Original Article

Validation study of postoperative liver failure and mortality risk scores after liver resection for perihilar cholangiocarcinoma

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Background: Surgery for perihilar cholangiocarcinoma (PHCC) remains a challenging procedure with high morbidity and mortality. The Academic Medical Center (Amsterdam UMC) and Memorial Sloan Kettering Cancer Center proposed a postoperative mortality risk score (POMRS) and post-hepatectomy liver failure score (PHLFS) to predict patient outcomes. This study aimed to validate the POMRS and PHLFS for PHCC patients at Hokkaido University.

Methods: Medical records of 260 consecutive PHCC patients who had undergone major hepatectomy with extrahepatic bile duct resection without pancreaticoduodenectomy at Hokkaido University between March 2001 and November 2018 were evaluated to validate the PHLFS and POMRS.

Results: The observed risks for PHLF were 13.7%, 24.5%, and 39.8% for the low-risk, intermediate-risk, and high-risk groups, respectively, in the study cohort. A receiver-operator characteristic (ROC) analysis revealed that the PHLFS had moderate predictive value, with an analysis under the curve (AUC) value of 0.62. Mortality rates based on the POMRS were 1.7%, 5%, and 5.1% for the low-risk, intermediate-risk, and high-risk groups, respectively. The ROC analysis demonstrated an AUC value of 0.58.

Conclusions: This external validation study showed that for PHLFS the threshold for discrimination in an Eastern cohort was reached (AUC >0.6), but it would require optimization of the model before use in clinical practice is acceptable. The POMRS were not applicable in the eastern cohort. Further external validation is recommended.

Keywords: Perihilar cholangiocarcinoma (PHCC); post operative mortality score; post-hepatectomy liver failure score (PHLFS); validation study

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Introduction

Surgery for perihilar cholangiocarcinoma (PHCC) is challenging because of its high morbidity and mortality despite elaborate multidisciplinary perioperative management (1,2). Morbidity and mortality rates after surgery for patients with PHCC have been reported to range from 26% to 68% and 1.4% to 18%, respectively,

Table 1 Five risk factors and assigned points in PHCC patients based on the AMC/MSKCC scoring system

Variables	Points	All patients, N=254; n [%]	90-day mortality, N=11; n [%]	P
Age				0.902
<50 years	0	7 [3]	0	
50–59 years	1	27 [11]	1 [9]	
60–69 years	2	101 [40]	4 [36]	
70–79 years	3	111 [44]	6 [55]	
≥80 years	4	8 [3]	0	
Preoperative cholangitis				1.00
No	0	158 [62]	7 [64]	
Yes	2	96 [38]	4 [36]	
FLRV <30%				0.085
No	0	252 [99]	10 [91]	
Yes	1	2 [1]	1 [9]	
Incomplete drainage + FLR <50%				NA
No	0	254 [100]	11 [100]	
Yes	1	0	0	
Portal vein reconstruction				0.216
No	0	126 [49]	3 [27]	
Yes	1	128 [51]	8 [83]	

PHCC, perihilar cholangiocarcinoma; AMC/MSKCC, Academic Medical Center/Memorial Sloan Kettering Cancer Center; FLR, future liver remnant; NA, not assessed.

thus exceeding those of other hepato-biliary procedures (2). Previous reports have shown that post-hepatectomy liver failure (PHLF) is a common and serious complication, with a reported incidence of 22% to 33% and high mortality rates of 52% to 68% (3-6). Patients with PHCC usually have obstructive cholestasis and ultimately, jaundice due to the location of the tumour at the liver hilum (7-9). Cholestasis impairs the regenerative capacity of the liver after resection, which increases surgical risk, especially when the future liver remnant (FLR) volume (FLRV) is small (6,10,11). Therefore, it is essential to select candidates for PHCC surgery based not only on the tumour status but also on the patients' preoperative condition.

In 2016, two Western high-volume centres for PHCC [the Academic Medical Center of Amsterdam UMC (AMC) and the Memorial Sloan Kettering Cancer Center (MSKCC) in New York] proposed a postoperative mortality risk score (POMRS) for PHCC (12). They evaluated 228 PHCC patients and determined that postoperative mortality at 90 days was independently predicted by age, preoperative cholangitis, FLRV <30%, portal vein reconstruction (PVR), and incomplete FLRV drainage in patients with a FLRV volume <50% (*Table 1*). In 2017, the same team also proposed a PHLF risk score (PHLFS) (3). They evaluated a consecutive series of 217 patients who underwent major liver resection for PHCC. They showed that the risk factors for PHLF were FLRV volume <30% (small), FLRV of 30% to 45% (intermediate volume), jaundice at presentation, immediate preoperative bilirubin >50 mmol/L (>2.9 mg/dL), and preoperative cholangitis (*Table 2*). However, no external validation studies for both the POMRS and PHLFS have been reported.

