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ORIGINAL ARTICLE

# Minimum proportion of future liver remnant in safe major hepatopancreatoduodenectomy

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## Abstract

**Background and Aim:** Post-hepatectomy liver failure (PHLF) after major hepatopancreatoduodenectomy (HPD) is a challenge to overcome. However, the appropriate target proportion of the future liver remnant (pFLR) to prevent severe PHLF in major HPD remains uncertain. This study aimed to determine the minimum pFLR required for safe major HPD.

**Methods:** This retrospective study involved 48 major HPD patients. We assessed pFLR and remnant liver function scores (pFLR × albumin-bilirubin [ALBI] / albumin-indocyanine green evaluation [ALICE]/plasma clearance rate of indocyanine green [KICG]) as predictors for Grade B/C PHLF and established safety criteria.

**Results:** Grade B/C PHLF occurred in 40% of the patients ($n = 19$), leading to severe morbidity and two in-hospital deaths. pFLR was a good predictor of Grade B/C PHLF [area under the curve (AUC) 0.80, $p < 0.01$] with a 45% optimal cutoff. While all remnant liver function scores predicted PHLF, the remnant ALICE demonstrated the best predictability (AUC 0.85, $p < 0.01$), with the sensitivity and specificity at 89% and 83%, respectively, using −0.86 as the cutoff. Independent risk factors for Grade B/C PHLF were remnant ALICE ≥−0.86 and blood loss ≥1500 mL. Grade B/C PHLF developed in 14% with pFLR ≥45% but reached 64% with pFLR <45%. However, the rate could be reduced to 33% with remnant ALICE <−0.86.

**Conclusion:** To prevent Grade B/C PHLF, a pFLR ≥45% is recommended. Nevertheless, major HPD may be considered in patients with good remnant liver function.

KEYWORDS
albumin-indocyanine green evaluation, biliary cancer, hepatopancreatoduodenectomy, liver failure, liver volume

## 1 | INTRODUCTION

Major hepatopancreatoduodenectomy (HPD) has been introduced to achieve complete resection of advanced biliary tract and gallbladder cancers. Initially, there was considerable debate about whether to perform major HPD owing to its technical challenges and exceedingly high rates of complications as well as mortality.[1] However, advancements in standardizing operative procedures and the establishment of perioperative management have improved its safety. Moreover, reports from multiple institutions demonstrated that R0 resection in selected cases can lead to long-term survival.[2–5] Recently, major HPD has been recognized as the standard procedure for cases of biliary cancer in which complete resection cannot be achieved with major hepatectomy or pancreaticoduodenectomy alone, particularly in specialized hepatobiliary-pancreatic surgical centers.[6] Nonetheless, the rate of postoperative complication remains high, with post-hepatectomy liver failure (PHLF), a major cause of postoperative mortality occurring frequently following major HPD, even at high-volume centers.[2,4,7] In clinical practice, adjusting the proportion of the future liver remnants (pFLR) through portal vein embolization (PVE) is the most widely adopted method for preventing PHLF.[8] However, the appropriate pFLR target for major HPD remains unclear. Additionally, constructing a preoperative PHLF risk assessment system that considers FLR function is crucial for safer major HPD.

This study aimed to investigate the minimum required pFLR, considering remnant liver function, for safe major HPD.

## 2 | METHODS

### 2.1 | Patients and study design

This study enrolled a total of 48 patients who underwent major hepatectomy for cholangiocarcinoma or gallbladder cancer at Shinshu University Hospital, Matsumoto, Japan, between 1990 and 2022. Informed consent was obtained from each patient for treatment, and their medical records were retrospectively reviewed.

Grade B/C PHLF was established as the primary outcome of this study, and the following three studies were conducted. Study 1: The relationship between pFLR and the incidence of Grade B/C PHLF was examined using Receiver Operating Characteristic (ROC) curve analysis. Study 2: The scores, termed as "remnant liver function scores," were calculated by multiplying existing liver function assessment indicators [albumin-bilirubin (ALBI) score,[9] albumin-indocyanine green evaluation (ALICE) score,[10] and plasma clearance rate of indocyanine green (KICG)[8]] with the pFLR. The utility of these remnant liver function scores as predictors of Grade B/C PHLF was assessed using ROC curve and multivariate analyses. Study 3: To ensure safe HPD, the minimum required pFLR was investigated by considering the remnant liver function using a decision tree model analysis. In patients where PVE was performed, the FLR volume was calculated from the post-PVE liver volume. Liver function assessment indicators were calculated from the data obtained just before surgery.

### 2.2 | Indication for major hepatopancreatoduodenectomy

Major HPD was defined as a major liver resection involving the removal of three or more Couinaud segments, excluding segment 1, along with simultaneous pancreatoduodenectomy. The caudate lobe was resected in all major HPD cases. For cholangiocarcinoma, major HPD was indicated under the following tumor conditions where R0 resection is anticipated: (1) widespread extrahepatic cholangiocarcinoma involving the entire extrahepatic bile duct; (2) perihilar cholangiocarcinoma with caudal superficial spread or lymph node metastasis invading the pancreatic head or duodenum; (3) distal cholangiocarcinoma with cephalad superficial spreading. For gallbladder cancer, cases involving invasion into the lower bile duct, head of the pancreas, and duodenum were considered for major HPD. Additionally, in patients initially planned for major liver resection, concomitant pancreatoduodenectomy was performed if intraoperative assessment revealed the following: (1) tumor invasion into the head of the pancreas or duodenum and (2) a positive distal ductal margin on intraoperative frozen section pathology. Similarly, for patients initially scheduled for pancreatoduodenectomy, simultaneous major liver resection was performed if the intraoperative frozen section pathology indicated a positive proximal ductal margin and if liver function was assessed to be adequate to tolerate additional resection.

