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ORIGINAL ARTICLE

Usefulness of frailty to predict short- and long-term outcomes in patients who have undergone major hepatectomy for perihilar cholangiocarcinoma

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Abstract

Aim: The influence of frailty on outcomes after hepatectomy for perihilar cholangiocarcinoma (PHCC) remains unclear. This study aimed to investigate the impact of frailty on the incidence of postoperative complications and survival after major hepatectomy for PHCC.

Methods: A total of 87 patients who had undergone surgery for PHCC between 2007 and 2020 were enrolled in this study. Frailty was scored retrospectively using the Clinical Frailty Scale (CFS). The survival and incidence of postoperative complications were compared based on the degree of frailty, and their risk factors were analyzed.

Results: The overall survival of the CFS score 1-2 group was significantly higher than that of the CFS score 3-7 group ($P = .01$). The survival benefit was especially observed in stage I or II PHCC. Furthermore, there were significant differences between the CFS score 1-3 group and the CFS score 4-7 group in the incidence of Clavien–Dindo classification grade ≥ IIIa (39.4% vs 70.6%; $P = .03$). Frailty was an independent risk factor for severe postoperative complications (odds ratio, 4.11; 95% confidence interval, 1.18-15.20; $P = .03$) and the incidence of systemic complications ($P < .01$).

Conclusion: Frailty is a predictive factor for short- and long-term outcomes in patients who have undergone major hepatectomy for PHCC.

KEYWORDS
frailty, hepatectomy, perihilar cholangiocarcinoma, postoperative complications, survival analysis

1 | INTRODUCTION

The proportion of elderly patients requiring surgery for gastrointestinal cancer has increased over the last few decades[1] and is expected to continue increasing. Although aging is a contributing factor for short- and long-term outcomes, some patients have worse outcomes with age than expected. These patients are often associated with frailty—an impaired physiological condition resulting from aging that increases vulnerability to stress.[2,3] Recently, several studies have reported that frailty is a more significant risk factor than aging for postoperative complications or long-term survival after surgery for various cancers, including gastrointestinal cancer.[4–11]

Perihilar cholangiocarcinoma (PHCC) is the most common subtype of cholangiocarcinoma. This malignancy usually requires highly invasive surgical procedures with a relatively large volume of liver excision and biliary tract reconstruction. Therefore, it is generally not offered to the elderly population.[1,12–16] Several studies have evaluated surgery for PHCC in elderly patients.[1,12] Although these reports revealed that the rate of postoperative complications and long-term survival were not significantly different between elderly and younger patients, a less invasive surgical procedure was more frequently selected in elderly patients. While some studies have reported an association between the increased risk of mortality, morbidity, and prognosis with aging or frailty,[5–9,11] the influence of frailty on outcomes after hepatectomy for PHCC remains unclear.

This study was designed to investigate the impact of frailty on the incidence of postoperative complications and survival after major hepatectomy for PHCC.

2 | METHODS

2.1 | Patients

A total of 87 patients who had undergone major hepatectomy for pathologically proven PHCC at the Division of Gastroenterological, Hepato-Biliary-Pancreatic, Transplantation and Pediatric Surgery, Department of Surgery, Shinshu University Hospital between January 2007 and December 2020 were enrolled in this study. Four patients who had undergone limited surgery were excluded. R2 resection and peri-EQUATION operative deaths were also excluded from the survival analysis.

The study protocol was approved by the Shinshu University Hospital Ethics Committee (approval number: 4999), and the study conformed to the provisions of the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out on the website, and those who rejected were excluded.

2.2 | Frailty assessment

Frailty was scored retrospectively using the Canadian Study of Health and Aging Clinical Frailty Scale (CFS).[3] CFS scoring is as follows: CFS 1 = very fit; CFS 2 = fit; CFS 3 = managing well; CFS 4 = living with very mild frailty; CFS 5 = living with mild frailty; CFS 6 = living with moderate frailty; CFS 7 = living with severe frailty; CFS 8 = living with very severe frailty; and CFS 9 = terminally ill. CFS scores were evaluated using medical records at the initial visit or on admission, a summary of medicines recorded by the pharmacist, and fall prevention scores recorded by nurses. The CFS score was assessed by at least two investigators, and the lower score was applied in case of differences. All patients were blinded to the medical records, except for those mentioned above.

