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Prognostic Impact of Diabetes Mellitus and Extended Hepatectomy on Perihilar Cholangiocarcinoma

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Objective: To evaluate the prognostic impact of diabetes mellitus (DM) in patients who underwent resection for perihilar cholangiocarcinoma (PHCC) and the influence of remnant liver volumes on postoperative glycemic profiles and survival outcomes.

Background: The impact of DM and extended hepatectomy on survival outcomes of patients with PHCC remains unclear.

Methods: A total of 184 patients who underwent hepatectomy with extrahepatic bile duct resection for PHCC between 2002 and 2020 were retrospectively analyzed and divided into groups based on DM and future liver remnant (FLR) ≥40% or <40%. Survival outcomes and glycemic profiles were analyzed.

Results: Patients with DM (n = 34) had significantly worse overall survival compared with those without DM (n = 150; median survival time: 23.3 vs 46.7 months; $P = 0.003$) although cancer-specific survival was comparable ($P = 0.894$). Patients with DM had a higher incidence of death from infections ($P < 0.001$). Multivariate analysis identified DM as an independent prognostic factor (hazard ratio, 1.742; $P = 0.021$). DM with FLR <40% (n = 11) exhibited worse survival (median survival time: 13.7 vs 35.0 months; $P = 0.026$) and a higher incidence of death from infections ($P = 0.016$) compared with those with FLR ≥40% (n = 23). The median glucose fluctuation was larger in patients with DM and FLR <40% (80 vs 39 mg/dL; $P = 0.023$).

Conclusions: DM was an independent prognostic factor in patients with PHCC undergoing hepatectomy. DM and FLR <40% were associated with worse survival and larger glucose fluctuation postoperatively.

Keywords: perihilar cholangiocarcinoma, diabetes mellitus, extended hepatectomy, glucose fluctuation, future liver remnant

INTRODUCTION

Surgical resection is the only curative treatment for perihilar cholangiocarcinoma (PHCC).[1] Short-term outcomes for PHCC, historically associated with high morbidity and mortality, have improved considerably as a result of advances in the understanding of hepatobiliary anatomy, refinement of surgical indications, evolution of resection techniques, and development of multidisciplinary approaches to patient management.[1–4] In high-volume centers in Japan, the mortality rate for PHCC ranges between 1% and 4%.[1,5] However, the short-term outcomes have not yet been fully overcome, and the long-term outcomes remain unsatisfactory, with a 5-year survival rate of <40% after resection.[1]

In various cancers requiring surgical treatment, patients with diabetes mellitus (DM) are at increased risk of infections, metabolic derangements, and acute cardiovascular events, resulting in poor short-term outcomes.[6] Furthermore, abnormalities in glucose metabolism negatively impact long-term outcomes in patients with cancers, directly by promoting tumor progression through hyperinsulinemia and hyperglycemia and indirectly by causing treatment interruptions owing to infectious and cardiovascular events.[7] However, there are few reports on the postoperative outcomes and prognostic impact of DM in PHCC.

The liver plays an important role in maintaining glycemic homeostasis through glycogen storage, glycolysis, and gluconeogenesis.[8,9] Liver dysfunction is pathophysiologically associated with unstable glycemic control in DM owing to increased gluconeogenesis and decreased insulin sensitivity.[10] Hepatectomy, often requiring an extended resection, is essential for the excision of PHCC. However, the extent of liver resection must be carefully determined based on several critical factors. The most crucial consideration is the future liver remnant (FLR), as insufficient FLR leads to posthepatectomy liver failure (PHLF), a devastating complication with high mortality.[11] Notably, the critical FLR threshold varies significantly depending on underlying liver conditions: while 20% to 30% may be sufficient in normal liver, patients with compromised liver function due to cholestasis, chemotherapy, or chronic liver disease require 30% to 40% or more.[12] Therefore, various strategies have been developed to optimize FLR and reduce PHLF risk.[13] However, despite advances in surgical planning and perioperative management, the impact of extended hepatectomy and resultant FLR on specific patient populations, particularly those with DM, remains poorly understood. This is especially relevant given that the remnant liver volume may affect not only immediate postoperative

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liver function but also long-term glycemic control and oncological outcomes in patients with DM.

Thus, the purpose of this study was to evaluate the prognostic impact of DM in patients who underwent resection of PHCC and to investigate how remnant liver volumes affect postoperative glycemic profile and survival outcomes in patients with DM.

METHODS

Patients

A cholangiocarcinoma database prospectively maintained at Shizuoka Cancer Center was retrospectively reviewed to identify candidate patients. Among 282 patients who underwent hepatectomy combined with caudate lobectomy and extrahepatic bile duct resection of PHCC between November 2002 and December 2020, 98 patients were excluded: 79 underwent hepatopancreatoduodenectomy, 16 had other primary cancers, and 3 had incomplete data. Finally, 184 patients were included in this study. All procedures followed the Declarations of Helsinki and the ethical standards of the responsible committee on human experimentation (institutional approval no: J2023-228-2023-1-3).

Preoperative Evaluation

Tumor resectability and surgical strategy were determined by tumor status, general condition, and liver function. Tumor location, extension, lymph node metastasis, and distant metastasis were determined using multidetector-row computed tomography, ultrasonography, magnetic resonance imaging, biliary biopsy, and endoscopic or percutaneous transhepatic cholangiography.[14] Patients with obstructive jaundice underwent biliary drainage to the FLR via endoscopic or percutaneous approach. Hepatectomy was only performed once the total bilirubin levels were below 2.0 mg/dL. The liver functional reserve was assessed using the plasma clearance rate of indocyanine green (ICGK) and FLR. Specifically, patients with an ICGK-F (ICGK × proportion of FLR) >0.05 were considered candidates for resection.[15,16] Exercise tolerance, nutritional status, and organ function were evaluated via examination, laboratory tests, and physiological tests. Preoperative portal vein embolization was performed 2 to 4 weeks prior to surgery in patients scheduled for hepatectomy of at least 60% of total liver volume (mainly right hepatectomy and right or left trisectionectomy).

