

TBH score: a new model to predict and prevent severe liver damage after chemotherapy for cancer patients

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Purpose: To explore a quantitative predictive model for the risk of chemotherapy-induced severe liver damage (CISLD).

Materials and methods: In total, 3870 consecutive cancer patients initially treated with chemotherapy were retrospectively collected and randomly assigned to a training (n=2580) or internal validation (n=1290) set in a 2:1 ratio to construct and validate the model. Additional external validation was performed using another data set (n=413). A total of 486 patients were prospectively enrolled to assess the clinical significance of the model. CISLD was defined as grade ≥ 3 hepatotoxicity.

Results: CISLD was found in 255 (9.9%), 128 (9.9%) and 36 (8.7%) patients in the training, internal and external validation sets, respectively. Serum triglyceride, body mass index and history of hypertension formed the basis of the score model. Patients could be stratified into low, intermediate and high-risk groups with <10%, 10–30% and >30% CISLD occurrence, respectively. This model displayed a concordance index (C-index) of 0.834 and was validated in both the internal (C-index, 0.830) and external (C-index, 0.817) sets. The incidence of CISLD was significantly reduced in those who received preventive hepatoprotective drugs compared to those who did not among patients assessed as the intermediate risk group (8.9% vs 17.5%, $p=0.042$) and the high risk group (15.6% vs 55.8%, $p=0.043$).

Conclusions: The new score model can be used to accurately predict the risk of CISLD in cancer patients undergoing chemotherapy. Clinically, this can be translated into a reference tool for oncologists in the clinical decision-making process before chemotherapy to provide appropriate prevention and interventions for patients with a high risk of CISLD.

Keywords: chemotherapy, liver damage, predictive model

Background

All chemotherapeutic agents, whether used in monotherapy or combination therapy, can directly or indirectly cause liver toxicity due to hepatocellular injury, inflammation and/or cholestasis. Since most hepatotoxic drug reactions are idiosyncratic and can mechanistically be classified as immune (hypersensitive) or metabolic,¹ these reactions are usually unpredictable. Moreover, the degree of adverse liver reactions is heterogeneous due to the differences in susceptibility to drug-induced liver injury or capacity to recover from injury between individual patients. The clinical manifestations of chemotherapy-related hepatotoxicity can vary from asymptomatic transient liver biochemical abnormalities to acute diseases with jaundice.² Severe liver damage can lead to a dose reduction of the chemotherapeutic agents, treatment delays or

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interruptions, or even fatal adverse events. Dose reductions or course delays may reduce the effect of anti-tumor therapy,³ and fatal consequences are worthy of attention.^{4,5}

Previous literature and studies have reported several factors, including body mass index (BMI), age, sex, tobacco and alcohol intake, and treatment cycles, that may increase the risk of liver damage after chemotherapy.^{6–11} In addition to the above factors, chemotherapy-induced liver toxicity is often idiosyncratic and may also be affected by genetic factors, comorbidities, cancer subtypes and other factors.¹² Oncologists have already realized that the above factors are associated with potential severe liver damage after chemotherapy. However, thus far, not all individual factors have been combined to establish a quantitative predictive model for the risk of chemotherapy-induced severe liver damage (CISLD) that aims to guide the treatment choice before chemotherapy.

Therefore, we conducted a study to identify the high-risk factors for predicting CISLD and to develop a reliable prediction model by collecting as much comprehensive clinical data and laboratory data as possible from a large sample of patients. The model can be used as a reference tool for oncologists in the clinical decision-making process when selecting treatment agents and determining the dosages before chemotherapy.

Methods

Patients and design

The study retrospectively analyzed a total of 3870 patients diagnosed with primary cancer from January 1, 2010 to December 31, 2017 in the First Affiliated Hospital, Sun Yat-sen University. Patient consent to review their medical records was obtained from all patients entered in the study and supported by the Institutional Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University. The inclusion criteria were as follows: (1) 18 years or older; (2) confirmed cancer by histopathological examination; and (3) first treatment was chemotherapy and finished at least one cycle of chemotherapy. The exclusion criteria were as follows: (1) previous anticancer therapies; (2) missing necessary clinical information and laboratory data; and (3) no follow-up data. (4) known history of chronic liver disease. We randomly allocated these patients into a training cohort and an internal validation cohort in a 2:1 ratio. In addition, we included another 413 cancer patients with the same criteria from January 1, 2015 to December 31, 2016 from the Cancer Center, Sun Yat-sen

University, as the external validation cohort. The study was censored on January 31, 2018. The study was approved by the Institutional Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University. CISLD was defined when the grade or indices reflecting hepatic function was over 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) after chemotherapy.¹³ The liver functions is checked once a week during treatment and per one-three months during follow up. The time frames of hepatotoxicity was defined as any time in the future after chemotherapy, and the doctors judged whether the hepatotoxicity was related to the chemotherapy.

Data collection

The relevant data were retrieved from the medical records at the time of diagnosis and during the follow-up period. We collected the following background data: age; BMI; sex; history of smoking and alcoholism; history of hypertension, coronary heart disease (CHD) and diabetes; hepatitis B surface antigen (HBsAg); hepatitis C virus (HCV); nucleotide analogue medication; laboratory data (albumin [ALB], blood urea nitrogen [BUN], creatinine [Cr], uric acid [UA], blood glucose [GLU], alanine aminotransferase [ALT], aspartate aminotransferase [AST], ratio of alanine aminotransferase to aspartate aminotransferase [ALT/AST], cholesterol [CHOL], triglyceride [TG], C-reactive protein [CRP], cystatin C [Cys], hemoglobin [Hb], total bilirubin [TBIL], gamma-glutamyl transpeptidase [GGT], activated partial thromboplastin time [APTT], fibrinogen [Fbg], international normalized ratio [INR]); tumor type; tumor staging; liver metastasis; cycle of chemotherapy; and chemotherapeutics (oxaliplatin, cisplatin, carboplatin, irinotecan, gemcitabine, fluorouracil, paclitaxel, docetaxel, pemetrexed, doxorubicin).

