

# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2024 January 15; 16(1): 1-250



**EDITORIAL**

- 1 Present situation and prospect of immunotherapy for unresectable locally advanced esophageal cancer during peri-radiotherapy  
*Wang FM, Mo P, Yan X, Lin XY, Fu ZC*
- 8 Early gastric cancer recurrence after endoscopic submucosal dissection: Not to be ignored!  
*Zeng Y, Yang J, Zhang JW*

**REVIEW**

- 13 New trends in diagnosis and management of gallbladder carcinoma  
*Pavlidis ET, Galanis IN, Pavlidis TE*

**ORIGINAL ARTICLE****Clinical and Translational Research**

- 30 Mechanism of pachymic acid in the treatment of gastric cancer based on network pharmacology and experimental verification  
*Du YH, Zhao JJ, Li X, Huang SC, Ning N, Chen GQ, Yang Y, Nan Y, Yuan L*

**Retrospective Cohort Study**

- 51 Trends in colorectal cancer incidence according to an increase in the number of colonoscopy cases in Korea  
*Kim GH, Lee YC, Kim TJ, Hong SN, Chang DK, Kim YH, Yang DH, Moon CM, Kim K, Kim HG, Kim ER*

**Retrospective Study**

- 61 C-reactive protein to albumin ratio predict responses to programmed cell death-1 inhibitors in hepatocellular carcinoma patients  
*Li BB, Chen LJ, Lu SL, Lei B, Yu GL, Yu SP*
- 79 Impact of propofol and sevoflurane anesthesia on cognition and emotion in gastric cancer patients undergoing radical resection  
*Li AH, Bu S, Wang L, Liang AM, Luo HY*
- 90 Development and validation of a machine learning-based early prediction model for massive intraoperative bleeding in patients with primary hepatic malignancies  
*Li J, Jia YM, Zhang ZL, Liu CY, Jiang ZW, Hao ZW, Peng L*
- 102 Comparative study between Embosphere® and Marine gel® as embolic agents for chemoembolization of hepatocellular carcinoma  
*Kim HC, Choi JW*

- 110 Clinical value of oral contrast-enhanced ultrasonography in diagnosis of gastric tumors

*Wang CY, Fan XJ, Wang FL, Ge YY, Cai Z, Wang W, Zhou XP, Du J, Dai DW*

**Observational Study**

- 118 Prognostic significance and relationship of SMAD3 phospho-isoforms and VEGFR-1 in gastric cancer: A clinicopathological study

*Lv SL, Guo P, Zou JR, Chen RS, Luo LY, Huang DQ*

- 133 Colonoscopy plays an important role in detecting colorectal neoplasms in patients with gastric neoplasms

*Liu XR, Wen ZL, Liu F, Li ZW, Liu XY, Zhang W, Peng D*

**Basic Study**

- 144 Analysis of the potential biological value of pyruvate dehydrogenase E1 subunit  $\beta$  in human cancer

*Rong Y, Liu SH, Tang MZ, Wu ZH, Ma GR, Li XF, Cai H*

- 182 Colorectal cancer's burden attributable to a diet high in processed meat in the Belt and Road Initiative countries

*Liu G, Li CM, Xie F, Li QL, Liao LY, Jiang WJ, Li XP, Lu GM*

**SYSTEMATIC REVIEWS**

- 197 Comprehensive analysis of the role of ubiquitin-specific peptidases in colorectal cancer: A systematic review

*Al-Balushi E, Al Marzouqi A, Tavoosi S, Baghsheikhi AH, Sadri A, Aliabadi LS, Salarabedi MM, Rahman SA, Al-Yateem N, Jarrahi AM, Halimi A, Ahmadvand M, Abdel-Rahman WM*

**META-ANALYSIS**

- 214 Application of neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy in curative surgery for esophageal cancer: A meta-analysis

*Yuan MX, Cai QG, Zhang ZY, Zhou JZ, Lan CY, Lin JB*

**CASE REPORT**

- 234 Emerging role of liquid biopsy in rat sarcoma virus mutated metastatic colorectal cancer: A case report

*Gramaça J, Fernandes IG, Trabulo C, Gonçalves J, dos Santos RG, Baptista A, Pina I*

- 244 Comprehensive evaluation of rare case: From diagnosis to treatment of a sigmoid Schwannoma: A case report

*Li JY, Gao XZ, Zhang J, Meng XZ, Cao YX, Zhao K*

**ABOUT COVER**

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Wael M Abdel-Rahman, MD, PhD, Full Professor, Chairman, Department of Medical Laboratory Sciences, College of Health Sciences and Research Institute of Medical and Health Sciences, University of Sharjah, Sharjah 27272, United Arab Emirates. whassan@sharjah.ac.ae

**AIMS AND SCOPE**

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

**INDEXING/ABSTRACTING**

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGO* as 3.0; IF without journal self cites: 2.9; 5-year IF: 3.0; Journal Citation Indicator: 0.49; Ranking: 157 among 241 journals in oncology; Quartile category: Q3; Ranking: 58 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2022 is 4.1 and Scopus CiteScore rank 2022: Gastroenterology is 71/149; Oncology is 197/366.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Xiang-Di Zhang; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Oncology*

**ISSN**

ISSN 1948-5204 (online)

**LAUNCH DATE**

February 15, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Monjur Ahmed, Florin Burada

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

**PUBLICATION DATE**

January 15, 2024

**COPYRIGHT**

© 2023 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



Retrospective Study

# Development and validation of a machine learning-based early prediction model for massive intraoperative bleeding in patients with primary hepatic malignancies

Jin Li, Yu-Ming Jia, Zhi-Lei Zhang, Cheng-Yu Liu, Zhan-Wu Jiang, Zhi-Wei Hao, Li Peng

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): D  
Grade E (Poor): 0

**P-Reviewer:** Ahmed M, United States; Ker CG, Taiwan; Wani I, India

**Received:** August 22, 2023

**Peer-review started:** August 22, 2023

**First decision:** September 26, 2023

**Revised:** October 12, 2023

**Accepted:** December 1, 2023

**Article in press:** December 1, 2023

**Published online:** January 15, 2024



**Jin Li, Yu-Ming Jia, Zhi-Lei Zhang, Cheng-Yu Liu, Li Peng,** Department of Hepatological Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, Hebei Province, China

**Zhan-Wu Jiang, Zhi-Wei Hao,** Department of General Surgery II, Baoding First Central Hospital, Baoding 071000, Hebei Province, China

**Corresponding author:** Li Peng, MD, Director, Doctor, Department of Hepatological Surgery, The Fourth Hospital of Hebei Medical University, No. 12 Health Road, Chang'an District, Shijiazhuang 050011, Hebei Province, China. [pengli555555@163.com](mailto:pengli555555@163.com)

## Abstract

### BACKGROUND

Surgical resection remains the primary treatment for hepatic malignancies, and intraoperative bleeding is associated with a significantly increased risk of death. Therefore, accurate prediction of intraoperative bleeding risk in patients with hepatic malignancies is essential to preventing bleeding in advance and providing safer and more effective treatment.

### AIM

To develop a predictive model for intraoperative bleeding in primary hepatic malignancy patients for improving surgical planning and outcomes.

