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A nomogram prediction of postoperative surgical site infections in patients with perihilar cholangiocarcinoma

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Abstract

Surgical site infection (SSI) is one of the major morbidities after radical resection for perihilar cholangiocarcinoma (PHCC). This study aimed to clarify the risk factors and construct a nomogram to predict SSIs in patients with PHCC.

A total of 335 consecutive patients who underwent hepatectomy combined with hepaticojejunostomy between January 2013 and December 2015 were analyzed retrospectively. SSIs, including incisional (superficial and deep) and space/organ infection, were defined according to the Centers for Disease Control and Prevention (CDC)'s National Nosocomial Infection Surveillance (NNIS) system. Risk factors associated with postoperative SSIs were analyzed by univariate and multivariate analyses. A nomogram was developed on the basis of results from the multivariate logistic model and the discriminatory ability of the model was analyzed.

PHCC patients had higher organ/space SSI rate than incisional SSI rate after radical resection. Multivariate analysis showed that risk factors indicating postoperative overall SSIs (incisional and organ/space) included coexisting cholangiolithiasis [odds ratio (OR): 6.77; 95% confidence interval (95% CI): 2.40–19.11; $P < .001$], blood loss >1500 mL (OR: 4.77; 95% CI: 1.45–15.65; $P = .010$), having abdominal surgical history (OR: 5.85; 95% CI: 1.91–17.97; $P = .002$), and bile leakage (OR: 15.28; 95% CI: 5.90–39.62; $P < .001$). The β coefficients from the multivariate logistic model were used to construct the model for estimation of SSI risk. The scoring model was as follows: −4.12 +1.91 × (coexisting cholangiolithiasis = 1) + 1.77 × (having previous abdominal surgical history = 1) +1.56 × (blood loss >1500 mL = 1) + 2.73 × (bile leakage = 1). The discriminatory ability of the model was good and the area under the receiver operating characteristic (ROC) curve (AUC) was 0.851.

In PHCC patients, there may be a relationship between postoperative SSIs and abdominal surgical history, coexisting cholangiolithiasis, bile leakage, and blood loss. The nomogram can be used to estimate the risk of postoperative SSIs in patients with PHCC.

Abbreviations: AJCC = American Joint Committee on Cancer, ALT = alanine transaminase, ASA = American Society of Anesthesiologists, AST = aspartate transaminase, AUC = area under ROC curve, CDC = Centers for Disease Control and Prevention, COPD = chronic obstructive pulmonary disease, ENBD = endoscopic nasobiliary drainage, ERBD = endoscopic retrograde biliary drainage, FLR = functional liver remnant, ICG-R15 = indocyanine green retention rate at 15 minutes, MRSA = Methicillin-resistant *Staphylococcus aureus*, MSKCC = Memorial Sloan Kettering Cancer Center, NNIS = National Nosocomial Infection Surveillance, PHCC = perihilar cholangicarcinoma, POD = postoperative day, PTCD = percutaneous transhepatic cholangial drainage, PVE = Portal vein embolization, ROC = receiver operating characteristic curve, SSI = Surgical site infection, TB = total bilirubin, TNM = tumor node metastasis.

Keywords: nomogram, perihilar cholangiocarcinoma, surgical site infection

1. Introduction

Perihilar cholangicarcinoma (PHCC), also known as Klatskin tumor, is a type of epithelial cancer arising from the right and left hepatic ducts, the confluence of the right and left hepatic bile ducts, and above cystic duct openings. Complete resection of the invaded hepatic bile duct and hepatic parenchyma combined with hepaticojejunostomy is the most commonly used procedure. Vascular resection and reconstruction are essential when major portal structures including the hepatic artery and portal vein are infiltrated. As a consequence of these complicated procedures, patients with PHCC often have high postoperative morbidity and mortality rates.[1–3] Patients with postoperative infectious complications such as SSIs often have longer hospital stay and worse prognosis.[4–7] Several studies have reported on the risk factors associated with SSIs (incisional and organ/space infection) in patients undergoing hepatectomies. Higher American Society of Anesthesiologists (ASA) scores,[8] the presence of diabetes mellitus,[9] longer operative time,[10] bile leakage,[4] and some

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other factors were demonstrated to be risk factors indicating postoperative SSIs in patients with liver malignancy following hepatectomies. However, for PHCC patients, few studies have reported on the negative prognostic factors associated with postoperative SSIs.