Diagnosis for DM

Patients who met the following criteria at their initial visit to our hospital were diagnosed with DM: (1) use of oral hypoglycemic agents and/or using insulin or (2) hemoglobin A1c (HbA1c) ≥6.5% and fasting plasma glucose levels ≥126 mg/dL or casual plasma glucose levels ≥200 mg/dL. Patients without a history of DM and who did not meet these criteria were diagnosed to be without DM. Until March 2012, HbA1c was measured based on the Japan Diabetes Society (JDS). From April 2012, HbA1c was measured based on the National Glycohemoglobin Standardization Program (NGSP). HbA1c measured by the JDS was standardized to the NGSP using the following correction formula: HbA1c (NGSP) (%) = 1.02 × HbA1c (JDS) (%) + 0.25%.[17]

Surgical Procedure and Postoperative Complications

Hepatectomy combined with caudate lobectomy and extrahepatic bile duct resection was performed for PHCC, as reported previously.[14,18] Right or left hemihepatectomy, central bisectionectomy, and right or left trisectionectomy were performed according to the tumor location.[19] A combination of vascular resection and reconstruction was performed for patients with macroscopic vascular invasion.[5,14]

All postoperative complications and in-hospital mortality were recorded and graded according to the Clavien-Dindo classification.[20] Postoperative bile leakage and PHLF were classified according to standard definitions by the International Study Group of Liver Surgery.[11,21]

Investigation of Postoperative Glycemic Profile in Patients With DM

Postoperative blood glucose (BG) levels were measured before each meal by pricking a needle in the fingertip to absorb the required amount of blood into the BG meter's sensor. In principle, patients with DM continued BG measurement until discharge. However, BG measurement for some patients with DM was completed before discharge in patients whose general condition and food intake had been stable, diabetic medications had been resumed, and short-term complications had been overcome. The average values for 3 days immediately before the end of BG measurements were used to evaluate the glycemic profiles of patients with DM. Glucose fluctuation was defined as the maximum BG level of the day minus the prebreakfast BG level because the prebreakfast BG level was not affected by the sliding scale.

Adjuvant Chemotherapy, Follow-Up, and Definition of Postoperative Events and Deaths

Adjuvant therapy was not generally administered except for patients enrolled in clinical trials.[22,23] Patients were followed up once every 3 to 6 months postoperatively for physical examination, blood tests, and computed tomography scans. Recurrence was determined based on radiological or histological evidence.

Postoperative cardio/cerebrovascular events included myocardial infarction, angina pectoris, cardiomyopathy, and stroke. Postoperative infectious events included pneumonia, cholangitis, and liver abscess. Cholangitis was diagnosed according to the diagnostic criteria of Tokyo Guidelines 2018.[24] "Death from cancer" was defined as any death in patients with recurrent cancer whose general condition had worsened due to cancer progression and additional treatment, such as chemotherapy, was impossible. "Death from other diseases" was defined as any death that was not categorized as "Death from cancer," including the death of patients with recurrent cancer with good general health. "Death from infections" was included in "Death from other diseases" and referred to deaths from sepsis owing to cholangitis or liver abscess.

Statistical Analysis

All statistical analyses were performed using the JMP software program version 18 (SAS Institute, Cary, NC, USA). Continuous variables are presented as medians with interquartile ranges and were compared using the Mann-Whitney *U* test. Categorical variables were compared using the Fisher exact probability test or the Pearson χ^2 test. The overall survival (OS), cancer-specific survival (CSS), and cumulative incidence rate of death from infections and other diseases were calculated using the Kaplan-Meier analysis. Differences in survival were measured using the log-rank test. Subgroup analyses were performed to examine the impact of FLR volume on survival outcomes, using the cut-off value of 40% according to previous reports.[25,26] Univariate and multivariate analyses for prognostic factors associated with OS were performed using a Cox proportional hazard regression model. A matched analysis was performed to minimize bias due to prognostic factors other than DM and validate the results. Patients with and without DM were matched in a 1:1 ratio based on independent prognostic factors other than DM.

Table 1.

Clinicopathological Factors and Postoperative Outcomes in Patients With and Without DM