### METHODS

The retrospective analysis enrolled patients diagnosed with primary hepatic malignancies who underwent surgery at the Hepatobiliary Surgery Department of the Fourth Hospital of Hebei Medical University between 2010 and 2020. Logistic regression analysis was performed to identify potential risk factors for intraoperative bleeding. A prediction model was developed using Python programming language, and its accuracy was evaluated using receiver operating characteristic (ROC) curve analysis.

### RESULTS

Among 406 primary liver cancer patients, 16.0% (65/406) suffered massive intraoperative bleeding. Logistic regression analysis identified four variables as associated with intraoperative bleeding in these patients: ascites [odds ratio (OR): 22.839;  $P < 0.05$ ], history of alcohol consumption (OR: 2.950;  $P < 0.015$ ), TNM

staging (OR: 2.441;  $P < 0.001$ ), and albumin-bilirubin score (OR: 2.361;  $P < 0.001$ ). These variables were used to construct the prediction model. The 406 patients were randomly assigned to a training set (70%) and a prediction set (30%). The area under the ROC curve values for the model's ability to predict intraoperative bleeding were 0.844 in the training set and 0.80 in the prediction set.

## CONCLUSION

The developed and validated model predicts significant intraoperative blood loss in primary hepatic malignancies using four preoperative clinical factors by considering four preoperative clinical factors: ascites, history of alcohol consumption, TNM staging, and albumin-bilirubin score. Consequently, this model holds promise for enhancing individualised surgical planning.

**Key Words:** Primary liver cancer; Intraoperative bleeding; Machine learning; Model

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** A prediction model for significant intraoperative blood loss in patients with primary hepatic malignancies was constructed in this retrospective analysis. Logistic regression analysis identified four preoperative clinical factors associated with intraoperative bleeding: ascites, history of alcohol consumption, TNM staging, and albumin-bilirubin score. These factors were used to construct a prediction model that demonstrated good accuracy in assessing the risk of intraoperative bleeding. Implementation of this model has the potential to enhance personalized surgical planning, leading to safer and more effective treatment for patients with hepatic malignancies.

**Citation:** Li J, Jia YM, Zhang ZL, Liu CY, Jiang ZW, Hao ZW, Peng L. Development and validation of a machine learning-based early prediction model for massive intraoperative bleeding in patients with primary hepatic malignancies. *World J Gastrointest Oncol* 2024; 16(1): 90-101

**URL:** <https://www.wjgnet.com/1948-5204/full/v16/i1/90.htm>

**DOI:** <https://dx.doi.org/10.4251/wjgo.v16.i1.90>

## INTRODUCTION

Primary liver cancer is a common cancer type worldwide, but especially in developing countries[1]. Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the two most prevalent primary hepatic malignancies, followed by combined HCC and cholangiocarcinoma[2]. HCC accounts for the vast majority of primary hepatic malignancies and is the third leading cause of cancer-related fatalities worldwide and the second leading cause of cancer-related death in China[3,4], whereas ICC accounts for an estimated 5%-10% of all liver malignancies[5]. Hepatitis B virus infection is responsible for up to 80% of liver cancer cases in China[6,7]. Previously published studies demonstrated that infectious liver disease and intraoperative bleeding > 1000 mL were independent factors that increased the odds of major complications. Age over 70 years, metastatic liver tumor, difficult liver resection, liver cirrhosis, and right hepatectomy were also factors that independently influenced prolonged postoperative length of stay after laparoscopic liver resection on multivariate analysis. In general, the prognosis for primary liver cancer is dismal, and especially so for cases with vascular metastases. Patients with early-stage HCC have a median life expectancy of 6-20 mo following diagnosis, with 3- and 5-year postoperative survival rates of 72% and 50%, respectively, and 5-year post-liver transplantation survival rates ranging from 48% to 61%[8-10].

Surgical resection is the primary treatment for hepatic malignancies[11-13], and intraoperative blood loss and transfusion requirements are closely related to perioperative morbidity and mortality in patients undergoing liver cancer surgery[14]. Hepatic portal blocking is usually necessary to control intraoperative bleeding[15]. In 1977, Foster and Berman published the results of a multicenter analysis of 621 patients who underwent hepatectomy for various indications, which showed that operative mortality rates exceeding 13% and 20% for hepatectomy and extended hepatic resection, respectively, with 20% of deaths resulting from bleeding[14,16]. Lei *et al*[15] conducted a retrospective study involving 643 consecutive patients who underwent hepatic resection for HCC. The study identified several risk factors associated with major intraoperative blood loss in these patients. These risk factors included male gender, elevated alanine aminotransferase levels (> 55 U/dL), decreased prothrombin time (< 95%), resection of more than 3 Couinaud segments, *en bloc* resection, low case volume of the surgeon (< 65 cases), and central location of the tumor.

Therefore, it is imperative to develop a precise methodology for the anticipation of intraoperative hemorrhaging in individuals afflicted with hepatic malignancies, in order to facilitate the implementation of tailored therapeutic interventions for these patients. Developing a scientifically rigorous methodology to predict the probability of intraoperative hemorrhage in individuals with hepatic malignancies would not only optimize the selection of appropriate surgical interventions but also improve the allocation of limited resources. In the present study, through retrospective analysis of the clinical and preoperative data of patients with primary hepatic malignancies, factors associated with intraoperative bleeding were identified. The identified factors were then incorporated into the development of a

prognostic model designed to predict cases of significant intraoperative hemorrhage. Validation of this model was conducted using various statistical methods, confirming its effectiveness. The utilization of this model has the potential to improve personalized surgical planning.

## MATERIALS AND METHODS

### Study population

Patient data for individuals with primary hepatic malignancies who underwent radical resection in the Department of Hepatobiliary Surgery of the Fourth Hospital of Hebei Medical University from 2010-2020 were analyzed retrospectively. Patients were included in this study according to the following criteria: (1) Both male and female participants between the ages of 18 and 75 years; (2) Good overall health condition and ability to tolerate anesthesia, pneumoperitoneum, and laparoscopic liver resection; (3) Liver function classification according to Child-Pugh score A or B, with a residual liver volume to standard liver volume ratio greater than 40%; (4) Presence of a single HCC with a tumor size not exceeding 10 cm; and (5) No evidence of tumor invasion or thrombosis in major hepatic vessels, and no intrahepatic or extrahepatic metastasis. Patients were excluded if they met any of the following exclusion criteria: (1) A history of esophageal variceal hemorrhage, severe hypersplenism syndrome, or refractory ascites; (2) Any preoperative anticancer treatments including transcatheter arterial chemoembolization, radiofrequency ablation, radiotherapy; (3) Postoperative pathology suggested metastatic liver cancer or primary liver cancer of another tissue type; (4) Previous or concomitant malignancies; (5) In patients who have a prior history of increased bleeding risk or are known to have tumor-related coagulopathy; and (6) Presence of preoperative tumor ruptured. This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. Rigorous adherence to a confidentiality policy was observed in all data manipulations, and the present investigation adhered to the principles outlined in the Declaration of Helsinki. The hospital ethics committee waived the requirement for written, informed patient consent due to the retrospective study design.

