ORIGINAL ARTICLE

Risk factors for a high Comprehensive Complication Index score after major hepatectomy for biliary cancer: a study of 229 patients at a single institution

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Abstract

Background: The Comprehensive Complication Index (CCI) is a new tool to evaluate the postoperative condition by calculating the sum of all complications weighted by their severity. The aim of this study was to identify independent risk factors for a high CCI score (≥40) in 229 patients after major hepatectomies with biliary reconstruction for biliary cancers.

Methods: The CCI was calculated online via www.assessurgery.com. Independent risk factors were identified by multivariable analysis.

Results: 57 (25%) patients were classified as having CCI ≥ 40. On multivariable analysis, volume of intraoperative blood loss (≥2.5 L) (p = 0.004) and combined pancreatoduodenectomy (PD) (p = 0.006) were independent risk factors for CCI ≥ 40. A high level of maximum serum total bilirubin was identified as independent risk factors for a high volume of intraoperative blood loss. Liver failure (p = 0.046) was more frequent in patients with combined PD than in those without.

Discussion: Patients who undergo preoperative external biliary drainage for severe jaundice might have impaired production of coagulation factors. When blood loss during liver transection becomes difficult to control, surgeons should consider various strategies, such as second-stage biliary or pancreatic reconstruction. In patients planned to undergo major hepatectomy with combined PD, preoperative portal vein embolization is mandatory to prevent postoperative liver failure.

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Introduction

For patients with biliary cancers, including perihilar cholangiocarcinoma or gallbladder carcinoma, surgical resection offers the only possibility of cure.[1] However, hepatectomy for these diseases is more difficult than for hepatocellular carcinoma or metastatic disease to the liver. The increased complexity comes from the need for biliary tract reconstruction and, on occasion, the need to resect and reconstruct the portal vein or hepatic artery, or add pancreatoduodenectomy (PD).[1–3] Therefore, it is possible that risk factors for postoperative complications in patients who undergo such complex procedures are different from those who undergo simple hepatectomy. Few reports have examined independent risk factors for morbidity or mortality in patients who have undergone hepatectomy for cholangiocarcinoma (Table 1).[1,4–9]

In recent years, the Clavien–Dindo classification (CDC) grade has become the standard for reporting postoperative complications. This classification grades complications according to the most severe complication or events judged to be relevant.[10] By this system, complications of lesser magnitude, as well as the total number of complications, are not accounted for. To address this issue, in 2013, Slankamenac *et al.* presented a new tool for

Table 1 Independent risk factors for morbidity or mortality of patients who underwent resection for perihilar cholangiocarcinoma or tumor in previous reports

Risk factor for endpoints	Endpoint	
	Morbidity	Mortality
	No. Reference	
Variable		
Preoperative cholangitis	4	1,5,9
Intraoperative blood loss or blood transfusion	[8](>900 ml)	[1](≥2500 ml),[6] (blood transfusion)
Low liver function or %FLR[a]		1,9
Preoperative bilirubin (>3 mg/dL)	7	

[a] Plasma disappearance rate of indocyanine green (ICGK) < 0.14(1), FLR < 30%.[9]

scoring, the so-called "Comprehensive Complication Index (CCI)".[11,12] The CCI is calculated as the sum of all complications weighted by severity (available at www.assessurgery.com).[10,13] The formula for the CCI yields a continuous scale to rank the severity of any combination of complications from 0 (no complications) to 100 (death) in a single patient. For example, a patient with a CCI of 8.7 would have a single CDC grade I complication, one with a CCI of 20.6 would have a grade II complication, one with a CCI of 26.2 would have a grade IIIa complication, one with a CCI of 33.7 would have a grade IIIb complication, one with a CCI of 44.2 would have a grade IVa complication, and one with a CCI of 46.2 would have a grade IVb complication. In addition, the formula for the CCI can calculate the summative severity of several complications in a single patient. For example, the CCI index for the sum of one CDC grade I and two CDC grade II complications in a single patient is 30.8. There have been no reports that have identified risk factors for a severe postoperative CCI score (CCI > 40) in a large cohort of patients undergoing hepatectomy for malignant biliary disease.

The aim of this study was to identify predictive factors for patients who developed a severe postoperative CCI score following major hepatectomy with biliary reconstruction for biliary cancer.