Previous studies have reported significant differences in treatment and outcomes of Western (e.g., Europe, Northern America) and (South-East) Asian centres (e.g., Japan, Korea, and China) (2). To determine the differences

Table 2 Risks predicted by the PHLF risk score of Hokkaido University and AMC/MSKCC

Group	Total points	Hokkaido University			AMC/MSKCC		
		Number of patients/PHLF	Predicted risk of PHLF (%)	Observed PHLF rate (%)	Number of patients (%)	Predicted risk of PHLF (%)	Observed PHLF rate (%)
Low risk	0	40/6	4	13.7	34	4	5
	1	11/1			10	7	
Intermediate risk	2	81/17	14	24.5	44	12	14
	3	29/10			20	20	
High risk	4	65/22	44	39.8	53	33	44
	5	27/14			18	48	
	6	1/1			11	64	
	7	0			1	67	
	8	0			7	87	

PHLF, post-hepatectomy liver failure; AMC/MSKCC, Academic Medical Centre/Memorial Sloan Kettering Cancer Center.

between Western and Asian PHCC treatments, we recently performed a comparative study (13). This study showed, despite more aggressive surgery (with concomitant vascular resection) undertaken in the Asian cohort, that the 90-day mortality rate was lower (Asian cohort, 7%; Western cohort, 14%; P=0.066). This discrepancy could be explained by differences in patients' characteristics, such as the American Society of Anaesthesiologists (ASA) score, use of preoperative biliary drainage, and indication for portal vein embolization (PVE).

The results also raised the clinical question whether the PHLFS and POMRS, which were established based on Western-centre cohorts with patient backgrounds different from those in Asia, can be applied to a cohort of a South-East Asian-centre. The objective of this study was to validate the POMRS and PHLFS for PHCC patients at Hokkaido University, which is a high-volume centre for PHCC in Japan. We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-660/rc).

Methods

Ethics

The study was approved by the institutional review board of Hokkaido University (No. 018-0429) and conducted according to the Declaration of Helsinki (as revised in 2013). It was registered at the UMIN-CTR (No. UMIN000036229).

Data collection

This retrospective study was conducted from March 2019 to June 2019.

Patients

The PHLFS and POMRS were validated for 260 consecutive PHCC patients subjected to major hepatectomy with extrahepatic bile duct resection without pancreaticoduodenectomy at Hokkaido University, Dept. of Gastroenterological Surgery II between March 2001 and November 2018.

Control group

To compare with previous results of the PHLFS and POMRS, we referred to published data of AMC/MSKCC's PHLFS and POMRS (3,12).

Preoperative diagnosis

The details of preoperative diagnosis of PHCC have been described previously (6,7,14,15). The diagnosis of PHCC was based on clinical presentation, imaging studies using enhanced computed tomography (CT), magnetic resonance imaging (MRI), direct cholangiography, and biopsy.

Biliary drainage

Biliary drainage procedures have been described in previous reports (7). The aim of preoperative biliary drainage at Hokkaido University was complete drainage of the FLRV. All PHCC patients had undergone surgery with complete drainage of the FLRV at Hokkaido University (6). Preoperative biliary decompression was performed to reduce the serum bilirubin concentration to <2 mg/dL in all patients with jaundice and to control segmental cholangitis. Before 2005, single or multiple percutaneous transhepatic biliary drainage (PTBD) was performed (14). As of 2005, selective single or double endoscopic naso-biliary drainage (ENBD) of the FLR was adopted as the initial drainage procedure. Additional second ENBD catheters were placed to drain the biliary tree in future remnant livers that were not decompressed by the first catheter or to control cholangitis when this occurred. Alternatively, PTBD was used when drainage with ENBD was not effective or if a third catheter was required (16).

Cholangitis

Preoperative cholangitis was defined when all of the following criteria were fulfilled: fever with body temperature higher than 38 ℃, decrease of temperature after new placement of a drainage catheter, and/or liver abscess formation with fever.