### Data extraction

For all included patients, baseline characteristics, laboratory parameters, and pathological tumor features were collected. Demographic variables included gender, age, height, weight, and history of alcohol consumption. Laboratory parameters included platelet count, hemoglobin level, alanine aminotransferase level, prothrombin time, aspartate aminotransferase level, albumin level, direct bilirubin level, total bilirubin level, methemoglobin level, unconjugated bilirubin level, and carcinoembryonic antigen level. Tumor characteristics included pathologic staging, number of lesions, maximum lesion diameter, and cancer emboli. Similarly, coexisting infections such as hepatitis B virus infection, cirrhosis, and ascites were also considered. The TNM stage was used for the cancer stage, and the patient's general health was represented by the Eastern Cooperative Oncology Group score. Liver function was assessed using Child-Pugh grade, albumin bilirubin score (ALBI), and ALBI grade. The rate of massive intraoperative bleeding was calculated based on 28 indicators, as published previously, and our clinical experience. According to the available data, the etiology of primary liver cancer in each patient was evaluated and classified.

### Statistical analysis

Python software (version 3.7.1) and R language software (version 3.6.3) were used for calculations and analyses. Continuous variables are expressed as mean  $\pm$  SD or median and interquartile range. Categorical variables are expressed as total and percentage. The Kruskal-Wallis test was applied to compare continuous variables between two groups, and the Chi-square test for variance was used to compare categorical variables between two groups. Two-tailed *P* values  $<$  0.05 were assumed to indicate a statistically significant difference.

Logistic regression analysis was performed to screen variables associated with intraoperative massive bleeding and transfusion requirements. Based on the scikit-learn algorithm of the machine learning (ML) library, a prediction model based on the identified variables was constructed using Python[17]. We conducted an evaluation of the area under the curve (AUC) values for five distinct ML models in order to ascertain the most appropriate model for our study, as depicted in [Supplementary Figure 1](#). According to the findings, logistic regression exhibited superior AUC compared to the other four models within the medical domain. R software was used to develop the nomogram, perform logistic regression analysis, and generate decision-making, calibration, and clinical impact curves.

## RESULTS

### Baseline characteristics of the included liver cancer patients

A retrospective screening was conducted on data for a cohort of 445 patients diagnosed with primary hepatic malignancies. Through the screening process, a total of 406 patients were identified as meeting the predetermined inclusion criteria for the study ([Figure 1](#)). The clinical data for all 406 patients are presented in [Supplementary Table 1](#). Blood loss exceeding 1000 mL was defined as massive bleeding. Among the 406 patients, 65 (16.0%) suffered massive intraoperative bleeding ( $>$  1000 mL), while the median bleeding volume among patients was measured at 1267.4 mL, 291 (71.7%) had a history of hepatitis B, and 290 (71.4%) had cirrhosis.

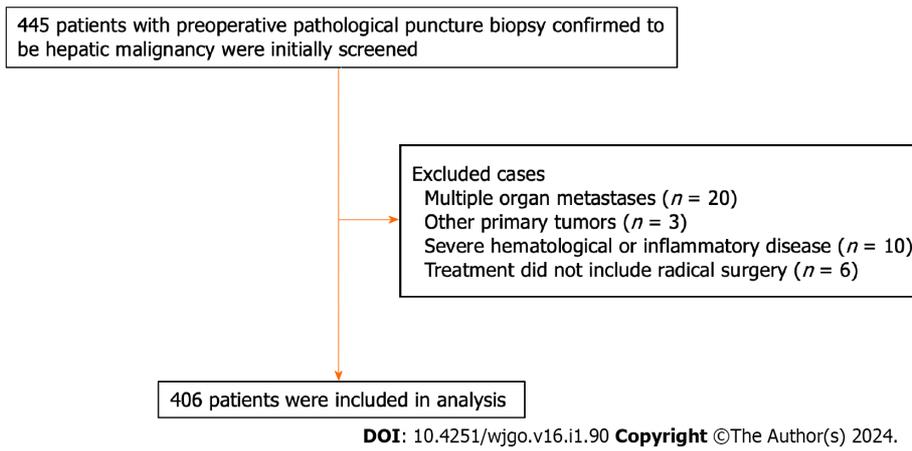


Figure 1 Flow chart of patient inclusion.

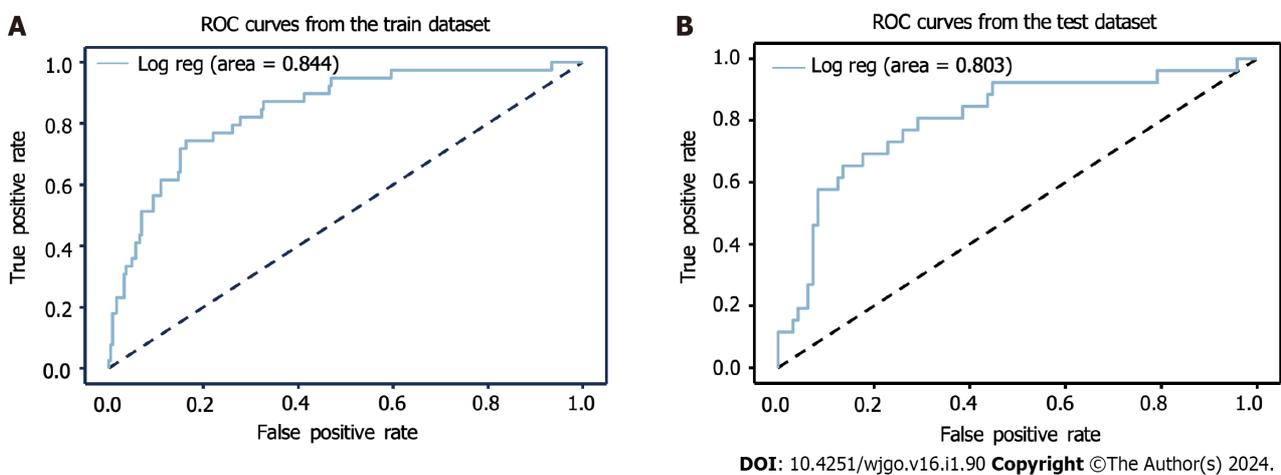


Figure 2 Predictive performance of the developed model. Model discrimination was evaluated based on area under the curve values, which were (A) 0.844 in the training set and (B) 0.803 in the prediction set. ROC: Receiver operating characteristics.

The study cohort was divided randomly into two sets: 70% of cases to the training set, which was utilized for model training, and the remaining 30% of cases to the prediction set, which was used for model testing. Comparison of the basic and clinical characteristics of patients in the training and prediction sets showed no statistically significant differences (Table 1). Notably, 14% of the training set (39/284) and 21% of the prediction set (26/122) exhibited indications of substantial intraoperative hemorrhage.

### Development and evaluation of prediction model

Among the 28 variables described in the Methods section, 21 associated with massive intraoperative bleeding based on clinical experience were included in the univariate analysis (Table 1). Variables for which  $P < 0.2$  on univariate analysis were included in the subsequent multivariate analysis (Table 2). Then the ML model was constructed using the variables for which  $P < 0.05$  on multivariate analysis. Four variables were identified as predictors of massive intraoperative bleeding and transfusion requirements: ascites [odds ratio (OR): 22.839;  $P < 0.05$ ], history of alcohol consumption (OR: 2.950;  $P < 0.015$ ), TNM staging (OR: 2.441;  $P < 0.001$ ), and ALBI score (OR: 2.361;  $P < 0.001$ ). From receiver operating characteristic curve analysis, the AUC values for the ability of the developed model to predict massive intraoperative bleeding were 0.844 in the training set and 0.803 in the test set (Figure 2). The predictive performance of the model (AUC = 0.844) was found to be significantly higher compared to the individual factors of history of alcohol consumption (AUC = 0.603), ascites (AUC = 0.612), and ALBI score (AUC = 0.580; Figure 3). The analysis also encompassed the examination of correlations among the variables incorporated in the study, as depicted in Figure 4.

