A nomogram for acute pancreatitis in patients with acute lymphoblastic leukemia under CCLG-ALL regimen

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is the most common malignant neoplasm in children. Although the prognosis is good, complications caused by chemotherapy are still a large challenge for clinicians. Among them, pancreatitis is one of the most serious complications after the application of asparaginase, which is an important part of treatment. The occurrence of pancreatitis may affect chemotherapy tolerance and prognosis of ALL. We intend to establish a predictive model for the risk of pancreatitis in children with ALL during chemotherapy based on clinical data. Method: Collect clinical data of ALL patients under CCLG-ALL, screen variables that may be related to the occurrence of pancreatitis through lasso regression, divide the total patient into a training set and a validation set in a ratio of 8:2, build a prediction model in the training set, and evaluate prediction ability through area under the receiver operating characteristic curve (AUC) and calibration curve. External validation is done in the validation set. Results: A total of 321 patients with ALL were included in this study, including 58 patients with pancreatitis and 263 patients in the control group. Risk factors related to pancreatitis were elevated total bilirubin, direct bilirubin and induction chemotherapy. C statistic and AUC obtained in the training set of this model was 0.862 and 0.86, and the AUC of this model in the validation set was 0.95. Conclusion: This study constructs a risk prediction model for pancreatitis in children with acute lymphoblastic leukemia receiving chemotherapy, and the results suggest that the prediction ability is good. A nomogram based on this model was developed. Among the risk factors, increased total bilirubin and direct bilirubin may indicate that pancreatitis may be related to biliary obstruction, and induction chemotherapy may indicate that children may have predisposing factors for pancreatitis. Further research may be needed in these two aspects in the future.

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The authors of this study declare that they have no conflicts of interest.

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The ethics committee of Beijing Children's Hospital reviewed and approved this study.

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Abstract:

Introduction: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. While treatment outcomes have improved, chemotherapy complications remain a significant challenge for clinicians. Pancreatitis, a serious side effect of asparaginase, a crucial drug in ALL treatment, can impact chemotherapy tolerance and patient prognosis. This study aims to develop a clinical model that predicts pancreatitis risk in children with ALL undergoing chemotherapy, using clinical data.

Method: This study used clinical data from ALL patients enrolled in the CCLG-ALL trial. Lasso regression was employed to identify potential risk factors for pancreatitis. The patients were randomly divided into training and validation sets (80% and 20%, respectively). A predictive model was developed using the training set, and its performance was evaluated based on the area under the receiver operating characteristic curve (AUC) and calibration curve. The model's predictive ability was then externally validated using the validation set.

Results: This study included 321 ALL patients, with 58 experiencing pancreatitis and 263 serving as controls. Elevated total bilirubin, direct bilirubin, and induction chemotherapy were identified as risk factors for pancreatitis. The model's performance, evaluated using the training set, yielded a C-statistic of 0.862 and an AUC of 0.86. The model's predictive ability was confirmed in the validation set, with an AUC of 0.95.

Conclusion: This study developed a predictive model for pancreatitis in children with ALL undergoing chemotherapy, demonstrating strong predictive ability. A nomogram was created based on this model, identifying elevated total bilirubin and direct bilirubin, as well as induction chemotherapy, as significant risk factors. These findings suggest a possible link between pancreatitis and biliary obstruction (due to elevated bilirubin levels), and a potential predisposition to pancreatitis during induction chemotherapy. Further research is warranted to explore these associations in greater depth.

