Original Article

Factors associated with pulmonary complications after hepatectomy and establishment of nomogram: A real-world retrospective study

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ABSTRACT

Background and Aims: Hepatectomy is currently the most effective way to treat liver diseases, and its safety has observably improved. However, the incidence of postoperative complications (POCs) remains high. Therefore, exploring the related influencing factors helps identify high-risk groups early and improve patient prognosis. **Methods:** Clinical data were retrospectively collected from a real-world setting. Patients were divided into two groups based on the incidence of postoperative pulmonary complications (PPCs). Univariate analysis, LASSO regression, and logistic regression were applied to analyse the correlation between PPCs and perioperative indicators. A nomogram prediction model was constructed, whose discrimination, accuracy, and clinical effectiveness were evaluated. **Results:** The incidence of PPCs was 36.33% among the 1244 patients in this study. The total length of hospital stay and perioperative mortality in the PPCs group were markedly higher ($P < 0.001$) than in the non-PPCs group. Logistic regression showed that surgical method [odds ratio (OR) =2.469 (95% CI: 1.665, 3.748); $P < 0.001$], duration of surgery [OR = 1.003 (95% CI: 1.002, 1.005); $P < 0.001$], postoperative patient destination [OR = 1.453 (95% CI: 1.115, 1.893); $P = 0.006$], and postoperative international normalised ratio (INR) [OR = 2.245 (95% CI: 1.287, 4.120); $P = 0.007$] were independent risk factors of PPCs; the number of clamping [OR = 0.988 (95% CI: 0.980, 0.995); $P = 0.001$] was an independent protective factor of PPCs. The area under the receiver operating characteristic (ROC) curve was 0.675 (95% CI: 0.638, 0.703), the consistency index of the calibration curve was 0.675 (95% CI: 0.641, 0.703), and the Hosmer-Lemeshow goodness-of-fit test yielded $P = 0.327$. **Conclusions:** In this study, the incidence of PPCs after hepatectomy was the highest. Our nomogram model can predict the probability of PPCs after hepatectomy.

Keywords: Factors, hepatectomy, nomogram, postoperative pulmonary complications, real-world study, univariate analysis

INTRODUCTION

The 21st century is an era in which data guides decision-making. Medical institutions worldwide have built medical information databases based on patient clinical data. Therefore, real-world studies (RWS) have also begun to receive widespread attention.[1-3]

Liver cancer remains the sixth most common cancer in the world and the third largest cause of cancer-related deaths globally,[4] accounting for more than half of the new and fatal cases each year in China.[5] Surgery is a potentially curative treatment for liver cancer.[6] Most patients achieve good results after surgery, and

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the 5-year survival rate is as high as 60%–80%.[7] Hepatectomy refers to the removal of diseased liver by surgical resection, such as liver segments, lobes, or hemilivers, with preservation of liver tissue sufficient to maintain normal physiological function,[8] which has been rapidly developed in China since the 1950s.[9] Although the safety of hepatectomy has greatly improved, the mortality rate has been significantly lower than before, usually less than 3%,[10,11] and the incidence of postoperative complications (POCs) remains high, ranging from 20% to 50%.[10,12] The greater perioperative pathophysiological changes in hepatectomy have different degrees of effects on respiration, circulation, and coagulation systems, which may be an important cause of complications after hepatectomy in patients. After the occurrence of POCs, the rehabilitation process of patients is seriously hindered, the treatment cycle is prolonged, and the treatment cost increases, which not only causes physical and mental pain to the patients themselves but also increases the burden on their families and society. Therefore, identifying perioperative factors, identifying high-risk groups earlier, and providing preventive measures are important to reduce the occurrence of POCs and improve the prognosis of hepatectomy patients.

The nomogram is a reliable tool that can effectively assist clinical diagnosis and treatment[13] and has received extensive applications in medical research. Nomograms with intuitive and understandable characteristics can transform the results of complex regression equations into readable visual graphs that facilitate evaluation.[14] In this study, we first analysed patients' perioperative data to understand the incidence and mortality of complications after hepatectomy. Then, we analysed the influencing factors of the highest-incidence postoperative pulmonary complications (PPCs) and established an individualised prediction model to provide a clinical reference for standardising the perioperative management of hepatectomy and preventing and treating PPCs.

METHODS

The clinical data of 1570 patients who underwent hepatectomy between 2014 and 2021 were obtained through the Biological Sample Information Resource Centre of the First Affiliated Hospital of Xi'an Jiaotong University and the electronic medical record system of the hospital. This study conformed to the Declaration of Helsinki and was approved by the Ethics Review Board (approval number: XJTU1AF2022LSK-032, dated 25 February 2022). The exclusion criteria were as follows: (1) important information missing from clinical case data; (2) history of drug abuse, mental illness, or alcoholism before surgery; (3) significant abnormal preoperative heart, lung, liver, kidney, and other important organ functions; (4) age <18 years; and (5) duration of surgery <120 minutes.

Demographic and preoperative baseline information was collected from the patients and were collectively referred to as preoperative indicators: (1) age, gender, height, weight, body and mass index (BMI); (2) preoperative comorbidities (hypertension, diabetes, cardiovascular disease, chronic liver/kidney disease, and lung disease) and smoking history; (3) liver primary diseases (hepatocellular carcinoma, cholangiocarcinoma, recurrence liver cancer, secondary liver cancer, gallbladder cancer, benign liver tumours, intrahepatic and extrahepatic bile duct stones, cholangitis, hepatic echinococcosis, and others), Child-Pugh stage, hepatitis B virus (HBV)/hepatitis C virus (HCV), and liver cirrhosis preoperative hospital stay; (4) preoperative last laboratory test before surgery: albumin (ALB), total bilirubin (TBIL), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), blood urea nitrogen (BUN), serum potassium (K), serum sodium (Na), serum calcium (Ca), thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), international normalised ratio (INR), D-dimer, fibrinogen (FIB), haemoglobin (Hb), red blood cell (RBC) count, white blood cell (WBC) count, platelet (PLT) count, monocyte count, neutrophil count, lymphocyte count, haematocrit (HCT), and plateletcrit (PCT).