From the perspective of liver function, the feasibility of performing major HPD was determined based on the evaluation of liver function by indocyanine green retention rate at 15 min (ICGR15) and remnant liver volume by computed tomography (CT) volumetry. If liver function was normal (ICGR15 < 10%) with pFLR > 40%, PVE was not deemed essential, and major HPD was indicated. At our institution, PVE was indicated for patients with: (1) normal liver function (ICGR15 < 10%) and a pFLR of 35%–40%, or (2) mildly impaired liver function (ICGR15 of 10%–19%) and a pFLR of 40%–50%. The pFLR was reevaluated 2–3 weeks after PVE, and surgery was subsequently performed. The pFLR value referenced in this study was calculated just before surgery.[2]

### 2.3 | Pre and postoperative management and surgical procedure

Cholangiography, CT, magnetic resonance imaging (MRI), and intraductal ultrasonography were routinely performed to evaluate the tumor progression. Preoperative biliary drainage (PBD) was performed in patients with jaundice using either percutaneous transhepatic or endoscopic retrograde biliary drainage. A drainage tube was inserted into the future liver remnant and managed so that the total bilirubin level decreased to <2 mg/dL. Liver function was evaluated using ICGR15 after jaundice was reduced. If preoperative cholangitis developed, antibiotic therapy was administered based on the results of the bile culture, and surgery was performed after the inflammation was controlled.

The detailed standard procedure for major HPD at our hospital has been previously described.[2,11] Pancreatogastrostomy was initially the principal method for pancreatic reconstruction when the HPD was introduced. However, owing to the high incidence of postoperative pancreatic fistulas, the standard procedure was modified to involve complete external drainage of pancreatic juice, to subsequently perform a second-stage pancreatojejunostomy. Since 2012, the choice between pancreatojejunostomy and complete external drainage of pancreatic juice has been at the discretion of the surgeon.

For postoperative management, biochemical blood tests and bedside ultrasonography were performed daily for the first week postoperatively and thereafter, as required, based on the patient's condition. Bilirubin and amylase levels in the drainage fluid from each abdominal drain were monitored three times per week until drain removal. If any abnormalities were detected in these tests, additional examinations, such as CT or contrast studies, were performed to evaluate complications.

Regarding adjuvant chemotherapy, gemcitabine hydrochloride alone was administered after April 2006, gemcitabine hydrochloride + S-1 after 2016, and S-1 alone after 2022. However, in cases of poor performance status after surgery, severe postoperative complications, or patient refusal, the treatment team decided to forgo administration.

### 2.4 | Definition of complications

Postoperative complications were graded according to the Clavien–Dindo classification.[12] PHLF, posthepatectomy bile leakage, and postoperative pancreatic fistulas (POPF) were diagnosed and graded according to the criteria of the International Study Group of Liver Surgery and the updated criteria of the International Study Group on Pancreatic Surgery.[13–15] For PHLF, cases where clinicians performed non-invasive therapeutic interventions such as the administration of fresh frozen plasma (FFP) or diuretics to control liver failure were diagnosed as Grade B PHLF. Other complications were diagnosed by the attending physician based on a comprehensive assessment of clinical symptoms, laboratory tests, and imaging findings.

### 2.5 | Statistical analysis

Data were presented as medians (interquartile ranges) for continuous variables and numbers (%) for categorical variables. Mann–Whitney *U* test was used for continuous variables, and the $\chi^2$ test or Fisher's exact test for categorical variables. Statistical significance was set at $p<0.05$. To identify independent risk factors for Grade B/C PHLF, multivariate logistic regression analyses were conducted using the forward selection of covariates with a cutoff *p*-value of 0.10 in the univariate analysis. All statistical analyses were performed using the JMP software, version 16.2 (SAS Institute, Cary, NC, USA).

## 3 | RESULTS

### 3.1 | Patient characteristics, surgical details, and short-term outcomes with/without post-hepatectomy liver failure

Patient characteristics, surgical details, and short-term outcomes are summarized in Table 1. The median age of the entire cohort was 67 years; 40 patients had cholangiocarcinoma and eight had gallbladder cancer. Nearly all patients (98%) had an American Society of Anesthesiologists score of 1 or 2. Grade B/C PHLF was observed in 19 patients (40%); among them, two patients who developed Grade C PLHF necessitated intensive care, and both of them, unfortunately, resulted in in-hospital deaths.

Grade B/C PHLF was more common in patients with gallbladder cancer (32% vs. 7%; $p=0.048$), and in the early era of major HPD introduction, more than two-thirds of the patients developed this condition. Although most preoperative comorbidities were equivalent in both groups, there was a trend toward a higher prevalence of diabetes in patients with Grade B/C PHLF. Standard and total liver volumes were comparable in both groups; however, pFLR was significantly lower in patients with Grade B/C PHLF (42% vs. 48%, $p<0.001$), and 79% of them underwent PVE. There were no significant differences in PBD or cholangitis between the groups. In patients with Grade B/C PHLF, liver function assessments based on ALBI, ALICE, Child–Pugh, and KICG were generally impaired. Regarding the type of hepatectomy, no instances of Grade B/C PHLF were observed among patients who underwent left hemihepatectomy. Patients with Grade B/C PHLF underwent more extensive liver resection, concomitant vascular resection, increased blood loss, and higher RBC/FFP transfusion rates. With regard to postoperative complications, patients with Grade B/C PHLF had a higher incidence of pleural effusion, sepsis, and intra-abdominal infections. Consequently, these patients also experienced a higher rate of severe complications (Clavien–Dindo Grade III, IV, V) and longer postoperative hospital stays.