Assessment of the remnant liver function, portal vein embolization, and surgical indications

Liver function of all patients was evaluated preoperatively using methods similar to those used by the Nagoya University group (17). To evaluate whole liver function, an indocyanine green (ICG) regression test was performed before surgery (6). The plasma disappearance rate of ICG (ICGK) was calculated using a linear regression analysis of plasma ICG concentration, as previously described (6,17). FLR plasma clearance rate of ICG (ICGK-F) values were calculated by multiplying ICGK by the proportion of the FLRV. The proportion of the FLRV was calculated by CT-volumetry, which was also performed preoperatively.

Preoperative PVE of the liver lobe to be resected was indicated when subsequent right hepatectomy, right trisectionectomy, or left trisectionectomy was planned (15,18). Methods for PVE at our institution have been described previously (19). Two or 3 weeks after PVE, the ICGK-F was re-evaluated and surgery was performed. When the ICGK-F value did not fulfil the Nagoya criteria (≥0.05) (17), surgery was postponed.

Surgery

The surgical procedures for PHCC have been described previously (14,18,20,21). Briefly, radical resection included en bloc excision of the liver hilum with (extended) hemi-hepatectomy, including the caudate lobe in most cases, complete lymphadenectomy of the hepatoduodenal ligament, and excision and reconstruction of each or both the portal vein and hepatic artery if necessary. The portal vein was reconstructed by HPB surgeons; however, the hepatic artery was reconstructed by plastic surgeons (until 2015) or cardiovascular surgeons (from 2016 to present).

Definition of complications

Postoperative complications consistent with Clavien-Dindo classification ≥ IIIa were defined as morbidity (22). Ninety-day in-hospital death after surgery was defined as mortality. PHLF was defined as International Study Group of Liver Surgery (ISGLS) grade B or C (23).

Statistical analysis

Statistical calculations were performed using JMP version 14 (SAS, Cary, NC, USA), and statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) and R version 2.15.3 (http://www.r-project.org/) software packages.

The chi-square test, Fisher's exact test, and Mann-Whitney U test were used as appropriate. P<0.05 was considered significant. To develop POMRS and PHLFS at Hokkaido University, cases were calculated based on the statistical methods previously used by AMC/MSKCC. The AUC value was calculated to estimate how well the model discriminated between patients with and without postoperative mortality or PHLF.

Results

Six patients were excluded from the study because of missing preoperative liver volume data; thus, 254

Table 3 Patient characteristics in univariate analysis of post hepatectomy liver failure (PHLF) in the Hokkaido University series

Characteristics	Hokkaido University				AMC/MSKCC 2017 (PHLFS)	
	All patients (n=254)	Without PHLF (n=183)	With PHLF (n=71)	P value	Without PHLF (n=165)	With PHLF (n=52)
Sex (male/female) n [%]	176 [69]/78 [31]	129 [70]/54 [30]	47 [66]/24 [34]	0.506	106 [64]/59 [36]	40 [77]/12 [23]
Age (years); median [range]	68 [43–86]	68 [43–86]	69 [48–79]	0.313	64 [56–70]	66 [48–79]
Body mass index; median [range]	22.0 [14.3–32.7]	22.0 [14.3–32.7]	21.9 [16.7–30.7]	0.780	25 [23–28]	25 [22–27]
FLRV (mL); median [range]	602 [295–1,427]	666 [305–1,427]	556 [295–1,040]	<0.001	–	–
FLRV (%); median [range]	54.6 [22–95.4]	61.6 [31.3–95.4]	49.1 [22–85.2]	<0.001	60 [34–75]	37 [26–61]
Large (>45%); n [%]	185 [73]	141 [77]	44 [62]	0.008	–	–
Intermediate (30–45%); n [%]	67 [26]	42 [23]	25 [35]		–	–
Small (<30%); n [%]	2 [1]	0	2 [3]		–	–
Jaundice (yes/no); n [%]	199 [78]/55 [22]	136 [74]/47[26]	63 [89]/8 [11]	0.012	109 [66]/56 [34]	46 [88/6[12]
FLR drainage (complete/incomplete); n	254/0	183/0	71/0	NA	–	–
Preoperative cholangitis (yes/no); n [%]	96 [38]/158 [62]	59 [32]/124 [68]	37 [52]/34 [48]	0.004	37 [22]/128 [78]	28 [54]/24 [46]
Preoperative PVE (yes/no); n [%]	117 [46]/137 [54]	68 [37]/115 [63]	49 [69]/22 [31]	<0.001	–	–
Type of liver resection; n [%]						
Central	1	0	1	<0.001	1	1
Left (Ex)	109 [43]	96 [52]	13 [18]		65 [27]	11 [6]
L3	17 [7]	10 [5]	7 [10]		–	–
Right (Ex)	115 [45]	71 [39]	44 [62]		24 [48]	8 [26]
R3	12 [5]	6 [3]	6 [8]		–	–
Operative time (min); median [range]	681 [385–1,252]	663 [385–1,127]	732 [479–1,252]	<0.001	–	–
Operative bleeding (mL); median [range]	1670 [390–40,070]	1500 [390–10,735]	2210 [780–40,070]	<0.001	–	–
Portal vein reconstruction (yes/no); n [%]	128 [51]/126 [49]	84 [46]/99 [54]	44 [62]/27 [38]	0.021	24 [15]/141 [85]	14 [27]/38 [73]
Hepatic artery reconstruction (yes/no); n [%]	32 [13]/222 [87]	23[13]/160 [87]	9 [13]/62 [87]	0.982	–	–