	DM−		DM+		
Variable	**n = 150**		**n = 34**		***P***
Preoperative factors					
Age, yr	71	(65–75)	75	(68–78)	**0.012**
Sex, male, n (%)	104	(69.3)	23	(67.7)	0.848
Body mass index, kg/m^2	22.0	(20.2–23.7)	22.1	(21.2–24.3)	0.290
≥25, n (%)	21	(14.0)	4	(11.8)	1.000
Comorbidity, n (%)					
Metabolic diseases	67	(44.7)	21	(61.8)	0.072
Cardiovascular diseases	13	(8.7)	3	(8.8)	1.000
Cranial nerve diseases	8	(5.3)	5	(14.7)	0.068
Liver diseases	8	(5.3)	1	(2.9)	1.000
Kidney diseases	1	(0.7)	1	(2.9)	0.336
Bismuth type, IV, n (%)	55	(36.7)	9	(26.5)	0.260
Biliary drainage, n (%)	106	(70.7)	25	(73.5)	0.739
Portal vein embolization, n (%)	81	(54.0)	20	(58.8)	0.610
FLR (%)	46.9	(38.9–62.8)	45.5	(37.3–62.4)	0.524
HbA1c,* %	5.5	(5.1–5.8)	6.6	(6.0–7.2)	**<0.001**
Preoperative therapy for DM, oral/insulin/exercise, and diet			16/3/15		
Creatinine clearance, mL/min	74.7	(61.5–88.5)	74.2	(54.0–87.7)	0.216
CA19-9, U/mL	47	(13–165)	47	(23–136)	0.385
Surgical factors and outcomes					
Type of hepatectomy, n (%)					0.852
Right hemihepatectomy	48	(32.0)	14	(41.2)	
Right trisectionectomy	16	(10.7)	3	(8.8)	
Left hemihepatectomy	54	(36.0)	10	(29.4)	
Left trisectionectomy	31	(20.6)	7	(20.6)	
Central bisectionectomy	1	(0.7)	0	(0.0)	
Operation time, min	511	(441–604)	523	(472–615)	0.628
Blood loss, g	1297	(891–1874)	1230	(891–1684)	0.620
Postoperative complication, C–D ≥IIIa, n (%)	61	(40.7)	14	(41.2)	0.956
In-hospital mortality, n (%)	2	(1.3)	3	(8.8)	**0.045**
Bile leakage, ISGLS grade ≥B, n (%)	34	(22.7)	5	(14.7)	0.361
Liver failure, ISGLS grade ≥B, n (%)	14	(9.3)	5	(14.7)	0.355
Postoperative hospital stays, d	21	(16–31)	23	(18–34)	0.332
Pathological factors					
Histological grade,† G1, n (%)	49	(32.7)	7	(20.6)	0.167
T category,† ≥T3, n (%)	79	(52.7)	18	(52.9)	0.977
N category,† N1/2, n (%)	62	(41.3)	15	(44.1)	0.766
Lymphatic invasion, n (%)	106	(70.7)	27	(79.4)	0.304
Venous invasion, n (%)	66	(44.0)	18	(52.9)	0.345
Perineural invasion, n (%)	127	(84.7)	33	(97.1)	0.086
Surgical margin, R1, n (%)	32	(21.3)	9	(26.5)	0.516
Postoperative factors and events					
Adjuvant chemotherapy, n (%)	24	(16.0)	4	(11.8)	0.791
Recurrence, n (%)	96	(64.0)	24	(70.6)	0.467
Cardio/cerebrovascular events, n (%)	7	(4.7)	6	(17.7)	**0.008**

Significant values are given in boldface. Continuous variables are presented as medians, and interquartile ranges are shown in parentheses.

*Patients with available data were analyzed. n = 127 (DM−: n = 93; DM+: n = 34).

†According to the eighth edition of the Union for International Cancer Control Staging.

CA19-9 indicates carbohydrate antigen 19-9; C–D, Clavien-Dindo classification; ISGLS, International Study Group of Liver Surgery.

Variables that showed statistical significance in univariate analysis were included in the multivariate model. The Spearman correlation analysis was used to assess the correlation between FLR and glucose fluctuation. All statistical tests were 2-sided, and $P < 0.05$ were considered statistically significant.

RESULTS

Clinicopathological Factors and Postoperative Outcomes According to DM Status

Of the 184 patients, 34 (18.5%) were diagnosed with DM. Table 1 shows the clinicopathological factors and postoperative outcomes in patients with and without DM. In preoperative factors, the median age of patients with DM was significantly higher than that of patients without DM. The in-hospital mortality rate of patients with DM was significantly higher than that of those without DM (8.8% vs 1.3%). Among the patients with DM, 16 (47.1%) were treated with oral hypoglycemic agents, 3 (8.8%) were treated with insulin therapy, and 15 (44.1%) were managed through exercise and diet therapy. There were no significant differences in metabolic, cardiovascular, cranial nerve, liver, or kidney comorbidities between the 2 groups. None of the 184 patients included in this study had a creatinine clearance <30 mL/min. In the non-DM group, 1 patient succumbed to PHLF and another to sepsis, whereas, in the DM group, 1 patient died from PHLF, 1 from sepsis, and an additional one from pneumonia. Concerning postoperative factors and events, adjuvant chemotherapy and recurrence rates were similar between the groups. Notably, patients with DM showed a higher incidence of cardio/cerebrovascular events than those without DM (17.7% vs 4.7%).