### Prediction nomogram construction

Based on the four variables identified by the logistic regression analysis, a nomogram was developed to predict the massive intraoperative bleeding among patients with hepatic malignancy (Figure 5). The calibration curve demonstrated a high level of concordance between the projected incidence derived from the logistic regression model and the observed outcomes within the cohort (Figure 6). The nomogram demonstrates reliable predictive ability for estimating the

**Table 1** Baseline characteristics of primary liver cancer patients in the training and prediction sets

	Training dataset ( <i>n</i> = 284)			Testing dataset ( <i>n</i> = 122)		
	Non-hemorrhage (245)	Hemorrhage (39)	<i>P</i> value	Non-hemorrhage (96)	Hemorrhage (26)	<i>P</i> value
Gender, male, <i>n</i> (%)	195 (79.6)	32 (82.1)	0.888	77 (80.2)	20 (76.9)	0.925
Age (yr)	59.0 [52.0, 65.0]	55.0 [50.5, 62.0]	0.133	59.0 [53.0, 64.0]	59.0 [53.0, 66.0]	0.834
Alcohol, <i>n</i> (%)			0.024			
No	151 (61.6)	16 (41.0)		58 (60.4)	15 (57.7)	
Yes	94 (38.4)	23 (59.0)		38 (39.6)	11 (42.3)	
Ascites, <i>n</i> (%)			< 0.001			0.001
No	237 (96.7)	29 (74.4)		94 (97.9)	20 (76.9)	
Yes	8 (3.3)	10 (25.6)		2 (2.1)	6 (23.1)	
Cirrhosis, <i>n</i> (%)			0.755			0.957
No	72 (29.4)	13 (33.3)		24 (25.0)	7 (26.9)	
Yes	173 (70.6)	26 (66.7)		72 (75.0)	19 (73.1)	
HBV, <i>n</i> (%)			0.061			0.957
No	67 (27.3)	17 (43.6)		24 (25.0)	7 (26.9)	
Yes	178 (72.7)	22 (56.4)		72 (75.0)	19 (73.1)	
HBG (g/L)	145.0 [133.6, 154.5]	139.0 [125.0, 154.0]	0.275	145.0 [135.0, 153.5]	134.0 [125.0, 146.0]	0.012
PT (s)	12.1 [11.5, 12.7]	12.0 [11.1, 12.6]	0.379	12.0 [11.4, 12.8]	11.9 [11.2, 13.1]	0.710
ALT (U/L)	27.0 [18.0, 40.0]	31.0 [23.0, 44.9]	0.100	29.7 [19.9, 49.0]	26.9 [20.8, 35.1]	0.332
AST (U/L)	27.0 [20.5, 40.0]	30.9 [26.1, 43.8]	0.053	26.9 [19.8, 41.0]	28.1 [22.8, 42.0]	0.524
Albumin (g/L)	42.7 [38.9, 45.5]	41.2 [36.7, 45.5]	0.274	43.3 [40.1, 45.6]	41.5 [37.8, 44.2]	0.075
TBIL (μmol/L)	13.3 [10.5, 17.9]	17.7 [13.3, 25.1]	0.001	13.6 [10.4, 17.1]	15.6 [11.9, 20.4]	0.086
DBIL (μmol/L)	5.0 [3.4, 7.0]	6.8 [4.2, 10.4]	0.002	4.9 [3.4, 6.7]	5.8 [3.5, 9.4]	0.314
IBIL (μmol/L)	8.1 [6.6, 11.4]	9.6 [6.8, 12.0]	0.152	8.4 [6.4, 10.8]	8.9 [7.1, 11.4]	0.440
AFP (ng/mL)	13.4 [4.2, 352.6]	10.6 [3.9, 365.6]	0.990	33.3 [4.9, 531.6]	77.7 [7.1, 571.7]	0.514
CEA (ng/mL)	2.6 [1.8, 4.1]	2.4 [1.6, 3.7]	0.498	2.6 [1.7, 3.7]	2.5 [2.1, 3.4]	0.883
No. of lesions, <i>n</i> (%)			0.462			0.534
1	205 (83.7)	35 (89.7)		83 (86.5)	21 (80.8)	
> 1	40 (16.3)	4 (10.3)		13 (13.5)	5 (19.2)	
Size of main tumor, <i>n</i> (%)			0.002			0.002
< 5 cm	144 (58.8)	12 (30.8)		58 (60.4)	6 (23.1)	
≥ 5 cm	101 (41.2)	27 (69.2)		38 (39.6)	20 (76.9)	
Tumor thrombus, <i>n</i> (%)			0.136			0.329
No	209 (85.3)	29 (74.4)		85 (88.5)	21 (80.8)	
Yes	36 (14.7)	10 (25.6)		11 (11.5)	5 (19.2)	
Pathological type, <i>n</i> (%)			0.760			0.558
HCC	207 (84.5)	31 (79.5)		80 (83.3)	22 (84.6)	
CCA	32 (13.1)	7 (17.9)		10 (10.4)	4 (15.4)	
HCC-CCA	2 (0.8)			3 (3.1)		
Other	4 (1.6)	1 (2.6)		3 (3.1)		

TNM, <i>n</i> (%)			< 0.001			< 0.001
I	175 (71.4)	11 (28.2)		70 (72.9)	9 (34.6)	
II	38 (15.5)	6 (15.4)		13 (13.5)	4 (15.4)	
III	27 (11.0)	19 (48.7)		10 (10.4)	12 (46.2)	
IV	5 (2.0)	3 (7.7)		3 (3.1)	1 (3.8)	
Child-Pugh grade, <i>n</i> (%)			0.002			0.021
A	234 (95.5)	31 (79.5)		92 (95.8)	21 (80.8)	
B	11 (4.5)	8 (20.5)		4 (4.2)	5 (19.2)	
ALBI score	-2.9 [-3.1, -2.5]	-2.7 [-3.1, -2.2]	0.108	-3.0 [-3.1, -2.6]	-2.8 [-3.0, -2.1]	0.059
ALBI grade, <i>n</i> (%)			< 0.001			0.398
1	177 (72.2)	21 (53.8)		73 (76.0)	17 (65.4)	
2	68 (27.8)	16 (41.0)		23 (24.0)	9 (34.6)	
3		2 (5.1)				

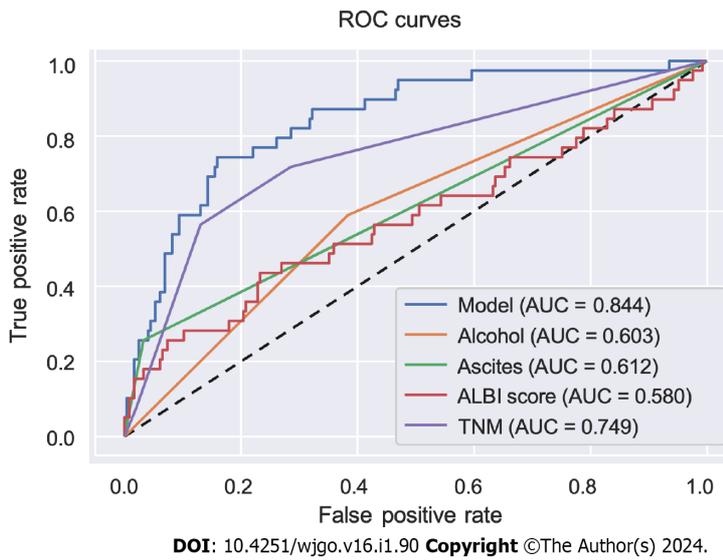
HBV: Hepatitis B virus; HBG: Hemoglobin; PT: Prothrombin time; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Unconjugated bilirubin; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; HCC: Hepatocellular carcinoma; CAA: Cholangio carcinoma; HCC-CCA: Combined hepatocellular-cholangiocarcinoma; ALBI: Albumin bilirubin.

