RESEARCH ARTICLE

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Predictive Factors for Post-Hepatectomy Liver Failure in Patients with Cholangiocarcinoma

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Abstract

Background: Cholangiocarcinoma (CCA) is a cancer of biliary tract with a different incidence across the globe. The northeast part of Thailand has the highest incidence of CCA. Post-hepatectomy liver failure (PHLF) is the most severe and life-threatening complication in CCA patients. The aim of this study was to identify factors related to PHLF incidence in patients with CCA. **Methods:** An analytical cross-sectional study was performed in a university hospital in northeast Thailand between January 1, 2014 and December 31, 2020. PHLF grading criteria was used according to the international study group of liver surgery definition for PHLF. Multiple Logistic Regression with a stepwise forward method was employed to identify the predictive factors related to PHLF. **Result:** The study findings revealed that 185 patients developed PHLF, of whom 56.22% experience grade A, 36.76% grade B, and 7.06% grade C PHLF. Based on our findings, seventeen factors were significantly correlated with PHLF incidence, namely age, cholangiocarcinoma type, hepatectomy type, preoperative biliary drainage, cholangitis, Child-Turcotte-Pugh grade, operation time, total blood loss, total blood transfusion, level of serum albumin, total bilirubin, direct bilirubin, alanine transaminase, aspartate transaminase, alkaline phosphatase, prothrombin time, and level of international normalized ratio. Total bilirubin (adjusted OR=14.07, 95% CI 7.54-26.27), Child-Turcotte-Pugh grade (adjusted OR=3.34, 95% CI 1.43-7.81), total blood transfusion (adjusted OR=2.32, 95% CI 1.19-4.54), and operation time (adjusted OR=1.77, 95% CI 1.05-2.97) could significantly predict PHLF incidence with a positive predictive value of 86.03% and a negative predictive value of 80.23%, while the accuracy of prediction was 81.88%. **Conclusion:** The findings of this study identified total bilirubin, Child-Turcotte-Pugh grade, total blood transfusion, and operation time as clinical predictive factors of PHLF. Therefore, modification of these factors is recommended to reduce the probability of liver failure in CCA patients.

Keywords: Cholangiocarcinoma- post-hepatectomy liver failure- predictive factor

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Introduction

Cholangiocarcinoma (CCA) accounts for 13% of the total cancer mortality worldwide. The incidence of CCA in Southeast Asia is much higher than other regions of the world. Moreover, CCA is one of the most common cancers in Thailand, especially in the Northeastern region (Kamsa-ard et al, 2018; Insamran and Sangrajrang, 2020). In Khon Kaen, Thailand, the overall age-standardized incidence rates (ASR) from 1989 to 2018 for all ages in males was 36.1 per 100 000 person-years (95% CI; 35.3 to 36.8), while it was 14.4 per 100,000 person-years in females (95% CI; 13.9 to 14.8) (Kamsa-ard et al., 2021). Liver resection is the only treatment that can permanently cure early-stage CCA (Blechacz, 2017; Cillo et al., 2019; Lee et al., 2020). In addition, the highest survival prediction for individuals with CCA was associated with surgery as the basis of treatment (Chanchai, et al., 2019). However, liver resection is associated with various complications, including post-hepatectomy liver failure (PHLF), bile leak, infection, thrombosis, and acute kidney failure. PHLF is a most severe complication that can be found in the sufferers. The incidence of PHLF is approximately 1% to 34% worldwide (Liu et al., 2020; Rahnemai-Azar et al., 2018). In Srinagarind, a university teaching hospital in Thailand, the incidence of PHLF in CCA patients was 38% (Medical Record Unit, 2017-2019). Additionally, the mortality rate of PHLF is approximately 5% to 10% worldwide (Andreatos et al., 2017; Gilg et al., 2018).

PHLF is defined by deterioration in the ability of the liver to perform its previous functions after surgery due to the imbalance created in the circulation system of the remnant liver (Tsoris and Marlar, 2022). Previous studies revealed various factors associated with PHLF, including

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gender, age, comorbidities, malnutrition, cholangitis, cirrhosis, neoadjuvant (Sultana et al., 2018), abnormal liver function tests such as serum bilirubin levels, albumin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), coagulation values: prothrombin time levels (PT) , international normalized ratio (INR) (Rahbari et al., 2011; Lee et al., 2020), type of liver resection, and future liver remnant. The International Study Group of Liver Study (ISGLS) defines PHLF as loss of liver function after liver resection for five days along with increase of serum bilirubin and coagulation levels higher than the standard value . The severity of PHLF is classified into three levels of A, B, and C. The mortality rate for PHLF in levels A, B, and C is 0%, 12%, and 54%, respectively (Rahbari et al., 2011).