Values are presented as n or median (range in Hokkaido University; and interquartile range in PHLFS). "–"; not shown; PHLF, post hepatectomy liver failure; FLRV, future liver remnant volume; FLR, future liver remnant; PVE, portal vein embolization; central, central hepatectomy; left, left hepatectomy; L3, left trisectionectomy; right, right hepatectomy; R3, right trisectionectomy; Ex, extended hepatectomy including trisectionectomy; AMC, Academic Medial Center; MSKCC, Memorial Sloan Kettering Cancer Center; PHLFS, post hepatectomy liver failure score (Olthof *et al.* 2017).

patients with PHCC were included in the analysis. The postoperative pathological examination confirmed PHCC in all 254 patients. *Table 3* shows the characteristics of the patients involved in this study and the characteristics of patients with or without PHLF.

The preoperative status, such as FLRV (percentage or volume), jaundice at presentation, and preoperative cholangitis, as well as intraoperative factors, such as PVR, longer operative time, and/or higher volume of operative bleeding, were associated with PHLF (*Table 3*). The incidence of PHLF was almost similar in the AMC/MSKCC and Hokkaido University cohorts (i.e., 24% and 28%, respectively; P=0.345). None of the patients in the Hokkaido University cohort had preoperative bilirubin levels exceeding 50 μmol/L (2.9 mg/dL).

The risks predicted by the PHLFS for the AMC/

MSKCC and Hokkaido University cohorts are shown in *Table 2*. The predicted risk score for the Hokkaido University cohort was almost the same as that of the AMC/MSKCC cohort; the observed risks for PHLF in the Hokkaido University cohort were 13.7%, 24.5%, and 39.8% for the low-risk, intermediate-risk, and high-risk groups, respectively. Receiver-operator characteristic (ROC) analysis revealed that the PHLFS had moderate predictive value, as demonstrated by an analysis of the AUC value of 0.62 for PHLF in the Hokkaido University cohort.

Next, we evaluated POMRS. The univariate analysis revealed that FLRV, operative time, operative bleeding, and PHLF influenced 90-day mortality in the Hokkaido University series (*Table 4*). However, patient age, preoperative cholangitis, and PVR, which were independent risk factors for 90-day mortality in the POMRS, were not associated with 90-day mortality in the Hokkaido University cohort (*Table 1*). Mortality rates based on POMRS in this cohort were 1.7%, 5%, and 5.1% for the low-risk (n=59), intermediate-risk (n=120), and high-risk (n=75) patients, respectively (*Table 5*). The ROC analysis revealed that the POMRS was not useful for predicting the 90-day mortality in the Hokkaido University cohort, as demonstrated by an AUC value of 0.58.

Discussion

In this study, the PHLFS and POMRS, which were established in Western high-volume centres for PHCC, were validated in an Asian cohort. The results showed that the PHLFS was only partially represented in the South-East Asian, high volume centre cohort whereas the POMRS was not applicable in this cohort.

PHLF is the most severe, life-threatening complication after PHCC surgery (2,3,8). Although there were differences in patient and treatment characteristics in the Asian and Western cohorts, as determined previously (12), the present study showed that the incidences of PHLF were similar in both groups. A previous systematic review also supports this result (2).