The patients' anaesthesia and surgery-related data were collected during surgery and were referred to as intraoperative indicators: (1) surgery-related indicators: type of surgery, name of surgery, duration of surgery, number of clamping, and time of clamping; (2) anaesthesia-related indicators: a. American Society of Anesthesiologists (ASA) Physical Status Classification; b. midazolam, sufentanil, etomidate, rocuronium, propofol, cisatracurium, remifentanil, dexmedetomidine, and sevoflurane; c. total input, crystal input, colloid input, RBC and other blood product input, blood loss volume, urine volume, total output, and net volume.

The patients' postoperative prognosis and relevant information were collected and referred to as postoperative indicators: (1) postoperative patient destination (post-anaesthesia care unit (PACU)/ surgical intensive care unit (SICU)) and perioperative mortality; (2) first postoperative laboratory test: ALB, TBIL, ALP, ALT, AST, Scr, BUN, serum K, serum Na, serum Ca, TT, PT, APTT, INR, D-dimer, FIB, Hb, RBC count, WBC count, PLT count, monocyte count, neutrophil count, lymphocyte count, HCT, and PCT; (3) POCs: PPCs and others (post-hepatectomy liver failure (PHLF), post-hepatectomy haemorrhage (PHH), bile leakage (BL), hepatic encephalopathy (HE), postoperative delirium (POD), cardiovascular complications, postoperative gastrointestinal dysfunction (POGD), acute kidney injury (AKI), thrombotic complications, and infectious complications).

The POC observation time was within 30 days after the operation. The incidence of PPCs was the primary outcome measure. PPCs refer to a series of respiratory symptoms experienced by patients after surgery and include respiratory infection, pneumonia, pleural effusion, pneumothorax, atelectasis, respiratory failure, bronchospasm, aspiration pneumonia, acute respiratory distress syndrome (ARDS), and pulmonary embolism. We diagnosed PPCs according to the guidelines for European Perioperative Clinical Outcome (EPCO) definitions issued by the European Society of Anaesthesiology (ESA) and the European Society of Intensive Care Medicine (ESICM) joint task force in 2015[15] [Table 1]. The incidence of other POCs, total hospital stay, and perioperative mortality are secondary outcome measures.

Data were first processed using Statistical Package for Social Sciences (SPSS) software (version 26.0, IBM SPSS, Armonk, NY, USA). Data were pre-processed, variables with more than a 3% missing proportion were removed, and data with less than a 3% missing proportion were filled using the mean/median of each variable. Enumeration data were expressed in frequency and analysed using the Chi-square or Fisher's exact test. Continuous data were analysed by independent sample t-tests when they met normal distribution, and homogeneous variance was expressed as mean (standard deviation (SD). Non-parametric tests were used when they did not meet normal distribution and/or variance heterogeneity and expressed as median (interquartile range (IQR). Univariate analysis was performed to compare preoperative, intraoperative, and postoperative indicators between the PPCs and non-PPCs groups. The criterion for determining the statistical significance of differences was $P < 0.05$. Then, the least absolute shrinkage and selection operator (LASSO) analyses were conducted using the R 4.2.0 software (R Foundation for Statistical Computing, Vienna, Austria) to reduce the risk of multi-collinearity and overfitting. The variables with $P < 0.05$ in the

Table 1: Definitions of PPCs

	Definitions
Respiratory infection	Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, WBC count >12×10^9/L.
Respiratory failure	PaO_2<8 kPa (60 mmHg) on room air, a PaO_2:FIO_2 ratio <40 kPa (300 mmHg), or arterial oxyhaemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy.
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in the upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows.
Atelectasis	Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm towards the affected area and compensatory over-inflation in the adjacent non-atelectatic lung.
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura.
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators.
Aspiration pneumonia	Acute lung injury after the inhalation of regurgitated gastric contents.
Pneumonia	Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease): (1) new or progressive and persistent infiltrates, (2) consolidation, and (3) cavitation. At least one of the following: (1) fever (>38°C) with no other recognised cause (2) leukopenia (WBC count <4 × 10^9/L) or leucocytosis (WBC count >12×10^9/L) (3) for adults >70 years old, altered mental status with no other recognised cause. And at least two of the following: (1) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements (2) new onset or worsening cough, or dyspnoea, or tachypnoea (3) rales or bronchial breath sounds (4) worsening gas exchange (hypoxemia, increased oxygen requirement, increased ventilator demand).
ARDS	Within 1 week of a known clinical insult or new or worsening respiratory symptoms. Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor presently.
Pulmonary embolism	New blood clots or thrombi in the pulmonary arterial system.

WBC: white blood cell; PaO_2: partial pressure of oxygen in arterial blood; FIO_2: fraction of inspired oxygen; ARDS: acute respiratory distress syndrome

univariate analysis were re-evaluated, and the selected best predictor variables were put into a logistic regression model, with $P < 0.05$ considered to have statistical significance. A nomogram was constructed based on the results of logistic regression analysis, and the discriminatory ability was measured by the ROC curve and the area under the ROC curve (AUC). The model was validated internally by bootstrap resampling 500 times, and the calibration curve was drawn to calculate the C-index. The Hosmer-Lemeshow test reflected the accuracy of the model, with $P > 0.05$ indicating a high accuracy of the model. The clinical effectiveness of the model was evaluated using decision curve analysis (DCA).

