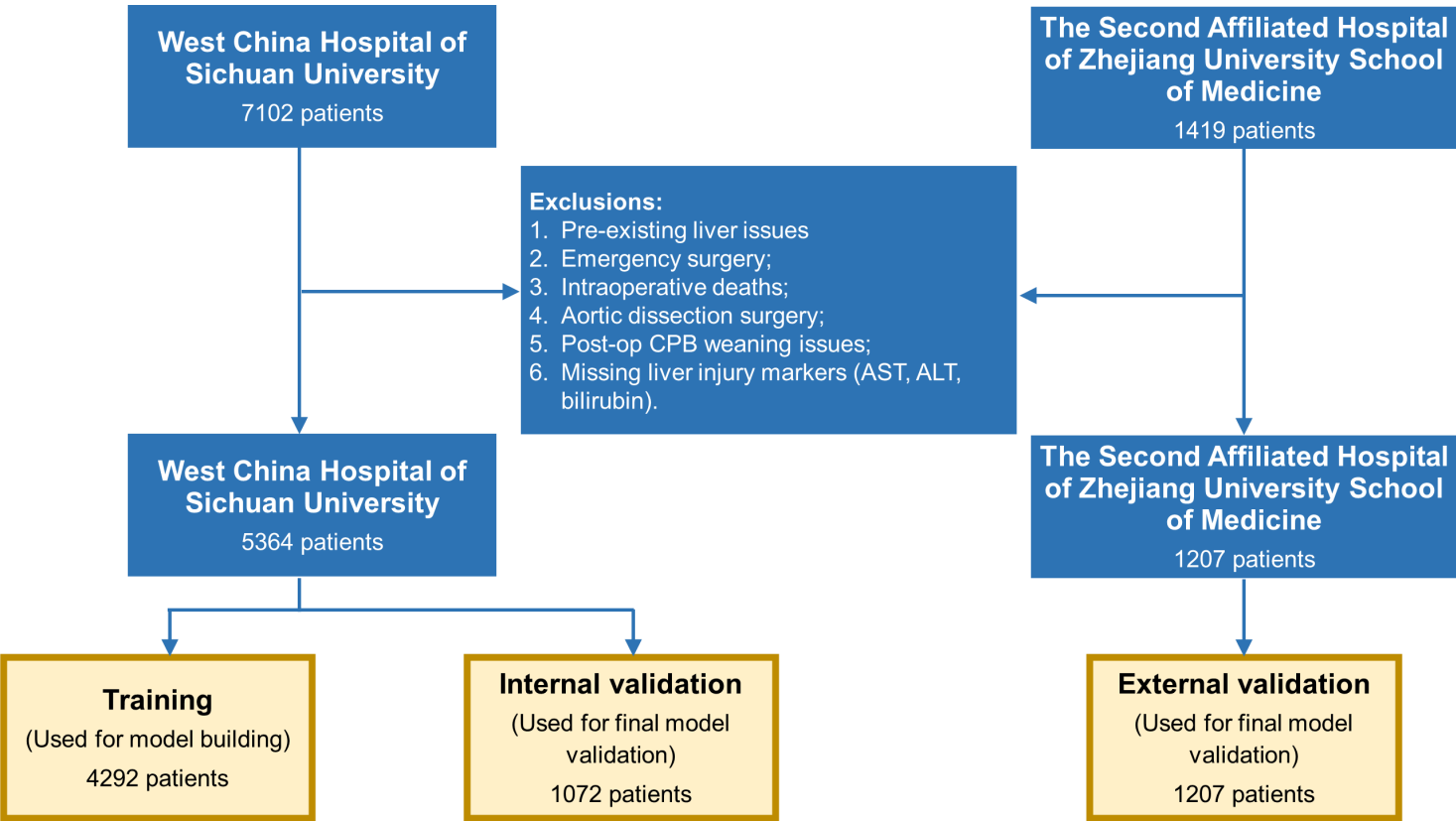


Figure 1

Flowchart of the Sample Selection Process and Dataset Definition.