2.3 | Endpoint assessment and data collection

The survival and incidence of postoperative complications were compared between the frailty and nonfrailty groups, and their risk factors were analyzed.

Patient demographics, perioperative factors, postoperative outcomes, tumor characteristics, and survival were retrospectively collected from the medical records. The final pathologic stage was identified using the eighth edition of the *TNM Classification of Malignant Tumors* by the Union for International Cancer Control (UICC).[17] Postoperative complications were categorized according to the Clavien–Dindo classification (CD).[18] Posthepatectomy liver failure (PHLF) and posthepatectomy biliary leakage (PHBL) were defined according to the International Study Group of Liver Surgery standards in 2011.[19,20]

2.4 | Perioperative management and surgical procedure

Upon the development of obstructive jaundice, biliary drainage of the future liver remnant was initiated, and bile collected by the drainage catheter was taken orally until surgery. The indocyanine green (ICG) test has been routinely performed postoperatively along with general blood sampling. Indications for hepatectomy were determined according to Makuuchi's criteria,[21] ICG clearance of the remnant liver,[22] and the remnant hepatocellular uptake index.[23] Major hepatectomy with resection of the caudate lobe and extrahepatic bile duct has been routinely performed for PHCC. Drinking water was initiated on postoperative day (POD) 1 along with symbiotics, and no enteral tube was used. Postoperative rehabilitation was also initiated on POD 1.

Hematological examination was performed daily in the first week after hepatectomy, and the bilirubin concentration in the abdominal drainage fluid was routinely measured on postoperative d 1 and 3.

2.5 | Statistical analysis

The results are presented as median values with ranges. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, and quantitative variables were analyzed using the Mann–Whitney *U* test. Variables with $P < .10$ by univariate analysis were included in multivariate analyses using the multiple logistic regression model. Quantitative variables were categorized into two groups according to the cutoff value obtained from the receiver operating characteristic curve. Odds ratios (ORs) and 95% confidence intervals (CIs) for the incidence of postoperative complications were also calculated. Survival after surgery was estimated using the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using JMP version 13.2.1 (SAS Institute, Inc.). $P < .05$ was considered statistically significance.

3 | RESULTS

3.1 | Baseline characteristics and survival after surgery

The distribution of CFS scores among the 87 surveyed patients is shown in Figure 1. Preoperative demographics, operative outcomes, and pathological characteristics of patients with a CFS score of 1-2 and 3-9 are summarized in Tables 1 and 2, respectively. The preoperative variables and surgical outcomes were similar between the two groups, except for the American Society of Anesthesiologists physical status score. Pathologically, the UICC T factor, N factor, and UICC TNM stage of the CFS score 3-9 group were significantly higher than those of the CFS score 1-2 group. The R0 resection rate or application rate of adjuvant chemotherapy was not significantly different between the two groups.

The overall survival (OS) of the CFS score 1-2 group was significantly higher than that of the CFS score 3-9 group (5-year OS rate: 41.8% vs 10.2%, *P* = .01; Figure 2). This trend was also observed in disease-specific survival (Figure S1). When patients in both groups were stratified into two subgroups according to TNM stage (0-II or III/IV), the difference in OS was larger in stage 0-II patients (5-year OS rate: 44.5% vs 13.0%; *P* = .02; Figure 3A). Meanwhile, there was no significant difference in OS between the two groups in stage III/IV patients (5-year OS rate: 40.0% vs 0%, *P* = .46; Figure 3B).