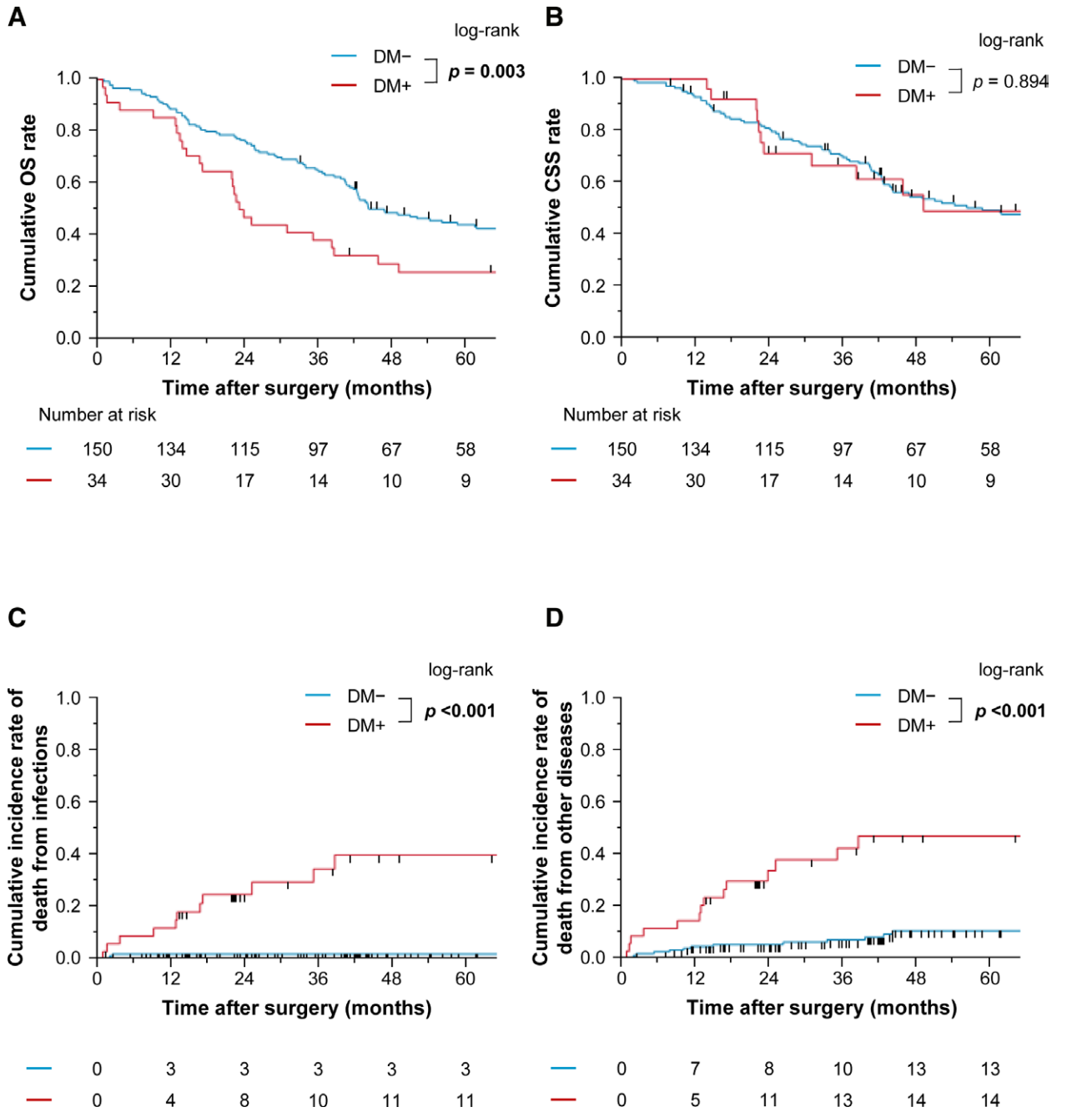

Figure 1. Kaplan-Meier curves of survival outcomes according to DM status. A, Kaplan-Meier curves for OS. B, Kaplan-Meier curves for CSS. C, Kaplan-Meier curves for incidence of death from infections. D, Kaplan-Meier curves for incidence of death from other diseases. The differences were calculated using the log-rank test.

Survival Outcomes According to DM Status and Preoperative Therapy for DM

The median observation period in the censored cases was 76.8 (range, 33.0–176.5) months. Figure 1 shows the survival outcomes of patients with and without DM. The OS of patients with DM was significantly worse than that of patients without DM (median survival time: 23.3 vs 46.7 months; $P = 0.003$; Fig. 1A). However, the CSS of patients with DM was comparable to that of patients without DM ($P = 0.894$; Fig. 1B), and the cumulative incidence rate of death from infections was significantly higher in patients with DM than in those without DM ($P < 0.001$; Fig. 1C). Thirty-four patients died from other diseases, as detailed in Supplemental Table 1, http://links.lww.com/AOSO/A471. The proportion of deaths from infectious events was high, particularly among patients with DM. The cumulative incidence of death from other diseases was significantly higher in patients with DM than in patients without DM ($P < 0.001$; Fig. 1D).

Supplemental Figure 1, http://links.lww.com/AOSO/A469, shows the survival outcomes of patients with DM according to preoperative therapy for DM. There were no differences in OS among patients with DM according to preoperative therapy for DM.

Prognostic Factors

Prognostic factors for OS were analyzed (Table 2). Univariate and multivariate analyses identified pathological lymph node metastasis (hazard ratio [HR], 2.215; $P < 0.001$), DM (HR, 1.742; $P = 0.021$), venous invasion (HR, 1.705; $P = 0.006$), and

Table 2.

Univariate and Multivariate Analyses Associated With OS

Variable		MST, mo	Univariate *P*	Multivariate HR	Multivariate 95% CI	Multivariate *P*
Age, yr	≥70	40.4	**0.030**	1.448	0.997–2.130	0.052
	<70	52.0				
Body mass index, kg/m^2	≥25	42.6	0.547			
	<25	43.5				
Metabolic diseases	Present	42.2	0.915			
	Absent	44.0				
Cardiovascular diseases	Present	42.2	0.715			
	Absent	42.6				
Cranial nerve diseases	Present	42.5	0.817			
	Absent	43.5				
Liver diseases	Present	68.2	0.884			
	Absent	42.6				
Kidney diseases	Present	23.8	0.184			
	Absent	43.5				
DM	Present	23.3	**0.006**	1.742	1.090–2.705	**0.021**
	Absent	46.7				
Bismuth type	IV	41.4	0.400			
	I/II/III	45.6				
FLR, %	<40	40.3	0.382			
	≥40	43.9				
Creatinine clearance, mL/min	<60	42.5	0.885			
	≥60	43.5				
CA19-9, U/mL	>37	36.2	**<0.001**	1.551	1.075–2.261	**0.019**
	≤37	78.1				
Postoperative complication, C–D	≥IIIa	42.2	0.060			
	≤II	49.0				
Histological grade*	Other	40.6	**0.031**	1.346	0.903–2.050	0.146
	G1	44.2				
Pathological T category*	≥T3	40.4	0.113			
	≤T2	46.7				
Pathological N category*	N1/2	32.6	**<0.001**	2.215	1.472–3.362	**<0.001**
	N0	78.5				
Lymphatic invasion	Present	40.1	**0.005**	1.250	0.738–2.053	0.398
	Absent	78.5				
Venous invasion	Present	36.2	**<0.001**	1.705	1.166–2.507	**0.006**
	Absent	68.2				
Perineural invasion	Present	40.3	**<0.001**	1.853	0.902–4.127	0.095
	Absent	196.3				
Surgical margin	R1	37.0	**0.009**	1.320	0.862–1.979	0.197
	R0	46.8				
Adjuvant therapy	Absent	42.6	0.875			
	Present	42.2				

Significant values are given in boldface.