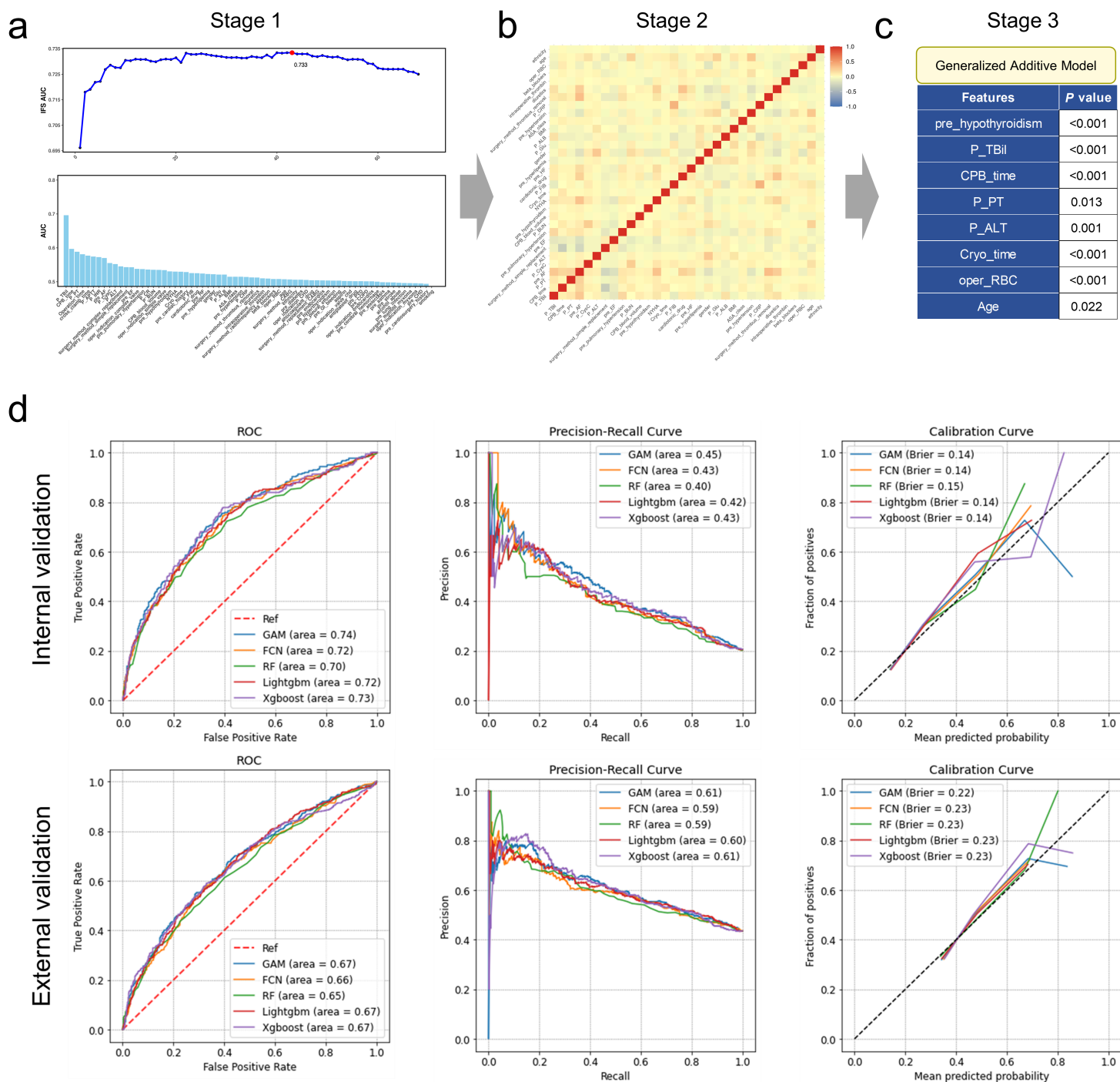


Figure 2

The illustration of the flow chart used for feature selection and prediction performance assessment in determining the risk of postoperative new-onset liver injury. The three-step feature screening scheme is depicted from parts a to c: **a**. Stage 1 presents an Incremental Feature Selection (IFS) curve (shown in blue) generated based on the AUROC ranking of individual features. The red dots on the blue curve indicate the maximum AUROC values. The bar chart represents various features within subsets, differentiated by color, where the height of each bar denotes the AUROC value of the individual feature. **b**. Stage 2 utilizes a heat map to display the Pearson correlations among pairwise features. These features

have been screened out based on their correlation coefficients and AUROC values. **c.** Stage 3 involves inputting the features screened in Stage 2 into a Generalized Additive Model (GAM) to calculate the P -values from Wald Chi-square tests for each variable. Variables with P -values less than 0.05 are retained for inclusion in the final model construction.