CCA patients with PHLF experience a prolonged length of hospital stay in intensive care unit, increased in-hospital mortality, and 90-day mortality (Arisaka et al., 2020; Lee et al., 2020). Identifying the risk factors of PHLF in CCA patients can improve post-liver resection outcomes. A previous study investigated patients with different types of CCA who suffered from combined gallbladder cancer. It was found that serum albumin level and indocyanine green retention ratio at 15 minutes were associated with PHLF (Miyazaki et al., 2019). Another study was done on patients with intrahepatic CCA. Tumor size, serum bilirubin levels, neutrophil-to-lymphocyte ratio, and cancer antigen 19-9 level were reported as risk factors associated with PHLF in the aforementioned study (Sasaki et al., 2016). Lee et al., in their study on patients with perihilar CCA found that future liver remnant/body weight (FLR/BW) and portal vein resection could act as predictors of PHLF (Lee et al., 2020). Ishii et al., identified preoperative type IV collagen 7S as a significant independent factor associated with both PHLF and postoperative long-term recovery of liver function(Ishii et al., 2020). Preoperative type IV collagen 7S; however, there are still contrasting findings about predictive factors of PHLF.

From the excellence center of CCA at a university hospital in northeast Thailand, patients who underwent liver resection, a preoperative phase have been evaluated for general risk factors, and the possibility for liver resection for the specific risk factors of PHLF would not be included. Therefore, this study aimed to discover possible risk factors of PHLF in CCA patients admitted to a university hospital in northeast Thailand.

Materials and Methods

This analytical cross-sectional study was conducted by reviewing personal data records, evaluating patients' outcome, and severity using PHLF grading criteria by the international study group of liver surgery in a university hospital in northeast Thailand between January 1, 2014 and December 31, 2020. A total of 480 cases at different stages and with different type of CCA were included in the present study. Inclusion criteria were not having liver failure before surgery, age≥ 18 years , and being candidate of liver resection. Patients who had history of palliative surgery were excluded. The sample size was estimated under the logistic regression for the binary outcome (Hsieh et al., 1998) with a significant maximum odd ratio of International normalized ratio (INR) for predicting PHLF from a previous study (Odd ratio = 4.08, 95% CI 2.14-7.78) (Dasari et al., 2018), 5% statistical significance and 80% power of the study . Thirteen percent of the sample size missed in the previous study (Dasari et al., 2018) was used to cover incomplete data.

The study was approved by the Human Ethics Committee of Khon Kaen University, Khon Kaen, Thailand (HE 641173) (Approved on 22 March 2021).

Outcome and measurement

PHLF was diagnosed based on definition and grading of PHLF proposed by the international study group of liver study (ISGLS) (Rahbari et al., 2011). The inter-rater reliability tests showed good reliability (ICC = 0.60 and 0.77, respectively). Patients' outcome after liver resection was assessed and recorded the personal data record form, which was reviewed by three experts in hepatobiliary. The content validity was assessed using index of item-objective congruence and acceptable value was obtained (IOC= 0.97).

Statistical analysis

The study data were analyzed using SPSS (version 26) (KKU Microsoft Campus License). Categorical variables were expressed as frequencies and percentages, and continuous variables were represented as means ±standard deviation (SD) and medians with quartile range (Q1-Q3). Univariable analysis was performed using simple logistic regression, and multivariable analysis was performed by multiple logistic regression with forwarding stepwise (Likelihood ratio) method used for defining factors associated and predicted post hepatectomy liver failure. Factors with statistical significance (P-value < 0.05) on univariable analysis were included in the multivariable model, a multicollinearity test was applied to independent factors, adjusted odds ratio (Adjusted OR) and 95% confidence intervals (95% CI) apply for reported as a result.

Results

A total of 480 cases were included in this study. They were predominantly male (66%), their mean age was 62.11 years (SD 9.14). The participants' mean body mass index (BMI) was 22.07 (SD 3.06) kg/m2. The majority of the participants were diagnosed with intrahepatic CCA (64.58%) and had no comorbidity (76.04%), abnormality of the liver before the operation (94.79%), and cholangitis before the operation. Cirrhosis of the liver was the most frequent abnormality in the patients before undergoing surgery (2.92%). Endoscopic nasobiliary drainage (ENBD) was the most common preoperative procedure in the patients prior undergoing liver resection (6.67%). Fourteen patients (2.92%) had preoperative neoadjuvant chemotherapy. Regarding liver function status, 28 patients (5.83%) were diagnosed with indocyanine green retention ratio at 15 minutes (ICGR-15) before liver resection. Before operation, most of the patients (83.33%) had the

Child-Turcotte-Pugh grade A. Approximately, half of the patients (46.46%) received right hepatectomy. The patients' characteristics are shown in details in Table 1.