RESULTS

This study selected 1570 patients who underwent hepatectomy in the Department of Hepatobiliary Surgery as the study subjects. Of these, 326 cases were excluded according to the exclusion criteria, 311 cases had missing important information on clinical case data, four cases were aged <18 years, and 11 cases had a duration of surgery <120 min. Finally, 1244 valid cases were included [Figure 1]. The mean age was 55.67 (SD: 11.58) years, including 713 (57.32%) male patients and 531 (42.68%) female patients. The types of primary liver diseases are shown in Figure 2.

A total of 576 patients (46.30%) had POCs. The incidence of pulmonary complications was 36.33% (some patients had two or more types), including 232 cases of pneumonia, 18 cases of respiratory failure, 416 cases of pleural effusion, 177 cases of atelectasis, six cases of pneumothorax, and six cases of pulmonary embolism. Two hundred eighty patients (22.51%) had other POCs (some patients also had pulmonary complications) [Table 2]. Because the incidence of PPCs is much higher than other complications, we used it as the primary observation indicator. All patients were divided into two groups according to whether PPCs developed after hepatectomy. Compared with the non-PPCs group, the total hospital stay after hepatectomy was prolonged in the PPCs group [24.52 (SD: 12.00) vs 17.78 (SD: 6.84) days, $P < 0.001$]. The perioperative mortality of patients in the PPCs group was significantly higher than that of patients in the non-PPCs group (4.2% vs 0.88%, $P < 0.001$) [Table 3].

The preoperative indicators of the PPCs and non-PPCs groups were analysed using univariate analysis [Table 4]. There were statistically significant differences in age, diabetes, chronic liver disease, HBV, liver cirrhosis, preoperative primary liver disease, preoperative hospital stay, serum Ca, PT, D-dimer, Hb, RBC count, and HCT between the two groups ($P < 0.05$). Among the intraoperative indicators, type of surgery, name of surgery, duration of surgery, number of clamping, time of clamping, total input, crystal input, colloid input, RBC input, total output, blood loss volume, urine volume, net volume, etomidate, rocuronium, propofol, cisatracurium, remifentanil, and dexmedetomidine between the two groups were statistically different ($P < 0.05$) [Table 5].

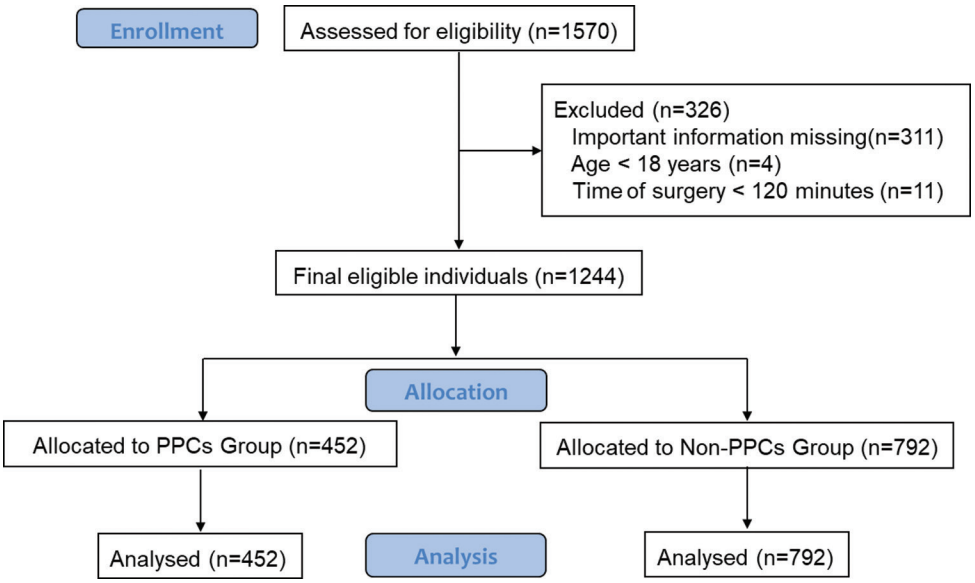

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow. PPCs: postoperative pulmonary complications

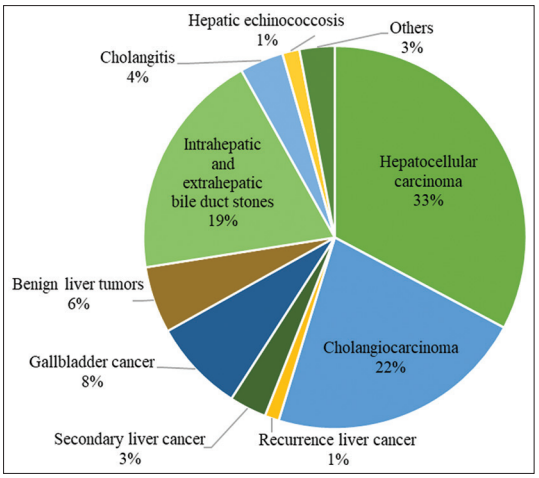

Figure 2: Distribution map of preoperative liver primary disease

Table 2: Incidence of postoperative complications

	n (%)
Postoperative complications	576 (46.30)
Pulmonary complications	452 (36.33)
Other complications	280 (22.51)

Data are presented as numbers (percentages)

Table 3: Comparison of postoperative rehabilitation between the two groups

	PPCs (*n*=452)	No PPCs (*n*=792)	*P*
Total hospital stay (day)	24.52 (12.00)	17.78 (6.84)	<0.001
Perioperative mortality, *n* (%)	19 (4.20)	7 (0.88)	<0.001

Data are presented as mean (standard deviating) and number (percentage). *n*=Number of patients, PPC=postoperative pulmonary complications. PPCs=postoperative pulmonary complications

The results of the two groups about postoperative indicators are presented in Table 6. Postoperative patient destination (PACU/SICU), ALB, TBIL, ALT, AST, serum K, serum Na, PT, APTT, INR, FIB, D-dimer, Hb, RBC count, WBC count, PLT count, monocyte count, neutrophil count, HCT, and PCT were statistically different between the two groups ($P < 0.05$).