PHCC patients seem to have higher postoperative SSI rates resulting from injured preoperative liver function and more complicated surgical procedures. In the present study, we aimed to investigate risk factors related to postoperative incisional and organ/space SSIs and develop a scoring model to estimate the risk of postoperative SSIs in patients with PHCC. Furthermore, we also reported the management and outcomes of incisional and organ/space SSIs in the present series.

2. Patients and methods

A total of 335 consecutive PHCC patients were reviewed retrospectively. These patients underwent hepatectomy combined with hepaticojejunostomy between January 2013 and December 2015 in the West China Hospital. The surgeries were performed by professors in our liver surgery center and all surgeons have performed liver resections for more than 500 cases of liver malignancy. The diagnosis of PHCC was confirmed by postoperative histopathological examination. Patients with unresectable PHCC (e.g., main portal vein involvement, bilateral spread to secondary biliary radicles, and intrahepatic or extrahepatic disseminated metastasis) were excluded.[11] Parts of these patients in advanced stage received internal biliary drainage such as endoscopic retrograde biliary drainage (ERBD), and/or external biliary drainage including endoscopic nasobiliary drainage (ENBD) and percutaneous transhepatic cholangial drainage (PTCD). Patients with poor liver function [Child–Pugh class C or indocyanine green retention rate at 15 minutes (ICG-R15) >20%] were excluded for the high risk of postoperative complications and death. Patients undergoing simultaneous procedures such as colorectal resection were excluded. Patients in type I (Bismuth classification) without hepatectomy were excluded. The classification of PHCC was based on the seventh edition of American Joint Committee on Cancer (AJCC) cancer staging manual and Memorial Sloan Kettering Cancer Center (MSKCC) staging system.[12] Pre-, intra-, and postoperative clinical characteristics associated with postoperative organ/space SSIs and overall (incisional and organ/space) SSIs were analyzed by univariate analyses (Table 1). And all statistically significant factors in univariate analyses were included in multivariate analyses. This study was approved by the Ethical Committee of the West China Hospital.

2.1. Perioperative management and surgical procedures

Biliary drainage including PTCD (n = 167) and ENBD (n = 148) was necessary for patients with clinically evident jaundice before surgery [preoperative total bilirubin (TB) should be less than 100 μmol/L]. Portal vein embolization (PVE; n = 10) should be carried out preoperatively for patients with anticipated functional liver remnant (FLR) less than 50% of the functional liver volume. Antibiotics (cefuroxime 1.5 g intravenous drip) were used 30 minutes before skin incision and additional doses of antimicrobial agents were used every 3 hours. Reversed "L" shaped incision was adopted in 312 patients and "J" shaped incision in 23 patients. The main surgical procedures before hepatectomy included freeing and ligating the distal bile duct just above the pancreatic head; dividing and ligating the portal

Table 1

Clinicopathologic variables of PHCC patients by occurrence of overall SSI (incisional and organ/pace).

Variables	Overall SSI (n = 34, 10.15%)	Non-SSI (n = 301, 89.85%)	*P*
Sex, M/F	15/19	145/156	.654
Age, y, ≤65/>65	23/11	181/120	.395
Child–Pugh grade A/B/C	31/17/0	297/149/0	.780
ICG-R15 (%) ≤10/>10	30/4	294/7	.016
Background liver			
Normal/fatty/obstructive jaundice	8/11/15	80/60/141	.347
Coexisting medical conditions yes/no			
Cholangiolithiasis	13/21	35/266	<.0001
Diabetes mellitus	3/31	23/278	1.000
Hypertension	5/29	21/280	.110
Pulmonary diseases	4/30	18/283	.355
Renal insufficiency	2/32	5/296	.318
Cardiovascular diseases	3/31	8/293	.160
Previous treatment yes/no			
PTCD	22/12	145/156	.068
ENBD	11/23	137/164	.143
ERBD	3/31	11/290	.329
PVE	2/32	8/293	.606
Previous abdominal surgical history			
Yes/no	10/24	19/282	<.0001
BMI, kg/m^2 ≤25/>25	8/26	141/160	.010
ASA score 1/2/3	4/16/14	83/134/84	.090
Smoking history yes/no	8/26	98/203	.283
Preoperative serum TB, μmol/L			
≤34.2/>34.2	8/26	88/213	.485
Preoperative serum albumin, g/L			
≤30/>30	3/31	32/269	.975
Preoperative serum AST, IU/L			
≤80/>80	26/8	280/21	.001
Preoperative serum ALT, IU/L			
≤100/>100	27/7	277/24	.016
Preoperative serum CA-199, IU/mL			
≤1000/>1000	23/11	169/132	.199
Bismuth–Corlette type			
I-II/III-IV	7/27	34/267	.117
AJCC TNM stage			
Stage 0-II/stage III-IV	28/6	242/59	.785
MSKCC stage T1/T2/T3	29/3/2	267/26/8	.575
No. of segments resected			
≤4/>4	4/30	34/267	1.000
Vascular reconstruction yes/no	7/27	33/268	.101
Hepatic ischemic time, min			
≤60/>60	31/3	290/11	.329
Operation duration, min			
≤360/>360	24/10	171/130	0.123
Blood loss, mL			
≤1500/>1500	25/9	279/22	<.0001
Perioperative blood transfusion			
Yes/no	13/21	103/198	.641
Tumor size, cm ≤2/>2	18/16	177/124	.511
Resection margin R0/R1	32/2	295/6	.415
Ascites yes/no	9/25	46/255	.095
Bile leakage yes/no	21/13	44/257	<.0001
Liver failure yes/no	2/32	6/295	.415
Coexisting PPI yes/no	6/28	21/280	.030
Median hospital stay, d	34 (14–49)	15 (8–44)	<.001
90-day mortality dead/alive	2/32	2/299	.068