**Table 2 Results of multifactor analysis of variables associated with intraoperative bleeding in primary liver cancer patients**

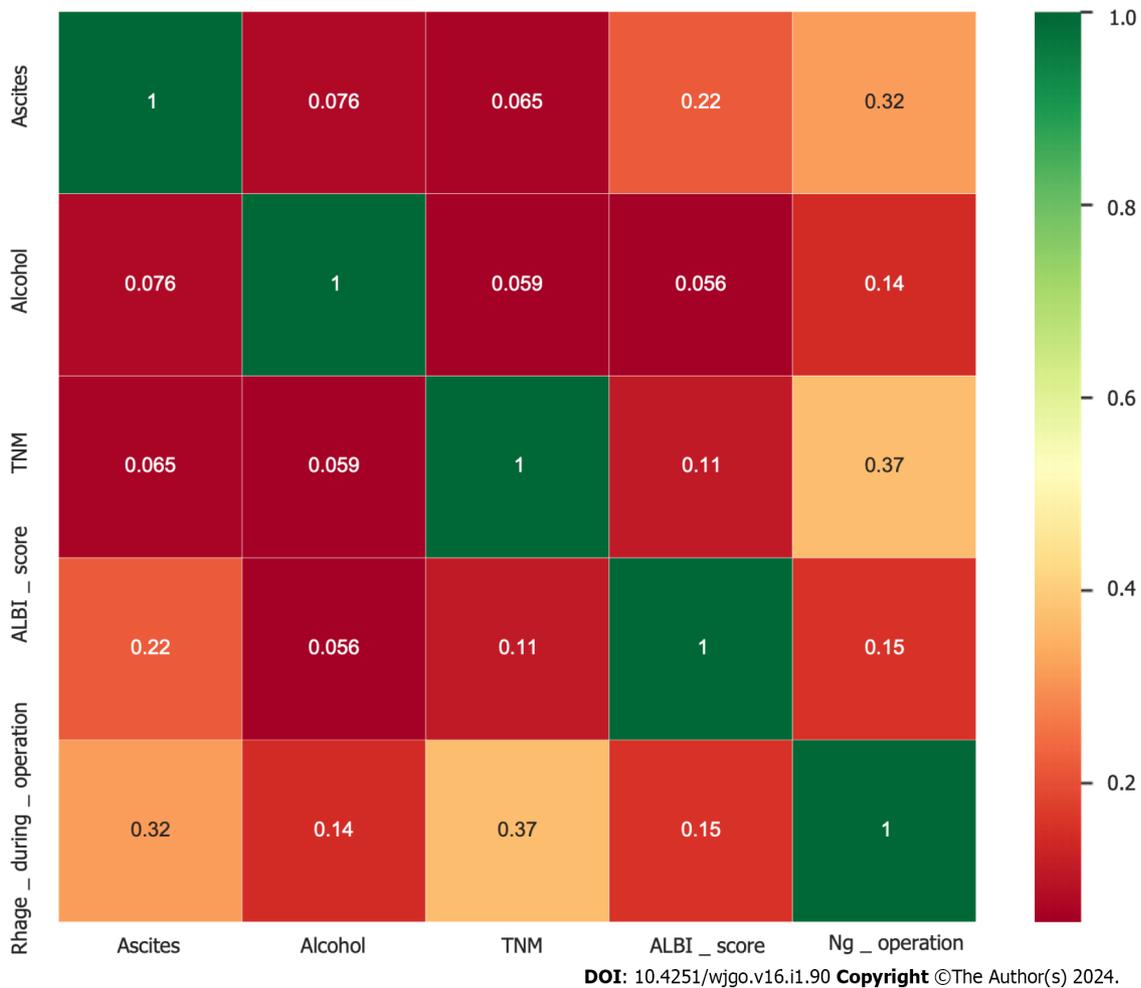
	97.5%CI lower	97.5%CI upper	OR	P value
Alcohol	1.231	7.068	2.950	0.015
Ascites	5.358	97.359	22.839	< 0.001
HBV	0.197	1.158	0.478	0.102
TBIL	0.947	1.456	1.174	0.144
DBIL	0.706	1.087	0.877	0.229
IBIL	0.725	1.144	0.911	0.421
Size of main tumor	0.865	5.798	2.239	0.097
Tumor thrombus	0.292	2.549	0.862	0.789
TNM	1.527	3.900	2.441	< 0.001
Child-Pugh_grade	0.035	1.402	0.223	0.11
ALBI score	1.426	3.909	2.361	0.001
ALBI grade	0.147	1.124	0.406	0.083
Age	0.879	1.091	0.979	0.384
AST	0.872	1.139	0.996	0.255
ALT	0.969	1.001	0.985	0.343

HBV: Hepatitis B virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Unconjugated bilirubin; ALBI: Albumin bilirubin.

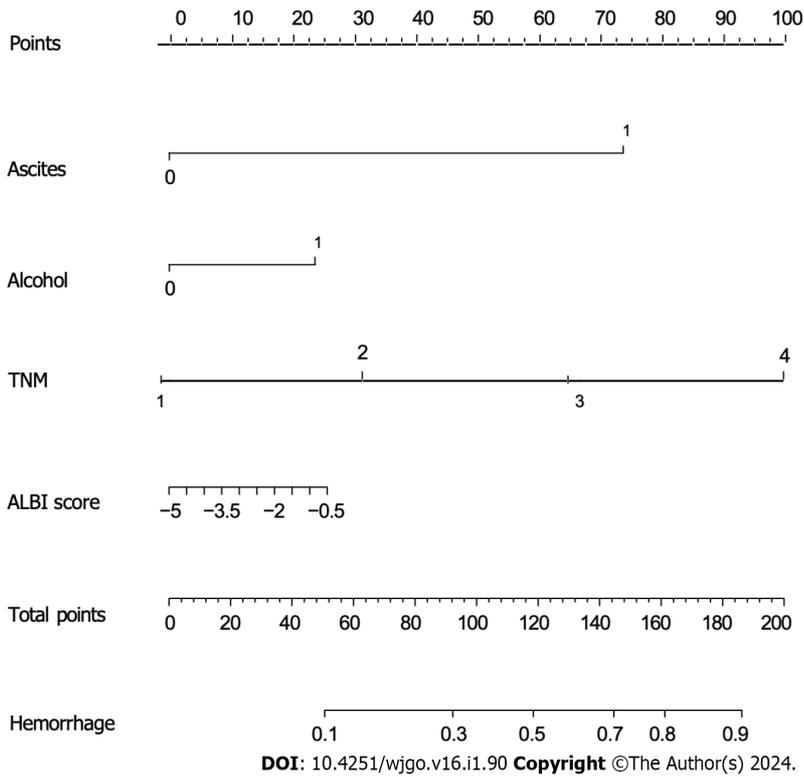
likelihood of significant intraoperative bleeding in patients with hepatic malignancies. According to the clinical impact curves, the model demonstrated superior standardized net benefits for predicting patient outcomes compared to the individual factors of ascites, alcohol consumption history, TNM stage, and ALBI score (Figure 7).