Statistical analysis

Statistical analysis was conducted using R studio software (version 1.0.153, <https://www.rstudio.com/products/rstudio/>). The R packages used in the study include the glmnet, Hmisc and rms packages. Continuous variables are presented as the mean±standard deviation, while categorical variables are presented as the frequencies and percentages of events. Continuous variables were compared using Student's *t*-test or Kruskal-Wallis H test (variables with an abnormal distribution), and categorical variables were compared using the χ^2 test or Fisher's exact test. The least absolute shrinkage and selection

operator (LASSO) method was used to primarily identify features for predicting hepatic function damage in the training cohort. Then, the significant variables identified by LASSO were incorporated into further multivariate logistic regression analysis to build the final prediction model. The nomogram was constructed based on the results of the multivariate logistic regression analysis following LASSO. The predictive performance of the nomogram was evaluated by the concordance index (C-index) and calibration curve. The C-index was an equivalent variable of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve for censored data. A calibration curve was applied to assess the agreement between the nomogram-predicted result and the actual observed result. In addition, internal and external validation was performed by applying the derived nomogram in the validation cohorts. The C-index and calibration curve were also used in the validation cohorts. All statistical tests were two-sided with a statistical significance level set at $p < 0.05$. Moreover, the regression coefficients of the significant variables were multiplied by 10 and rounded to acquire point numbers facilitating the bedside calculation of a risk score. The risk score was utilized to assign patients into different risk groups.

Results

Patient characteristics and outcomes

The patient characteristics of the training and internal validation cohorts are listed in [Table 1](#). In total, 3870 patients diagnosed with cancer during the study period were enrolled in this study. Among these patients, 2580 were assigned to the training cohort, while the other 1290 were assigned to the internal validation cohort. As shown in [Table 1](#), the training and internal validation cohorts showed good agreement in all variables. In total, 276 patients received a nucleotide analogue for hepatitis B infection; among whom, 188 (7.9%) were in the training cohort, and 88 (6.8%) were in the validation cohort. The patient characteristics of the external cohort are listed in [Table S1](#). CISLD was found in 255 (9.9%), 128 (9.9%) and 36 (8.7%) patients in the training, internal and external validation cohorts, respectively. The median time of developing severe hepatic function damage from the first dose of chemotherapy in the three sets of patients was 27 d, 30 d, and 29 d, respectively. The details of hepatic function damage are listed in [Tables S2](#) and [S3](#).

Feature selection using LASSO and multivariate logistic regression analysis was performed in the training

cohort. After LASSO analysis, 42 features were reduced to 3 potential predictors based on the 2870 patients in the training cohort. [Figures S1](#) and [S2](#) show the process of selecting features using LASSO. The optimized lambda (λ) determined in [Figure S1](#) was utilized to identify features with nonzero coefficients from the coefficient profile plot in [Figure S2](#). LASSO identified TG, BMI and history of hypertension as potential prognostic variables that predict CISLD. After incorporating the three variables into the multivariate logistic regression analysis, TG (hazard ratio [HR], 2.269; 95% confidence interval [CI], 1.937–2.661; $p < 0.001$), BMI (HR, 10.274; 95% CI, 7.047–15.476; $p < 0.001$) and history of hypertension (hazard ratio [HR], 2.028; 95% confidence interval [CI], 1.407–2.895; $p < 0.001$) showed statistical significance. The details of the LASSO method and multivariate analysis are shown in [Table 2](#).

Development of the prognostic nomogram in the training cohort

The final three variables were incorporated into the nomogram to predict CISLD in patients after chemotherapy ([Figure 1](#)). The nomogram included two background characteristics (BMI and history of hypertension) and one laboratory test (TG). Every value of the variables was assigned a specific score. To use the nomogram, an individual patient's value is located on the axis of each variable, and a line is drawn upwards to determine the number of points assigned to each variable value. The sum of these numbers is located on the total point axis, and a line is drawn downwards to the risk axis to determine the likelihood of hepatic function damage.

Predictive performance of the prognostic nomogram in the training and internal/external validation cohorts

The C-index of the nomogram for predicting CISLD was 0.834 (95% CI: 0.815–0.854), which is greater than 0.7, suggesting that the new model has advanced suitability. The calibration plot demonstrated good agreement between the actual observations and the nomogram predictions for the risk of hepatic function damage in the training cohort ([Figure 2](#)). In the internal validation cohort, the nomogram displayed a C-index of 0.830 (95% CI: 0.803–0.857) for estimating the risk of hepatic function damage. Good calibration was also observed in the internal validation cohort ([Figure 3](#)). In the external validation

Table 1 Baseline characteristics of patients in the training and internal validation cohort