*According to the eighth edition of the Union for International Cancer Control Staging.

CA19-9 indicates carbohydrate antigen 19-9; C–D, Clavien-Dindo classification; CI, confidence interval; MST, median survival time.

carbohydrate antigen 19-9 (HR, 1.551; $P = 0.019$) as independent prognostic factors.

Validation After Matching

Patients with and without DM were matched based on independent prognostic factors, including pathological lymph node metastasis, venous invasion, and carbohydrate antigen 19-9 level. Supplemental Table 2, http://links.lww.com/AOSO/A472, reports the clinicopathological factors and postoperative outcomes in patients with and without DM following matching. The median age of patients with DM was significantly higher than that of patients without DM. Furthermore, survival outcomes before and after matching were similar between the 2 groups (Supplemental Figure 2, see http://links.lww.com/AOSO/A470).

Survival Outcomes According to DM and FLR Status

To investigate the impact of DM and remnant liver volume on the postoperative outcomes, patients were divided into four groups based on the presence or absence of DM and FLR ≥40% or <40% as follows: DM–/FLR ≥40% group (n = 106), DM–/FLR <40% group (n = 44), DM+/FLR ≥40% group (n = 23), and DM+/FLR <40% group (n = 11). The OS in the DM+/FLR <40% group was significantly worse than in the other 3 groups (Fig. 2A). The CSS in the DM+/FLR <40% group tended to be worse than that in the DM+/FLR ≥40% group; however, the difference was not significant ($P = 0.107$; Fig. 2B). The cumulative incidence rate of death from infections was comparable in the DM–/FLR ≥40% and DM–/FLR <40% groups ($P = 0.866$), whereas it was significantly higher in the DM+/FLR <40% group than in the DM+/FLR ≥40% group ($P = 0.016$; Fig. 2C). The cumulative incidence of death from other diseases tended to be higher in the DM+/FLR <40% group than in the DM+/FLR ≥40% group ($P = 0.116$; Fig. 2D).

Clinicopathological Factors and Postoperative Outcomes According to DM and FLR Status

Table 3 shows the clinicopathological factors and postoperative outcomes in patients with DM according to FLR. As for preoperative factors, the median body mass index and proportion of portal vein embolization were significantly lower and higher in the FLR <40% group than in the FLR ≥40% group. The FLR <40% group had a higher rate of right hepatectomy and a lower rate of left hepatectomy.

An additional analysis of readmission due to postoperative infectious events was performed for 31 patients, excluding 3 patients who died of surgical complications. The readmission rate, the number of readmissions, and the duration of readmission due to postoperative infectious events were significantly higher and longer in the FLR <40% group than in the FLR ≥40% group.

Supplemental Table 3, http://links.lww.com/AOSO/A473, presents the clinicopathological factors and postoperative outcomes in patients with FLR <40% according to DM. There were no significant differences in clinicopathological factors or postoperative outcomes between the groups.

Glycemic Profiles of Patients With DM According to FLR

The correlation between glycemic profile and FLR in patients with DM was analyzed (Table 4). Among the 34 patients with DM, 26 were included in the analysis, excluding 5 patients without postoperative BG data and 3 patients who died from surgical complications. Hypoglycemia <70 mg/dL or hyperglycemia >400 mg/dL did not occur. The maximum BG levels and glucose fluctuation were significantly higher and larger in the FLR <40% group than in the FLR ≥40% group. In patients with available data (n = 19), HbA1c levels from discharge to 6 months postoperatively were significantly higher in the FLR <40% group and tended to remain elevated up to 1 year postoperatively.

Only 11 patients (FLR ≥40% group: n = 5; FLR <40% group: n = 6) had glycemic profile data available for patients without DM under the same condition. The median prebreakfast BG levels (145 vs 130 mg/dL; $P = 0.382$), maximum BG levels (169 vs 161 mg/dL; $P = 0.482$), average BG levels (144 vs 135 mg/dL; $P = 0.522$), and glucose fluctuation (24 vs 46 mg/dL; $P = 0.482$) were not significantly different between the FLR ≥40% and FLR <40% groups.