Two in-hospital deaths in this cohort were due to PHLF. The first case involved a 72-year-old man with both perihilar cholangiocarcinoma and duodenal papilla carcinoma. He experienced recurrent cholangitis before surgery and had been administered antibiotics several times. The pFLR was 41.5% with an ALICE Grade of 3, resulting in a remnant ALICE score of −0.50 (poor). However, with a remnant KICG of 0.056, PVE was not performed, and a right hemihepatectomy with pancreatoduodenectomy was carried out. The hepatoduodenal ligament was hardened due to inflammation, rendering the lymph node dissection challenging. The liver was severely fibrotic and prone to bleeding. The surgery lasted 1297 min, with a hepatic ischemia duration of 122 min and

TABLE 1 Patient characteristics, surgical details, and short-term outcomes with/without post-hepatectomy liver failure.

| Variable | Whole cohort (*n* = 48) median (IQR)/*n* (%) | Grade B/C PHLF (*n* = 19) median (IQR)/*n* (%) | Grade A/No PHLF (*n* = 29) median (IQR)/*n* (%) | *p*-Value |
|---|---|---|---|---|
| Age, years | 67 (61–71) | 67 (62–72) | 66 (61–71) | 0.519 |
| Sex | | | | |
| Male | 35 (72.9) | 13 (68.4) | 22 (75.9) | 0.572 |
| Female | 13 (27.1) | 6 (31.6) | 7 (24.1) | |
| Diagnosis | | | | |
| Perihilar cholangiocarcinoma | 25 (52.1) | 10 (52.6) | 15 (51.7) | 0.048 |
| Distal cholangiocarcinoma | 15 (31.3) | 3 (15.8) | 12 (41.4) | |
| Gallbladder cancer | 8 (16.7) | 6 (31.6) | 2 (6.9) | |
| Era of surgery | | | | |
| 1990–1999 | 17 (35.4) | 12 (70.6) | 5 (29.4) | 0.004 |
| 2000–2009 | 15 (31.3) | 3 (20.0) | 12 (80.0) | |
| 2010–2022 | 16 (33.3) | 4 (25.0) | 12 (75.0) | |
| Body mass index, kg/m$^2$ | 21.0 (19.4–23.9) | 21.9 (19.9–24.0) | 20.2 (19.1–23.4) | 0.171 |
| Standard liver volume, mL | 1103 (1041–1183) | 1095 (998–1177) | 1118 (1054–1191) | 0.435 |
| American Society of Anesthesiologists score | | | | |
| 1 | 20 (41.7) | 8 (42.1) | 12 (41.4) | 0.618 |
| 2 | 27 (56.3) | 10 (52.6) | 17 (58.6) | |
| 3 | 1 (2.1) | 1 (5.3) | 0 (0) | |
| Hypertension | 16 (33.3) | 6 (31.6) | 10 (34.5) | 0.834 |
| Diabetes | 5 (10.4) | 4 (21.1) | 1 (3.5) | 0.051 |
| Cardiovascular disease | 3 (6.3) | 1 (5.3) | 2 (6.9) | 0.817 |
| Pulmonary disease | 2 (4.2) | 1 (5.3) | 1 (3.5) | 0.761 |
| Preoperative biliary drainage | 44 (91.7) | 17 (89.5) | 27 (93.1) | 0.660 |
| Preoperative cholangitis | 14 (29.2) | 6 (31.6) | 8 (27.6) | 0.767 |
| Portal vein embolization | 30 (62.5) | 15 (79.0) | 15 (51.7) | 0.052 |
| ALBI score | −2.40 (−2.63 to −2.21) | −2.26 (−2.57 to −2.15) | −2.42 (−2.79 to −2.31) | 0.098 |
| ALICE score | −2.05 (−2.27 to −1.85) | −1.91 (−2.17 to −1.78) | −2.22 (−2.35 to −1.93) | 0.017 |
| Child–Pugh score | 5 (5–6) | 6 (5–6) | 5 (5–6) | 0.137 |
| ICGR15, % | 10.0 (6.8–13.8) | 12.0 (8.5–15.0) | 8.4 (5.6–12.5) | 0.054 |
| KICG | 0.157 (0.140–0.183) | 0.145 (0.132–0.171) | 0.170 (0.145–0.201) | 0.022 |
| Standard liver volume, mL | 1103 (1041–1183) | 1095 (998–1177) | 1118 (1054–1191) | 0.435 |
| Total liver volume, mL | 1053 (966–1288) | 1062 (872–1300) | 1043 (996–1284) | 0.462 |
| Volume of the future liver remnant, mL | 533 (406–616) | 407 (366–573) | 572 (476–640) | 0.017 |
| Proportion of the future liver remnant, % | 44 (40–52) | 42 (37–44) | 50 (44–63) | <0.001 |
| Type of hepatectomy | | | | |
| Right hemihepatectomy | 33 (68.8) | 17 (89.5) | 16 (55.2) | 0.001 |
| Left hemihepatectomy | 12 (25.0) | 0 (0) | 12 (41.4) | |
| Left trisectionectomy | 1 (2.1) | 1 (5.3) | 0 (0) | |
| Central bisectionectomy | 2 (4.2) | 1 (5.3) | 1 (3.5) | |
| Concomitant vascular resection | 8 (16.7) | 6 (31.6) | 2 (6.9) | |
| Portal vein | 8 (16.7) | 5 (26.3) | 1 (3.5) | 0.025 |
| Hepatic artery | 2 (4.2) | 1 (5.3) | 1 (3.5) | |