Patient's Characteristics	Total (n=3870)	Training cohort (n=2580)	Internal validation cohort (n=1290)	p-value
Background data				
Age, yr	50.6±11.9	50.6±11.9	50.4±11.9	0.548
BMI, kg/m ²	22.9±2.7	22.9±2.7	22.8±2.7	0.639
Gender (male/female)	2129/1741 (55.0%/45.0%)	1408/1172 (54.6%/45.4%)	721/569 (55.9%/44.1%)	0.437
History of smoking (Yes/No)	754/3116 (19.5%/80.5%)	483/2097 (18.7%/81.3%)	271/1019 (21.0%/79.0%)	0.090
History of hypertension (Yes/No)	395/3475 (10.2%/89.8%)	269/2311 (10.4%/89.6%)	126/1164 (9.8%/90.2%)	0.523
History of CHD (Yes/No)	30/3840 (0.8%/99.2%)	16/2564 (0.6%/99.4%)	14/1276 (1.1%/98.9%)	0.120
History of diabetes (Yes/No)	117/3753 (3.0%/97.0%)	82/2498 (3.2%/96.86%)	35/1255 (2.7%/97.3%)	0.426
History of alcoholism (Yes/No)	1021/2849 (26.4%/73.6%)	670/1910 (26.0%/74.0%)	(27.2%/72.8%)	0.409
History of HBV infection (Yes/No)	549/3421 (14.2%/85.8%)	369/2211 (14.3%/85.7%)	180/1110 (13.9%/86.1%)	0.807
History of HCV infection (Yes/No)	67/3803 (1.7%/98.3%)	41/2539 (1.6%/98.4%)	25/1265 (1.9%/98.1%)	0.693
Nucleotide analogue medicine (Yes/No)	276/3594 (7.1%/92.9%)	188/2392 (7.9%/92.1%)	88/1202 (6.8%/93.2%)	0.643
Laboratory data				
ALB, g/l	42.7±4.3	42.7±4.3	42.7±4.3	0.637
BUN, mmol/l	4.7±1.4	4.7±1.4	4.8±1.5	0.115
Cr, μmol/l	70.5±16.9	70.5±17.0	70.6±16.7	0.799
UA, μmol/l	318.9±97.8	318.6±98.2	319.6±97.1	0.759
GLU, mmol/l	5.7±1.4	5.7±1.3	5.8±1.5	0.164
ALT, U/L	22.1±14.7	22.1±15.0	22.2±14.2	0.912
AST, U/L	22.1±9.7	22.1±10.1	22.0±8.7	0.884
ALT/AST	1.0±0.4	1.0±0.4	1.0±0.4	0.971
CHOL, mmol/l	5.2±1.0	5.2±1.0	5.2±1.0	0.266
TG, mmol/l	1.5±0.9	1.5±0.9	1.5±0.9	0.575
CRP, mg/l	11.5±23.5	11.1±21.1	12.3±27.6	0.190
Cys, mg/l	0.9±0.2	0.9±0.2	0.9±0.2	0.640
Hb, g/l	132.4±16.5	132.2±16.6	132.8±16.3	0.255
TBIL, μmol/l	17.9±5.2	17.9±5.1	17.8±5.2	0.610
GGT, U/L	173.7±147.3	172.3±144.6	176.4±152.7	0.419
APTT, s	32.9±4.8	32.9±4.8	33.0±4.9	0.339
Fbg, g/l	4.3±1.1	4.3±1.1	4.3±1.1	0.284
INR	1.1±0.1	1.1±0.1	1.1±0.1	0.328
Other data				
Tumor type				
Gastrointestinal	740 (19.1%)	495 (19.2%)	245 (19.0%)	0.331

(Continued)

Table 1 (Continued).

Patient's Characteristics	Total (n=3870)	Training cohort (n=2580)	Internal validation cohort (n=1290)	p-value
Breast	507 (13.1%)	354 (13.7%)	153 (11.9%)	
Head/neck	1115 (28.8%)	729 (28.3%)	386 (29.9%)	
Lung	688 (17.8%)	448 (17.4%)	240 (18.6%)	
Gynecologic	422 (10.9%)	281 (10.9%)	141 (10.9%)	
Hematologic	297 (7.7%)	209 (8.1%)	88 (6.8%)	
Others	101 (2.7%)	64 (2.5%)	37 (2.9%)	
Liver metastasis (Yes/No)	425/3445 (11.0%/89.0%)	289/2561 (11.2%/88.8%)	136/1154 (10.5%/89.5%)	0.699
Tumor staging				
II	752 (19.4%)	514 (19.8%)	238 (18.4%)	0.601
III	1505 (38.9%)	996 (38.6%)	509 (39.5%)	
IV	1613 (41.7%)	1070 (41.5%)	543 (42.1%)	
Cycle of chemotherapy				
≤2	1308 (33.8%)	865 (33.5%)	443 (34.3%)	0.461
3 or 4	1402 (36.2%)	952 (36.9%)	450 (34.9%)	
>4	1160 (30.0%)	763 (29.6%)	397 (30.8%)	
Chemotherapeutics				
Oxaliplatin (Yes/No)	366/3504 (9.5%/90.5%)	251/2329 (9.7%/90.3%)	115/1175 (8.9%/91.1%)	0.415
Irinotecan (Yes/No)	374/3496 (9.7%/90.3%)	262/2318 (10.1%/89.9%)	112/1178 (8.9%/91.1%)	0.149
Gemcitabine (Yes/No)	227/3643 (5.9%/94.1%)	140/2440 (5.4%/94.6%)	87/1203 (6.7%/93.3%)	0.100
Platinum (Yes/No)	1910/1960 (49.4%/50.6%)	1269/1311 (49.2%/50.8%)	641/649 (49.7%/50.3%)	0.768
Fluorouracil (Yes/No)	1066/2804 (27.5%/72.5%)	722/1858 (28.0%/72.0%)	344/946 (26.7%/73.3%)	0.387
Doxorubicin (Yes/No)	72/13149 (18.6%/81.4%)	502/2078 (19.5%/80.5%)	219/1071 (17.0%/83.0%)	0.062
Paclitaxel (Yes/No)	567/3303 (14.7%/85.3%)	383/2197 (14.8%/85.2%)	184/1106 (14.3%/85.7%)	0.664
Docetaxel (Yes/No)	378/3508 (9.8%/90.2%)	249/2331 (9.7%/90.3%)	129/1161 (10.0%/90.0%)	0.731
Penmetrexed (Yes/No)	45/13419 (11.7%/88.3%)	285/2295 (11.0%/89.0%)	166/1124 (12.8%/87.2%)	0.100

Note: Data are presented as n (%), mean ± SD.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HBV, hepatitis B virus; HCV, hepatitis C virus; ALB, albumin; BUN, urea nitrogen; Cr, creatinine; UA, uric acid; GLU, blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALT/AST, ratio of alanine aminotransferase to aspartate aminotransferase; CHOL, cholesterol; TG, triglyceride; CRP, C-reactive protein; Cys, cystatin C; Hb, hemoglobin; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; APTT, activated partial thromboplastin time; Fbg, fibrinogen; INR, international normalized ratio.

Table 2 LASSO-multivariate logistic regression results of predicting hepatic function damage after chemotherapy in training cohort

Variables	LASSO-multivariate logistic regression		
	β	p-value	Hazard ratio (95% CI)
TG	0.819	<0.001*	2.269 (1.937, 2.661)
BMI	2.330	<0.001*	10.274 (7.047, 15.476)
History of hypertension	0.341	<0.001*	2.028 (1.407, 2.895)

Note: *Statistically significant at alpha =0.05.
Abbreviations: TG, triglyceride; BMI, body mass index.

cohort, the nomogram displayed a C-index of 0.817 (95% CI: 0.752–0.882) for estimating the risk of hepatic function damage. Good calibration was also observed in the external validation cohort (Figure S3).