Patients and methods

Patients

Between March 1999 and March 2013, 255 patients underwent hepatectomy with biliary reconstruction for biliary cancer (perihilar cholangiocarcinoma or gallbladder carcinoma) with curative intent at the Department of Gastroenterological Surgery II, Hokkaido University Hospital. Twenty-six (10%) patients were excluded from the present study due to a lack of clinical records (n = 10), having a history of surgery including biliary reconstruction (n = 11), or undergoing minor hepatectomy (n = 5). Thus, 229 (90%) patients were included for the further study. This study was approved by the Institutional Review Board of Hokkaido University Hospital (No. 014-0374).

Preoperative preparation

The patients were treated in accordance with departmental guidelines, which were established in 1999 for patients with hilar cholangiocarcinoma.[14,15] Pre-operative biliary decompression was performed to reduce serum bilirubin concentrations below 34 μmol/L (2 mg/dL) for all patients with jaundice and to control segmental cholangitis. Previously, percutaneous transhepatic biliary drainage (PTBD) was used for drainage. Beginning in 2005, endoscopic nasobiliary drainage (ENBD) of the future remnant liver was adopted for initial drainage.

Preoperative portal vein embolization (PVE) of the liver to be resected was considered when right hepatectomy or right- or left-trisectionectomy was planned.[16] More than 2 weeks after PVE, the patients' liver volumes were semi-automatically measured using contrast-enhanced computed tomography imaging data (volume data or 5-mm-thick axial imaging data).[16] The basic decision criteria for the ratio of the future liver remnant volume/total liver volume (%FLR) limit for each type of hepatectomy are shown in Fig. 1.

Surgical technique

In patients with gallbladder carcinoma and intrahepatic cholangiocarcinoma, before radical resection, para-aortic lymphadenectomy and pathological examination by frozen sections were performed immediately after laparotomy to decide whether radical resection should be performed.[17–19] For patients with extrahepatic cholangiocarcinoma, para-aortic lymphadenectomy

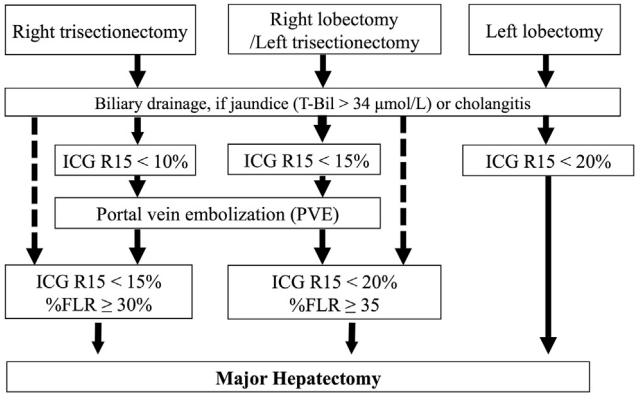


Figure 1 Decision criteria for the strategy for preoperative management of major hepatectomy in biliary cancer. Preoperative biliary decompression is performed to reduce the serum bilirubin concentration to below 2 mg/dL. When the value of the indocyanine green retention rate at 15 min (ICG R15) after relief of jaundice meets the requirements, limited PE is performed. At 2 weeks after PVE, patients with ICG R15 and the appropriate ratio of the future liver remnant volume/total liver volume (%FLR) are considered candidates for major hepatectomy with biliary reconstruction

was performed for nodes with suspected metastases on preoperative imaging findings. Systematic lymphadenectomy of the hepatoduodenal ligament, including the nodes around the head of the pancreas, was routinely performed in all three types of biliary carcinoma. Portal vein resection and reconstruction with macroscopic infiltration by the tumor were completed before hepatic parenchymal dissection and hepatic ductal division.[20,21] Hepatic arteries that were determined to have cancer invasion were resected en bloc with the bile duct and reconstructed by direct end-to-end anastomosis of the hepatic arteries or *in situ* grafting of the right epigastric artery or the gastroduodenal artery using a microscopic technique. When infiltration of tumor proceeded too peripherally to allow reconstruction, arterioportal shunting was performed.[22] Liver transection was performed using the forceps clamp crushing method during both hepatic artery and portal vein clamping for 15 min with 5-min intervals. Biliary tract reconstruction was performed by bilioenterostomy using a Roux-en-Y jejunal limb.[23]

Evaluation of postoperative complications

The information about complications was acquired from medical records in all patients. Each postoperative event during the hospital stay in each patient was assessed and graded according to the CDC.[10] The CCI was then calculated as the sum of all complications online by free access at www.assessurgery.com. In this study, a severe postoperative condition was defined as CCI $\geq$ 40, because it was thought that severe postoperative conditions corresponded to one or more CDC grade IV (life-threatening) complications.