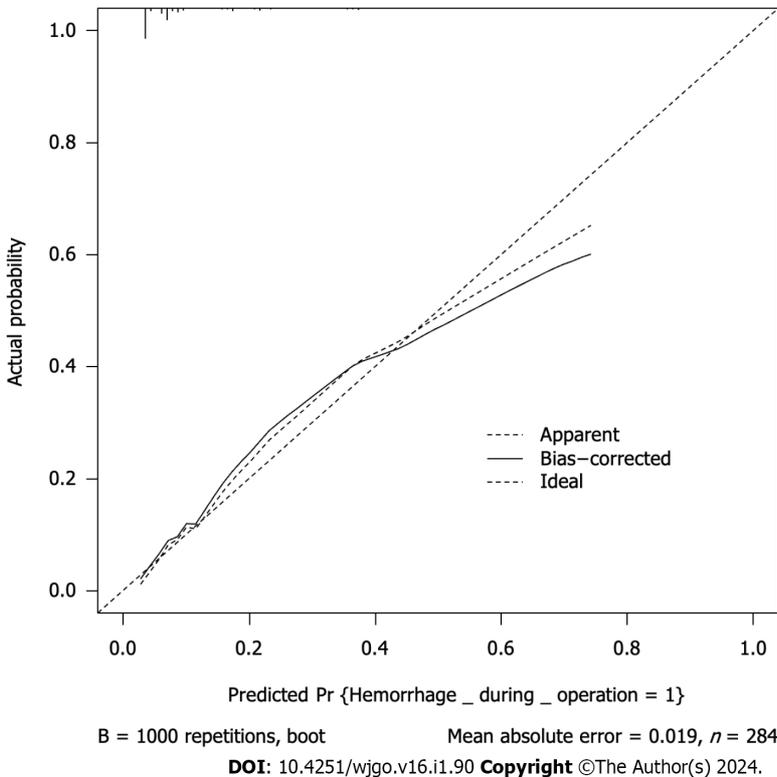
**Figure 3** Receiver operating characteristics curves for the prediction model compared with the individual variables included in the model. ROC: Receiver operating characteristics; AUC: Area under the curve; ALBI: Albumin bilirubin.



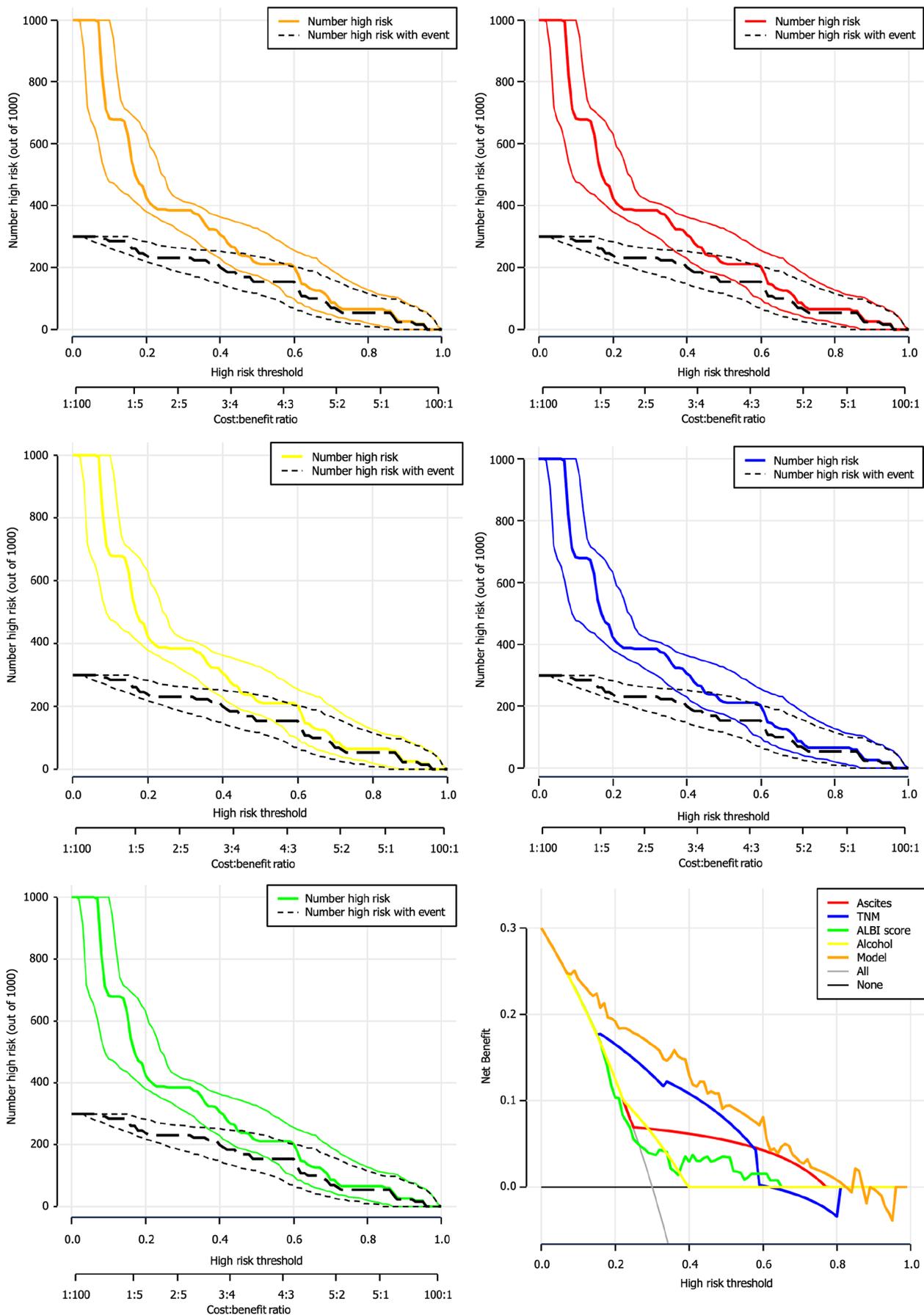
**Figure 4** Correlogram demonstrating the correlation between variables in the prediction model. ALBI: Albumin bilirubin.



**Figure 5** Nomogram for the prediction of intraoperative bleeding in patients with primary hepatic malignancies based on significant variable identified by the logistic regression model. ALBI: Albumin bilirubin.



**Figure 6** Calibration curves for the prediction of intraoperative bleeding in patients with primary hepatic malignancies. Nomogram-predicted intraoperative bleeding in patients with primary hepatic malignancies is plotted on the X-axis, and actual intraoperative bleeding in patients with primary hepatic malignancies is plotted on the Y-axis.