Key word: leukemia, pancreatitis, nomogram, prediction model

Introduction:

Acute lymphoblastic leukemia (ALL) is the most common malignancy among children. It has a good prognosis after regular treatment. However, the current treatment of this disease has encountered certain challenges, one of which is the side effects of chemotherapy drugs associated with treatment intolerance, including chemotherapy-related pancreatitis. Asparaginase is significantly associated with pancreatitis, which is important for the treatment of lymphocytic leukemia and can significantly improve prognosis. However, the use of asparaginase may be restricted by the occurrence of drug-induced pancreatitis, which may result in serious infection, disorder of circulation, pancreatic injury and multiple organ dysfunction, and may also affect the prognosis of ALL. [1-3]

Many studies have shown that the incidence of asparaginase-associated pancreatitis varies from 1.5% to 18%,[4-8] and have explored the risk factors for pancreatitis in patients receiving chemotherapy, such as age and the cumulative dosage of asparaginase, etc. But there are still other drugs associated with pancreatitis and possible risk factors. Assessment before chemotherapy of the risk of pancreatitis may be good for preventing pancreatitis from happening, and improving the prognosis of ALL. This study seeks to develop a tool that can predict the risk of pancreatitis in children with leukemia treated with the China Children's Leukemia Group(CCLG)-ALL regimen, potentially aiding in early detection and intervention.

Method:

1). Patient: This retrospective study included 321 children diagnosed with acute lymphoblastic leukemia (ALL) at Beijing Children's Hospital between November 2016 and May 2023. All patients were identified from the hospital's case management system. ALL diagnosis was confirmed through bone marrow morphology. Acute pancreatitis was defined based on the presence of at least two out of three criteria: acute gastrointestinal symptoms, serum lipase or amylase levels at least three times the upper limit of normal, and characteristic imaging findings. Patients were excluded if they had pre-existing organ failure, a history of pancreatic surgery, prior pancreatitis, liver cirrhosis, hepatitis, or incomplete information in the case management system. The control group consisted of patients without pancreatitis. The study was deemed minimal risk by the ethics committee, and therefore informed consent was waived.

2). Data collection: demographic and other characteristics of the patients were collected, including age, gender, weight, Immunophenotyping, risk classification, chemotherapy phase, cumulative dose of asparaginase administered (usually Pegaspargase in our center), MRD level after induction therapy, presence of infection prior to chemotherapy, presence of pancreatic morphologic abnormalities as indicated by ultrasound, liver and kidney function, lipids, bilirubin, pancreatin, C-reactive protein, etc.

3). Statistical analysis: To build the predictive model, variables with over 20% missing data were excluded. The remaining missing data were addressed using multiple imputation with the "mice" package in R software. Patients were randomly divided into training (80%) and validation (20%) cohorts. The predictive model was developed using the training data and then evaluated for accuracy using the validation data. Descriptive statistics for continuous variables included mean and standard deviation or median and interquartile range, while categorical variables were presented as percentages. Chi-square or Fisher's exact test was used to compare categorical variables between groups, while t-tests were employed for continuous variables.

Independent risk factors for pancreatitis were screened by lasso regression which were further output for the construction of nomogram model. To prepare the independent variables for analysis, disordered categorical variables were converted into dummy variables. Continuous variables underwent standardization before being included in the regression analysis. The predictive model's performance was evaluated using the area under the receiver operating characteristic curve (AUC). An AUC exceeding 0.7 indicated a useful model, while an AUC between 0.8 and 0.9 suggested high diagnostic accuracy.[9, 10] To assess the calibration of the prediction model, a calibration curve was generated. [11]

Statistical significance was defined as a p-value less than 0.05, and all analyses were performed using R version 4.0.3.

The local ethics committee of Beijing Children's Hospital approved this study.

Result:

We enrolled 321 children with ALL in this study. Of these, 58 had pancreatitis, while 263 served as controls. The median age of the participants was 5.25 years (IQR: 3.5-8.66 years). There are 190(59%) male patients and 131(41%) female patients.

Results of univariate comparison between pancreatitis group and control group

Table 1 presents the results of univariate analysis comparing children with pancreatitis to the control group. No significant differences were observed in the following indicators, such as gender, age, weight, immunological typing, and post-induction MRD levels between the two groups and the results of pre-chemotherapy evaluation between the two groups are also listed. Variables are screened by lasso regression for Multicollinearity exists among indicators, such as chemotherapy phase and asparaginase dosage. The importance of different indicators for pancreatitis is shown in Figure 1.