After univariate analysis, 52 indicators ($P < 0.05$) were analysed in the LASSO regression for further analysis [Figure 3]. A total of 10 variables were selected as potential influencing factors, namely type of surgery, name of surgery, duration of surgery, number of clamping, propofol, total input, colloid input, postoperative patient destination (PACU/SICU), postoperative INR, and postoperative ALB. The 10 variables selected using LASSO regression were analysed using the two-way stepwise logistic regression to screen further the variables that were finally entered into the model. Ultimately, a total of six variables were selected, as shown in Table 7, of which open surgery [OR = 2.469 (95% confidence interval (CI): 1.665, 3.748); $P < 0.001$],

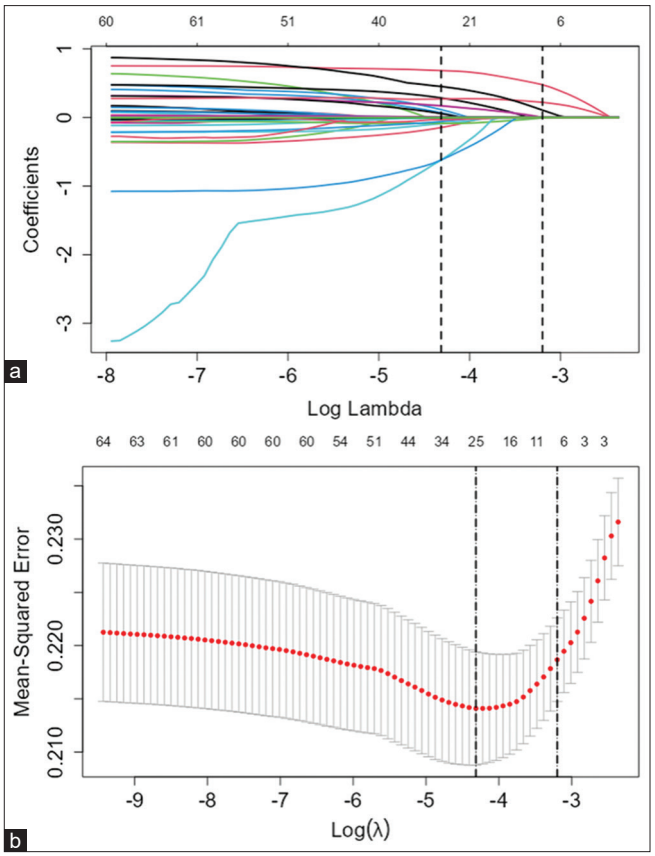

Figure 3: Variable selection by the LASSO regression model. a. LASSO coefficient profiles of the 52 variables were produced against the Log Lambda sequence. b. Cross-validation curve of LASSO regression (10-fold). The X-axis is the logarithm of the penalty coefficient Lambda (λ), the Y-axis is the mean-squared error. The top number is the number of variables left in the equation for different λ. The dashed line on the left is λ min, meaning λ with the smallest prediction error, which means that the model fitting effect is the highest. The dashed line on the right is λ-1se, meaning 1 standard error to the right of the smallest λ. At this λ value, the model is simpler with a good fitting effect, too

longer duration of surgery [OR = 1.003 (95% CI: 1.002, 1.005); $P < 0.001$], postoperative patient destination (SICU) [OR = 1.453 (95% CI: 1.115, 1.893); $P = 0.006$], and higher postoperative INR [OR = 2.245 (95% CI: 1.287, 4.120); $P = 0.007$] were independent risk factors of PPCs; the number of clamping [OR = 0.988 (95% CI: 0.980, 0.995); $P = 0.001$] was an independent protective factor of PPCs.

A nomogram for predicting PPCs after hepatectomy was built through logistic regression [Figure 4]. The ROC curve for the nomogram predicting PPCs [Figure 5] showed an AUC of 0.675 (95% CI: 0.638, 0.703). Using the Youden index, the cutoff value was 0.343. Sensitivity was 68.8%, and specificity was 56.2% at this point when the corresponding nomogram had a risk of PPCs of 34.3%.