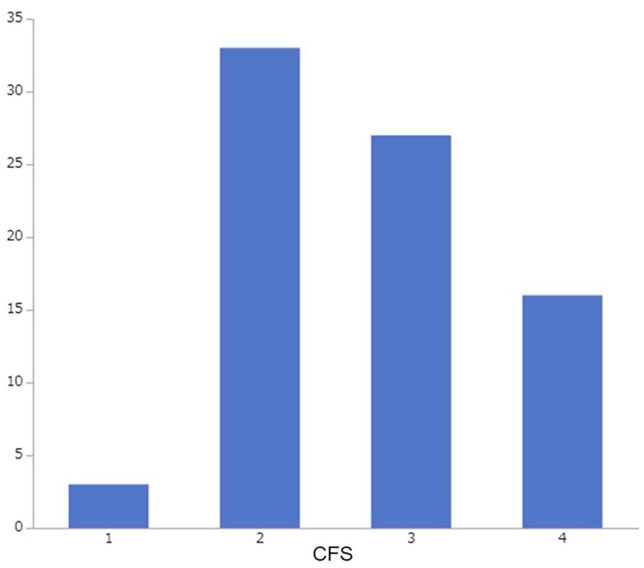

FIGURE 1 The distribution of CFS scores among the 87 surveyed patients. CFS, Clinical Frailty Scale

3.2 | Analysis of prognostic factors

Clinicopathological factors were assessed to identify prognostic factors in this population. Univariate analysis revealed that an operation time >663 mins (*P* = .04) and CFS score 3-9 (*P* = .01) were significantly associated with OS. Although there was no significant difference, the OS of patients with stage III/IV UICC was longer than that of patients with UICC stage I/II (*P* = .09). Confounding factors with the above three factors (UICC T factor, UICC N factor, and the value of bilirubin) were excluded from the multivariate analysis of prognostic factors. Multivariate analysis using the Cox proportional hazards model revealed that a CFS score of 3-9 was an independent prognostic factor for OS (hazard ratio, 2.31; 95% CI, 1.14-4.87; *P* = .02; Table 3).

3.3 | Incidence and risk factors of major postoperative complications

The incidence of postoperative complications of CD grade ≥IIIa and ≥IIIb were compared using a CFS score of 1-2 and 3-9 or a CFS score of 1-3 and 4-9 (Figure S2). There was a significant difference in the incidence of postoperative complications between the two groups. In the latter population, preoperative variables and outcomes were similar between the CFS score 1-3 group and the CFS score 4-9 group, except for the history of hypertension and the level of serum albumin (Table S1).

The incidence of mortality was 2.4% (n = 2 patients who died due to liver failure). The incidence of postoperative complications of CD all grade, grade ≥IIIa, and ≥IIIb were 81.9% (n = 68), 45.8% (n = 38), and 12.0% (n = 10 [intraabdominal abscesses formation after PHBL (n = 3), PHLF (grade C) (n = 2), intraabdominal bleeding (n = 1), intractable ascites (n = 1), anastomotic leakage (n = 1)]), respectively. The incidence of postoperative complications was significantly higher in the CFS score 4-9 group than in the CFS score 1-3 group both for CD grade ≥IIIa complications (CFS score 1-3: 39.4% vs CFS score 4-9: 70.6%, *P* = .03) and CD grade ≥IIIb complications (7.6% vs 29.4%, *P* = .03; Table 4).

In multivariate analysis, frailty (CFS score 4-9) was identified as an independent risk factor for CD grade ≥IIIa (severe) postoperative complications (OR, 4.11; 95% CI, 1.11-15.20; *P* = .03), >10% ICG retention at 15 minutes (OR, 3.87; 95% CI, 1.36-11.00; *P* = .01), and concomitant resection with pancreaticoduodenectomy (OR, 7.15; 95% CI, 1.67-30.52; *P* = .01; Table 5).

3.4 | Detailed assessment of postoperative complications

Postoperative complications were categorized into two groups: (a) surgery-related complications (complications associated with the operative procedure), such as PHLF, PHBL, surgical site infection (SSI), and bleeding, and (b) nonsurgery-related complications (systemic complications not associated directly with the operative