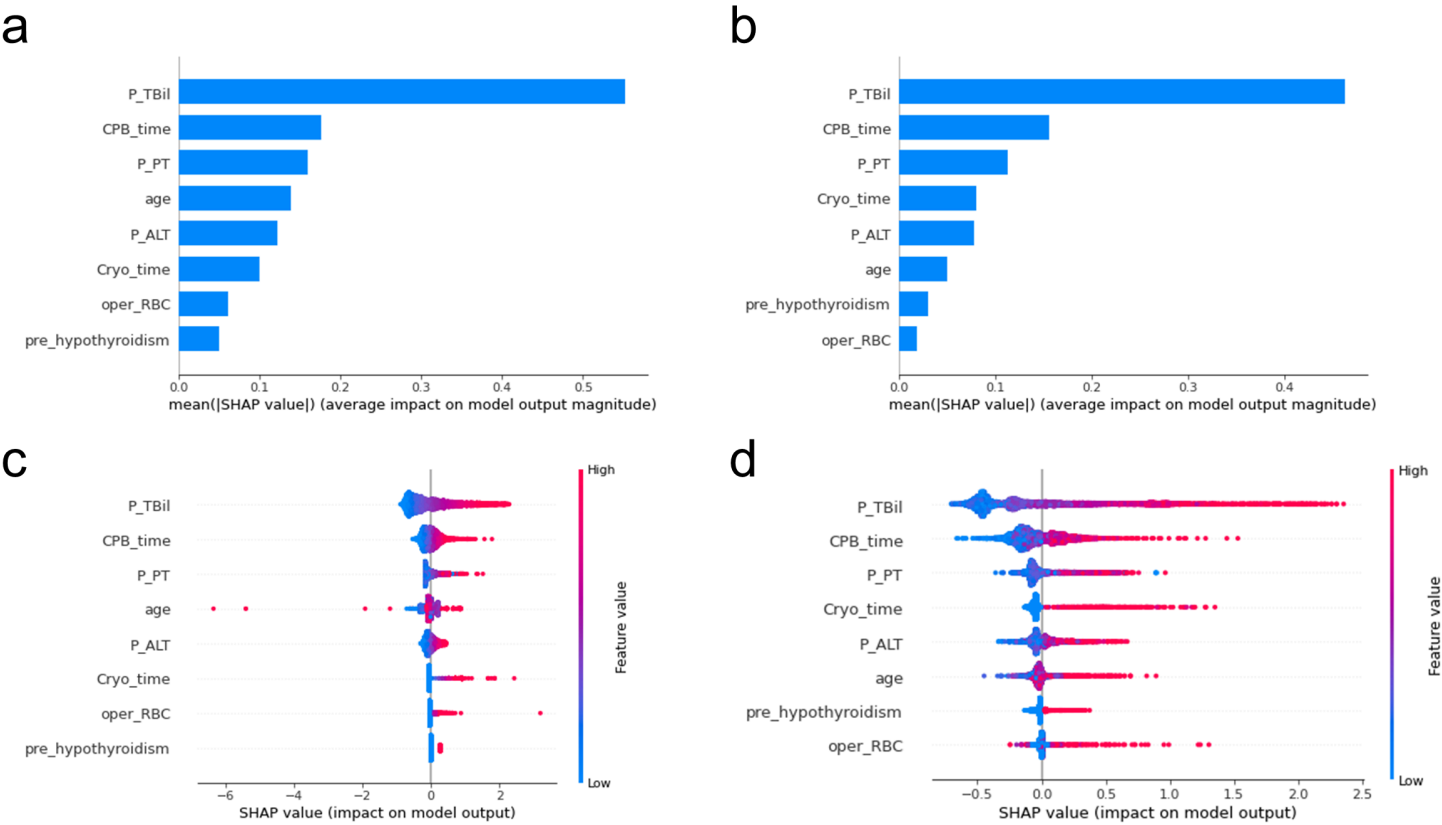


Figure 3

Statistical analysis of risk factors for postoperative new-onset liver injury. **a.** SHAP summary plot for the GAM model. **b.** SHAP summary plot for the XGBoost model. **c.** Bee swarm plot of SHAP values for the GAM model. **d.** Bee swarm plot of SHAP values for the XGBoost model.