Table 4: Preoperative risk factors associated with PPCs

	PPCs (*n*=452)	No PPCs (*n*=792)	*P*
Age (year)	58 (49, 65)	55 (48, 64)	0.002*
Gender			0.434
Male, *n* (%)	252 (55.75)	461 (58.21)	
Female, *n* (%)	200 (44.25)	331 (41.79)	
Height (m)	1.65 (1.60, 1.70)	1.65 (1.60, 1.70)	0.929
Weight (kg)	62.00 (55.00, 70.00)	61.00 (55.00, 70.00)	0.660
BMI (kg/m^2)	22.82 (3.11)	22.69 (3.10)	0.842
Comorbidities, *n* (%)			
Hypertension	97 (21.46)	142 (17.93)	0.148
Diabetes	59 (13.05)	66 (8.33)	0.010*
Cardiovascular disease	29 (6.41)	44 (5.56)	0.620
Chronic liver disease	130 (28.72)	298 (37.63)	0.002*
Chronic kidney disease	5 (1.11)	5 (0.63)	0.511
Lung disease	108 (23.95)	184 (23.23)	0.845
Smoking history, *n* (%)			0.938
Smoking	89 (19.69)	150 (18.94)	
No smoking	329 (72.79)	580 (73.23)	
Quit smoking	34 (7.52)	62 (7.83)	
Child-Pugh stage, *n* (%)			0.108
A	347 (76.77)	644 (81.32)	
B	103 (22.79)	146 (18.43)	
C	2 (0.44)	2 (0.25)	
HBV, *n* (%)	117 (25.94)	275 (34.72)	0.001*
HCV, *n* (%)	10 (2.22)	18 (2.27)	0.945
Liver cirrhosis, *n* (%)	79 (17.52)	189 (23.86)	0.007*
Preoperative liver primary diseases, *n* (%)			<0.001*
Hepatocellular carcinoma	120 (26.55)	288 (36.36)	
Cholangiocarcinoma	126 (27.88)	147 (18.56)	
Recurrent liver cancer	7 (1.55)	8 (1.01)	
Secondary liver cancer	15 (3.32)	24 (3.03)	
Gallbladder cancer	41 (9.07)	56 (7.07)	
Benign liver tumours	14 (3.10)	56 (7.07)	
Intrahepatic and extrahepatic bile duct stone	84 (18.58)	157 (19.82)	
Cholangitis	20 (4.42)	26 (3.28)	
Hepatic echinococcosis	7 (1.55)	11 (1.39)	
Others	18 (3.98)	19 (2.40)	
Preoperative hospital stay (day)	7.57 (4.38)	6.84 (3.58)	0.005*
ALB (g/L)	36.85 (4.89)	36.83 (4.62)	0.732
TBIL (umol/L)	17.20 (11.20, 38.60)	15.45 (10.80, 25.45)	0.143
ALP (U/L)	124.00 (87.00, 222.00)	113.00 (79.64, 193.25)	0.491
ALT (U/L)	36.00 (20.20, 70.00)	33.00 (22.00, 61.00)	0.804
AST (Ul/L)	32.00 (21.00, 52.00)	30.00 (22.00, 49.75)	0.507
Scr (umol/L)	53.00 (44.00, 62.00)	51.00 (43.00, 61.60)	0.613
BUN (mmol/L)	4.81 (3.81, 5.90)	4.69 (3.76, 5.63)	0.652
Serum K (mmol/L)	3.96 (3.67, 4.21)	3.97 (3.73, 4.24)	0.233
Serum Na (mmol/L)	141.00 (138.00, 142.43)	141.00 (139.00, 143.00)	0.172
Serum Ca (mmol/L)	2.24 (2.15, 2.32)	2.25 (2.16, 2.34)	0.025*
TT (s)	15.45 (1.02, 17.60)	16.30 (1.04, 18.30)	0.682
PT (s)	13.40 (12.70, 14.10)	13.20 (12.40, 13.90)	0.009*
APTT (s)	36.25 (32.98, 39.23)	36.20 (32.80, 38.90)	0.146
INR	1.04 (0.98, 1.11)	1.03 (0.93, 1.10)	0.064
D-dimer (mg/L)	0.76 (0.47, 1.40)	0.60 (0.31, 1.18)	0.002*
FIB (g/L)	3.43 (2.72, 4.26)	3.21 (2.48, 4.16)	0.075
Hb (g/L)	124.28 (17.72)	127.44 (19.37)	0.008*
RBC count (×10^{12}/L)	4.05 (0.57)	4.19 (0.65)	0.001*
WBC count (×10^9/L)	5.39 (4.21, 6.98)	5.45 (4.14, 6.91)	0.955
PLT count (×10^9/L)	186.00 (137.50, 241.00)	192.00 (142.50, 248.00)	0.201

Contd...

Table 4: Contd...			
	PPCs (*n*=452)	No PPCs (*n*=792)	*P*
Monocyte count (×10^9/L)	0.34 (0.25, 0.44)	0.33 (0.25, 0.42)	0.237
Neutrophil count (×10^9/L)	3.47 (2.53, 4.88)	3.49 (2.42, 4.67)	0.692
Lymphocyte count (×10^9/L)	1.27 (0.96, 1.69)	1.34 (1.01, 1.74)	0.283
HCT (%)	37.90 (34.10, 41.50)	38.70 (34.80, 42.50)	0.005*
PCT (%)	0.21 (0.16, 0.26)	0.21 (0.16, 0.26)	0.192

Data are presented as mean (SD), median (IQR) and number (percentage); * indicates *P*<0.05; PPCs: postoperative pulmonary complications; BMI: body mass index; HBV: hepatitis B virus; HCV: hepatitis C virus; ALB: albumin; TBIL: total bilirubin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Ser: serum creatinine; BUN: blood urea nitrogen; TT: thrombin time; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalised ratio; FIB: fibrinogen; Hb: haemoglobin; RBC: red blood cell; WBC: white blood cell; PLT: platelet; HCT: haematocrit; PCT: plateletcrit