TABLE 1 Preoperative demographics and operative outcomes

	CFS score 1-2 n = 35		CFS score 3-9 n = 44		*P* value
Age, median (range), year	71	(42-81)	72	(59-88)	.098
Sex					
Male	25	(71.4)	27	(61.4)	.347
Female	10	(28.6)	17	(38.7)	
Body mass index[a], kg/m^2	21.2	(17.4-31.7)	21.9	(16.7-30.9)	.312
ASA score					
1	9	(25.7)	2	(4.6)	.010
2	26	(74.3)	40	(90.9)	
3	0	(0)	2	(4.6)	
Comobidity					
Hypertension	16	(45.7)	25	(56.8)	.326
Diabetes mellitus	6	(17.1)	9	(20.5)	.708
Previous operation	11	(31.4)	19	(43.2)	.283
Preoperative cholangitis	10	(28.6)	17	(38.6)	.347
Preoperative biliary drainage	30	(85.7)	40	(90.9)	.472
Remnant liver volume[a], %	52.5	(36.2-87.8)	46.5	(31.0-81.0)	.198
Portal vein embolization	15	(42.9)	14	(31.8)	.312
Lymphocyte[a], /μL	1420	(610-3000)	1310	(600-3070)	.336
Albumin[a], g/dL	3.7	(2.7-4.4)	3.5	(2.3-4.6)	.109
C-reactive protein[a], mg/dL	0.18	(0.02-7.24)	0.29	(0.02-5.02)	.604
Total bilirubin[a], mg/dL	0.70	(0.3-1-2.27)	0.89	(0.35-2.15)	.145
Indocyanine green test[a], %	8.2	(3.5-18.0)	8.7	(3.0-21.0)	.914
Operative procedure					
Right hemihepatectomy	19	(54.3)	27	(61.4)	.724
Left hemihepatectomy	15	(42.9)	15	(34.1)	
Left trisectionectomy	1	(2.9)	2	(4.6)	
Concomitant resection					
Pancreaticoduodenectomy	5	(14.3)	9	(20.5)	.472
Vascular resection (portal vein or artery)	5	(14.3)	6	(13.6)	.934
Other organ resection	1	(2.9)	2	(4.6)	.693
Stomach	1	(2.9)	1	(2.3)	
Kidney	0	(0)	1	(2.3)	
Operation time[a], min	674	(443-1330)	656	(490-1153)	.650
Blood loss[a], mL	550	(120-3500)	675	(130-4000)	.441
Blood transfusion	12	(34.3)	22	(50.0)	.159
Postoperative hospital stay[a], day	29	(14-187)	35	(12-198)	.242

Note: Figures in parentheses are percentage unless otherwise specified.
Abbreviations: ASA, American Society of Anesthesiologists; CFS, Clinical Frailty Scale.
[a]Median (range).

procedure), such as pneumonia, arrhythmia, or delirium. The results of the statistical tests and descriptive information about postoperative complications are summarized in Table 4.

The incidence of surgery-related postoperative complications did not differ between the CFS score 1-3 group and the CFS score 4-9 group. There was no significant difference in the incidence of PHLF,

TABLE 2 Pathological characteristics

	CFS score 1-2 n = 35		CFS score 3-9 n = 44		P value
UICC T factor, 8th edition					
0	1	(2.9)	0	(0)	.039
1	8	(22.9)	2	(4.6)	
2	19	(54.3)	31	(70.5)	
3	5	(14.3)	4	(9.1)	
4	2	(5.7)	7	(15.9)	
UICC N factor, 8th edition					
0	25	(71.4)	21	(47.3)	.032
1	10	(28.6)	23	(52.3)	
UICC stage, 8th edition					
0	1	(2.9)	0	(0)	.049
I	7	(20.0)	1	(2.3)	
II	13	(37.1)	16	(36.4)	
III	11	(31.4)	21	(47.7)	
IV	3	(8.6)	6	(13.6)	
Microscopic residual disease					
R0	28	(80.0)	32	(72.7)	.450
R1	7	(20.0)	12	(27.3)	
Adjuvant chemotherapy					
Yes	25	(71.4)	31	(70.5)	.925
No	10	(28.6)	13	(71.4)	

Note: Figures in parentheses are percentage unless otherwise specified.
Abbreviations: CFS, Clinical Frailty Scale; UICC, Union for International Cancer Control.