(Continues)

TABLE 1 (Continued)

| Variable | Whole cohort ($n=48$) median (IQR)/$n$ (%) | Grade B/C PHLF ($n=19$) median (IQR)/$n$ (%) | Grade A/No PHLF ($n=29$) median (IQR)/$n$ (%) | $p$-Value |
|---|---|---|---|---|
| Reconstruction of pancreas | | | | |
| Complete external drainage for two-stage reconstruction | 34 (70.8) | 14 (41.2) | 20 (58.8) | 0.006 |
| Primary pancreatojejunostomy | 10 (20.8) | 1 (10.0) | 9 (90.0) | |
| Primary pancreatogastrostomy | 4 (100) | 4 (100) | 0 (0) | |
| Operation time, min | 868 (746–984) | 927 (800–1125) | 806 (720–948) | 0.075 |
| Liver ischemia time, min | 59 (45–72) | 46 (30–70) | 60 (45–75) | 0.540 |
| Intraoperative bleeding, mL | 1075 (893–1770) | 1680 (1000–2060) | 1000 (850–1215) | 0.014 |
| Intraoperative RBC transfusion | 12 (25.0) | 8 (42.1) | 4 (13.8) | 0.028 |
| Intraoperative FFP transfusion | 36 (75.0) | 17 (89.5) | 19 (65.5) | 0.050 |
| Pleural effusion | 19 (39.6) | 11 (57.9) | 8 (27.6) | 0.036 |
| Sepsis | 3 (6.3) | 3 (15.8) | 0 (0) | 0.015 |
| Intra-abdominal infection | 23 (47.9) | 13 (68.4) | 10 (34.5) | 0.020 |
| Postoperative pancreatic fistula (Grade B/C) | 16 (33.3) | 9 (47.4) | 7 (24.1) | 0.096 |
| Post-hepatectomy bile leak (Grade B/C) | 4 (8.3) | 2 (10.5) | 2 (6.9) | 0.660 |
| Delayed gastric emptying | 3 (6.3) | 0 (0) | 3 (10.3) | 0.076 |
| Clavien–Dindo classification | | | | |
| Grade I | 23 (47.9) | 8 (42.1) | 15 (51.7) | 0.514 |
| Grade II | 31 (64.6) | 14 (73.7) | 17 (58.6) | 0.281 |
| Grade III | 27 (56.3) | 14 (73.7) | 13 (44.8) | 0.046 |
| Grade IV | 3 (6.3) | 3 (15.8) | 0 (0) | 0.015 |
| Grade V (in-hospital death) | 2 (4.2) | 2 (10.5) | 0 (0) | 0.050 |
| Postoperative hospital stay days | 53 (40–72) | 78 (48–111) | 49 (36–58) | 0.002 |
| R0 resection | 38 (80.9) | 15 (79.0) | 23 (82.1) | 0.785 |
| Adjuvant chemotherapy | 10 (20.8) | 2 (10.5) | 8 (27.6) | 0.140 |
| 1-year survival | 40 (83.3) | 13 (68.4) | 27 (93.1) | 0.025 |

Abbreviations: ALBI, albumin-bilirubin; ALICE, albumin-liver stiffness and platelet count evaluation; FFP, fresh frozen plasmaICGR15, indocyanine green retention rate at 15 min; interquartile ranges (IQR); KICG, plasma clearance rate of indocyanine green; PHLF, post-hepatectomy liver failure; RBC, red blood cell.

blood loss of 2500 mL, necessitating four units of RBC transfusion. On postoperative day 5, the patient developed an intra-abdominal abscess and sepsis caused by Enterobacter, which was resistant to the prophylactic antibiotic Ceftazidime Hydrate. This was followed by Grade C PHLF. Despite intensive treatment, PHLF remained uncontrollable, and the patient passed away on postoperative day 21. The second case involved a 72-year-old man diagnosed with extensive cholangiocarcinoma affecting both the hepatic artery and portal vein. PVE was performed, achieving a preoperative pFLR of 50%, remnant KICG of 0.072, and a remnant ALICE score of −0.79 (poor). Subsequently, he underwent a left trisectionectomy with reconstruction of the hepatic artery and portal vein. The operation lasted 1200 min, including a hepatic ischemia time of 78 min and resulted in blood loss of 1800 mL, requiring six units of intraoperative RBC transfusion. Hepatic artery reconstruction posed challenges, leading to 208 min of hepatic artery ischemia. By postoperative day 4, the patient developed respiratory failure and Grade C PHLF, necessitating admission to the intensive care unit. Subsequently, the patient developed intractable ascites due to concurrent liver and renal failure. Despite intensive treatment, PHLF did not improve, and he ultimately succumbed to multiple organ failure on postoperative day 209.

Additionally, while the R0 resection rates were comparable between the two groups, there was a trend toward a lower rate of adjuvant chemotherapy administration in the PHLF group, and the 1-year survival rate was significantly poorer (68.4% vs. 92.9%, $p=0.029$). Among the eight patients who died within 1 year following surgery, excluding two patients who succumbed to Grade C PHLF, all deaths resulted from cancer recurrence. None of these patients were able to receive adjuvant chemotherapy or additional treatment courses. The causes of death were as follows: within the PHLF group, there were six patients (Grade C PHLF $n=2$, recurrence $n=4$ [2 peritoneum, liver, lung]), and in the Non-PHLF group, there were two patients (recurrence $n=2$ [abdominal wall, liver]).