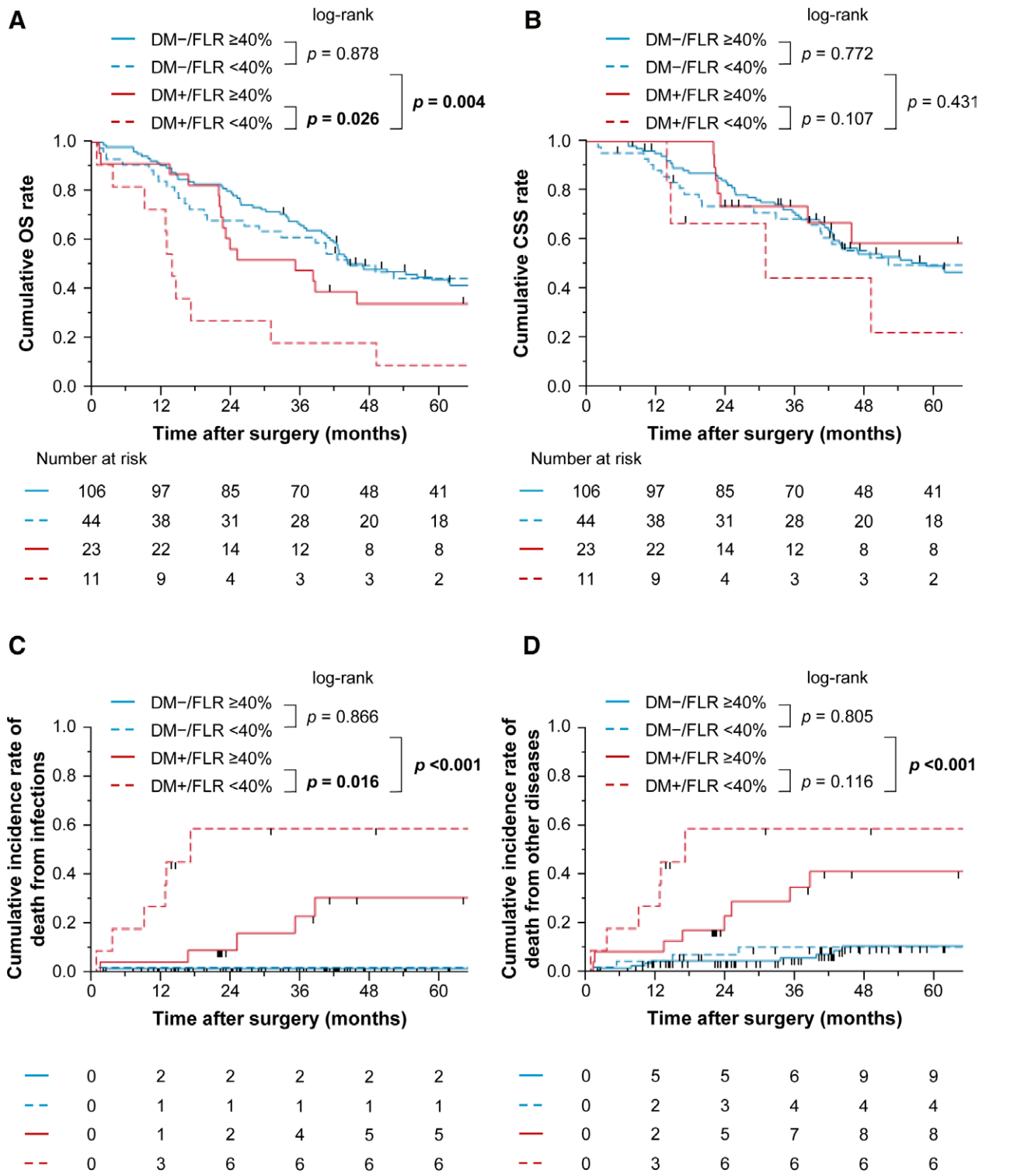

Figure 2. Kaplan-Meier curves of survival outcomes according to DM and FLR status. A, Kaplan-Meier curves for OS. B, Kaplan-Meier curves for CSS. C, Kaplan-Meier curves for incidence of death from infections. D, Kaplan-Meier curves for incidence of death from other diseases. The differences were calculated using the log-rank test.

Figure 3 illustrates the correlation between FLR and glucose fluctuation in 26 patients with DM who had postoperative BG data and did not experience mortality from surgical complications. The Spearman rank correlation coefficient ($\rho = -0.463$) indicates a significant negative correlation between FLR and glucose fluctuation ($P = 0.017$), suggesting that as FLR increases, glucose fluctuation tends to decrease.

DISCUSSION

The present study demonstrated that patients with PHCC and DM, especially those with FLR <40%, had poor OS and a high cumulative incidence rate of death from infections and other diseases. Patients with DM exhibited a higher rate of surgical mortality and incidence of postoperative cardio/cerebrovascular events than those without DM. In the DM group, the

Table 3.

Clinicopathological Factors and Postoperative Outcomes in Patients With DM According to Future Liver Remnant

	FLR ≥40%		FLR <40%		
Variable	**n = 23**		**n = 11**		***P***
Preoperative factors					
Age, yr	76	(66–78)	72	(69–78)	0.825
Sex, male, n (%)	15	(65.2)	8	(72.7)	1.000
Body mass index, kg/m^2	23.9	(21.8–24.8)	21.4	(19.5–21.9)	**0.002**
≥25, n (%)	4	(17.4)	0	(0.0)	0.280
Comorbidity, n (%)					
Metabolic diseases	15	(65.2)	6	(54.6)	0.709
Cardiovascular diseases	3	(13.0)	0	(0.0)	0.535
Cranial nerve diseases	4	(17.4)	1	(9.1)	1.000
Liver diseases	1	(4.4)	0	(0.0)	1.000
Kidney diseases	0	(0.0)	1	(9.1)	0.324
Bismuth type, IV, n (%)	6	(26.1)	3	(27.3)	1.000
Biliary drainage, n (%)	16	(69.6)	9	(81.8)	0.682
Portal vein embolization, n (%)	10	(43.5)	10	(90.9)	**0.011**
HbA1c, %	6.6	(6.0–7.1)	6.8	(5.6–7.8)	0.796
Preoperative therapy for DM, oral/insulin/exercise, and diet	10/2/11		6/1/4		0.812
Creatinine clearance, mL/min	76.2	(54.2–87.7)	57.8	(45.0–79.8)	0.232
CA19-9, U/mL	44	(20–231)	66	(37–104)	0.377
Surgical factors and outcomes					
Type of hepatectomy, n (%)					**0.038**
Right hemihepatectomy	7	(30.4)	7	(63.6)	
Right trisectionectomy	1	(4.4)	2	(18.2)	
Left hemihepatectomy	10	(43.5)	0	(0.0)	
Left trisectionectomy	5	(21.7)	2	(18.2)	
Operation time, min	525	(493–616)	508	(452–592)	0.840
Blood loss, g	1250	(824–2013)	1144	(913–1506)	0.519
Postoperative complication, C–D ≥IIIa, n (%)	8	(34.8)	6	(54.6)	0.458
In-hospital mortality, n (%)	2	(8.7)	1	(9.1)	1.000
Bile leakage, ISGLS Grade ≥B, n (%)	4	(17.4)	1	(9.1)	1.000
Liver failure, ISGLS grade ≥B, n (%)	3	(13.0)	2	(18.2)	1.000
Postoperative hospital stays, d	22	(18–34)	23	(19–34)	0.768
Pathological factors					
Histological grade,* G1, n (%)	4	(17.4)	3	(27.3)	0.656
T category,* ≥T3, n (%)	11	(47.8)	7	(63.6)	0.477
N category,* N1/2, n (%)	10	(43.5)	5	(45.5)	1.000
Lymphatic invasion, n (%)	18	(78.3)	9	(81.8)	1.000
Venous invasion, n (%)	13	(56.5)	5	(45.5)	0.717
Perineural invasion, n (%)	22	(95.7)	11	(100.0)	1.000
Surgical margin, R1, n (%)	7	(30.4)	2	(18.2)	0.682
Postoperative factors and events					
Adjuvant chemotherapy, n (%)	3	(13.0)	1	(9.1)	1.000
Recurrence, n (%)	16	(69.6)	8	(72.7)	1.000
Cardio/cerebrovascular events, n (%)	3	(13.0)	3	(27.3)	0.363
Readmission due to postoperative infectious events,† n (%)	12	(57.1)	10	(100.0)	**0.030**
Number of readmissions due to postoperative infectious events,† n (%)	1	(0–1)	2	(1–5)	**0.010**
Hospital stays for readmission due to postoperative infectious events, d†	6	(0–34)	32	(19–117)	**0.020**