TBH score calculation to identify different risk groups

The calculated regression coefficients were multiplied 10 times and rounded to facilitate the calculation of a risk score (TBH, TG-BMI-history of Hypertension score) (Table 3). We then calculated the TBH score for patients in the training cohort (n=2870) and identified three subgroups with distinct outcomes. Patients whose TBH score was ≤ 16 points (1488/2580, 57.7%) had a rate of

CISLD <10%, which was significantly different from that of patients with a TBH score of 16 to ≤ 39 points (861/2580, 33.3%), who had a rate of CISLD of 10–30%. In contrast, patients with a TBH score >39 points (231/2580, 9.0%) had a rate of CISLD >30%. Since the average rate in the whole population is approximately 9.9%, we defined patients with TBH scores ≤ 16 as the low-risk group, 16 to ≤ 39 points as the moderate-risk group and >39 points as the high-risk group. Crucially, the TBH score was validated in the internal (n=1290) and external (n=413) validation cohorts. Among the 1290 patients in the internal validation cohort, the number of patients with TBH scores ≤ 16 points, 16 to ≤ 39 points, >39 points were 759 (58.8%), 433 (33.6%) and 98 (7.6%), respectively. The corresponding possibility of CISLD for the patients in each group was <10%, 10–30%, and >30%, respectively. Among the 413 patients in the external validation cohort, the number of patients with TBH scores ≤ 16 points, 16 to ≤ 39 points, >39 points were 261 (63.2%), 140 (33.9%) and 12 (2.9%), respectively. The corresponding possibility of CISLD for the patients in each group was <10%, 10–30%, >30%, respectively. The percentage of CISLD and 95% Confident Interval of the low, intermediate and high-risk group for internal and external datasets were showed in Table 4.

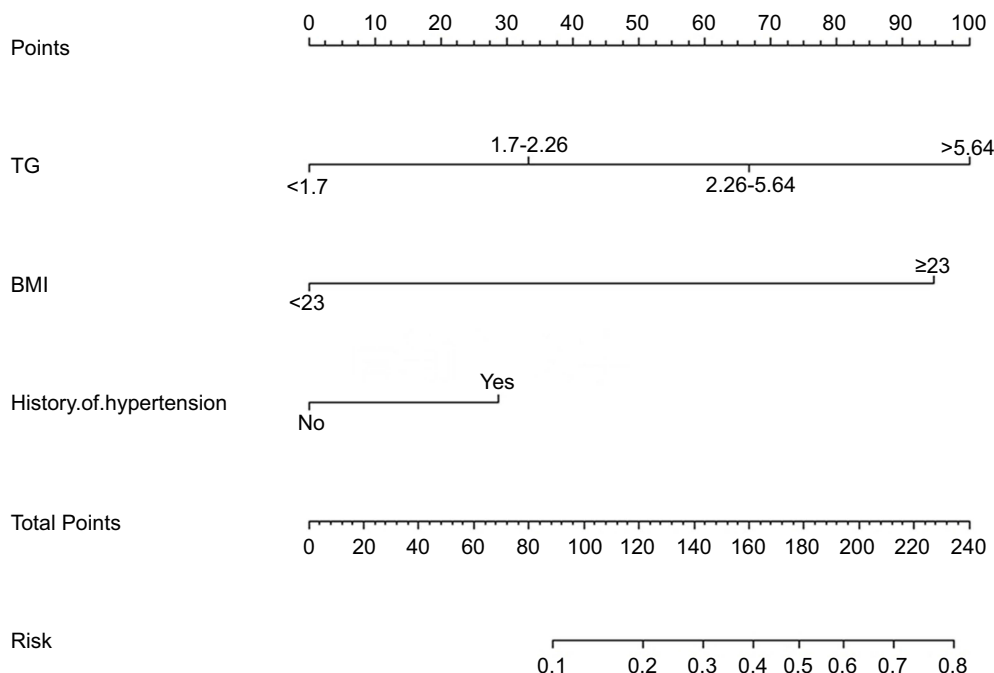


Figure 1 Nomogram for predicting hepatic function damage in patients after chemotherapy.
Abbreviations: TG, triglyceride; BMI, body mass index.