Table 1. Characteristics of the 480 Study Patients

Characteristics	No. (%)
Gender	
Male	317 (66.00)
Female	163 (34.00)
Age (mean 62.11, SD 9.14)	
≤ 60 years	175 (36.46)
≥ 60 years	305 (63.54)
Body mass index (mean 22.07, SD 3.06)	
< 30 kg/m^2	433 (98.54)
≥ 30 kg/m^2	7 (1.46)
Type of cholangiocarcinoma	
Intrahepatic CCA	310 (64.58)
Perihilar CCA	167 (34.79)
Perihilar and distal CBD CCA	3 (0.63)
Comorbidities	
Diabetes mellitus	33 (6.88)
Hypertension	42 (8.75)
Diabetes mellitus and hypertension	40 (8.33)
None	365 (76.04)
Liver abnormalities	
Cirrhosis	14 (2.92)
Fatty liver disease	6 (1.25)
Liver abscess	5 (1.04)
None	455 (94.79)
Cholangitis before operation	
Having	29 (6.04)
None	451(93.96)
Preoperative biliary drainage	
Percutaneous Transhepatic Biliary (PTBD)	72 (15)
Endoscopic Nasal Bile Drainage (ENBD)	32 (6.67)
Internal stent	9 (1.88)
None	367 (76.45)
Neoadjuvant	
Received	14 (2.92)
None	466 (97.08)
ICGR-15 level before operation	
Testing	28 (5.83)
None	452 (94.16)
Child-Turcotte-Pugh grading	
Grade A	400 (83.33)
Grade B & C	80 (16.67)
Type of liver surgery	
Extend right hepatectomy	78 (16.25)
Extend left hepatectomy	28 (5.83)
Right hepatectomy	223 (46.46)
Left hepatectomy	151 (31.46)

CCA, cholangiocarcinoma; CBD, common bile duct; ICGR-15, indocyanine green retention ratio at 15 minutes

Factors related to post-hepatectomy liver failure

Based on our findings, 185 patients (38.5%) developed PHLF. In terms of severity, 104 patients experienced grade A of PHLF (56.22%), 68 grade B (36.76%), 13 grade C (7.02%). Following univariable analysis, 17 factors related to PHLF with a p-value < 0.05 were identified. Serum direct bilirubin (OR 38.14, 95% CI 17.08-85.17; P < 0.001), serum total bilirubin level (OR 25.28, 95% CI 14.42-44.34; P < 0.001), Child-Turcotte-Pugh grade (OR 17.35, 95% CI 8.64-34.83; P < 0.001), and preoperative biliary drainage (OR 8.11, 95% CI 5-13.16; P < 0.001) were identified as four risk facors of PHLF. In contrast, based on our findings, patients younger than 60 years had significantly decreased risk of PHLF (OR 0.65, 95% CI 0.44-0.95; P = 0.025). A few samples were found for neoadjuvant chemotherapy and ICGR-15 level and maybe not be feasible to evaluate their associated effect on PHLF. Results on factors related to post- hepatectomy liver failure are shown in Table 2.

Predictive factors of post-hepatectomy liver failure

Following univariable analysis and multicollinearity checking, 14 significant independent variables were included in multiple logistic regression model. Three multicollinearity independent variables (direct bilirubin, ALT, and PT) were excluded. The model showed that total bilirubin level (adjusted OR = 14.07, 95% CI = 7.54-26.27, P < 0.001), Child-Turcotte-Pugh grade (adjusted OR = 3.34, 95% CI = 1.43-7.81, P = 0.005), total blood transfusion (adjusted OR = 2.32, 95% CI = 1.19-4.54, P = 0.014), and operation time (adjusted OR = 1.77, 95% CI = 1.05-2.97, P = 0.031) remained as statistically significant risk factors of post-hepatectomy liver failure (Table 3). To create an equation to predict the chance of post-hepatectomy liver failure, it can be done in the intersection point at 0.5 by the predictive equation as : P (Y = 1) = 1/1-e-w. In the predictive equation, a function of predictive factors (w) = -1.893 + 2.644 (XTB) + 1.205 (XCTP grade) + 0.842 (Xtotal blood transfusion) + 0.570 (Xoperation time), X = 1 when an independent variable has a value in Table 3, X = 0 for any values. Accordingly, evaluated ability of predictive equation performed with predicted factors, retested with a sample for positive predictive value (PPV) 86.03%, negative predictive value (NPV) 80.23%, and the accuracy 81.88%.