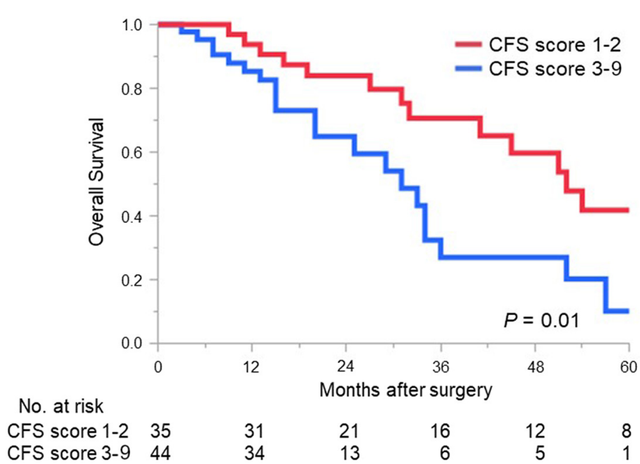

FIGURE 2 Kaplan–Meier curve of OS in the CFS score 1-2 group and the CFS score 3-9 group. The OS of the CFS score 1-2 group was significantly higher than that of the CFS score 3-7 group ($P = .01$). CFS, Clinical Frailty Scale; OS, overall survival

PHBL, SSI, or bleeding. In contrast, the incidence of nonsurgery-related postoperative complications was significantly higher in the CFS score 4-9 group (16.7% vs 76.5%; $P < .01$).

In contrast, there was a significant difference in the incidence of infectious complications except for incisional SSI (39.4% vs 70.6%, $P = .02$).

4 | DISCUSSION

The present study demonstrated the relationship between frailty and the rate of severe postoperative complications of major hepatectomy for PHCC using CFS, which is a simple and useful measurement system for frailty.[3–5,11]

Frailty is defined as a clinical state associated with impaired physiological conditions and vulnerability to stress. It results from aging-related decline or disease, and various scores have been reported for its assessment. Several studies have revealed the association between poor outcomes and high frailty scores in patients with various disorders, such as cardiovascular diseases,[24] infectious diseases,[25] liver disease,[26] or malignant diseases including gastrointestinal cancer.[4–8,27] As for hepatic resection, 11 studies[5–11,13–16] are available to date, among which 10 showed the usefulness of frailty scoring in predicting mortality, morbidity, or prognosis after hepatectomy. Tanaka et al[7] conducted a prospective multicenter study using the Kihon checklist and demonstrated that high frailty was an independent risk factor for age-related events (major respiratory complications, major cardiac events, delirium requiring medication, transfer to rehabilitation facility, and dependency). In addition, Gani et al,[6] McKechnie et al,[10] Chen et al,[13] van der Windt et al,[14] and Dauch et al[15] described that frailty measured using the revised frailty index, modified frailty index, or risk analysis index was a predictor of morbidity and/or mortality after liver surgery. Louwers et al[9] and Okabe et al[11] revealed a significant association between frailty and postoperative complications of CD grade III/IV. Moreover, Yamada et al[7] and Tokuda et al[16] described the usefulness of frailty assessed by CFS to estimate the prognosis of hepatocellular carcinoma (HCC) or colorectal liver metastasis after hepatectomy. Although Milliken et al[8] reported no significant difference with the degree of frailty in short- and long-term outcomes after hepatectomy, it is reasonable to suggest—based on the findings of other previous studies—that frailty serves some degree of influence on outcomes after hepatectomy. However, the subjects of investigation in these studies were HCC, colorectal liver metastasis, and all types of liver cancer (HCC, PHCC, liver metastases), and, to the best of our knowledge, this is the first report to demonstrate the potency of frailty in predicting postoperative outcomes and prognosis for patients who have undergone surgery for PHCC.

In this study we used the CFS score to assess frailty. CFS is a nine-point scale for assessing frailty, which is scored by evaluating comorbidity, function, and cognition.[3] Although the CFS is a semiquantitative scale that does not include preoperative test results, it provides a more detailed assessment, including cognitive function, than the ECOG-PS, and various studies have reported an association between CFS and clinical outcomes.[4,5,11,16,28] The