## 3.2 | Study 1: Association between proportion of the future liver remnant and grade B/C post-hepatectomy liver failure

Subsequently, we analyzed the association between pFLR and Grade B/C PHLF. There was no statistical difference in the incidence of Grade B/C PHLF between the groups with pFLR ≥40% and <40% (33% [*n*=12] vs. 58% [*n*=7], *p*=0.176), and both Grade C patients had pFLR ≥40% (Figure 1A). In contrast, ROC analysis demonstrated that pFLR favorably predicted Grade B/C PHLF (area under the curve [AUC] 0.81, *p*=0.004), and the optimal cutoff value by Youden index was 45% (Figure 1B). Remarkably, only 13% (*n*=3) of patients with pFLR ≥45% experienced PHLF, whereas 64% (*n*=16) of patients with pFLR <45% developed Grade B/C PHLF (Figure 1A).

## 3.3 | Study 2: Utility of the remnant liver function scores as predictors for grade B/C post-hepatectomy liver failure

Next, we assessed the utility of the remnant liver function scores (pFLR×[ALBI/ALICE/KICG]) as predictors of Grade B/C PHLF. Although the liver function scores alone (ALBI/ALICE/KICG) did not significantly detect Grade B/C PHLF, all remnant liver function scores considering pFLR showed significant predictive ability for Grade B/C PHLF (Figure 2A–C). Notably, the predictive ability of the remnant ALICE (pFLR×ALICE) and ALBI scores (pFLR×ALBI) drastically increased compared to that of the ALICE/ALBI scores alone. Moreover, the remnant ALICE score demonstrated the highest predictive ability for Grade B/C PHLF among the three scores, with a sensitivity of 89% and specificity of 83% when using −0.86 as the cutoff.

Early era of surgery, operation time ≥870 min, red blood cell transfusion, concomitant vascular resection, pFLR <45%, remnant ALICE score ≥−0.86, remnant ALBI score ≥−0.99, and remnant KICG ≤0.061 were risk factors for Grade B/C PHLF in the univariate analysis. In the multivariate analysis after stepwise selection, a remnant ALICE score ≥−0.86 and intraoperative bleeding ≥1500 mL were identified as the independent risk factors for Grade B/C PHLF in major HPD (Table 2).

## 3.4 | Study 3: Minimum proportion of the future liver remnant considering remnant liver function for safe major HPD

Finally, we explored the minimum required pFLR, considering remnant liver function, and developed a decision tree model to perform major HPD safely (Figure 3). With a pFLR ≥45%, only three patients (13%) developed Grade B/C PHLF, indicating that major HPD could be performed safely. Interestingly, all three patients exhibited a remnant ALICE score of ≥−0.86. Conversely, with a pFLR <45%, the incidence of Grade B/C PHLF increased to 64%. However, in patients with a remnant ALICE score <−0.86, the incidence could be reduced to 33%. In the case group with a remnant ALICE score ≥−0.86, the incidence of Grade B/C PHLF was extremely high at 72%; therefore, major HPD is not acceptable under these conditions.

POPF is a distinctive surgical complication in HPD, not typically observed in major hepatectomy. In this study, we defined clinically relevant (Grade B/C) POPF as such. Sixteen patients (33%) developed POPF, and these patients exhibited a significantly higher incidence of intra-abdominal infection (69% vs. 38%, *p*=0.039) and tended to experience more severe postoperative complications of CD grade ≥III (75% vs. 50%, *p*=0.09). Additionally, there was a

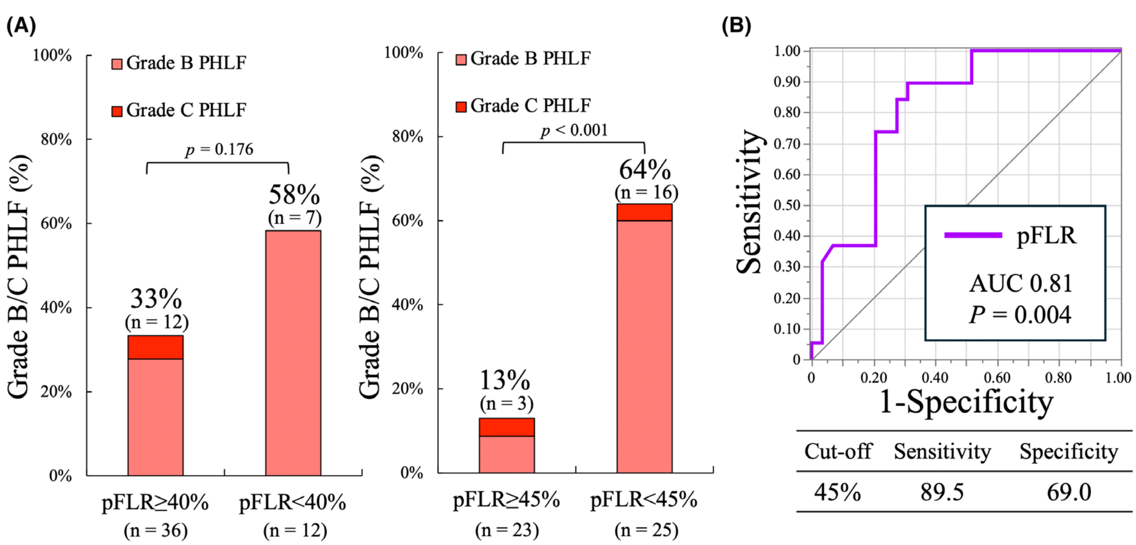



**FIGURE 1** Association between pFLR and grade B/C PHLF. (A) Comparison between pFLR ≥40% and pFLR <40% (Left panel), pFLR ≥45% and pFLR <45% (Right panel). (B) Receiver operating characteristic analysis evaluating predictive ability of pFLR for Grade B/C PHLF. AUC, area under the curve. pFLR, proportion of the future liver remnants; PHLF, post-hepatectomy liver failure.