A lasso-logit prediction model

Increased total bilirubin, direct bilirubin and chemotherapy phase of induction are screened out as independent risk factors for pancreatitis by lasso regression. The variation of the variable coefficients in the lasso-logit

regression model is visualized in Figure 2A. To optimize model performance, we employed a 10-fold cross-validation procedure, identifying an optimal model with both high performance and minimal variable count when the regularization parameter (lambda) was set to 0.015 (Figure 2B). This selected set of variables was then used to construct a logistic regression model (Table 2). The resulting predictive model demonstrated robust performance, achieving a c-statistic of 0.862. The calibration curve (Figure 3) further indicates good predictive accuracy, with a low mean absolute error (MAE) of 0.029, signifying a close agreement between predicted and observed probabilities. As can be seen from table2 and the nomogram (Figure 4), patients with higher total and direct bilirubin levels during induction phase are more likely to develop pancreatitis.

External validation

The prediction model, developed on a training set, achieved an AUC of 0.86 on the training set and 0.95 on an independent validation set, suggesting good generalizability.

Discussion:

The intracellular aspartic acid is removed by L-asparaginase through hydrolysis, and tumor cells cannot synthesize aspartic acid, thus preventing protein synthesis and inducing apoptosis. Asparaginase is a crucial drug used in chemotherapy for ALL. It may have many side effects, among which pancreatitis is one of the most serious one. Pancreatitis may affect the tolerance of chemotherapy and the prognosis of ALL. Understanding the risk factors and predicting the occurrence of acute pancreatitis is essential for improving clinical management.

The risk factors for pancreatitis in children with ALL undergoing chemotherapy remain unclear. Some reports suggest that the dosage of asparaginase is an independent risk factor. [12] However, no significant association has been reported between asparaginase use and the development of pancreatitis.[13] The incidence of pancreatitis in our study did not differ significantly between genders, consistent with prior findings.[14, 15] The results of univariate analysis in this study suggest that the pancreatitis group used less asparaginase than the control group, which may be related to discontinuing asparaginase application after pancreatitis. In the pancreatitis group, the proportion of abnormal pancreatic morphology was higher, but the results of multivariate analysis showed that it was not an independent risk factor.

This study developed a model to predict acute pancreatitis risk in ALL patients undergoing chemotherapy, using baseline and pre-treatment data. Independent risk factors included increased total bilirubin, direct bilirubin, and induction phase. These data are easy to obtain before chemotherapy, increasing the feasibility of its clinical application, and all patients are uniformly treated with CCLG-ALL regimen, which can reduce confounding interference. The model also proved to have good predictive power in external validation. Consistent with prior research, the high rate of pancreatitis observed during induction therapy, often following the first few doses of asparaginase, suggests a potential predisposing factor or genetic susceptibility for pancreatitis.[16] The elevated level of bilirubin may be related to hepatopancreatic ampullary edema and bile excretion disorder, suggesting that pancreatitis after asparaginase administration may be related to obstruction of biliary tract.[17] Oxidative stress is implicated in pancreatitis, and given bilirubin's antioxidant capacity, low total bilirubin levels could be associated with severe pancreatitis.[18] Further studies may be required to determine the relationship between the severity of post-chemotherapy pancreatitis and bilirubin levels and whether pancreatitis is associated with obstruction of biliary tract.