AJCC = American Joint Committee on Cancer, ALT = alanine transaminase, ASA = American Society of Anesthesiologists, AST = aspartate transaminase, BMI = Body mass index, COPD = chronic obstructive pulmonary disease, ENBD = endoscopic nasobiliary drainage, ERBD = endoscopic retrograde biliary drainage, ICG-R15 = indocyanine green retention rate at 15 min, MSKCC = Memorial Sloan Kettering Cancer Center, PHCC = perihilar cholangicarcinoma, PPI = postoperative pulmonary infection, PTCD = percutaneous transhepatic drainage, PVE = portal vein embolization, SSI = surgical site infection, TB = total bilirubin, TNM = tumor node metastasis.

pedicles of the resected side; and ligating the short hepatic veins if possible. If portal vein and hepatic artery were infiltrated, vascular reconstruction was necessary. Portal vein reconstruction was performed by wedge resection (n = 11), end-to-end anastomosis (n = 10), or reconstruction with autologous vessels (n = 12). Hepatic artery reconstruction was performed by end-to-end anastomosis (n = 4), and replacement with autologous vessels (n = 3). The range of liver resection was determined by preoperative imaging examination and intraoperative abdominal exploration. Liver parenchyma transection was carried out with the Kelly-crush technique or other instruments, including CUSA (Valleylab Corp., Somerville, NJ) or Harmonic scalpel (Johnson & Johnson Corp., Princeton, NJ). Roux-en-Y biliary enteric anastomosis was performed on the residual bile duct to the jejunum. In principle, 2 abdominal drainage tubes were positioned at the Winslow hiatus and the cut surface of the liver, respectively. Abdominal incisions including fascia and skin were closed in 3 layers with interrupted sutures, using monofilament absorbable sutures. Antibiotics (cefuroxime 1.5 g q8 h, intravenous drip) were routinely managed for prophylaxis for 3 days after liver resection. The abdominal drainage tubes were pulled out on postoperative day (POD) 3 or 4 when no bile leakage, organ/space infection, or other situations needing abdominal drainage occurred.

2.2. Definitions

Obstructive jaundice was defined as a preoperative TB concentration ≥51.3 μmol/L.[13] Cholangiolithiasis was classified as intra- and extrahepatic bile duct stones and was diagnosed by preoperative imaging examinations and intraoperative findings by the surgeons. Hepatolithiasis was defined as the presence of stones in the intrahepatic duct and choledocholithiasis were defined as stones in the common bile duct. Diagnosis of diabetes mellitus and hypertension was based on the World Health Organization criteria.[14,15] Renal insufficiency was defined as an increase of serum urea and/or creatinine level (50% above the baseline). In the present study, preoperative cardiovascular diseases mainly included coronary heart disease and valvular heart disease. Preoperative pulmonary diseases mainly included pulmonary infection and chronic obstructive pulmonary disease (COPD). All coexisting preoperative chronic medical diseases were diagnosed by specialist physicians.

SSIs, including incisional (superficial and deep) and space/organ infection, were defined according to the CDC's NNIS system.[16] On the basis of these criteria, SSI was defined as conditions that occurred within 30 days postoperatively. The criteria of SSIs included at least one of the followings: pus discharged from the incision (superficial or deep) or drainage tubes in the abdominal cavity; organisms were isolated from an aseptically obtained culture of fluid or tissue in the incision or organ/space; diagnosis of an incisional or organ/space SSI by surgeons at the time of reoperation or percutaneous drainage.