The finding that this validation study did not completely reproduce previous results is possibly explained by several factors. First, amongst the four risk factors of PHLFS, jaundice at presentation and preoperative cholangitis were also risk factors for PHLF in the Hokkaido University cohort. However, the other two risk factors, FLRV <30% and immediate preoperative bilirubin >50 µmol/L (2.9 mg/dL), were not identified as risk factors. Very few patients had FLRV <30% (2/254) and none had an immediate preoperative bilirubin level >50 µmol/L (2.9 mg/dL) at Hokkaido University. As mentioned above, preoperative biliary drainage was performed routinely in jaundiced patients, and surgery for PHCC was not performed for patients with an preoperative bilirubin level >34.2 µmol/L (2 mg/dL) at Hokkaido University. Second, PVR was one of the risk factors in the Hokkaido University cohort, but it was not a risk factor in the PHLFS. PVR is associated with longer operative times and higher volumes of operative blood loss, which could be associated with PHLF. Third, PVE was associated with PHLF in the Hokkaido University cohort (*Table 3*). In general, PVE is also associated with a small future remnant liver and the type of hepatectomy, and such patients are also at higher risk for PHLF (6,15). Therefore, high-risk patients are under-represented in many high volume Asian centres including Hokkaido University (1), and these differences between Asia and the West potentially lead to a relatively lower AUC level (0.62).

One important problem is the lack of a definitive definition of PHLF for PHCC surgery (6,24). Recently, Kawamura *et al*. reported that the ISGLS criteria are inferior to other grading systems for PHLF after PHCC surgery, such as the maximum total bilirubin level criteria (maximum total bilirubin level >7 mg/dL on postoperative day 7), 3-4-50 criteria (total bilirubin >4 mg and prothrombin time <50% on postoperative day 3), and 50-50 criteria for predicting PHLF-related mortality (6). This study showed that when PHLF was defined using the ISGLS criteria for PHCC surgery, it showed high sensitivity but had low specificity for PHLF-related death. This was also shown in our results presented in *Table 2*. It appears that the PHLFS underpredicted PHLF in the low and intermediate risk groups in the Hokkaido cohort, but was predictive in the high risk. Although the reasons for this discrepancy are uncertain, we suspect that the use of the ISGLS criteria led to false positive cases in patients with low or intermediate risk. Furthermore, because there are significant differences between regular hepatectomies and large resections for PHCC—the latter requiring major hepatectomy with extra-hepatic bile duct resection and lymphadenectomy (25,26)—further validation studies using a modified PHLF definition are needed to confirm the usefulness of the PHLFS.

The POMRS consisted of five patient characteristics: age, preoperative cholangitis, FLRV (<30%), incomplete drainage + FLRV <50%, and PVR (12); however, these risk

Table 4 Univariate analysis of 90-day mortality in the Hokkaido University series