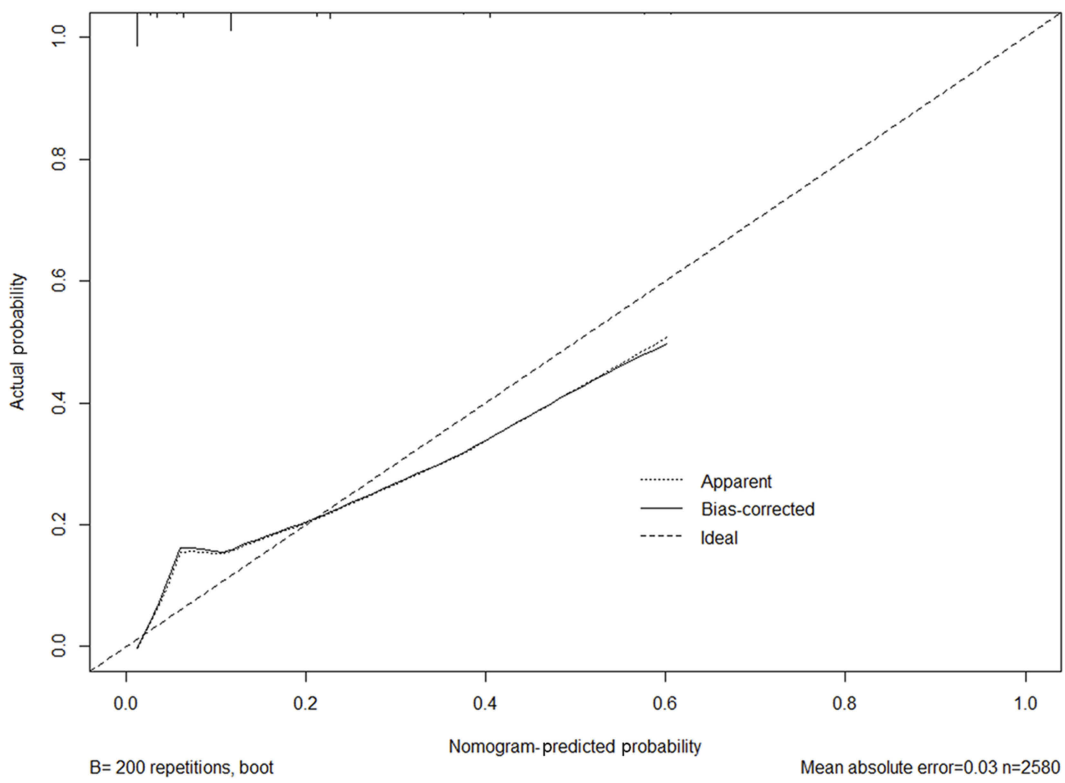


Figure 2 The calibration plot for the risk of hepatic function damage in the training cohort.

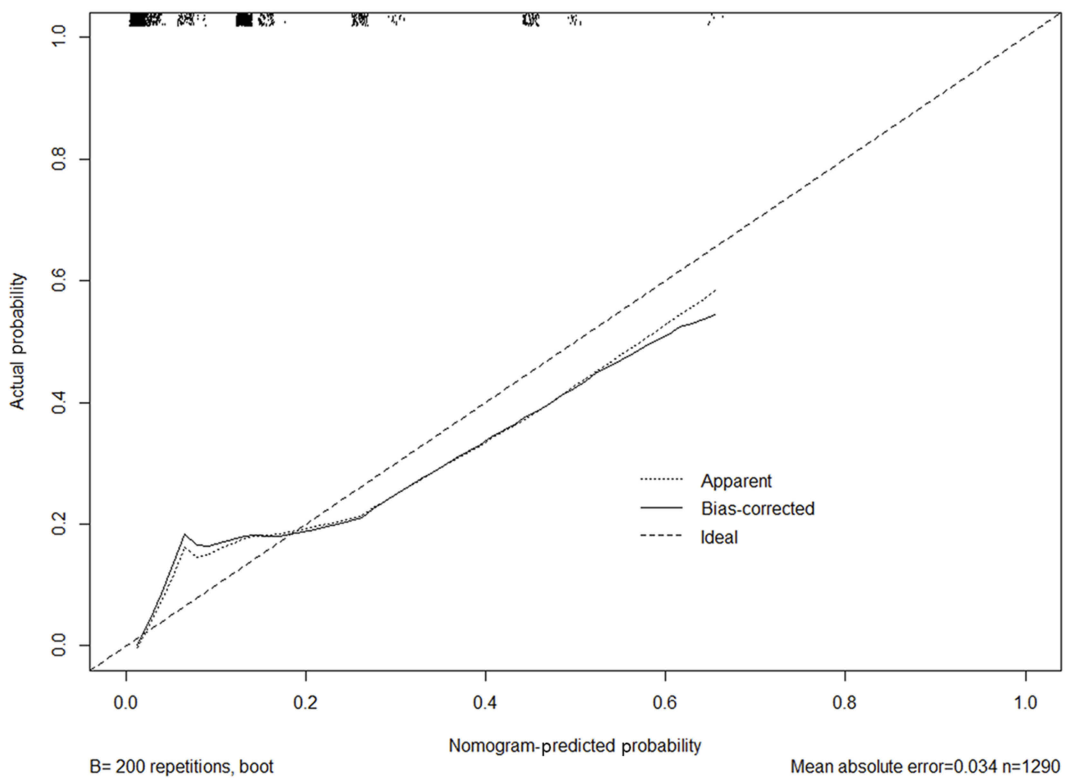


Figure 3 The calibration plot for the risk of hepatic function damage in the internal validation cohort.

Table 3 Stratification of significant variables used to calculate bedside TBH (TG-BMI-history of Hypertension) score

Variables	Stratification	β	TBH score points [#]	p-value*
TG (mmol/l)	<1.7	–	0	
	1.7–2.26	0.423	4	0.031*
	2.26–5.64	1.576	16	<0.001*
	≥5.64	3.248	32	<0.001*
BMI (kg/m ²)	<23	–	0	
	≥23	2.371	24	<0.001*
History of hypertension	No	–	0	
	Yes	0.732	7	<0.001*

Notes: [#]The regression coefficients (β) were multiplied by 10 and rounded in order to facilitate the bedside calculation of the TBH score. *Statistically significant at alpha =0.05.

Abbreviations: TG, triglyceride; BMI, body mass index.

Table 4 The percentage of CISLD and 95% confident interval of the low, intermediate and high-risk group for internal and external datasets

Groups	CISLD, % (95% confident interval)		
	Internal-training set	Internal-validation set	External set
Low	1.40 (1.27, 1.53)	1.42 (1.25, 1.60)	0.87 (0.64, 1.10)
Intermediate	16.23 (15.79, 16.67)	15.87 (15.24, 16.49)	15.40 (14.43, 16.38)
High	44.07 (43.05, 45.09)	44.09 (42.57, 45.62)	51.63 (44.50, 58.75)

Abbreviation: CISLD, chemotherapy induced severe liver damage.

Clinical significance of the TBH score

From January 1, 2017 to June 30, 2017, 486 patients in these two centers with the same inclusion criteria were prospectively enrolled. Among these patients, 302 patients routinely received one or two kinds of protective medications for liver function to prevent CISLD (prevention group), and the other 184 patients did not receive medications (nonprevention group). There were 175, 96, 31 patients with TBH scores ≤16 points, 16 to ≤39 points, and >39 points in the prevention group, respectively. The corresponding numbers were 104, 64, and 16 patients in the nonprevention group. Polyene phosphatidylcholine and glutathione were used in the prospective study to prevent CISLD. On the censored day of the study on January 31, 2018, the CISLD rates were 2.5%, 8.9%, and 15.6% in the prevention group, and the corresponding figures were 4.3%, 17.5%, and 55.8% in the nonprevention group. There were significant differences in the CISLD rates between these two groups for patients with TBH scores of 16 to ≤39 points (8.9% vs 17.5%, $p=0.042$) and >39 points (15.6% vs 55.8%, $p=0.043$).