Clavien–Dindo classification was used to classify organ/space SSIs.[17] Liver failure was defined as peak bilirubin concentration >7 mg/dL, peak international normalized ratio >2.0, refractory ascites, or encephalopathy.[18] Bile leakage was defined as a drain fluid-to-serum TB concentration ratio ≥3.0 on or after POD 3.[19] Clinically significant ascites was defined when abdominal drainage was more than 500 mL/day for longer than 3 days. Postoperative mortality was defined as any death during postoperative hospitalization or within 90 days after surgery.

2.3. Statistical analysis

The clinicopathologic features and surgical outcomes of all patients were compared between groups with and without SSIs. Categorical variables were shown as numbers and tested by Chi-square test or Fisher exact test. Continuous variables were presented as mean (range) and tested by 1-way analysis of variance (ANOVA) (Student–Newman–Keuls test was used when ANOVA was significant) or Kruskal–Wallis H rank test when appropriate. Independent risk factors indicating postoperative SSIs were analyzed by univariate and multivariate binary logistic regression analysis. The final model selection for the nomogram was performed by a backward step-down selection process using a threshold of $P < .05$, and some factors without clinical significance were also excluded from the model. ROC curves were used to find the cut-off value and evaluate the discriminatory ability of the model. All statistical analyses were 2-tailed and P values $< .05$ were deemed statistically significant. The nomogram and time-dependent ROC were established with R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA). Other analyses were performed by SPSS 19.0 statistical software (SPSS Company, Chicago, IL).

3. Results

3.1. Risk factors for SSIs in patients with PHCC

During the period of study, 335 patients (160 male; 175 female) with PHCC who underwent hepatectomy combined with hepaticojejunostomy were analyzed. Overall SSI (incisional and organ/space) rate was 10.15% (n = 34). Five patients showed both incisional and organ/space SSIs. Univariate analysis showed that risk factors associated with overall SSIs were coexisting cholangiolithiasis ($P < .0001$), having abdominal surgical history ($P < .0001$), body mass index (BMI) >25 kg/m^2 ($P = .010$), preoperative serum aspartate transaminase (AST) >80 IU/L ($P = .001$), preoperative serum alanine transaminase (ALT) >100 IU/L ($P = .016$), blood loss >1500 mL ($P < .0001$), and bile leakage ($P < .0001$) (Table 1). Cholangiolithiasis included extrahepatic cholangiolithiasis (n = 27), intrahepatic cholangiolithiasis (n = 31), and both (n = 10). Previous abdominal surgeries included hepatectomy (n = 10), cholecystectomy (n = 12), surgeries on choledocholithiasis (n = 15), hepaticojejunostomy (n = 3), pancreaticoduodenectomy (n = 2), and appendicectomy (n = 3). Factors showing no significant difference included gender, age, preoperative ICG-R15, preoperative TB, albumin, serum CA-199, background liver (normal, fatty, and obstructive jaundice), coexisting medical conditions except for cholangiolithiasis, previous treatment (PTCD, ENBD, and PVE), number of vascular reconstruction, AJCC and MSKCC stage, hepatic ischemic time, tumor size and other factors listed in Table 1 (all; $P > .05$). Total organ/pace SSI rate (n = 22) was 6.57%. Univariate analysis revealed that coexisting cholangiolithiasis ($P = .002$), having abdominal surgical history ($P < .0001$), ascites ($P = .044$), and bile leakage ($P < .0001$) were risk factors related to organ/space SSIs (Table 2).

Multivariate analysis [including ICG-R15, coexisting cholangiolithiasis, previous abdominal surgical history, BMI, blood loss, bile leakage, coexisting PPI (postoperative pulmonary infection), and hospital stay] showed that risk factors indicating overall postoperative SSIs included coexisting cholangiolithiasis (OR: 6.77; 95% CI: 2.40–19.11; $P < .001$), blood loss >1500 mL (OR: 4.77; 95% CI: 1.45–15.65; $P = .010$), having abdominal

Table 2

Clinicopathologic variables of PHCC patients by occurrence of organ/pace SSI.