Post-hepatectomy liver failure, intra-abdominal hemorrhage, and bile leakage that occurred during a patient's hospital stay were evaluated according to the definitions and grading of the International Study Group of Liver Surgery (ISGLS).[24–26] Grade B or C of the ISGLS of the 3 above complications was defined as positive in this study. Similarly, a pancreatic fistula that occurred during a patient's hospital stay was evaluated according to the International Study Group of Pancreatic Fistula (ISGPF),[27] and grade B or C was defined as positive. For liver failure, bile leakage, and pancreatic fistula, evaluation was performed at or after postoperative day (POD) −5,[24] on POD 3,[26] and on POD 5,[27] respectively.

Statistics

Univariable and multivariable analyses were performed using logistic regression. On multivariable analysis, factors identified as $p < 0.30$ on univariable analyses were examined. $P < 0.05$ was considered significant. Analyses were performed using JMP software (version 8.0.2, SAS Institute, Inc., Cary, NC, USA).

Results

Patients

The median age was 67 years (range, 40–86 years), and 151 (66%) patients were men. The primary lesion involved the extrahepatic bile duct in 150 (66%) patients, the intrahepatic bile duct in 41 (18%) patients, and the gallbladder, including the cystic duct, in 38 (17%) patients. A total of 128 (56%) patients, including 5 (2%) patients whose portal veins were occluded by tumor, underwent preoperative PVE. The data for %FLR before PVE in 105 (82%) of 128 patients who underwent PVE were obtained. In those 105 patients, the mean ± SD increase rate of % FLR after PVE compared with that before PVE was 10.8% ± 5.5%. The mean ± standard deviation (SD) final %FLR in each type of major hepatectomy and the combinations of vascular resection and PD with each type of major hepatectomy are shown in Table 2.

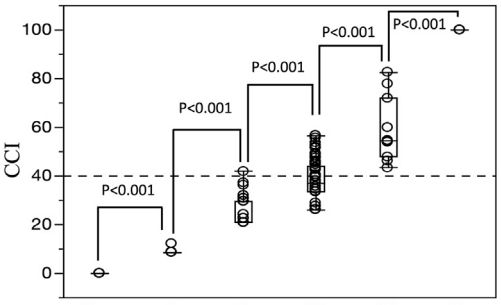
The highest CDC grade complication during the hospital stay was no complication in 14 (6%), grade I in 20 (9%), grade II in 89 (39%), grade III in 81 (35%), grade IV in 11 (5%), and grade V (hospital death) in 14 (6%) patients. The median hospital stay after surgery of 14 patients with CDC grade V was 76 days (range, 2–147 days).

The median CCI of the 229 patients was 28 (range, 0–100). The number of patients with CCI $\geq$ 40 was 57 (25%). The associations between CCI and the highest CDC grade of individual patients' complications are shown in Fig. 2.

Table 2 Surgical procedures performed

	Type of major hepatectomy			
	Right hepatectomy (S 1, 5, 6, 7, 8)	**Right trisectionectomy (S1, 4, 5, 6, 7, 8)**	**Left hepatectomy (S1, 2, 3, 4)**	**Left trisectionectomy (S1, 2, 3, 4, 5, 8)**
%FLR (mean ± SD, %)	47.9 ± 8.6	36.3 ± 8.2	70.4 ± 10.1	47.6 ± 11.3
Number of patients	122	10	82	15
Combined procedure				
PVR	86	4	28	8
AR	1	0	17	7
PD	29	2	8	2

S, Couinaud's hepatic segment; %FLR, ratio of the future liver remnant/total liver volume; SD, standard deviation; PVR, portal vein reconstruction; AR, artery reconstruction; PD, pancreatoduodenectomy.



No. of patients	None	I	II	III	IV	V
Total	14	20	89	81	11	14
Median	0	8.7	20.9	37.1	44.2	100
(range)	(0)	(8.7-12.2)	(20.9-41.8)	(26.2-56.7)	(43.3-82.6)	(100)
CCI ≥40	0	0	1	31	11	14

Figure 2 **Associations between the highest CDC grade and CCI.** CCI according to the highest CDC grade of complications that occurred in each patient. Box-and-whisker plots display median, interquartile range, and extreme values. *p*-Values were calculated using the Mann–Whitney *U*-test

The results of comparisons of risk factors between CCI < 40 and CCI ≥ 40 on univariable and multivariable analyses are shown in Table 3.

Associations between large volume of intraoperative blood loss (≥2.5 L) and various pre- or intra-operative factors were examined. The results are shown in Table 4.

Postoperative complications of patients with combined PD

Frequencies of 4 representative in-hospital complications (ISGLS grade B or C of postoperative liver failure, bile leakage, intra-abdominal hemorrhage, and ISGPF grade B or C of pancreatic fistula) were compared between patients who underwent major hepatectomy with and without PD. The results are shown in Table 5.