DOI: 10.4251/wjgo.v16.i1.90 Copyright ©The Author(s) 2024.

Figure 7 Decision and clinical impact curves for use of the nomogram to predict intraoperative bleeding in patients with primary hepatic

**malignancies.** The model showed superior standardized net benefit over the individual factors included (ascites, alcohol consumption, TNM staging, and albumin bilirubin score). ALBI: Albumin bilirubin.

## DISCUSSION

As of present, efficacious treatment modalities for primary hepatic malignancies remain limited to hepatectomy[18]. Although advancements in perioperative management as well as hepatectomy techniques have led to better outcomes for patients[19,20], massive intraoperative blood loss remains a common complication with these procedures that can adversely affect postoperative outcomes[14,21]. In a comprehensive investigation conducted by Melendez *et al*[22], including a cohort of 496 individuals who underwent hepatectomy, it was observed that the median blood loss was 645 mL. However, the mean blood loss was higher at 848 mL, with a considerable degree of variability observed among patients, ranging from 40 to 9000 mL. Thus, given the considerable variability in blood loss, it is necessary to develop a predictive model to estimate the probability of massive intraoperative bleeding in patients diagnosed with primary hepatic malignancies. Despite previous studies investigating variables associated with severe intraoperative bleeding after hepatectomy, there has been a scarcity of research focusing on prediction models specifically for major intraoperative bleeding in patients with primary hepatic malignancies. In a study of 438 patients by Kawaguchi *et al*[23], hypertensive disease, preoperative chemotherapy, posterior superior resection, and partial hepatectomy were independent risk factors for increased bleeding during hepatectomy[23]. A distinct study revealed that male gender and decreased prothrombin activity were correlated with an increased risk of experiencing higher blood loss during hepatectomy[24]. Katz *et al*[25] applied multivariate analysis to identify factors that contribute significantly to blood loss during hepatectomy in patients diagnosed with hepatocellular malignancy. The variables identified as significant predictors include male sex, major hepatectomy, operating time, and vascular invasion, and they also reported that significantly increased bleeding during hepatectomy for hepatocellular malignancy was an independent prognostic factor for tumor recurrence and death[25]. The present research differs significantly from prior studies in that patients in the previous studies had partial hepatectomy for a variety of reasons, while all patients in the current study had primary hepatic malignancies. In contrast to previous studies that considered both preoperative and intraoperative factors, the current study specifically aimed to identify preoperative variables associated with intraoperative bleeding in patients with primary hepatic malignancies. This approach was adopted to develop a prediction model applicable before surgical intervention for these patients. In our investigation, a prognostic model was formulated utilising four clinical variables (ascites, history of alcohol consumption, TNM staging, and ALBI score), its efficacy for predicting substantial intraoperative haemorrhaging in individuals diagnosed with primary hepatic malignancies was evaluated. The model was subsequently validated to ensure its reliability and accuracy. Multiple statistical methodologies were employed to verify the satisfactory performance of the model. Using the predicted risk of significant intraoperative hemorrhage determined by the patient's nomogram score, this model has the potential to notify and alert the attending physician and surgeon. Consequently, they can implement proactive and effective treatment interventions before and during the surgical procedure for patients who show a heightened vulnerability to substantial intraoperative bleeding.

### Limitations

This study has several limitations that need to be acknowledged. Firstly, it was a single-center study with internal validation only, lacking external validation, which restricts the generalizability of the model. Therefore, larger multicenter studies are required to validate these findings. The impact of tumor location within the liver on intraoperative bleeding was not considered in the study design. Furthermore, while the study focused on preoperative factors, the inclusion of intraoperative factors could provide valuable insights for guiding intraoperative decision-making regarding bleeding control methods. Hence, further analyses incorporating intraoperative factors are warranted. Lastly, prospective studies with longer follow-up periods are crucial to confirm and enhance the performance of the developed prediction model.

## CONCLUSION

In summary, screening of preoperative clinical factors in patients with primary hepatic malignancies identified four variables associated with massive intraoperative bleeding, which were then used to construct a model and corresponding nomogram for the preoperative prediction of such bleeding in these patients. The developed model has the potential to improve individualized surgical planning for patients with primary hepatic malignancies, leading to enhanced outcomes and optimal utilization of limited medical resources.

## ARTICLE HIGHLIGHTS

### Research background

Surgical removal is the primary treatment for hepatic malignancies, but intraoperative bleeding poses a significant risk to patients with hepatic malignancies. Accurate prediction of intraoperative bleeding is crucial for preventing complications

and improving treatment outcomes.

### **Research motivation**

This study aimed to develop a predictive model for significant intraoperative blood loss in patients with primary liver malignancies. By identifying preoperative factors associated with intraoperative bleeding, we can improve surgical planning and provide safer and more effective treatment for these patients.

### **Research objectives**

This study aimed to identify risk factors for intraoperative bleeding in primary liver malignancies and develop a predictive model to estimate significant intraoperative blood loss.

### **Research methods**

A retrospective analysis was conducted on primary liver malignancy patients who underwent surgery at the Hepatobiliary Surgery Department of the Fourth Hospital of Hebei Medical University between 2010 and 2020. Logistic regression analysis was used to identify risk factors for intraoperative bleeding. A predictive model was developed using Python programming. The model's accuracy was evaluated using receiver operating characteristic (ROC) curve analysis.

### **Research results**

Among 406 patients with primary liver cancer, 16.0% (65/406) experienced significant intraoperative bleeding. Logistic regression analysis revealed four variables that were significantly associated with intraoperative bleeding: Ascites, alcohol consumption history, TNM staging, and albumin-bilirubin score. These variables were utilized to construct a predictive model. The model demonstrated good predictive accuracy, as evidenced by area under the ROC curve values of 0.844 in the training set and 0.80 in the prediction set.

### **Research conclusions**

This study successfully developed and validated a predictive model for significant intraoperative blood loss in patients with primary liver malignancies, using preoperative clinical factors. Implementation of this model has the potential to enhance personalized surgical planning and improve patient outcomes.

### **Research perspectives**

Further research is needed to assess the impact of implementing the predictive model on surgical decision-making, patient safety, and overall clinical outcomes to determine its real-world effectiveness and benefits.

---

## **FOOTNOTES**

**Author contributions:** Li J, Peng L and Jia YM conceived and designed research; Zhang ZL, Liu CY and Jiang ZW collected data and conducted research; Li J, Peng L and Hao ZW analyzed and interpreted data; Li J, Jia YM and Peng L wrote the initial draft; Li J and Peng L revised the manuscript; Li J had primary responsibility for final content; all authors read and approved the final version of the manuscript.

**Institutional review board statement:** This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Informed consent statement:** Due to the retrospective study design, the need for written, informed patient consent was waived by the hospital ethics committee.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Data sharing statement:** The datasets generated and analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**Country/Territory of origin:** China

**ORCID number:** Jin Li 0009-0004-1989-2309; Yu-Ming Jia 0000-0001-8796-2605; Zhi-Lei Zhang 0009-0004-0591-9056; Cheng-Yu Liu 0000-0003-2140-2706; Zhan-Wu Jiang 0000-0001-8690-2635; Zhi-Wei Hao 0009-0008-2550-0438; Li Peng 0009-0003-1568-9760.