Significant values are given in boldface. Continuous variables are presented as medians, and interquartile ranges are shown in parentheses.

*According to the eighth edition of the Union for International Cancer Control Staging.

†Patients with surgical mortality were excluded from the analysis. n = 31 (FLR ≥40%: n = 21; FLR <40%: n = 10).

CA19-9 indicates carbohydrate antigen 19-9; C–D, Clavien-Dindo classification; ISGLS, International Study Group of Liver Surgery.

readmission rate, the number of readmissions, and the duration of readmission due to postoperative infectious events were higher and longer in the FLR <40% group. Analysis of glycemic profiles of patients with DM in the stable postoperative state showed that glucose fluctuation was larger in patients with FLR <40%, and HbA1c levels remained high 6 months to 1 year after hepatectomy. Moreover, FLR and glucose fluctuation were negatively correlated. These findings indicate that adequate glycemic control may be necessary for patients with PHCC and DM not only in the perioperative period but also over a long period after surgery, especially for patients who have undergone extended hepatectomy. This underscores the need for enhanced postoperative glycemic monitoring and infection control measures in patients with DM and low FLR undergoing resection of PHCC, given the increased mortality from infections associated with these factors.

In this study, DM was identified as an unfavorable prognostic factor in patients undergoing hepatectomy for PHCC. Existing literature has noted the correlation between DM and survival outcomes in patients with cancer, indicating that DM can affect survival outcomes directly and indirectly.[7,27] Direct pathways include the promotion of tumor growth by elevated levels of insulin and insulin-like growth factors, as well as the facilitation of a metastatic milieu via increased reactive oxidative species production and structural alterations in the basement membrane.[9,28] Indirectly, survival outcomes may be compromised by suboptimal treatment efficacy or by delays and disruptions in treatment because of diabetic complications such as renal dysfunction and peripheral neuropathy, infections, and severe cardio/cerebrovascular incidents. In this study, patients with DM exhibited worse OS and a higher mortality rate of other diseases than those without DM. Nonetheless, the CSS of patients with

Table 4.

Glycemic Profiles of Patients With DM According to Future Liver Remnant

Variable		FLR ≥40% n = 18		FLR <40% n = 8		*P*
Postoperative, d	Hospital stays	20	(18–31)	25	(17–44)	0.738
	End of BG measurement	17	(14–22)	25	(17–39)	0.106
Postoperative BG profile, mg/dL	Prebreakfast	119	(104–131)	116	(99–126)	0.523
	Maximum	172	(139–185)	197	(161–229)	**0.028**
	Average	145	(125–157)	156	(128–167)	0.267
	Glucose fluctuation	39	(32–72)	80	(60–96)	**0.023**
HbA1c, %	Preoperative	6.5	(6.0–7.0)	6.8	(6.6–8.1)	0.132
	Discharge to postoperative 6 months*	5.9	(5.6–6.7)	8.0	(6.5–10.0)	**0.018**
	Postoperative 6 months to 1 year†	6.4	(5.9–6.9)	7.5	(6.9–8.4)	0.069

Significant values are given in boldface. Continuous variables are presented as medians, and interquartile ranges are shown in parentheses.
*Patients with available data were analyzed. FLR ≥40%: n = 13; FLR <40%: n = 6.
†Patients with available data were analyzed. FLR ≥40%: n = 11; FLR <40%: n = 8.