Patients with definite diagnosis of acute pancreatitis were included in this study. During data collection, some patients exhibited mild pancreatic abnormalities and slightly elevated pancreatic enzyme levels before starting chemotherapy. These patients did not develop pancreatitis after chemotherapy, but also may affect the clinician's decision to use asparaginase, so it is necessary to evaluate the risk of pancreatitis of these patients in the future. Genetic factors, including variations in genes like PRSS1, PRSS2, SPINK1, CFTR, CTRC, CASR, CLDN2, CPA1, and HLA-DRB1*07:01, have been associated with an increased risk of pancreatitis. Future studies should include relevant genes as possible risk factors to assess their impact on the development of pancreatitis.[19-21] The small sample size, a consequence of the low incidence of pancreatitis, limits the generalizability of the study's findings. Larger studies are needed to validate these results.

Asparaginase is an essential component of chemotherapy treatment for patients with acute lymphoblastic leukemia. However, the occurrence of pancreatitis will affect the application of this drug, affecting the overall chemotherapy tolerance and disease prognosis. The construction of prediction model related to pancreatitis is beneficial to avoid treatment-related pancreatitis, improve treatment tolerance, and improve disease prognosis. Studies should also be conducted to compare the side effects and long-term outcomes of reuse versus discontinuation of asparaginase so that clinicians can weigh the pros and cons.[22]

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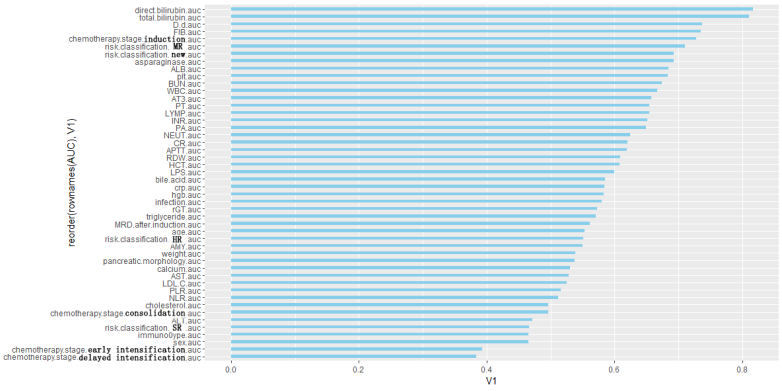

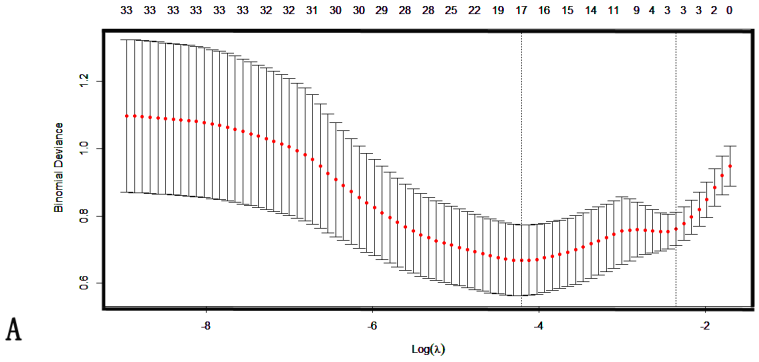

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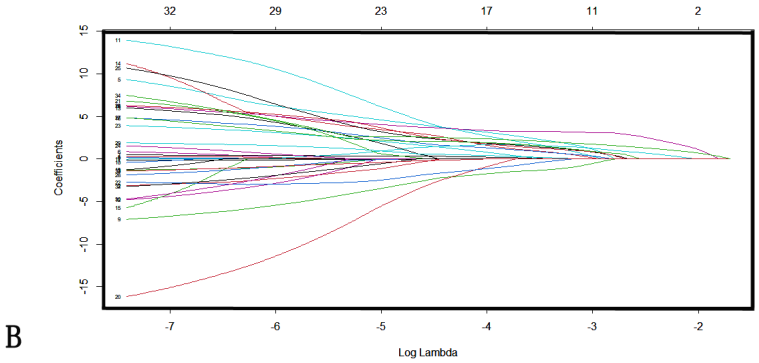