Discussion

Recently, postoperative courses have come to be evaluated based on a single complication that required the most invasive treatment using the CDC.[10] However, patients' conditions during the postoperative course include various complications. For example, it is possible that several CDC III or less grade complications provide patients more discomfort than a single Grade IV complication. Since CCI is a grading system that assesses the severity of postoperative conditions by the sum of all complications graded according to the CDC, the CCI enables comprehensive evaluations of patients' postoperative conditions more accurately and objectively than the conventional approach.[12]

The previous studies of independent risk factors for postoperative morbidity or mortality in cholangiocarcinoma from 6 institutions are shown in Table 1. Preoperative cholangitis was

Table 3 Risk factors for high CCI in 229 patients who underwent major hepatectomy for biliary cancer

Variable	CCI		Univariable, *p*	Multivariable		
	<40 (n = 172, 100%)	≥40 (n = 57, 100%)		Odds ratio	95% CI	*p*
Age (≥70 years)	78 (45%)	28 (49%)	0.621			
Male	110 (64%)	41 (72%)	0.266	1.26	0.63–2.61	0.516
Past history of upper abdominal laparotomy	17 (10%)	8 (14%)	0.400			
Diabetes mellitus	35 (20%)	11 (19%)	0.740			
Preoperative cholangitis	64 (37%)	32 (56%)	0.013	1.65	0.85–3.24	0.141
Body mass index (≥25 kg/m^2)	28 (16%)	10 (18%)	0.893			
Blood platelet count (≤15 × 10^4/mL)	14 (8%)	4 (7%)	0.783			
PT-INR (≥1.2)	24 (14%)	6 (11%)	0.498			
Preoperative serum albumin (<3.5 g/dL)	33 (19%)	14 (25%)	0.391			
Preoperative maximum serum T.Bil (≥100 μmol/L)	54 (31%)	21 (37%)	0.451			
ENBD or PTCD performed	134 (78%)	52 (91%)	0.017	2.36	0.86–7.75	0.100
ICG R15 (≥15%)	32 (19%)	6 (11%)	0.139	2.08	0.80–6.22	0.136
%FLR (<50%)	72 (42%)	34 (60%)	0.020	1.65	0.84–3.26	0.145
Combined gastrointestinal tract resection	11 (6%)	5 (9%)	0.551			
Combined portal vein resection and reconstruction	91 (53%)	35 (61%)	0.262	1.10	0.55–2.23	0.785
Combined hepatic artery resection and reconstruction	19 (11%)	6 (11%)	0.913			
Combined PD	22 (13%)	19 (33%)	<0.001	**2.98**	**1.38–6.43**	**0.006**
Volume of intraoperative blood loss (≥2.5 L)	38 (22%)	24 (42.1%)	0.004	**2.82**	**1.39–5.78**	**0.004**

CI, confidence interval; PT-INR, prothrombin-international ratio; ENBD, endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic biliary drainage; ICG R15, indocyanine green retention rate at 15 min; %FLR, ratio of the future liver remnant/the total liver volume.
Numerical values connected with significant factors in multivariable analysis shows bold.

Table 4 Risk factors for high volume of intraoperative blood loss in 229 patients who underwent major hepatectomy for biliary cancer

Variable	Volume of intraoperative blood loss		Univariable, *p*	Multivariable		
	<2.5 L (n = 167, 100%)	≥2.5 L (n = 62, 100%)		Odds ratio	95% CI	*p*
Age (≥70 years)	82 (49%)	24 (39%)	0.162	1.47	0.79–2.79	0.225
Male	103 (62%)	48 (77%)	0.027	2.19	1.11–4.53	0.029
Past history of upper abdominal laparotomy	17 (10%)	8 (13%)	0.558			
Diabetes mellitus	33 (20%)	13 (21%)	0.840			
Preoperative cholangitis	68 (41%)	28 (45%)	0.545			
Body mass index (≥25 kg/m^2)	26 (16%)	12 (19%)	0.495			
Blood platelets (≤15 × 10^4/mL)	8 (5%)	10 (16%)	0.007	3.63	1.26–10.87	0.018
PT-INR (≥1.2)	23 (14%)	7 (11%)	0.621			
Preoperative serum albumin (<3.5 g/dL)	32 (19%)	15 (24%)	0.323			
Preoperative maximum serum T.Bil (≥100 μmol/L)	47 (28%)	28 (45%)	0.016	2.08	1.09–3.99	0.027
ENBD or PTCD performed	136 (81%)	50 (81%)	0.892			
ICG R15 (≥15%)	23 (14%)	15 (24%)	0.063	1.5	0.66–3.29	0.327
%FLR (<50%)	76 (46%)	30 (48%)	0.698			
Combined gastrointestinal tract resection	11 (7%)	5 (8%)	0.697			
Combined portal vein resection and reconstruction	88 (53%)	38 (61%)	0.246	1.24	0.66–2.38	0.497
Combined hepatic artery resection and reconstruction	17 (10%)	8 (13%)	0.558			
Combined PD	29 (17%)	12 (19%)	0.727			