Discussion

This study explored the baseline characteristics prior to the first administration of chemotherapy of 3870 cancer patients

admitted to our hospital in relation to the risk of developing CISLD. Using 2580 patients as a training cohort, we developed a score system to estimate the risk of CISLD using information available about the patients prior to their first cycle of chemotherapy. The score system was validated both internally and externally. In our study, there was a nearly 10% chance of developing severe liver damage, both in the training cohort and in the validation cohorts. The results showed that some patients with certain characteristics had a very high risk of developing CISLD regardless of the regimen. For the first time, our study presents this prediction model and risk stratification score, which can be used to identify medium-to-high-risk groups of people who may develop CISLD prior to the first cycle of chemotherapy so that certain preventative interventions, modifications of the treatment agents or enhanced monitoring of liver function can be conducted to improve the safety of these patients.

Our score system showed very good accuracy in predicting the possibility of CISLD with a C-index of 0.834, 0.830, and 0.817 for the training cohort, internal validation cohort, and external validation cohort, respectively. BMI was found to be the strongest predictor of CISLD among the factors included in the final prediction model. Other studies also showed that high BMI values were closely

related to liver damage after chemotherapy, but these studies were also limited to patients with liver metastases of colorectal cancer who were undergoing preoperative chemotherapy.^{14–16} In contrast to these studies, the results in our study present that BMI, the strongest predictor of CISLD, is not limited to cancer types, tumor staging, chemotherapy regimens, and number of treatment cycles. In addition to BMI, another factor that influenced the incidence of CISLD is serum TG levels. A previous study suggested that BMI and TG were the most effective predictors of the severity of fatty liver and ultrasound scores in patients with nonalcoholic fatty liver disease (NAFLD).¹⁷ In addition, high blood pressure may induce fatty liver by triggering insulin resistance. Previous population studies have found that the prevalence of NAFLD in hypertensive patients was twice,¹⁸ or even three times, higher than that in patients with normal blood pressure.¹⁹ In animal experiments, it has also been found that hypertension may lead to increased oxidative stress and tissue damage in the liver, thereby affecting the progression of nonalcoholic steatohepatitis²⁰ or inducing liver injury and hepatic fibrosis.^{21,22} We can speculate that patients with overweight, hyperlipidemia or hypertension may have mild hepatic steatosis, NAFLD, or liver fibrosis. These preexisting hepatic pathological changes without clinical symptoms or abnormal liver biochemical indicators may be difficult to detect, but they may increase the susceptibility to CISLD.

The main significance of this study is to provide a reference tool for the oncologist's clinical decision-making process. The current dose of chemotherapeutic agents is still mainly based on the body surface area (BSA). However, BSA does not reflect the liver's capacity for metabolic clearance. Our model shows that patients with high BMIs are more susceptible to CISLD and should be treated carefully with reasonable reductions to the chemotherapeutic doses based on a large BSA. In addition, since BMI, TG and hypertension are all related to NAFLD, and patients with NAFLD may poorly tolerate chemotherapy and be prone to CISLD, we may routinely perform liver ultrasounds before chemotherapy to assess whether the patient has mild fatty liver disease that is not usually noticeable. For patients with moderate to high-risk TBH scores, we also have the option of using hepatoprotective drugs prophylactically. In our prospective data of patients assessed as being moderate to high risk, the incidence of CISLD was significantly reduced in those who prophylactically received protective medications for liver function compared to those who did not. Some studies have found that

several adjuvant drugs could prevent liver toxicity after chemotherapy, such as tiopronin,²³ magnesium isoglycyrrhizinate,²⁴ S-adenosylmethionine²⁵ and even the therapeutic drug bevacizumab.^{26,27} Nonetheless, patients using these drugs should also be closely monitored with liver function tests and follow-up examinations.

There are some limitations in this study. First, the study was a retrospective analysis, not a prospective study. Second, the data of the training group and the validation groups were collected from hospitals from China, which limits the region and race profile of the patients. In addition, we did not analyze the genetic polymorphisms and genotypes of the patients, which may also be related to the risks of CISLD.

Conclusion

For the first time, we stratified the risks of CISLD by using the TBH scoring system to easily identify high-risk patients and provided a reliable and operational tool for clinical use to improve the safety of chemotherapy in cancer patients.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Baseline characteristics of patients in the external validation cohort

Patient's characteristics	Total (n=413)
Background data	
Age, yr	54.3±12.4
BMI, kg/m ²	22.0±3.2
Gender (male/female)	254/159 (61.5%/38.5%)
History of smoking (Yes/No)	142/271 (34.4%/65.6%)
History of hypertension (Yes/No)	65/348 (15.7%/84.3%)
History of CHD (Yes/No)	15/398 (3.6%/96.4%)
History of HBV of infection (Yes/No)	67/346 (16.2%/83.8%)
History of HCV of infection (Yes/No)	5/408 (1.2%/98.8%)
Nucleotide analogue medicine (Yes/No)	37/376 (9.0%/91.0%)
History of diabetes (Yes/No)	33/380 (8.0%/92.0%)
History of alcoholism (Yes/No)	66/347 (16.0%/84.0%)
Laboratory data	
ALB, g/l	38.7±5.0
BUN, mmol/l	5.2±5.0
Cr, μmol/l	69.3±24.7
UA, μmol/l	298.8±97.1
GLU, mmol/l	5.7±4.2
ALT, U/L	26.6±22.9
AST, U/L	28.3±25.0
ALT/AST	1.0±1.6
CHOL, mmol/l	4.5±1.0
TG, mmol/l	1.2±0.8
CRP, mg/l	3.9±9.1
Cys, mg/l	0.8±0.2
Hb, g/l	120.6±23.6
TBIL, μmol/l	13.0±22.3
GGT, U/L	101.0±145.7
APTT, s	28.8±5.1
Fbg, g/l	4.4±1.5
INR	0.9±0.1
Other data	
Tumor type	
Gastrointestinal	146 (35.4%)
Breast	25 (6.1%)
Head/neck	37 (9.0%)
Lung	137 (33.2%)
Urinary tract	9 (2.2%)
Gynecologic	40 (9.7%)
Hematologic	7 (1.7%)
Others	12 (2.9%)
Liver metastasis (Yes/No)	41 (9.9%)/372 (90.1%)

(Continued)

Table S1 (Continued).