Table 5: Intraoperative risk factors associated with PPCs			
	PPCs (*n*=452)	No PPCs (*n*=792)	*P*
Type of surgery, *n* (%)			<0.001*
Open	417 (92.26)	620 (78.28)	
Laparoscope	35 (7.74)	172 (21.72)	
Name of surgery, *n* (%)			<0.001*
Simple left hemihepatectomy	91 (20.13)	206 (26.01)	
Simple right hemihepatectomy	114 (25.22)	191 (24.12)	
Simple partial hepatectomy	55 (12.17)	176 (22.22)	
Complex left hemihepatectomy	74 (16.37)	101 (12.75)	
Complex right hemihepatectomy	80 (17.70)	69 (8.71)	
Complex partial hepatectomy	38 (8.41)	49 (6.19)	
ASA class, *n* (%)			0.410
I	9 (1.99)	9 (1.14)	
II	285 (63.05)	515 (65.03)	
III	155 (34.29)	266 (33.59)	
IV	3 (0.66)	2 (0.25)	
Duration of surgery (min)	348.75 (117.03)	303.53 (99.46)	<0.001*
Number of clamping (time)	0 (0, 2)	0 (0, 2)	0.009*
Time of clamping (min)	0 (0, 20)	0 (0, 25)	0.016*
Total input (mL/kg)	62.5 (49.8, 76.7)	55.9 (43.9, 68.1)	<0.001*
Crystal input (mL/kg)	38.5 (30.8, 47.7)	34.9 (27.8, 43.7)	<0.001*
Colloid input (mL/kg)	27.7 (18.2, 42.0)	22.1 (14.3, 34.2)	<0.001*
RBC input (U)	2 (0, 4)	0 (0, 4)	<0.001*
Total output (mL)	1700 (1200, 2600)	1400 (900, 2100)	<0.001*
Blood loss volume (mL)	800 (500, 1300)	500 (300, 1000)	<0.001*
Urine volume (mL)	900 (600, 1200)	800 (500, 1100)	<0.001*
Net volume (mL)	1900 (1500, 2500)	1850 (1400, 2300)	0.016*
Anaesthetic			
Midazolam (mg/kg)	0.03 (0.03, 0.04)	0.03 (0.03, 0.04)	0.837
Sufentanil (ug/kg)	0.50 (0.40, 0.58)	0.49 (0.42, 0.58)	0.444
Etomidate (mg/kg)	0.21 (0.19, 0.26)	0.22 (0.19, 0.26)	0.014*
Rocuronium (mg/kg)	0.94 (0.67, 1.03)	0.97 (0.82, 1.05)	0.020*
Propofol (mg/kg)	22.6 (17.3, 28.3)	19.5 (14.9, 25.0)	<0.001*
Cisatracurium (mg/kg)	0.64 (0.48, 0.83)	0.57 (0.42, 0.76)	<0.001*
Remifentanil (ug/kg)	46.2 (35.8, 58.4)	40.0 (30.8, 50.6)	<0.001*
Dexmedetomidine (ug/kg)	1.45 (0.86, 1.92)	1.29 (0.81, 1.77)	0.013*
Sevoflurane (mL)	50 (40, 60)	50 (40, 60)	0.117

Data are presented as mean (SD), median (IQR) and number (percentage); * indicates *P*<0.05; PPCs: postoperative pulmonary complications; ASA: American Society of Anesthesiologists; RBC: red blood cell

Internal validation was performed using 500 bootstrap self-samplings, and calibration curves were plotted [Figure 6]. The concordance index was 0.670 (95% CI: 0.641, 0.703), which showed that the predicted probability was close to the actual probability, manifesting that the nomogram was higher calibrated.

We obtained $\chi^2 = 9.181$, $P = 0.327$ (>0.05) by the Hosmer-Lemeshow test, indicating that the nomogram's fitting effect was good and its accuracy was high. DCA evaluated the predictive model's clinical effectiveness, with a high benefit rate when clinical interventions were administered to patients who developed PPCs [Figure 7].

Table 6: Postoperative risk factors associated with PPCs

	PPCs (*n*=452)	No PPCs (*n*=792)	*P*
Postoperative patient destination, *n* (%)			<0.001*
PACU	234 (51.77)	556 (70.20)	
SICU	218 (48.23)	236 (29.80)	
ALB (g/L)	29.45 (6.23)	31.05 (5.41)	<0.001*
TBIL (umol/L)	34.70 (21.50, 59.80)	28.80 (19.45, 47.68)	<0.001*
ALP (U/L)	83.00 (62.00, 136.00)	77.00 (60.00, 115.00)	0.289
ALT (U/L)	166.00 (95.00, 313.00)	156.47 (88.25, 266.75)	0.010*
AST (UI/L)	192.00 (112.00, 367.00)	180.00 (101.50, 315.50)	0.004*
Scr (umol/L)	49.00 (39.00, 61.00)	48.00 (40.00, 59.00)	0.768
BUN (mmol/L)	4.34 (3.04, 5.75)	4.34 (3.31, 5.48)	0.571
Serum K (mmol/L)	3.90 (3.67, 4.21)	3.96 (3.68, 4.31)	0.023*
Serum Na (mmol/L)	138.18 (136.00, 141.03)	138.00 (135.70, 140.90)	0.016*
Serum Ca (mmol/L)	2.09 (1.97, 2.21)	2.11 (2.01, 2.19)	0.085
TT (s)	14.65 (0.98, 16.70)	14.60 (0.97, 17.20)	0.285
PT (s)	15.70 (14.38, 16.90)	14.90 (12.50, 16.40)	<0.001*
APTT (s)	37.50 (34.50, 41.50)	36.60 (33.40, 39.60)	0.006*
INR	1.28 (1.17, 1.42)	1.23 (1.12, 1.35)	<0.001*
D-dimer (mg/L)	2.22 (1.74, 2.98)	2.42 (1.90, 3.10)	0.025*
FIB (g/L)	5.12 (3.20, 8.35)	4.27 (2.82, 7.13)	0.001*
Hb (g/L)	112.99 (17.29)	115.47 (17.69)	0.015*
RBC count (×10^{12}/L)	3.65 (0.57)	3.76 (0.59)	0.001*
WBC count (×10^9/L)	11.40 (7.59, 15.14)	11.94 (8.91, 15.36)	0.021*
PLT count (×10^9/L)	145.00 (105.00, 199.50)	165.00 (123.00, 209.50)	0.002*
Monocyte count (×10^9/L)	0.42 (0.28, 0.62)	0.47 (0.30, 0.65)	0.023*
Neutrophil count (×10^9/L)	10.23 (6.35, 13.63)	10.84 (7.98, 13.91)	0.015*
Lymphocyte count (×10^9/L)	0.58 (0.38, 0.90)	0.57 (0.39, 0.83)	0.593
HCT (%)	33.90 (30.65, 37.30)	34.60 (31.20, 37.95)	0.049*
PCT (%)	0.17 (0.12, 0.22)	0.18 (0.14, 0.23)	0.001*