Characteristics	Hokkaido University			AMC/MSKCC 2015 (POMRS)	
	No 90-day mortality (n=243)	90-day mortality (n=11)	P	No 90-day mortality (n=247)	90-day mortality (n=40)
Sex (male/female), n [%]	171 [70]/75 [30]	8 [83]/3 [27]	0.821	151 [61]/96 [39]	31[78]/9[22]
Age (years)	68 [43–86]	69 [56–79]	0.478	61.9 ±10.9	67.4±10.6
<50, n [%]	7 [3]	6 [55]	0.903	–	–
50–59, n [%]	26 [11]	1 [9]		–	–
60–69, n [%]	97 [40]	4 [36]		–	–
70–79, n [%]	105 [43]	6 [55]		–	–
≥80, n [%]	8 [3]	0		–	–
Body mass index	21.9 [14.3–32.7]	23.1 [19.6–27.3]	0.198	–	–
FLRV (mL)	613 [300–1,427]	522 [295–730]	0.071	–	–
FLRV (%)	55.8 [28.5–95.4]	48.7 [22–64.6]	0.035	–	–
Large (>50%), n [%]	142 [58]	4 [36]	<0.001	105 [51]	10 [29]
Intermediate (30–50%), n [%]	100 [41]	6 [55]		66 [32]	10 [29]
Small (<30%), n [%]	1 [0.4]	1 [9]		37 [18]	15 [43]
Jaundice (yes/no), n [%]	188 [77]/55 [23]	11 [100]/0	0.128	202 [82]/47 [18]	–
FLR drainage, n [%] (complete/incomplete)	243 [100]/0	11[100]/0	NA	150 [72]/58 [28]	23 [66]/12 [34]
Preoperative cholangitis (yes/no), n [%]	92 [38]/151 [62]	4 [36]/7 [64]	1.00	49 [20]/193 [80]	10 [29]/25 [71]
Type of liver resection, n [%]					
Central	1 [0.4]	0	0.171	3 [1]	3 [1]
Left/Ext	107 [44]/0	2 [18]/0		90 [36]/31 [13]	12 [30]/5 [13]
L3	16 [2]	1 [9]		–	–
Right/Ext	109 [45]/0	6 [55]/0		40 [16]/83 [34]	6 [15]/17 [43]
R3	10 [4]	2 [18]		–	–
Operative time (min)	665 [385–1,252]	844 [607–1,250]	<0.001	–	–
Operative bleeding (mL)	1,550 [390–1,590]	3850 [2004–40,070]	<0.001	–	–
Portal vein reconstruction (yes/no), n [%]	120 [49]/123 [51]	8 [83]/3[27]	0.126	51[18]/236[82]	11[28]/29 [72]
Hepatic artery reconstruction (yes/no), n [%]	30 [12]/213 [88]	2 [18]/9 [82]	0.634	–	–
PHLF (yes/no), n [%]	62 [25]/181 [75]	9 [82]/2 [18]	<0.001	–	–

Values are presented as n or median [range]. NA, not assessed; FLRV, future liver remnant volume; FLR, future liver remnant; central, central hepatectomy; left, left hepatectomy; L3, left trisectionectomy; right, right hepatectomy; R3, right trisectionectomy; PHLF, post-hepatectomy liver failure.

Table 5 Risks predicted by the mortality risk scores determined in the Hokkaido University series and in the AMC/MSKCC series

Group	Total points	Hokkaido University				AMC/MSKCC 2015		
		n [%]	90-day mortality (n)	Predicted mortality risk [%]	Observed mortality rate [%]	n [%]	Predicted risk [%]	
Low risk	0	2 [1]	0	2	1.7	4 [2]	1	2
	1	15 [6]	0			23 [9]	2	
	2	42 [17]	1			45 [19]	3	
Intermediate risk	3	76 [30]	3	11	5.0	60 [25]	6	11
	4	44 [17]	3			55 [23]	14	
High risk	5	39 [15]	3	37	5.1	34 [14]	28	37
	6	34 [13]	1			16 [7]	47	
	7	2 [1]	0			5 [2]	67	
	8	0	0			1	82	
	9	0	0			0	NA	
Total		254	11		4.3	243	14	

AMC/MSKCC, Academic Medical Center/Memorial Sloan Kettering Cancer Center.

factors did not influence 90-day mortality in the present study. Therefore, this validation study could not reproduce the usefulness of the POMRS in the Hokkaido cohort. This may be explained by differences in the criteria for resection applied in Asia and the West. Very few patients (2/254) had FLRV <30% and none had incomplete drainage + FLRV <50% in the Hokkaido cohort. However, in the original Western study, 21% of the patients had FLRV <30% and 9% patients had incomplete drainage + FLRV <50%, while the mortality rates for these patients were 23% and 19%, respectively (12).

It is interesting that although both PVR and cholangitis were associated with PHLF in the Hokkaido University cohort (*Table 2*), these factors were not associated with 90-day mortality (*Table 1*). Possible reasons why these factors were not associated with 90-day mortality are active application of PVE and complete biliary drainage achieved in the Hokkaido cohort. Several previous reports showed that PVE contributed to an increase of FRLV, and that sustained cholangitis burdened liver regeneration (26,27). While previous reports showed that PHLF was associated with a mortality rate of approximately 50% (2,3), the present data showed lower mortality rates. As some authors have suggested, although PVE does not decrease the incidence of PHLF as defined by the ISGLS criteria, it could be useful for decreasing PHLF-related mortality (17,28,29). A previous study supports this hypothesis (30).