CI, confidence interval; PT-INR, prothrombin-international ratio; ENBD, endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic biliary drainage; ICG R15, indocyanine green retention rate at 15 min; %FLR, ratio of the future liver remnant/the total liver volume.

Table 5 Associations between representative postoperative complications and combined PD

Representative postoperative complication	Combined PD		*p*
	Without n = 187[a] (100%)	With n = 41	
Liver failure[b]	60 (32%)	20	0.046
Bile leakage[b]	28 (15%)	6	0.956
Intra-abdominal hemorrhage[b]	14 (8%)	7	0.074
Pancreatic fistula[c]	12 (6%)	28	<0.001

PD, pancreatoduodenectomy.
[a] One patient was excluded, because he died on postoperative day 2.
[b] Grade B/C of ISGLS definitions.
[c] Grade B/C of ISGPF definition.

identified as an independent risk factor for postoperative morbidity or mortality.[1,4,5] In the present study, preoperative cholangitis was associated with CCI ≥ 40 on the univariable analysis, but not on the multivariable analysis. The reason was thought to be that all patients in the current study with preoperative cholangitis were treated by biliary drainage, as shown in Fig. 1. Sakata *et al.* reported that the mortality rate was higher in patients who suffered from cholangitis until the date of definitive surgery than in those who were cured of cholangitis by the date of surgery.[5] Kanai *et al.* reported that, in patients who suffered from cholangitis, the morbidity rate after hepatectomy was significantly lower in patients who were treated with biliary drainage than in those not treated with biliary drainage.[28] As mentioned above, in patients who have preoperative cholangitis, the bile duct obstructed by tumor should be decompressed by biliary drainage immediately, and surgery should be delayed until the cholangitis is cured.

Volume of intraoperative blood loss (≥2.5 L) was found to be the most important risk factor for a severe postoperative condition after major hepatectomy with biliary reconstruction in the present study. Previous reports also have found that large intraoperative blood loss was associated with increased risk of complications, as shown in Table 1.[1,6,8] In the present study, preoperative risk factors for large volume of intraoperative blood loss (≥2.5 L) were identified as male sex, low blood platelet count, and high level of preoperative maximum serum total bilirubin, as shown in Table 4. The reason why a high level of preoperative maximum serum total bilirubin was identified as an independent risk factor for large volume of intraoperative blood loss was unclear. However, patients with severe obstructive jaundice are likely to have impaired production of coagulation factors because of loss of vitamin K. In addition to bile replacement,[29] administration of vitamin K might be useful for patients with obstructive severe jaundice to prevent a potential coagulation

disorder.[30] On the other hand, an attempt to identify intraoperative factors that are most closely associated with a large volume of intraoperative blood loss failed. However, blood loss usually occurs during the course of liver transection. Therefore, surgeons should make sufficient preparations prior to liver transection, such as optimization of hemodynamics, including the Pringle maneuver, clamping of the inferior vena cava,[31] and consideration of administration of tranexamic acid.[32] In patients in whom hepatopancreatoduodenectomy (HPD) is planned, liver transection might be done prior to pancreatic resection. When the amount of intraoperative blood loss is large at the completion of liver transection, one should consider delayed reconstruction, especially of the pancreatic anastomosis, in patients who undergo HPD.[33] In addition, preoperative consideration of ways to optimize %FLR is critical.[34,35] In a review of HPD by Ebata *et al.*, it was reported that the incidence of liver failure has decreased gradually in patients undergoing HPD since 2000. It was thought that this was due to the fact that PVE has been widely used in preoperative management.[36] It was also reported that in several departments in which PVE was aggressively used, lower mortality was seen in patients who underwent HPD than in those in whom PVE was not performed.[3]

In conclusion, to prevent the development of high CCI conditions in patients after major hepatectomy with biliary reconstruction for biliary cancer, surgeons should make every effort to optimize %FLR preoperatively and optimize surgical decision-making to minimize the risk of massive blood loss, including considering delayed reconstruction.

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Conflicts of interest

None declared.

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