Data are presented as mean (SD), median (IQR) and number (percentage); * indicates *P*<0.05; PPCs: postoperative pulmonary complications; PACU: post-anaesthesia care unit; SICU: surgical intensive care unit; ALB: albumin; TBIL: total bilirubin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Scr: serum creatinine; BUN: blood urea nitrogen; TT: thrombin time; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalised ratio; FIB: fibrinogen; Hb: haemoglobin; RBC: red blood cell; WBC: white blood cell; PLT: platelet; HCT: haematocrit; PCT: plateletcrit

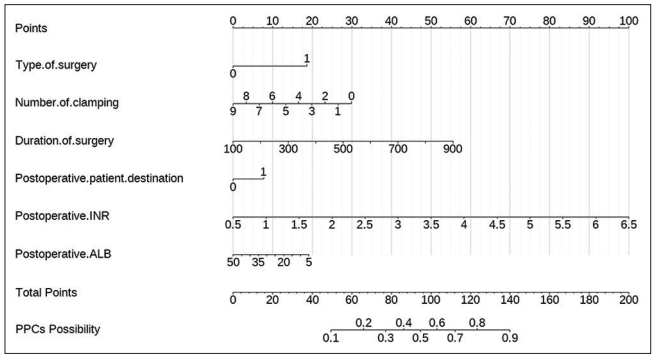

Figure 4: Nomogram model of predicting PPCs after hepatectomy. INR: international normalised ratio; ALB: albumin; PPCs: postoperative pulmonary complications

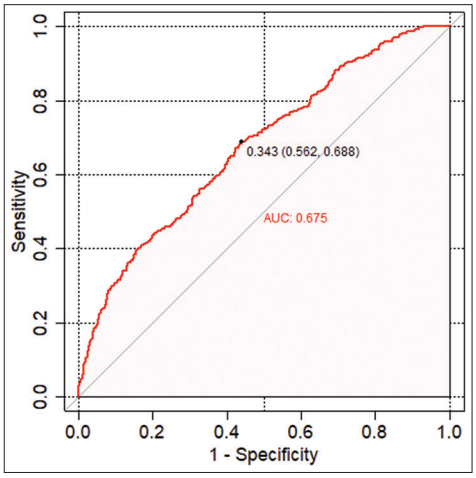

Figure 5: Receiver operating characteristic curve of the nomogram predicting PPCsAUC: area under the receiver operating characteristic curve

DISCUSSION

In this study, we found the highest incidence of PPCs after hepatectomy. It found that the total postoperative hospital stay and perioperative mortality of patients in the PPCs group were significantly higher than those in the non-PPCs group. It is reported that the mortality rate within 30 days after the occurrence of PPCs is 14%–30%, while that of patients without pulmonary complications is 0.2%–3%,[16] whose results are consistent with our study.

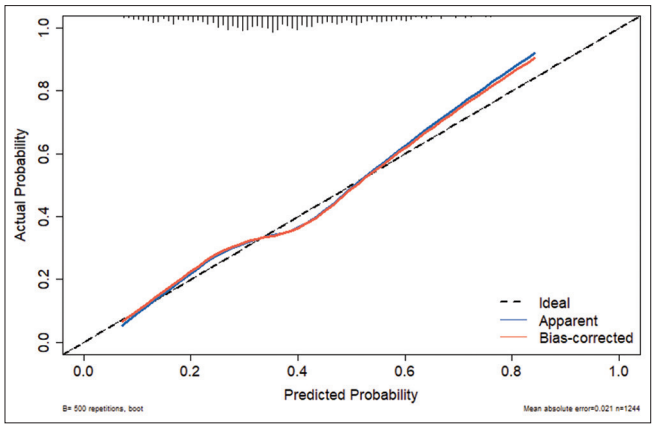

Figure 6: The calibration curve of the nomogram predicting PPCs (bootstrap 500 repetitions)