Variables	Organ/pace SSI (n = 22, 6.57%)	Non-SSI (n = 313, 93.43%)	P
Sex, M/F	10/12	150/163	.823
Age, y, ≤65/>65	15/7	189/124	.469
Child–Pugh grade A/B/C	20/13/0	308/153/0	.466
ICG R15 (%) ≤10/>10	19/3	305/8	.028
Background liver			
Normal/fatty/obstructive jaundice	5/6/11	83/65/145	.792
Coexisting medical conditions yes/no			
Cholangiolithiasis	8/14	40/273	.002
Diabetes mellitus	2/20	24/289	1.000
Hypertension	3/19	23/290	.514
Pulmonary diseases	2/20	20/293	.961
Renal insufficiency	1/21	6/307	.950
Cardiovascular diseases	2/20	9/304	.336
Previous treatment yes/no			
PTCD	16/6	151/162	.046
ENBD	8/14	140/173	.445
ERBD	2/20	12/301	.522
PVE	2/20	8/305	.274
Previous abdominal surgical history			
Yes/no	8/14	22/291	<.0001
BMI, kg/m^2 ≤25/>25	5/17	144/169	.034
ASA score 1/2/3	2/10/10	85/140/88	.095
Smoking history yes/no	6/16	100/213	.648
Preoperative serum TB, μmol/L			
≤34.2/>34.2	5/17	91/222	.525
Preoperative serum albumin, g/L			
≤30/>30	2/20	33/280	1.000
Preoperative serum AST, IU/L			
≤80/>80	18/4	288/25	.211
Preoperative serum ALT, IU/L			
≤100/>100	19/3	285/28	.724
Preoperative serum CA-199, IU/mL			
≤1000/>1000	15/7	177/136	.286
Bismuth–Corlette type			
I-II/III-IV	4/18	37/276	.587
AJCC TNM stage			
Stage 0-II/stage III-IV	19/3	251/62	.081
MSKCC stage T1/T2/T3	17/3/2	279/26/8	.139
No. of segments resected			
≤4/>4	2/20	36/277	1.000
Vascular reconstruction yes/no	4/18	36/277	.553
Hepatic ischemic time, min			
≤60/>60	19/3	302/11	.081
Operation duration, min			
≤360/>360	16/6	179/134	.153
Blood loss, mL			
≤1500/>1500	16/6	288/25	.003
Perioperative blood transfusion			
yes/no	8/14	108/205	.859
Tumor size, cm ≤2/>2	13/9	182/131	.931
Resection margin R0/R1	21/1	306/7	1.000
Ascites yes/no	7/15	48/265	.044
Bile leakage yes/no	17/5	48/265	<.0001
Liver failure yes/no	1/21	7/306	1.000
Coexisting PPI yes/no	3/19	24/289	.556
Median hospital stay, d	35 (16–49)	16 (8–44)	<.001
90-day mortality rate	2/20	2/311	.012

AJCC = American Joint Committee on Cancer, ALT = alanine transaminase, ASA = American Society of Anesthesiologists, AST = aspartate transaminase, BMI = Body mass index, COPD = chronic obstructive pulmonary disease, ENBD = endoscopic nasobiliary drainage, ERBD = endoscopic retrograde biliary drainage, ICG-R15 = indocyanine green retention rate at 15 min, MSKCC = Memorial Sloan Kettering Cancer Center, PHCC = perihilar cholangicarcinoma, PPI = postoperative pulmonary infection, PTCD = percutaneous transhepatic drainage, PVE = portal vein embolization, SSI = surgical site infection, TB = total bilirubin, TNM = tumor node metastasis.

Table 3

Multivariate analysis of risk factors for overall SSI (incisional and organ/pace).

Variables	β	OR (95% CI)	P
Coexisting cholangiolithiasis (yes vs no)	1.91	6.77 (2.40–19.11)	<.001
Blood loss (>1500 vs ≤1500 mL)	1.56	4.77 (1.45–15.65)	.010
Previous abdominal surgical history (yes vs no)	1.77	5.85 (1.91–17.97)	.002
Bile leakage (yes vs no)	2.73	15.28 (5.90–39.62)	<.001

Multivariate analysis of risk factors for overall SSI was performed by including ICG-R15, coexisting cholangiolithiasis, Previous abdominal surgical history, BMI (body mass index), blood loss, bile leakage, coexisting PPI (postoperative pulmonary infection) and hospital stay. β = regression coefficient, OR = odds ratio, SSI = surgical site infection.

surgical history (OR: 5.85; 95% CI: 1.91–17.97; $P = .002$), and bile leakage (OR: 15.28; 95% CI: 5.90–39.62; $P < .001$) (Table 3).