**S-Editor:** Yan JP

L-Editor: A

P-Editor: Zhang XD

## REFERENCES

- 1 **Zhang Y**, Ren JS, Shi JF, Li N, Wang YT, Qu C, Zhang Y, Dai M. International trends in primary liver cancer incidence from 1973 to 2007. *BMC Cancer* 2015; **15**: 94 [PMID: [25879744](#) DOI: [10.1186/s12885-015-1113-4](#)]
- 2 **Tang D**, Nagano H, Nakamura M, Wada H, Marubashi S, Miyamoto A, Takeda Y, Umeshita K, Dono K, Monden M. Clinical and pathological features of Allen's type C classification of resected combined hepatocellular and cholangiocarcinoma: a comparative study with hepatocellular carcinoma and cholangiocellular carcinoma. *J Gastrointest Surg* 2006; **10**: 987-998 [PMID: [16843869](#) DOI: [10.1016/j.gassur.2006.01.018](#)]
- 3 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: [15761078](#) DOI: [10.3322/canjclin.55.2.74](#)]
- 4 **Chen WQ**, Zheng RS, Zhang SW, Zeng HM, Zou XN. The incidences and mortalities of major cancers in China, 2010. *Chin J Cancer* 2014; **33**: 402-405 [PMID: [25011459](#) DOI: [10.5732/cjc.014.10084](#)]
- 5 **Dhanasekaran R**, Hemming AW, Zendejas I, George T, Nelson DR, Soldevila-Pico C, Firpi RJ, Morelli G, Clark V, Cabrera R. Treatment outcomes and prognostic factors of intrahepatic cholangiocarcinoma. *Oncol Rep* 2013; **29**: 1259-1267 [PMID: [23426976](#) DOI: [10.3892/or.2013.2290](#)]
- 6 **Nguyen VT**, Law MG, Dore GJ. Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. *J Viral Hepat* 2009; **16**: 453-463 [PMID: [19302335](#) DOI: [10.1111/j.1365-2893.2009.01117.x](#)]
- 7 **Merican I**, Guan R, Amarapuka D, Alexander MJ, Chutaputti A, Chien RN, Hasnian SS, Leung N, Lesmana L, Phiet PH, Sjalfoellah Noer HM, Sollano J, Sun HS, Xu DZ. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol* 2000; **15**: 1356-1361 [PMID: [11197043](#) DOI: [10.1046/j.1440-1746.2000.0150121356.x](#)]
- 8 **Hartke J**, Johnson M, Ghabril M. The diagnosis and treatment of hepatocellular carcinoma. *Semin Diagn Pathol* 2017; **34**: 153-159 [PMID: [2818047](#) DOI: [10.1053/j.semdp.2016.12.011](#)]
- 9 **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: [21374666](#) DOI: [10.1002/hep.24199](#)]
- 10 **Yoo HY**, Patt CH, Geschwind JF, Thuluvath PJ. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. *J Clin Oncol* 2003; **21**: 4329-4335 [PMID: [14581446](#) DOI: [10.1200/jco.2003.11.137](#)]
- 11 **European Association For The Study Of The Liver**; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: [22424438](#) DOI: [10.1016/j.jhep.2011.12.001](#)]
- 12 **Wu CC**, Ho WM, Cheng SB, Yeh DC, Wen MC, Liu TJ, P'eng FK. Perioperative parenteral tranexamic acid in liver tumor resection: a prospective randomized trial toward a "blood transfusion"-free hepatectomy. *Ann Surg* 2006; **243**: 173-180 [PMID: [16432349](#) DOI: [10.1097/01.sla.0000197561.70972.73](#)]
- 13 **Wu CC**, Cheng SB, Ho WM, Chen JT, Liu TJ, P'eng FK. Liver resection for hepatocellular carcinoma in patients with cirrhosis. *Br J Surg* 2005; **92**: 348-355 [PMID: [15672423](#) DOI: [10.1002/bjs.4838](#)]
- 14 **Jarnagin WR**, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, Corvera C, Weber S, Blumgart LH. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002; **236**: 397-406; discussion 406 [PMID: [12368667](#)]
- 15 **Lei L**, Wang Y, Xue Q, Tong J, Zhou CM, Yang JJ. A comparative study of machine learning algorithms for predicting acute kidney injury after liver cancer resection. *PeerJ* 2020; **8**: e8583 [PMID: [32140301](#) DOI: [10.7717/peerj.8583](#)]
- 16 **Foster JH**, Berman MM. Solid liver tumors. *Major Probl Clin Surg* 1977; **22**: 1-342 [PMID: [839860](#)]
- 17 **Abraham A**, Pedregosa F, Eickenberg M, Gervais P, Mueller A, Kossaiji F, Gramfort A, Thirion B, Varoquaux G. Machine learning for neuroimaging with scikit-learn. *Front Neuroinform* 2014; **8**: 14 [PMID: [24600388](#) DOI: [10.3389/fninf.2014.00014](#)]
- 18 **Adam R**, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg* 2000; **232**: 777-785 [PMID: [11088072](#) DOI: [10.1097/00000658-200012000-00006](#)]
- 19 **Sharma R**, Gibbs JF. Recent advances in the management of primary hepatic tumors refinement of surgical techniques and effect on outcome. *J Surg Oncol* 2010; **101**: 745-754 [PMID: [20512952](#) DOI: [10.1002/jso.21506](#)]
- 20 **Furrer K**, Deoliveira ML, Graf R, Clavien PA. Improving outcome in patients undergoing liver surgery. *Liver Int* 2007; **27**: 26-39 [PMID: [17241378](#) DOI: [10.1111/j.1478-3231.2006.01416.x](#)]
- 21 **Cunningham JD**, Fong Y, Shriver C, Melendez J, Marx WL, Blumgart LH. One hundred consecutive hepatic resections. Blood loss, transfusion, and operative technique. *Arch Surg* 1994; **129**: 1050-1056 [PMID: [7944934](#) DOI: [10.1001/archsurg.1994.01420340064011](#)]
- 22 **Melendez JA**, Arslan V, Fischer ME, Wuest D, Jarnagin WR, Fong Y, Blumgart LH. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. *J Am Coll Surg* 1998; **187**: 620-625 [PMID: [9849736](#) DOI: [10.1016/s1072-7515\(98\)00240-3](#)]
- 23 **Kawaguchi Y**, Nomi T, Fuks D, Mal F, Kokudo N, Gayet B. Hemorrhage control for laparoscopic hepatectomy: technical details and predictive factors for intraoperative blood loss. *Surg Endosc* 2016; **30**: 2543-2551 [PMID: [26310533](#) DOI: [10.1007/s00464-015-4520-3](#)]
- 24 **Nanashima A**, Abo T, Hamasaki K, Wakata K, Kunizaki M, Tou K, Takeshita H, Hidaka S, Sawai T, Tsuchiya T, Nagayasu T. Predictors of intraoperative blood loss in patients undergoing hepatectomy. *Surg Today* 2013; **43**: 485-493 [PMID: [23085968](#) DOI: [10.1007/s00595-012-0374-7](#)]
- 25 **Katz SC**, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR, Fong Y, D'Angelica MI, Blumgart LH, Dematteo RP. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg* 2009; **249**: 617-623 [PMID: [19300227](#) DOI: [10.1097/SLA.0b013e31819ed22f](#)]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