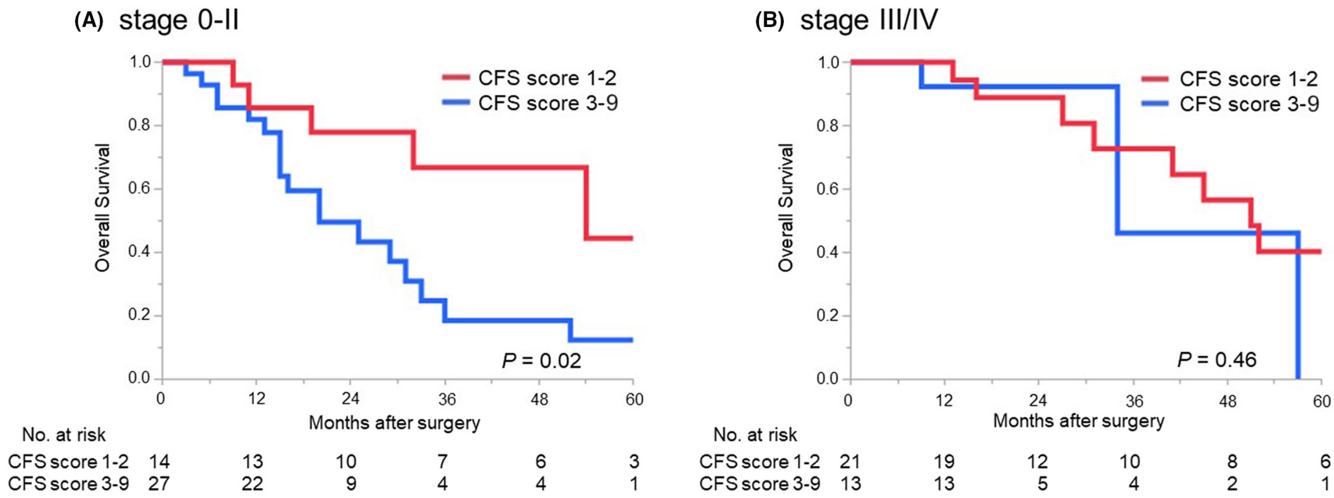

FIGURE 3 Kaplan–Meier curve of OS in the CFS score 1-2 group and the CFS score 3-9 group stratified according to TNM stage (0-II or III/IV). (a) The OS of the CFS score 1-2 group was significantly higher than that of CFS score 3-9 group in stage 0-II patients (*P* = .02). (b) A significant difference did not exist in stage III/IV patients (*P* = .46). CFS, Clinical Frailty Scale; OS, overall survival

TABLE 3 Univariate and multivariate analyses of prognostic factors for overall survival

	Univariate			Multivariate		
Variables	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
CFS score						
1-2	Ref			Ref		
3-9	2.46	1.23-5.13	.011	2.31	1.14-4.87	.020
Operation time, min						
>663	Ref			Ref		
≤663	2.03	1.04-4.22	.038	1.93	0.96-4.07	.065
UICC stage, 8th edition						
0-II	Ref			Ref		
III/IV	1.77	0.92-3.56	.087	1.29	0.64-2.68	.474

Abbreviations: CI, confidence interval; CFS, Clinical Frailty Scale; UICC, Union for International Cancer Control.

cutoff value of CFS varied among studies,[4,5,11,16] and even in this study, there is a difference in cutoffs for predicting prognosis and the development of complications. This may be due to differences in the impact of frailty on clinical outcomes, and we consider that a different cutoff value for each outcome may allow for a more rigorous evaluation.

Previous studies have suggested that frailty leads to increased postoperative complications, and some researchers have proposed various ideas for elucidating an accurate mechanism. Marcos-Perez et al[29] reported that frailty is associated with inflammatory mediators, and Lu et al[30] clarified the relationship between frailty and immunosuppression. In the present study, although there was no significant difference, the platelet-to-lymphocyte ratio was higher and the prognostic nutrition factor was lower in the frailty group (Figures S3 and S4), which were in line with the findings of the two aforementioned reports.[30] The incidence of nonsurgery-related postoperative complications was significantly higher in the frailty group, while the incidence of surgery-related complications did not differ between the frailty and nonfrailty groups. These findings indicate that the impact of frailty on postoperative complications is not the outcome of local tissue vulnerability, but that of systemic inflammation or immunosuppression. The significant association between frailty and infection in our study further supports this theory.

In the present study frailty was a significant prognostic factor associated with survival, especially in the early stage group. In general, immunosuppression is known to adversely affect the progression of malignancy, which may be explained by the above theories regarding the association between frailty and immunosuppression. The reasons for the lack of difference in survival rates in advanced stages are unclear but include the possibilities of the number of nonfrailty patients being too small to make valid comparisons, or the immunosuppressive effect of the tumor itself exceeding the immune effect of frailty due to the large tumor volume.