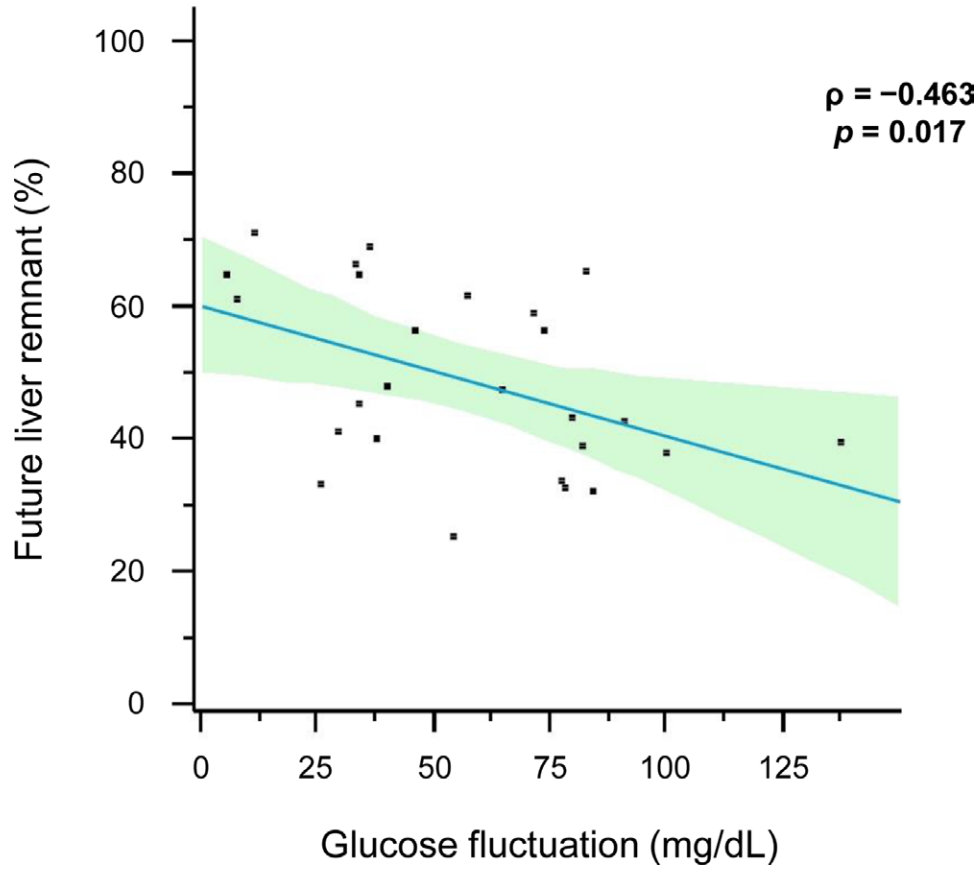

Figure 3. Spearman rank correlation analysis for the correlation between FLR and glucose fluctuation (n = 26).

DM was on par with that of patients without DM. Consequently, our results suggest that the indirect consequences of DM might exert a more profound influence on the survival outcomes of patients with PHCC compared with direct consequences.

Interestingly, the results of this study revealed that patients with DM and FLR <40% had particularly poor survival outcomes. Animal studies have shown metabolic changes, such as increased insulin and glucagon and large glucose fluctuation, after extended hepatectomy.[29,30] Similar outcomes were anticipated in this study. However, in patients without DM, the glycemic profile and incidence of death from infections and other diseases were comparable between the FLR <40% and FLR ≥40% groups. This suggests that the influence of remnant liver volume on BG levels might depend on the presence of DM. BG homeostasis is maintained by various organs, with the pancreas playing a crucial role. The glycemic profiles of patients without DM might remain stable even after extended hepatectomy, regulated by pancreatic hormones. In contrast, extended hepatectomy in patients with compromised pancreatic endocrine function, such as DM, could further destabilize glycemic control.

This study showed the clinical importance of remnant liver volume after hepatectomy in patients with DM. In general, the surgical procedure for hepatectomy is determined by the tumor location, with limited consideration given to remnant liver volume. Right hemihepatectomy is typically performed for bismuth type I/II PHCC.[31,32] However, a recent report has shown that left hemihepatectomy with arterial resection and reconstruction for bismuth type I/II PHCC results in a lower incidence rate of PHLF and yields survival outcomes comparable to that

via right hemihepatectomy,[14] and left hemihepatectomy is preferable to right hemihepatectomy in short-term outcomes.[33,34] Furthermore, our findings suggest that less extensive resections, such as left hemihepatectomy when feasible, could reduce deaths from other diseases, especially infectious diseases, in high-risk patients with DM. Future research could explore the balance between oncologic outcomes and metabolic stability in patients undergoing conservative resection, potentially guiding the choice between left resection and right resection based on preoperative assessment.

The previous discussion underscores the critical role of glycemic control in patients with PHCC, particularly those with DM who have undergone extended hepatectomy. Initially, it is essential to recognize that the glycemic profile of these patients is significantly altered, exhibiting a marked increase in glucose fluctuation. During the perioperative period, insulin-based glycemic management should adhere to the guidelines prescribed by the American Diabetes Association.[35] In the outpatient setting, regular monitoring of BG and HbA1c levels is imperative to assess whether DM treatments are effective. Postsurgery chemotherapy necessitates vigilance for hyperglycemia, induced by steroid administration, and hypoglycemia, which can result from reduced food intake because of nausea and vomiting. In cases of extended hepatectomy, the constrained selection of medications due to reduced liver volume and elevated glucose fluctuation may make glycemic control more difficult. Based on this recognition, attention, and evaluation, collaborating with physicians specializing in DM is vital to establish stringent goals and enhance postoperative glycemic management. Enhanced glycemic control may prevent deaths from other diseases, including deaths from infections, and this is a subject for future research.

This study has several limitations. First, this was a single-center retrospective study, and the sample size was relatively small, with a limited number of patients with DM and FLR <40%. Importantly, particular caution should be exercised when interpreting our results regarding the sensitivity analysis of FLR. Moreover, the period of this study was long and included a comprehensive analysis of the population affected by various changes in treatment patterns. Second, no standardized rules for BG management had been established, and treatment decisions were made by the physician in charge. Third, BG was measured by a single shot, not by continuous monitoring. Furthermore, due to the study design, the glycemic profile was only evaluated for 3 days immediately before the end of BG measurements. Thus, accurate glycemic trends might not be obtained. To address these limitations, validating these preliminary through long-term observations in a large multicenter cohort is warranted.

In conclusion, the results of this study showed that DM was an important prognostic factor for patients with PHCC and was strongly associated with death from infections and other diseases. In particular, patients requiring hepatectomy with FLR <40% were more likely to have impaired glucose tolerance and increased infectious events, and HbA1c levels remained high 6 months to 1 year after hepatectomy. Patients with PHCC and DM, especially those undergoing extended hepatectomy, may need appropriate glycemic control not only in the perioperative period but also over a long period after surgery.

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