Discussion

The finding of this study revealed that around 38% of patients who underwent liver resection suffered from PHLF, which was similar to the incidence of post-hepatectomy liver failure worldwide (Rahnemai-Azar et al., 2018; Liu et al., 2020). Our results revealed four predictors of PHLF in patients with CCA, namely total bilirubin levels, CTP grade, total blood transfusion, and operation time.

Serum total bilirubin levels greater than 1.2 mmol/dl increased the risk of PHLF. This finding could be explained by the fact that liver breaks down substances like bilirubin

Table 2. Factors Related to Post-Hepatectomy Liver Failure in Patients with Cholangiocarcinoma with Respect to Univariable Analysis (n = 480)

Factors	PHLF (n = 185) (%)	Non-PHLF (n = 295) (%)	OR (95% CI)	P value
Gender, Male	129 (40.69)	188 (59.31)	1.31 (0.89-1.94)	0.177
Age > 60 years	106 (34.75)	199 (52.55)	0.65 (0.44-0.95)	0.025*
Body mass index > 30 kg/m^2	5 (71.43)	2 (28.57)	4.07 (0.78-21.20)	0.096
Type of CCA				
extrahepatic CCA	109 (64.12)	61 (35.88)	5.50 (3.66-8.26)	< 0.001*
Type of liver surgery				
extend hepatectomy	58 (54.72)	48 (45.28)	2.35 (1.52-3.64)	< 0.001*
Comorbidities (DM, HT)	50 (43.48)	65 (56.52)	1.31 (0.86-2.01)	0.213
Liver abnormalities	11(44)	14(56)	1.27 (0.56-2.86)	0.565
Preoperative biliary drainage	85 (75.22)	28 (24.78)	8.11 (5-13.16)	< 0.001*
Cholangitis	18 (62.07)	11 (37.93)	1.65 (0.96-2.83)	< 0.001*
CTP grading (Grade B, C)	70 (87.5)	10 (12.5)	17.35 (8.64-34.83)	< 0.001*
Operation time > 300 min	146 (46.65)	167 (53.35)	2.87 (1.88-4.37)	< 0.001*
Total blood loss > 1,000 ml.	27 (67.5)	13 (32.5)	3.71 (1.86-7.39)	< 0.001*
Total blood transfusion > 500 ml.	44 (62.86)	26 (37.14)	3.23 (1.91-5.46)	< 0.001*
Neoadjuvant (n = 14)	4 (28.57)	10 (71.43)	1.36 (0.50-3.67)	0.545
ICGR-15	16 (57.14)	12 (42.86)	1.04 (0.92-1.16)	0.556
Albumin < 3.5 g/dl	48 (58.54)	34 (41.46)	2.69 (1.66-4.37)	< 0.001*
Total bilirubin > 1.2 mg/dl	115 (86.47)	18 (13.53)	25.28 (14.42-44.34)	< 0.001*
Direct bilirubin > 0.5 mg/dl	89 (92.70)	7(7.30)	38.14(17.08-85.17)	< 0.001*
ALT > 36 (U/L)	119 (50.42)	117 (49.58)	2.74 (1.88-4.01)	< 0.001*
AST > 32 (U/L)	118 (55.40)	95 (44.60)	3.71 (2.52-5.46)	< 0.001*
ALP > 121 (U/L)	146 (47.40)	162 (52.60)	3.07 (2.02-4.68)	< 0.001*
PT > 12.1 sec	87 (59.59)	59 (40.41)	3.55 (2.34-5.33)	< 0.001*
INR > 1.2	61 (69.32)	27 (30.68)	4.88 (2.96-8.06)	< 0.001*

OR, odd ratio; CI, confidence interval; CCA, cholangiocarcinoma; DM, diabetic mellitus, HT, hypertension, CTP grading, Child-Turcotte-Pugh grading; ICGR-15, indocyanine green retention ratio at 15 minutes, ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; PT, prothrombin time; INR, international normalized ratio; * p value < 0.05

Table 3. The Predictive Factors of Post-Hepatectomy Liver Failure in Patients with Cholangiocarcinoma with Respect to Multiple Logistic Regression Analysis Using Forward Stepwise Method (Likelihood ratio) (N = 480)