The main limitations of this study are its single-center, retrospective, nonrandomized design and its relatively small number of

TABLE 4 Postoperative short-term outcomes

	CFS score 1-3 n = 66		CFS score 4-9 n = 17		P value
Mortality	2	(3.0)	0	(0)	1.00
Morbidity					
All grade	50	(75.8)	17	(100)	.004
Clavien–Dindo classification grade ≥IIIa	26	(39.4)	12	(70.6)	.029
Clavien–Dindo classification grade ≥IIIb	5	(7.6)	5	(29.4)	.025
Surgery-related postoperative complications	45	(68.2)	11	(64.7)	.695
Posthepatectomy liver failure	21	(31.8)	7	(41.2)	.472
Grade A	11	(16.7)	2	(11.8)	
Grade B	8	(12.1)	5	(29.4)	
Grade C	2	(3.0)	0	(0)	
Posthepatectomy bile leakage	15	(22.7)	3	(17.7)	.644
Infectious complications	37	(56.1)	12	(70.6)	.517
Incisional SSI	27	(40.9)	6	(35.3)	.672
Infectious complications except for incisional SSI	26	(39.4)	12	(70.6)	.021
Bleeding	5	(7.6)	2	(11.8)	.594
Nonsurgery-related postoperative complications	11	(16.7)	13	(76.5)	<.001
Cardiovascular complications	0	(0)	3	(17.7)	.007
Respiratory complications	5	(7.6)	8	(47.1)	<.001
Delirium	5	(7.6)	7	(41.2)	<.001
Postoperative hospital stay, median (range), day	31.5	(12-287)	44	(17-198)	.139

Note: Figures in parentheses are percentage unless otherwise specified.
Abbreviations: CFS, Clinical Frailty Scale; SSI, surgical site infection.

TABLE 5 Univariate and multivariate analyses of risk factors for postoperative complications of Clavien–Dindo classification IIIa or more

	Univariate			Multivariate		
Variables	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
CFS score						
1-3	Ref			Ref		
4-9	3.69	1.16-11.71	.021	4.11	1.11-15.20	.034
Indocyanine green test						
<10.0%	Ref			Ref		
≥10.0%	3.50	1.38-8.88	.007	3.87	1.36-11.00	.011
Concomitant resection with Pancreaticoduodenectomy						
No	Ref			Ref		
Yes	7.28	1.88-28.07	.001	7.15	1.67-30.52	.008

Abbreviations: CI, confidence interval; CFS, Clinical Frailty Scale.

participants. Stage was not a prognostic factor in univariate and multivariate analysis, which might have occurred due to an insufficient sample size. However, the patients enrolled in this study showed considerable heterogeneity in characteristics, operative findings, and pathological outcomes. In addition, we used only CFS to assess frailty. A prospective study with a larger patient cohort is needed, and frailty should be assessed using other scoring systems. Hence, we have started assessing frailty using the Cardiovascular Health Study index,[2] Edmonton frail scale,[31] multidimensional frailty score,[32] and CFS to clarify the influence of frailty on postoperative outcomes after hepatobiliary and pancreatic surgery. To conclude, frailty is a predictive factor for short- and long-term outcomes in patients who have undergone major hepatectomy for PHCC.

DISCLOSURE

Funding: The authors received no specific funding for this study.
Conflict of Interest: The authors declare no conflicts of interest for this article.
Author Contributions: KH, AS, KK, TN, and YS were involved in study design and data interpretation. KH and KF were involved in

the drafting of the article. KH, HM, TY, HS, HH, and KY were involved in the data analysis. YS was involved in the study supervision. All authors critically revised the report, commented on drafts of the article, and approved the final report.

Ethics Statement: The protocol for this research project was approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. Committee of Shinshu University Hospital, Approval No. 4999. Informed consent was obtained from the subjects.