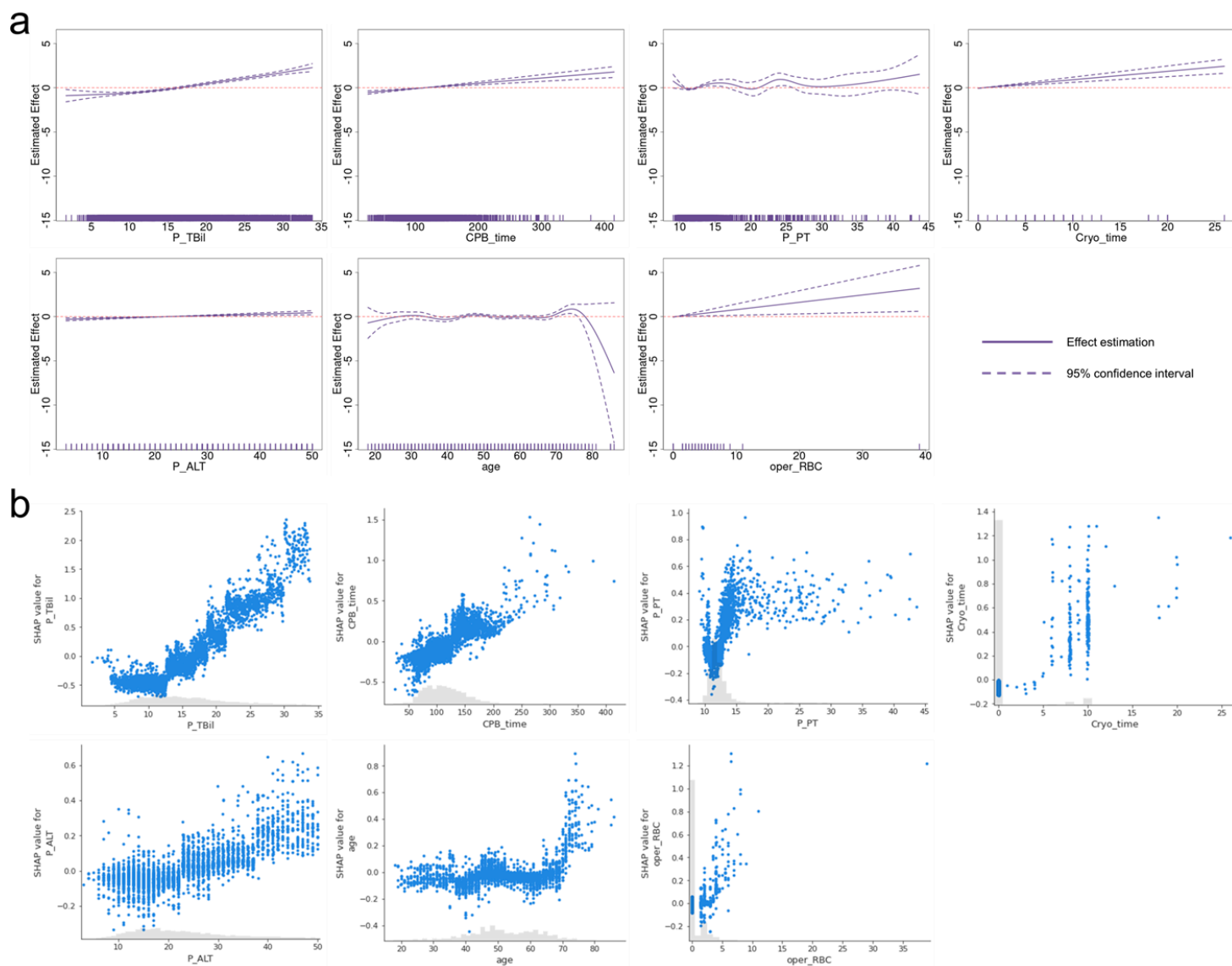


Figure 4

Visualization of the nonlinear relationships between continuous numerical variables and the risk of postoperative new-onset liver injury. **a.** Restricted cubic spline functions from the GAM model illustrate the relationships between continuous numerical variables and postoperative new-onset liver injury. **b.** Scatter plots showing the relationship between SHAP values and the values of continuous numerical variables, based on the XGBoost model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementary.docx](#)