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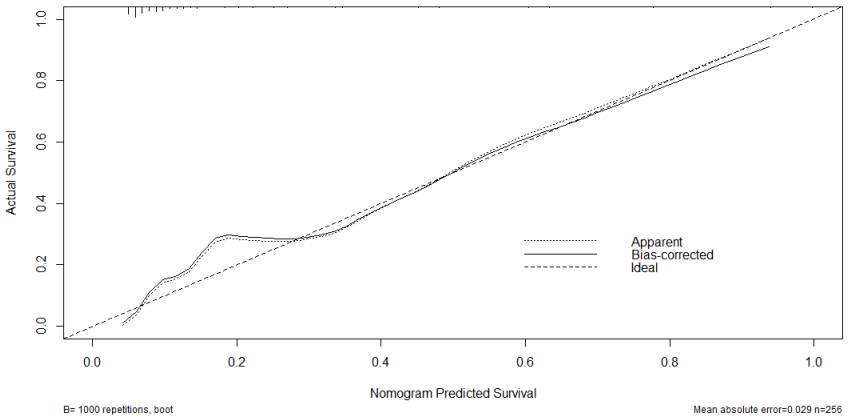

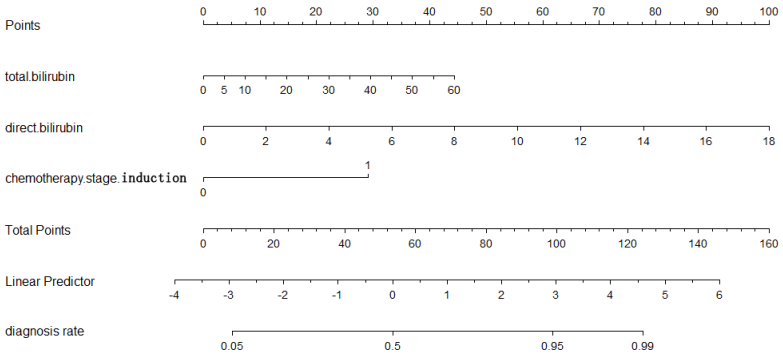

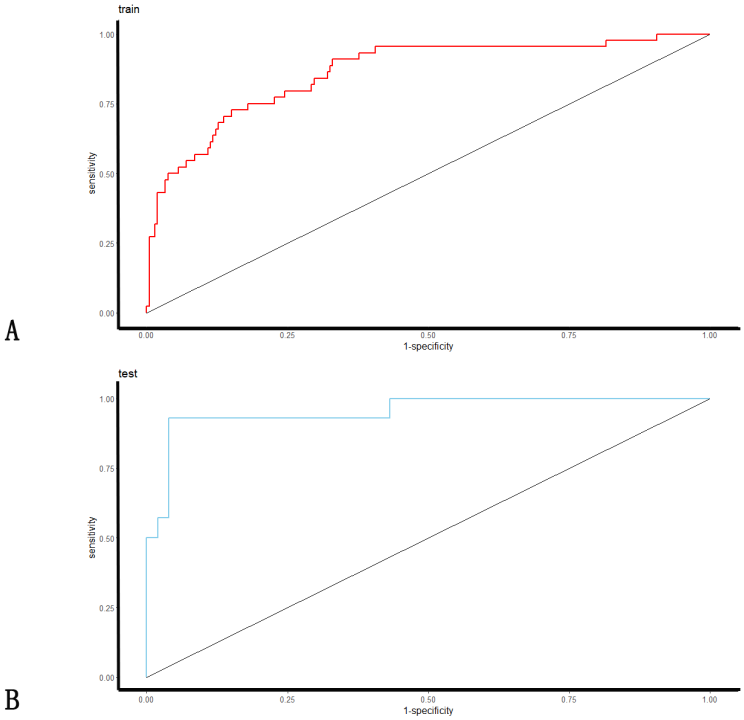

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