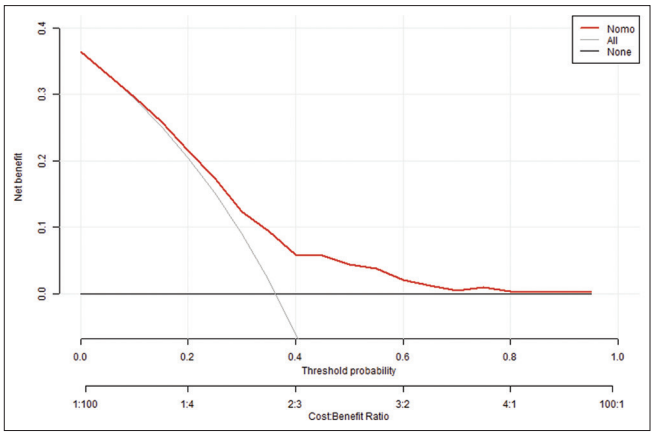

Figure 7: Decision curve analysis cure analysis of the model

Table 7: Multi-variate logistic analysis of PPCs

	β	SE	OR	95% CI	*P*
Type of surgery	0.904	0.20642	2.469	1.665, 3.747	<0.001*
Number of clamping	−0.161	0.04704	0.851	0.775, 0.932	0.001*
Duration of surgery	0.003	0.00062	1.003	1.002, 1.004	<0.001*
Postoperative patient destination	0.374	0.13501	1.453	1.114, 1.892	0.006*
Postoperative INR	0.809	0.29985	2.245	1.286, 4.119	0.007*
Preoperative ALB	−0.021	0.01296	0.980	0.954, 1.004	0.111

*indicates *P*<0.05; β: beta coefficient; SE: standard error; OR: odds ratio; 95%CI: 95% confidence interval; INR: international normalised ratio; ALB: albumin

Patients undergoing hepatectomy often have liver dysfunction, cirrhosis, viral hepatitis, and hypoproteinaemia before surgery, which increases the risk of postoperative pleural effusion, atelectasis, and pneumonia. Hepatic vascular clamping is a commonly used technique to reduce intraoperative bleeding. However, this technique inevitably leads to hepatic ischemia-reperfusion injury (HIRI) and haemodynamic changes, which even cause damage to distant organ function; the lung may be the most involved.[17,18] Studies have found that prolonged intraoperative ischemia time is a risk factor for PPCs within 7 days after hepatectomy, and the longer the ischemia time, the higher the incidence.[19] Prolonged occlusion predisposes to portal vein thrombosis and severe ischemia-reperfusion injury; thus, intermittent occlusion is commonly used in clinical practice.[20] This is consistent with our findings that in the absence of a difference in portal clamping time between the two groups, a greater number of clamping was associated with a lower incidence of PPCs.

Laparoscopic hepatectomy was first reported by Reich in 1991.[21] Compared with open hepatectomy, laparoscopic hepatectomy is increasingly used because of its many advantages, such as less invasive surgery, intraoperative blood loss, transfusion requirements, and lower incidence of POCs.[22,23] Matsuo *et al*. found that the overall incidence of pulmonary complications after laparoscopic hepatectomy was significantly lower than that after open hepatectomy.[24] We also found that the incidence of PPCs was higher in open hepatectomy than in laparoscopic surgery. This may be because the operation during open hepatectomy affects the function of the diaphragm or because a more severe postoperative inflammatory response affects lung function.[25,26]

Studies have found that anaesthetic methods, drugs, and management can also affect PPCs. Mechanical ventilation after anaesthesia can alter pulmonary defence mechanisms and reduce pulmonary surfactant, which increases the occurrence of pneumonia and other pulmonary complications. We found that the longer duration of surgery was associated with a higher incidence of PPCs after surgery, which may be due to the longer intraoperative mechanical ventilation. Still, the specific mechanism needs to be further explored with basic research. Furthermore, intraoperative inhalation of high concentrations of oxygen may lead to increased reactive oxygen species and pro-inflammatory factors, impaired gas exchange, oxygen-related lung injury, and increased occurrence of atelectasis.[27] Residual anaesthetic drugs or imperfect postoperative analgesia decrease the activity of respiratory muscles and compliance of the lung, leading to hypoventilation, ventilation/perfusion ratio disproportion, and increased hypoxemia.[28] As the study reports, implementing appropriate lung protective ventilation strategies during surgery may reduce barotrauma and volume injury caused by mechanical ventilation, improve local alveolar collapse, increase lung compliance, and reduce inflammatory

factors, thereby reducing lung injury.[29] Intraoperative fluid management is also an important part of anaesthetic management. Appropriate intraoperative fluid infusion to avoid tissue hypoperfusion and fluid overload can improve pulmonary function and tissue oxygenation and increase gastrointestinal motility and wound healing.[30,31] However, this study did not find the effect of anaesthetic drugs or intraoperative fluid infusion volume on PPCs in patients.

Numerous studies have demonstrated the good predictive power and clinical utility of nomograms in the diagnosis and prognosis of diseases.[32,33] Therefore, based on univariate, LASSO, and logistic regression analyses, the nomogram model was established in our study through multiple screening and analysis of common clinical indicators before, during, and after surgery. The model evaluated according the ROC curve and the C-index showed that the model had good discriminatory ability. The Hosmer-Lemeshow test[34] showed that the accuracy was high. In addition, the clinical decision curve[35] showed that patients with suspected PPCs screened according to this model could benefit from corresponding intervention measures. Overall, the study demonstrates that the established nomogram can predict the probability of PPCs after hepatectomy, which is feasible and worthy of further application in clinical practice.

This was a retrospective study, and the investigators were unable to control some interventions, such as intraoperative oxygen concentration and postoperative ventilation, which were adjusted according to the patient's condition. Therefore, they were not well captured in our study, which is indeed one of its limitations. In addition, our study is a single-centre study, and the study results have good reference value in our centre, but if we want to generalise to the entire population, a multi-centre study is also needed.

CONCLUSION

In this study, the incidence of PPCs after hepatectomy was 36.33%. The nomogram model constructed can effectively predict the occurrence of PPCs after hepatectomy.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

There are no conflicts of interest.

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