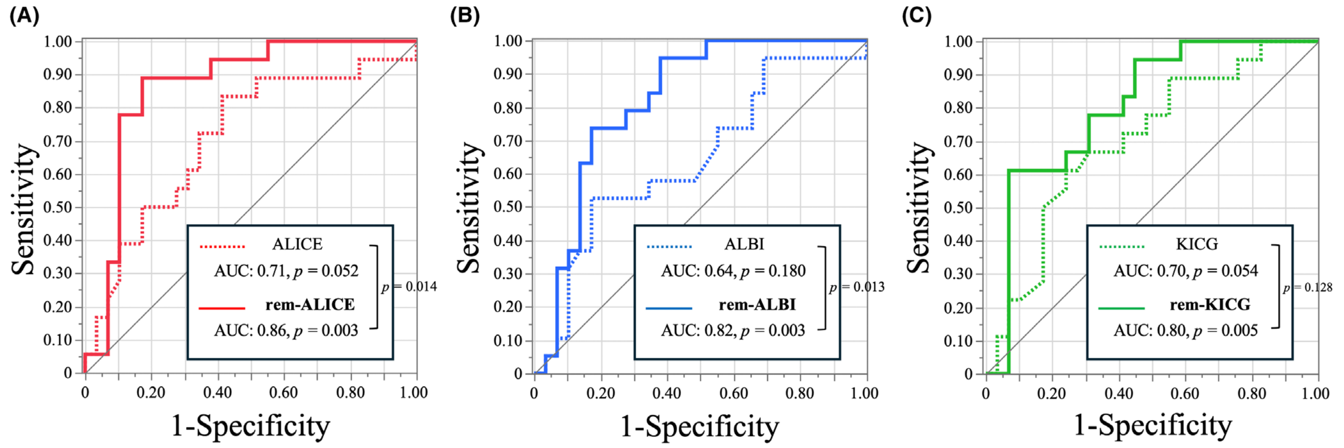



FIGURE 2 Remnant liver function scores as predictors for PHLF. Receiver operating characteristic analysis evaluating the predictive ability of (A) ALICE, (B) ALBI, and (C) KICG for Grade B/C PHLF. ALBI, albumin-bilirubin; ALICE, albumin-indocyanine green evaluation; AUC, area under the curve; KICG, plasma clearance rate of indocyanine green.

TABLE 2 Univariate and multivariate logistic regression analyses for Grade B/C post-hepatectomy liver failure.

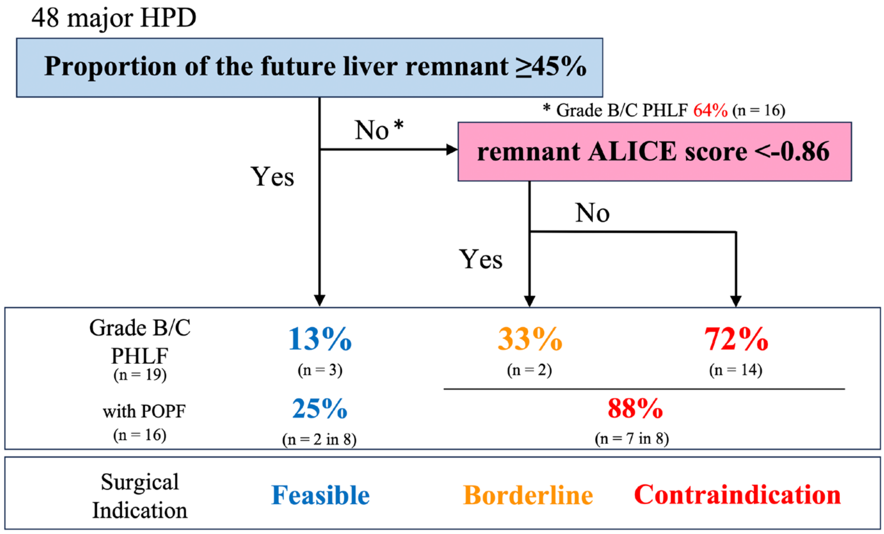
| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | OR | (95% CI) | *p*-Value | OR | (95% CI) | *p*-Value |
| Age at surgery ≥65 yrs | 1.98 | (0.56–6.97) | 0.281 | | | |
| Diagnosis | | | | | | |
| Perihilar cholangiocarcinoma | Reference | | | | | |
| Distal cholangiocarcinoma | 0.38 | (0.08–1.67) | 0.199 | | | |
| Gallbladder cancer | 4.5 | (0.75–26.93) | 0.099 | | | |
| Era of surgery | | | | | | |
| 1990–1999 | Reference | | | | | |
| 2000–2009 | 0.10 | (0.02–0.54) | 0.007 | | | |
| 2010–2022 | 0.13 | (0.03–0.65) | 0.012 | | | |
| Preoperative cholangitis | 1.21 | (0.34–4.29) | 0.766 | | | |
| Portal vein embolization | 3.50 | (0.93–13.12) | 0.063 | | | |
| Operation time ≥870 min[a] | 3.55 | (1.04–12.06) | 0.043 | | | |
| Intraoperative bleeding ≥1500 mL[a] | 6.94 | (1.73–27.81) | 0.004 | 11.32 | (1.08–118.97) | 0.043 |
| Intraoperative RBC transfusion | 4.55 | (1.13–18.32) | 0.033 | | | |
| Concomitant vascular resection | 6.23 | (1.10–35.21) | 0.038 | 4.35 | (0.43–44.24) | 0.215 |
| Proportion of the future liver remnant <45%[a] | 11.85 | (2.75–51.17) | <0.001 | | | |
| Remnant ALICE ≥−0.86[a] | 38.40 | (6.62–222.66) | <0.001 | 51.48 | (5.26–503.38) | <0.001 |
| Remnant ALBI ≥−0.99[a] | 13.44 | (3.30–54.72) | <0.001 | | | |
| Remnant KICG ≤0.061[a] | 12.38 | (2.66–57.56) | 0.001 | | | |