Patient's characteristics	Total (n=413)
Tumor staging	
II	71 (17.2%)
III	118 (28.6%)
IV	224 (54.2%)
Cycle of chemotherapy	
≤2	343 (83.1%)
3 or 4	70 (16.9%)
>4	0 (0)
Chemotherapeutics	
Oxaliplatin (Yes/No)	73/340 (16.9%/83.1%)
Irinotecan (Yes/No)	17/396 (4.1%/95.9%)
Gemcitabine (Yes/No)	38/375 (9.2%/90.8%)
Platinum (Yes/No)	108/305 (26.2%/73.8%)
Fluorouracil (Yes/No)	51/362 (12.3%/87.7%)
Doxorubicin (Yes/No)	50/363 (12.0%/88.0%)
Paclitaxel (Yes/No)	42/371 (10.2%/89.8%)
Docetaxel (Yes/No)	47/366 (11.3%/88.7%)
Pemetrexed (Yes/No)	41/372 (9.9%/90.1%)

Note: Data are presented as n (%), mean ± SD.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; ALB, albumin; BUN, urea nitrogen; Cr, creatinine; UA, uric acid; GLU, blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALT/AST, ratio of alanine aminotransferase to aspartate aminotransferase; CHOL, cholesterol; TG, triglyceride; CRP, C-reactive protein; Cys, cystatin C; Hb, hemoglobin; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; APTT, activated partial thromboplastin time; Fbg, fibrinogen; INR, international normalized ratio.

Table S2 Chemotherapy-induced severe liver damage in the training and internal validation cohort

Variables	Total (n=3870)	Training cohort (n=2580)	Internal validation cohort (n=1290)
ALT increased	210	146	64
AST increased	273	178	94
ALP increased	26	18	8
Bilirubin increased	33	21	12
GGT increased	41	26	15
Ascites	22	14	8
APTT prolonged	20	14	6
Fibrinogen decreased	20	11	9
INR increased	21	12	9
Total	666	440	225

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; GGT, gamma-glutamyl transpeptidase.

Table S3 Chemotherapy-induced severe liver damage in the external validation cohort

Variables	Training cohort (n=413)
ALT increased	21
AST increased	25
ALP increased	3
Bilirubin increased	2
GGT increased	4
Ascites	1
APTT prolonged	2
Fibrinogen decreased	1
INR increased	1
Total	60

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; GGT, gamma-glutamyl transpeptidase.

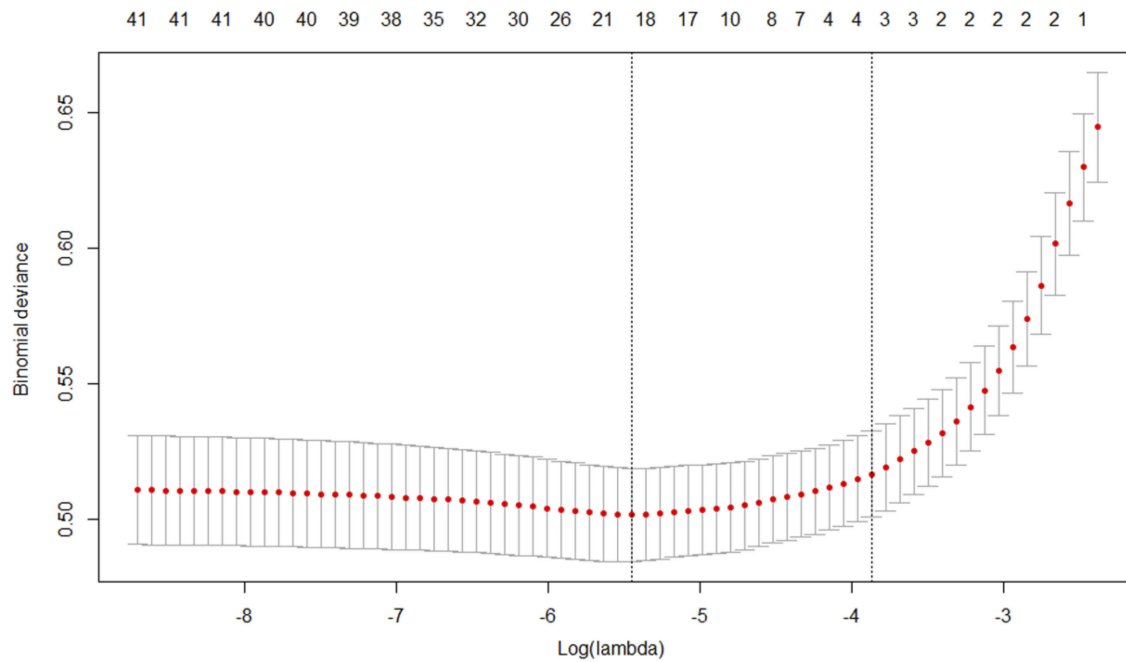


Figure S1 Features selection using the LASSO regression. Tuning parameter (λ) selection in the LASSO logistic model. The minimum criteria for tenfold cross validation were applied to λ selection. Using the 1 standard error (1-SE) criteria and the minimum criteria, the optimal values of the LASSO tuning parameter (λ) are indicated by the dotted vertical lines, and a value λ of 0.025 was chosen.