Factor	OR	95% CI	P value
TB			
> 1.2 mg/dl	14.07	7.54-26.27	< 0.001*
< 1.2 mg/dl	1		
CTP			
grading B, C	3.34	1.43-7.81	0.005*
grading A	1		
Total blood transfusion			
≥ 500 ml.	2.32	1.19-4.54	0.014*
< 500 ml.	1		
Operation time			
> 300 min.	1.77	1.05-2.97	0.031*
< 300 min.	1		

OR, odd ratio; CI, interval confidence; TB, total bilirubin; CTP, Child-Turcotte-Pugh; * P value < 0.05

from heme to the urinary and digestive system. Thus, hyperbilirubinemia is caused by obstruction of the intrahepatic or extrahepatic bile tract, leading to bilirubin congestion within the liver. As a result, an inflammatory reaction is activated, hence kupffer cells are destroyed. Moreover, hyperbilirubinemia indicates the ineffective function of liver in the pre-operative phase, which leads to reduced liver remnant recovery and an increased risk of liver failure after liver resection (van Mierlo et al., 2016). This result was consistent with two previous studies reporting that serum total bilirubin levels correlated with PHFL and could predict the occurrence of PHFL (Adjust OR= 4.29, 95 % CI = 1.72-10.73, P < 0.001) (Olthof et al., 2017) and the reporting by Wang et al (2018) (Adjust OR = 11.014, 95 % CI = 1.00-1.03 P = 0.17).

Child-Turcotte-Pugh grades B and C were associated with a higher risk of PHLF than grade A. This result could be used to estimate the severity of liver disease correlated with mortality rate. Similarly, a previos study showed that higher CTP grades could predict greater liver degeneration and loss of function in synthesis, excretion, and detoxification (Tsoris and Marlar, 2022). We found that CTP grades B and C increased the risk of liver

failure in concordance with the findings of a study done by Zheng et al., (2017). Zheng et al., (2017) yielded that 35 out of 40 patients of CTP grade B experienced PHLF. CTP had a significant correlation with PHFL (r = 0.43, P = 0.005), thus CTP can be used as prognosis predictors in PHLF patients.

The current study showed that receiving a blood transfusion of 500 ml. or more during liver surgery significantly increased the risk of PHLF. It is possible that receiving a blood transfusion may lead to exogenous bacterial infection and immunosuppression, ultimately resulting in a higher risk of infection after surgery and PHFL occurrence (Rahnemai-Azar et al., 2018). Similarly, previous studies indicated that receiving a blood transfusion during an operation significantly increased the risk of PHFL (Lee et al., 2017; Arisaka et al., 2020).

In addition, this study found that operation time could be regarded as a factor significantly associated with risk of developing PHLF. Those with a longer operation time of at least 300 minutes had higher risk of liver failure after hepatectomy. Findings of this study revealed that an operation time of 300 minutes or more was associated with a greater risk of post-hepatectomy liver failure. The duration of liver necrosis depends on the length of inflow occlusion, hepatectomy technique, and the time to reduce the blood pressure during surgery. A longer duration led to a higher chance of hepatic ischemia and hepatic hypoxia during surgery according to a previous study (Rahnemai-Azar et al., 2018)

Although the severity of PHLF (grades B and C) was associated with higher mortality rate, cases with grade A PHLF can also experience severe PHLF after liver resection. Therefore, patient monitoring and health education are necessary to remove risk factors in the pre-operative phase and consequently to prevent PHFL incidence. In addition, it was fund that the operation time of less than 300 minutes decreased the risk of PHFL in the intra-operative phase. Moreover, early detection, notification, and management in the post-operative phase can help decrease the severity of PHLF and morbidity rate in patients with CCA.

Author Contribution Statement

WK and BS contributed in study design, WK and BS performed data interpretation, analysis, and visualization. WK and AT collected and provided the clinical data. WK, BS, and PW drafted the first manuscript. All authors made substantial contributions, including interpretations of the findings and critical revisions of the manuscript. Before submission, the final version of the manuscript was approved by all authors.

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Ethical Declaration

The study was approved by the Center for Ethics in Human Research, Khon Kaen University, Khon Kaen, Thailand (HE641173) (Approved on 22 March 2021). This retrospective study adhered to Helsinki Declaration ethical principles and obtained permission from Srinagarind hospital in Khon Kaen, Thailand, Cholangiocarcinoma Research Institute (CARI).

Conflict of Interest

The authors have no conflicts of interest to declare.

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