Abbreviations: ALBI, albumin-bilirubin; CI, confidence interval; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; OR, odds ratio.

[a]The cutoff values were determined to maximize the Youden index using receiver operating characteristic curve analysis.

trend toward Grade B/C PHLF being twice as common in patients with POPF (56% vs. 31%, $p=0.10$), suggesting that POPF may pose a potential risk for PHLF. In the presented decision tree model, the incidence of PHLF in patients with POPF was 25% (two out of eight patients with POFP) in the Feasible group (pFLR ≥45%). In contrast, in the Borderline/Contraindication group (pFLR <45%), 88% (seven out of eight patients with POPF) developed Grade B/C PHLF. This suggests that in major HPD, patients with compromised remnant liver function who develop POPF are highly likely to experience Grade B/C PHLF.

FIGURE 3 Decision tree model of minimum pFLR considering remnant liver function for safe hepatopancreatoduodenectomy. ALICE, albumin-indocyanine green evaluation; PHLF, post-hepatectomy liver failure; POPF, postoperative pancreatic fistula.




## 4 | DISCUSSION

This study revealed that a pFLR of ≥45% represents an ideal target value for preventing Grade B/C PHLF in major HPD. Furthermore, our investigation of the remaining ALICE/ALBI/KICG scores, which concurrently consider liver function assessment systems and pFLR, demonstrated outstanding predictive capabilities for Grade B/C PHLF. Remarkably, the remaining ALICE scores exhibited the best predictive performance. Using a Decision Tree Model, it was suggested that even in patients with a pFLR <45%, those with favorable remnant liver function, as assessed by the remnant ALICE score, may undergo major HPD relatively safely.

PHLF is the most common and dreaded complication and the main cause of death following major HPD.[2,4,7,16] In this cohort, PHLF was the most frequent complication and the sole cause of death. Despite similar complete tumor resection rates, patients with PHLF had significantly lower 1-year survival rates than those without PHLF. Thus, when planning major HPD, it is crucial to evaluate the risk of severe PHLF to ensure complete tumor removal. In major HPD, compared with major hepatectomy, there is generally a higher incidence of risk factors associated with PHLF, such as significant bleeding, transfusions, POPF, and intra-abdominal infections.[2,17] A propensity score matching study comparing major HPD and major hepatectomy found a fourfold higher incidence of PHLF in major HPD, along with an increased mortality rate.[18] Therefore, it is essential to reevaluate PHLF risk factors and the required pFLR in major HPD cases, as the PHLF risk profiles for major hepatectomy and major HPD may fundamentally differ. This study confirmed that in patients with insufficiently secured pFLR (<45%) who developed POPF, Grade B/C PHLF almost invariably occurred. These findings underscore the distinct challenges of major HPD compared to major hepatectomy and highlight the necessity for special considerations, such as two-stage pancreatic reconstruction, in high-risk patients.

pFLR is the most crucial factor for PHLF that can be treated before surgery. The pFLR required for a safe hepatectomy depends closely on liver condition. Generally, it is recommended to ensure pFLR of ≥20% in normal liver, ≥30%–40% in severe fatty liver or cholestasis, and ≥40%–50% in cirrhosis.[19,20] However, in advanced biliary cancers eligible for major HPD, pFLR is often below 40%, except in cases undergoing left hemihepatectomy. PVE, introduced by Makuuchi, increases the pFLR by approximately 10%, making it an effective strategy for enhancing the safety and feasibility of major hepatectomies.[21] Ebata et al. reported a 75% reduction in the incidence of severe PHLF after introducing PVE before major hepatectomy.[22] The criteria for PVE before major HPD are controversial, with some recommending PVE with pFLR <30%,[23] <40%,[3] <40% and/or more than right hemiliver resection,[4] and <50%.[5] Generally, facilities that actively perform PVE have favorable mortality rates compared with those that do not. However, even in facilities that actively perform PVE, the incidence of PHLF is not always low, and the target pFLR just before surgery is not mentioned. Our results show that pFLR is strongly associated with PHLF and ensuring a pFLR ≥45% allows for the safe performance of major HPD with minimal experience with Grade B/C PHLF. This target pFLR was significantly higher than previously considered for cholestatic livers, emphasizing the high invasiveness of major HPD. However, one patient with Grade C PHLF resulting in death had a pFLR of 50%, suggesting potential risks in estimating PHLF based solely on pFLR. Moreover, for patients requiring a right hepatectomy or more, this target criterion may be considered stringent. Finally, the decision to perform HPD should carefully evaluate remnant liver function.