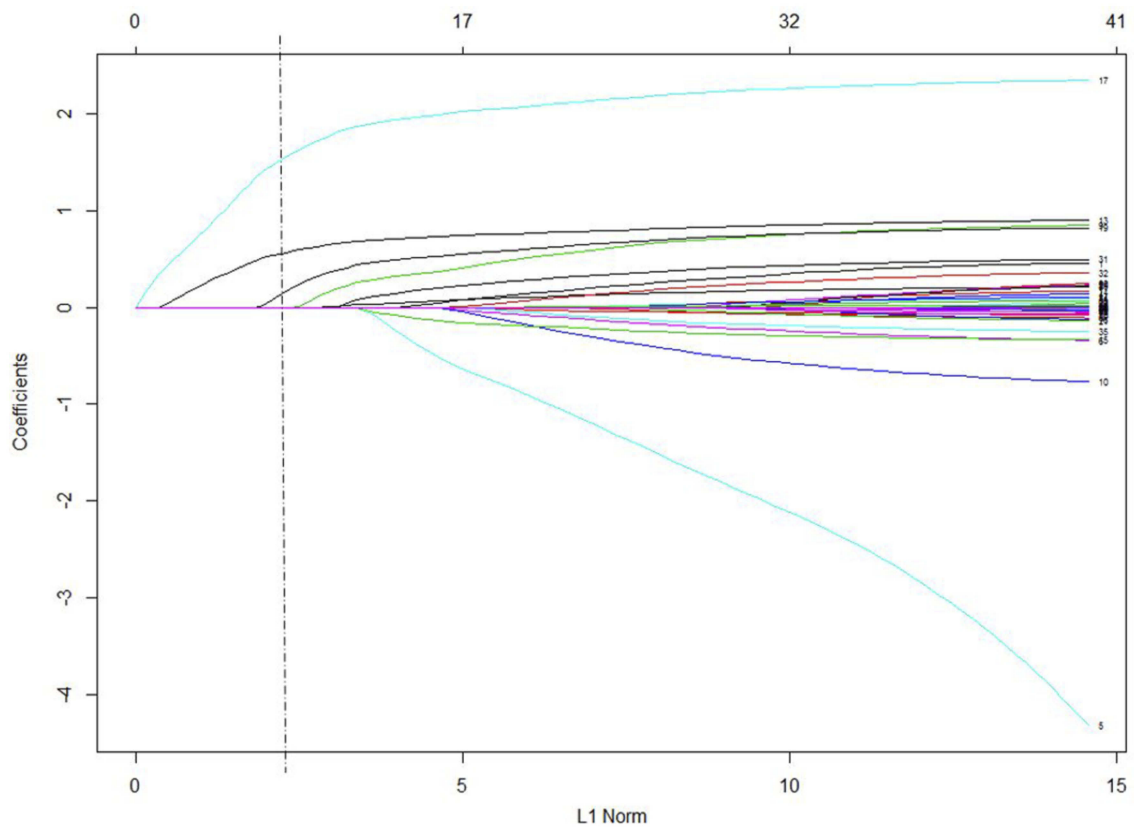


Figure S2 Features selection using the LASSO regression. The LASSO coefficients of the 42 features. A coefficient profile plot was generated against the L1 Norm sequence. Vertical line was drawn at the value selected using 10-fold cross-validation, where optimal λ resulted in 8 nonzero coefficients.

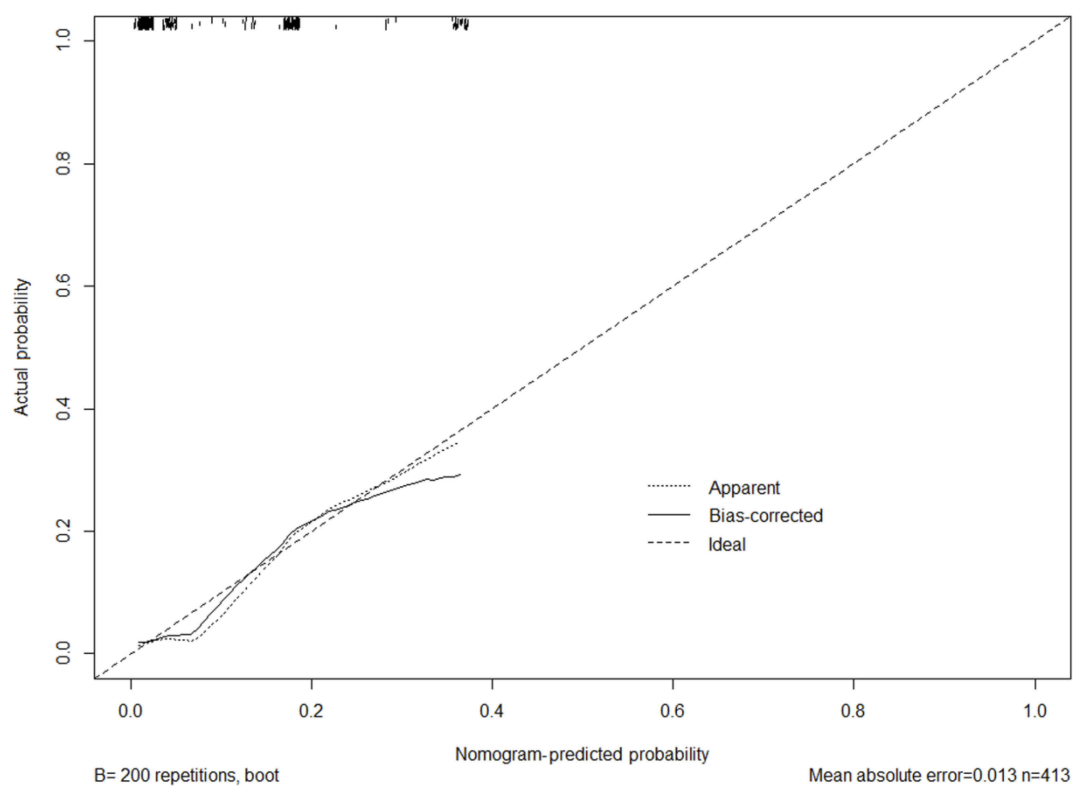


Figure S3 The calibration plot for risk of hepatic function damage in the external validation cohort.

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