3.2. The nomogram and its predictive performance

The regression coefficients (β) from the multivariate logistic model were used to construct the model for estimation of SSI risk. The scoring model was as follows: -4.12 +1.91*(coexisting cholangiolithiasis = 1) + 1.77*(having previous abdominal surgical history = 1) +1.56*(blood loss >1500 mL = 1) + 2.73*(bile leakage = 1). The performance of the nomogram was measured by ROC curves and the AUC was 0.851 (95% CI 0.777–0.925) in the model from observed data. The cut-off score was -2.28 with a sensitivity of 85.3% and a specificity of 74.1% (Fig. 1). The nomogram's predictive accuracy was also measured by the bootstrap (1000 resample) method and the AUC of the model from Bootstrap remained largely unchanged (AUC = 0.850).

3.3. Outcomes of patients with SSIs

The length of hospital stay in either overall SSI group or organ/space SSI group was longer than non-SSI group ($P < .001$). The 90-day mortality rate of overall SSI group was higher than non-SSI group but had no statistical significance ($P = .068$), while mortality rate of organ/space SSI group was significantly higher than non-SSI group ($P = .012$). Two patients in organ/space SSI group died from liver abscess. The other 2 patients in non-SSI group died from liver failure due to thrombogenesis in anastomotic portal vein and anastomotic leakage, respectively. No patients died from incisional infection (Fig. 2).

Twenty-two patients with organ/space SSIs were classified according to the Clavien–Dindo classification. Consequently, 8 patients were in grade II, 10 patients in grade III-a, 1 patient in III-b, 1 patient in grade IV-a, and 2 in grade V. Finally, 8 patients were successfully cured by percutaneous drainage, 1 patient by reoperation, 11 patients by irrigation of the pre-positioned drain, and 2 patients died from infectious shock (on POD 30) and liver failure (on POD 25), respectively.

3.4. Causative bacteria of incisional and organ/space SSIs

Fourteen patients with organ/space SSIs had positive culture results: *Escherichia coli* (n = 6), Klebsiella sp. (n = 1), Pseudomonas sp. (n = 2), Streptococcus sp. (n = 2), Enterococcus sp. (n = 1), Enterobacter sp (n = 1), and *Staphylococcus aureus* (n = 1). Ten

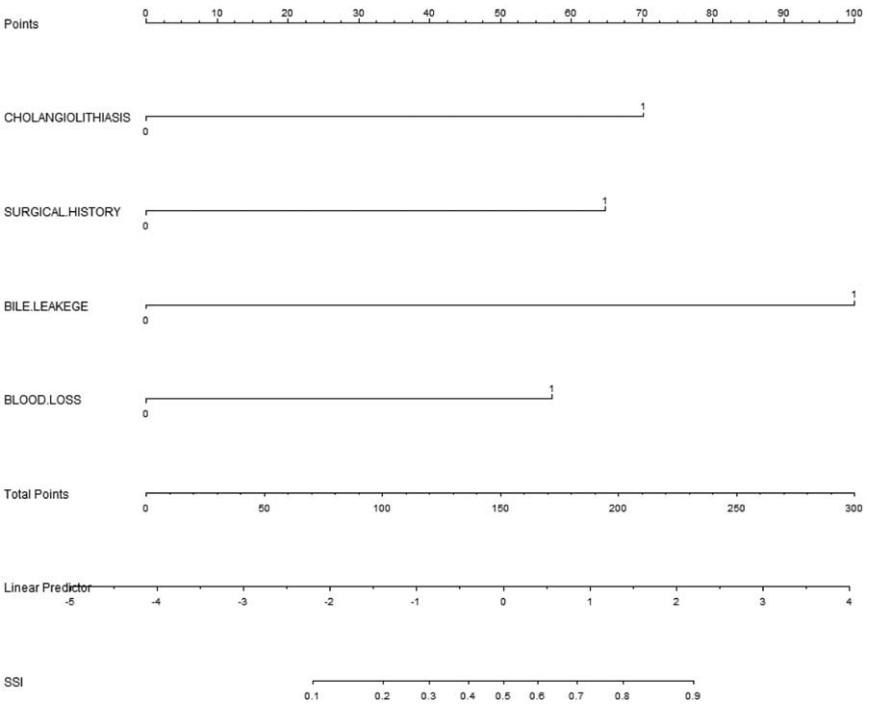

Figure 1. The nomogram to estimate the risk of SSI presence postoperatively in PHCC patients. To use the nomogram, find the position of each variable on the corresponding axis, draw a line to the points axis for the number of points, add the points from all of the variables, and draw a line from the total points axis to determine the SSI probabilities at the lower line of the nomogram.

patients with incisional SSIs had positive culture results: *S. epidermidis* (n = 3), Methicillin-resistant *S. aureus* (MRSA; n = 2), Streptococcus sp. (n = 2), Enterococcus sp (n = 1), Pseudomonas sp. (n = 1), and Klebsiella sp. (n = 1).