Among the qualitative tests for evaluating liver function, ICG test is considered one of the most reliable predictors of PHLF and surgery-related mortality.[24] Nagino reported that in patients undergoing liver resection for biliary cancer, a remnant KICG <0.05 was a risk factor for mortality.[8] In fact, with remnant KICG <0.05, more than half of the patients develop PHLF, which is considered a safety margin.[25] In this study, KICG was found to be valuable in predicting PHLF, similar to ALICE, when used alone. However, when assessing remnant liver function with pFLR, remnant KICG was less accurate in predicting severe PHLF compared to remnant ALICE. We comprehensively assessed HPD feasibility, including the ICG test. However, the results suggest that among our HPD-selected cases based on ICG, there might have been potential high-risk cases for Grade B/C PHLF.

The ALBI score/grade allows the assessment of liver function using only two routine blood parameters: albumin and total bilirubin.[9] Recent meta-analyses have indicated that the ALBI is also useful in predicting PHLF.[26] However, patients with biliary cancer eligible for major HPD typically undergo strict preoperative bilirubin level management via PBD. Therefore, the effectiveness of the ALBI grade may rely primarily on serum albumin levels. Despite the well-documented link between serum bilirubin levels and PHLF,[27] in this meticulously selected cohort based on post-biliary drainage bilirubin values, preoperative bilirubin levels showed no predictive capacity for PHLF (AUC 0.52).

The ALICE grading system assesses liver function, calculated from serum albumin levels and ICGR15, and was developed based on the long-term outcomes of HCC resection cases.[10] Miyazaki evaluated the predictive factors for PHLF in patients with biliary cancer, with the ALICE score showing a better predictive ability than the ALBI score.[28] Furthermore, a high ALICE grade combined with extensive liver resection is associated with an increased risk of severe PHLF and mortality.[29] Therefore, it is reasonable to assess the PHLF risk using the remnant ALICE score considering the pFLR. In our study, the remnant ALICE score was the best predictor of PHLF among other remnant liver function scores. Furthermore, one of the two cases that resulted in Grade C PHLF and subsequent mortality had a pFLR of 50% and a remnant KICG of 0.072. In this case, despite favorable pFLR and remnant KICG values, the remnant ALICE score was ≥−0.86, suggesting that this remnant ALICE criterion may provide a more accurate assurance of safe major HPD.

However, remnant liver function scores cannot be used to assess liver heterogeneity. Imaging studies may have the potential to predict PHLF more accurately. Notake et al. reported that the remnant hepatocellular uptake index using gadoxetate disodium-enhanced magnetic resonance imaging accurately predicted Grade B/C PHLF cases, including those in which conventional indicators, such as remnant KICG, could not.[30] In a subset analysis of 15 cases within our cohort for which data were available, using the proposed cut-off value of <0.410 for the remnant hepatocellular uptake index, Grade B/C PHLF was accurately predicted with a sensitivity of 100% and a positive predictive value of 83% (data not shown). Although the applicability of remnant liver function assessment via imaging studies is limited to facilities with access to these tests, given the advanced specialization of major HPD, it is worthwhile to further explore the potential benefits of using imaging-based remnant liver function assessment.

This study had some limitations. First, this was a retrospective, single-center study, which may have been influenced by regional and facility-specific factors. Additionally, although this study constituted a relatively larger cohort than previous reports, it involved a small number of cases statistically, and the results need to be validated through larger studies. Second, the study took place for a long period. Changes in surgical techniques and perioperative management may have influenced the patient outcomes. Notably, Grade B/C PHLF was observed more frequently in patients with gallbladder cancer and pancreaticogastrostomy, many of which were performed during the early period. This makes it challenging to assess their relationship with PHLF. Despite these limitations, we believe that the present study provides crucial information for enhancing the safety of this highly invasive procedure.

In conclusion, from the viewpoint of PHLF prevention, pFLR ≥45% is desirable for performing major HPD safely in biliary cancer. However, even in patients with a pFLR <45%, major HPD could be considered in cases with good remnant liver function scores, such as the remnant ALICE score.

## AUTHOR CONTRIBUTIONS

**Kentaro Umemura:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; validation; visualization; writing – original draft. **Akira Shimizu:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; resources; supervision; validation; writing – review and editing. **Tsuyoshi Notake:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; validation; visualization; writing – review and editing. **Koji Kubota:** Data curation; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing – review and editing. **Kiyotaka Hosoda:** Data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization; writing – original draft. **Koya Yasukawa:** Data curation; formal analysis; funding acquisition; investigation; methodology; software; supervision; validation; visualization; writing – original draft. **Atsushi Kamachi:** Data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization; writing – original draft. **Takamune Goto:** Data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization; writing – original draft. **Hidenori Tomida:** Data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization; writing – original draft. **Yuji Soejima:** Conceptualization; formal analysis; investigation; methodology; project administration; supervision; validation; writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

## DATA AVAILABILITY STATEMENT

The data cannot be shared publicly to protect personal information. However, the raw dataset will be made available upon reasonable request to the corresponding author.

## ETHICS STATEMENTS

Approval of the research protocol: This study was conducted following the Declaration of Helsinki and the Istanbul Declaration, and the protocol was approved by the Ethics Committee of Shinshu University (registration number: 5456).

Informed Consent: All informed consent was obtained from the patients for the treatment.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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