Other factors of the POMRS (older age and cholangitis) did not affect the 90-day mortality in the Hokkaido University cohort. This potentially leads to a mismatch between predicted mortality risk and observed mortality rate in the present study (*Table 5*). In general, elderly age is a potential risk factor for postoperative complications after any surgery. High age would be a considerable risk factor, especially in PHCC patients who require major hepatectomy, because aging has been associated with decreased liver function (31). In contrast, a recent study performed at Nagoya University Hospital showed that the surgical results of PHCC for octogenarians did not differ from those of younger generations (32). Our data support the reported results of the Nagoya University group. One possible reason for the age discrepancy could be the strict patient selection at Hokkaido University. In fact, patient selection criteria in the present series were stricter for older patients. Another possible reason might be ethnic differences; one of the longest life expectancies in the world have been recorded in Japan, with an average life expectancy of 82 years.

Because PHLF is the most serious complication after PHCC surgery, left hepatectomy, which leaves the largest FRLV, will be the ideal procedure. Recently, Sugiura *et al.* (33) showed that preoperative optimization strategies did not affect long term survival in Bismuth type I or II PHCC. On the other hand, previous authors suggested that right hepatectomy would be associated with better long-term survival because right hepatic pedicle resection enables better radicality compared with left resections (14,34,35). A recent review however, showed no survival benefit after either right or left resection for PHCC (36).

This study has several limitations. First, the small number of events is associated with statistical uncertainty. In addition, single-centre retrospective cohorts are subject to selection bias. Second, there is an obvious selection bias during the preoperative period. Some patients were denied surgery based on preoperative assessment. According to the selection criteria of Hokkaido University, no patients will undergo PHCC surgery without strict assessments of liver function using ICGK-F and patient's pre-operative status (e.g., serum CRP, nutrition status, and cholangitis). Therefore, there were few patients with FRLV <30% and no patients with preoperative bilirubin levels >50 μmol/L (2.9 mg/dL). Third, both the original study and this validation study did not evaluate intraoperative factors such as operative bleeding and operative time, which could be influenced by the surgical technique (3,6,12). Fourth, this validation study involved patients with different regional backgrounds. Our previous study showed that several differences existed between Asian and Western patients' backgrounds (13). Moreover, when validating the PHLFS, no patients in the present cohort had a preoperative bilirubin level exceeding 50 μmol/L (2.9 mg/dL), which was identified as an important factor for predicting PHLF in a previous study (3). It is possible that differences in preoperative management between Asian and Western countries resulted in the low AUC level for the validation of PHLFS. Especially, the lack of patients with preoperative bilirubin levels exceeding 50 μmol/L (2.9 mg/dL) in the validation set represents one of the most important limitations of this study. Therefore, one of the strongest reasons for the negative results in this study can be attributed to differences between Asia and the West, which makes it difficult to validate PORMS and PHLFS without variations (13).

Furthermore, several clinical questions have not been addressed in this study, such as whether preoperative biliary drainage is necessary in all PHCC patients. A previous report using the POMRS showed that jaundiced patients with no biliary drainage who had FRLV >50% and no cholangitis could undergo surgery with no mortality (12). As mentioned, in the present study all patients with jaundice with or without cholangitis underwent biliary drainage. This is not only common practice at Hokkaido University, but also at several Asian high volume centres (1,37). Further, this study could not determine who should undergo PVE for PHCC. The PHLFS suggested that not only patients with small FLRV (FLRV <30%) but also those with the other three factors (PHLFS 2) should be considered for PVE. In this study, all patients who underwent right hepatectomy or trisectionectomy had undergone PVE. This difference in preoperative preparation is also a major limitation of this study. To solve these issues, we should conduct further validation studies involving international participation and using strict criteria.

Despite these limitations and only partial representation of the PHLFS in the Asian cohort, the present study supports the applicability of the PHLFS in patients with PHCC considered for resection to assess surgical risk and to select patients for PVE. Previous data and the present results support preoperative application of PVE in patients undergoing trisectionectomy or right hepatectomy with PVR, even if they were categorised as low risk by the PHLFS. Conversely, to determine surgical risk using POMRS in patients with these different regional backgrounds appeared not to be feasible.

In conclusion, this external validation study showed that for PHLFS the threshold for discrimination in an Asian cohort was reached (AUC >0.6), but it would require optimization of the model before use in clinical practice is acceptable. Application of POMRS was not feasible in the Asian cohort. Further external validation is necessary to confirm whether the PHLFS and POMRS are applicable to Asian cohorts.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was performed in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Hokkaido University (No. 018-0429).

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