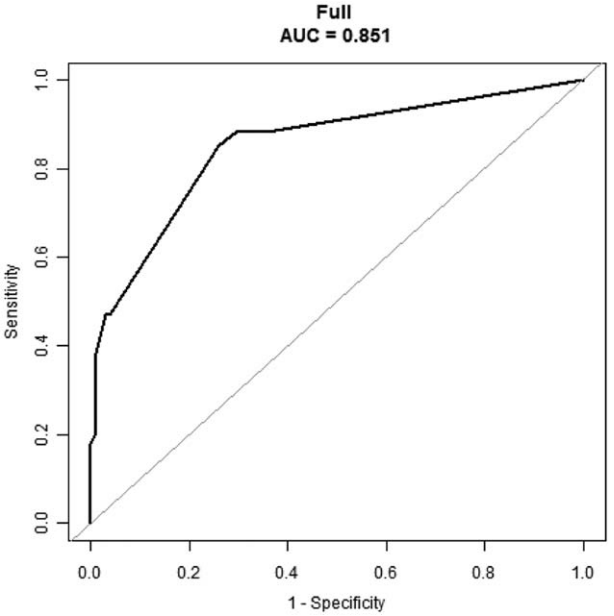

Figure 2. The AUC of the model from observed data (nomogram) was 0.851. The cut-off value was -2.28 with a sensitivity of 85.3% and a specificity of 74.1%. AUC = area under ROC.

4. Discussion

To our knowledge, few studies have demonstrated SSI rates of PHCC patients who underwent hepatectomy combined with hepaticojejunostomy and/or vascular reconstruction. In the present study, the total postoperative SSI rate for patients with PHCC was 10.15%, higher than SSI rates in other studies only performing hepatectomies for liver malignancies, which may be due to the concomitant biliary and bowel surgeries in PHCC patients.[20,21] Incisional SSI rate was generally higher than organ/space SSI rate in liver surgeries.[22] However, we found that organ/space infection rate was higher than incisional infection rate in PHCC patients following curative resection, thus identifying independent risk factors predicting postoperative SSIs had great significance. In this study, 4 factors were identified as risk indicators for postoperative overall SSIs in patients with PHCC. In addition, we developed a simple and easy-to-use prognostic nomogram integrating the 4 predictors to predict postoperative SSIs for these patients. The nomogram showed good predictive accuracy after internal validation (bootstrap).

Cholangiolithiasis was a predisposing factor associated with carcinogenesis of PHCC.[23,24] In the present study, cholangiolithiasis was observed in 13 of 34 PHCC patients with SSIs. Surgery is the primary treatment for both hepatolithiasis and PHCC. However, in multivariate analysis, hepatolithiasis was an independent risk factor indicating postoperative SSIs in patients with PHCC. Similarly, Yang et al[25] have shown that hepatolithiasis was an independent risk factor of both incisional and organ/space SSI after liver resection in 1 study including 7388 patients with different liver diseases. Cholangiolithiasis often resulted in bile infection and liver abscesses due to biliary obstruction, while preoperative hepatobiliary infection may be closely associated with postoperative SSIs.[26,27] On the basis of

these studies, liver resection should not be carried out in a septic condition and perioperative meticulous management was critical for these patients. We believed that it is significant to protect the incision and surgical field from intraoperative bacterial contamination, and postoperative sufficient peritoneal lavage and drainage may be beneficial to reduce SSI rate.[28] However, though preoperative biliary drainage is beneficial for liver function recovery, it predisposes to bile infection and postoperative SSIs, thus decision of biliary drainage before surgery should be repeatedly weighed.

To our knowledge, no previous studies have demonstrated a direct relation between abdominal surgical history and SSIs for patients with PHCC. Our data showed that previous abdominal surgical history was associated with postoperative SSIs. In our study, previous hepatobiliary surgeries for hepatolithiasis and cholecystolithiasis were the main procedures associated with SSIs after reoperations (radical resection of PHCC). It may be due to the longer operation time, more blood loss and transfusion, and higher postoperative morbidity (such as hemorrhage and bile leakage) rates for patients with PHCC undergoing reoperations. In the present study, bile leakage rate after curative resection in patients with PHCC was 19.4%, higher than patients only undergoing hepatectomy in other centers.[29,30] In multivariate analysis, postoperative bile leakage was also associated with overall SSIs and organ/space SSIs in the present study. In other studies, reoperation was also found to be a negative factor related to SSIs. Sadamori et al[31] demonstrated that repeat hepatectomy was an independent risk factor for bile leakage and organ/space SSIs after hepatectomy in hepatocellular carcinoma recurrence. Postoperative infections including SSIs also remain a significant problem among liver transplant recipients. Avkan-Oguz et al[32] demonstrated that reoperation was related to postoperative early bacterial infection (SSI: 20.2%) after liver transplantation. Consequently, for patients undergoing reoperations, postoperative SSIs was one of the major morbidities that may influence surgical outcomes and it should be focused on particular attention.

Similar to findings in several previous studies,[4–6] higher blood loss was a prognostic factor indicating SSIs by multivariate analysis in this study. Kobayashi et al[4] showed that blood loss >2000 mL was a risk factor for SSIs after hepatectomy. In our study, blood loss >1500 mL was identified as a risk factor for SSIs. In these patients, more blood loss usually resulted from concomitant vascular resections and reconstructions, and dividing abdominal adhesions for previous surgeries. Blood loss decreased the antibiotic concentration and it might be related to postoperative SSIs.[33] In our center, if intraoperative blood loss was more than 1500 mL, additional antibiotics were added for another dose to maintain therapeutic concentration. For patients undergoing hepatectomy and biliary reconstruction, postoperative continued antibiotic therapy may be effective to prevent SSIs.[34]

The clinical relevance of our study was that patients with PHCC had higher organ/space SSI rate than incisional SSI rate, which may be due to the special protection of the incision during the operation. Furthermore, risk factors indicating postoperative SSIs were different from those identified in liver malignancies,[4–6] which may be because of the different preoperative liver function, surgical procedures, and postoperative incidence of complications. In univariate analysis, preoperative biliary drainage was associated with postoperative organ/pace SSI. However, preoperative ERBD, ENBD, or ERBD (in fact, it is typical that the bile duct was contaminated through previous biliary drainage) was not risk factors predicting postoperative SSIs in multivariate analysis. Some studies demonstrated that patients with preoperative biliary drainage had an increased risk of incisional SSIs after pancreaticoduodenectomy.[35,36] In hepatobiliary surgery, the presence of biliary drainage catheter preoperatively was also found to be a specific risk factor for postoperative SSIs.[37] In the present study, preoperative biliary drainage was not a risk factor indicating SSIs. We suppose that bacterial culture may be necessary to explode the real bile infection rate after biliary drainage and the preoperative bile infection caused by biliary drainage may be an independent risk factor indicating postoperative SSIs.

In the present study, though most of postoperative SSIs have resolved after antimicrobial therapy or timely percutaneous tube drainage even for abdominal abscesses, there were still 2 patients who died from organ/space SSIs (both patients had liver abscess). Identify the risk factors related to SSIs was the precondition for reducing postoperative SSIs. In this study, a novel and practical nomogram was established to predict postoperative SSIs with good sensitivity and specificity. The nomogram showed a good performance for predicting the postoperative SSIs (AUC = 0.851). To our knowledge, we report here the first nomogram for predicting postoperative SSIs in PHCC patients. However, external validation of the nomogram is needed in further studies.

This study had several limitations. First, this was a retrospective study in a single center. Second, the data were obtained by reviewing medical records and thus it could have compromised quality because of the accumulation of inappropriate data. Third, only a small number of patients developed SSIs; thus, we did not perform subgroup multivariate analysis for incisional and organ/space SSIs, respectively, while the reasons for incisional and organ/space SSIs may be different.

In conclusion, PHCC patients had higher organ/space SSI rate than incisional SSI rate after radical surgery. Risk factors associated with postoperative overall SSIs included coexisting cholangiolithiasis, having abdominal surgical history, bile leakage, and blood loss >1500 mL. Special attention should be placed on these factors in the management of patients with PHCC. For example, for patients with postoperative bile leakage, timely drainage may be necessary and efficient for preventing SSIs. The surgeons should recognize and effectively prepare for risk of high blood loss and antibiotics should be redosed after large volumes of blood loss. We have developed a novel and practical nomogram that accurately predicts postoperative SSIs and the nomogram can be used to guide the frequency of postoperative surveillance as well as adjuvant therapy in patients at a high risk of postoperative SSIs.

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