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REFERENCES

1. Akashi K, Ebata T, Mizuno T, Yokoyama Y, Igami T, Yamaguchi J, et al. Surgery for perihilar cholangiocarcinoma from a viewpoint of age: is it beneficial to octogenarians in an aging society? Surgery. 2018;164(5):1023–9.
2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56.
3. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95.
4. Tanaka T, Suda K, Inaba K, Umeki Y, Gotoh A, Ishida Y, et al. Impact of frailty on postoperative outcomes for laparoscopic gastrectomy in patients older than 80 years. Ann Surg Oncol. 2019;26(12):4016–26.
5. Yamada S, Shimada M, Morine Y, Imura S, Ikemoto T, Arakawa Y, et al. Significance of frailty in prognosis after hepatectomy for elderly patients with hepatocellular carcinoma. Ann Surg Oncol. 2021;28(1):439–46.
6. Gani F, Cerullo M, Amini N, Buettner S, Margonis GA, Sasaki K, et al. Frailty as a risk predictor of morbidity and mortality following liver surgery. J Gastrointest Surg. 2017;21(5):822–30.
7. Tanaka S, Ueno M, Iida H, Kaibori M, Nomi T, Hirokawa F, et al. Preoperative assessment of frailty predicts age-related events after hepatic resection: a prospective multicenter study. J Hepatobiliary Pancreat Sci. 2018;25(8):377–87.
8. Milliken D, Curtis S, Melikian C. Predicting morbidity in liver resection surgery: external validation of the revised frailty index and development of a novel predictive model. HPB (Oxford). 2021;23(6):954–61.
9. Louwers L, Schnickel G, Rubinfeld I. Use of a simplified frailty index to predict Clavien 4 complications and mortality after hepatectomy: analysis of the National Surgical Quality Improvement Project database. Am J Surg. 2016;211(6):1071–6.
10. McKechnie T, Bao T, Fabbro M, Ruo L, Serrano PE. Frailty as a predictor of postoperative morbidity and mortality following liver resection. Am Surg. 2021;87(4):648–54.
11. Okabe H, Hayashi H, Higashi T, Nitta H, Ikuta Y, Yusa T, et al. Frailty predicts severe postoperative complication after elective hepatic resection. Gastrointest Tumors. 2019;6(1–2):28–35.
12. Takahashi Y, Ebata T, Yokoyama Y, Igami T, Sugawara G, Nagino M. Surgical treatment of perihilar cholangiocarcinoma in octogenarians: a single center experience. J Hepatobiliary Pancreat Sci. 2013;20(3):324–31.
13. Chen SY, Stem M, Cerullo M, Gearhart SL, Safar B, Fang SH, et al. The effect of frailty index on early outcomes after combined colorectal and liver resections. J Gastrointest Surg. 2018;22(4):640–9.
14. van der Windt DJ, Bou-Samra P, Dadashzadeh ER, Chen X, Varley PR, Tsung A. Preoperative risk analysis index for frailty predicts short-term outcomes after hepatopancreatobiliary surgery. HPB (Oxford). 2018;20(12):1181–8.
15. Dauch J, Hamidi M, Arrington AK, O'Grady CL, Hsu CH, Joseph B, et al. The impact of frailty on patients undergoing liver resection for colorectal liver metastasis. J Gastrointest Surg. 2022;26(3):608–14.
16. Tokuda K, Morine Y, Miyazaki K, Yamada S, Saito YU, Nishi M, et al. Frailty can predict prognosis after hepatectomy in patients with colorectal liver metastasis. Anticancer Res. 2021;41(9):4637–44.
17. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed. New Jersey: Wiley-Blackwell; 2016.
18. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187–96.
19. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the international study Group of Liver Surgery (ISGLS). Surgery. 2011;149(5):713–24.
20. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the international study Group of Liver Surgery. Surgery. 2011;149(5):680–8.
21. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. Semin Surg Oncol. 1993;9(4):298–304.
22. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg. 2006;243(3):364–72.
23. Notake T, Shimizu A, Kubota K, Ikehara T, Hayashi H, Yasukawa K, et al. Hepatocellular uptake index obtained with gadoxetate disodium-enhanced magnetic resonance imaging in the assessment future liver remnant function after major hepatectomy for biliary malignancy. BJS Open. 2021;5(4):zraa048.
24. Ida S, Kaneko R, Imataka K, Murata K. Relationship between frailty and mortality, hospitalization, and cardiovascular diseases in diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol. 2019;18(1):81.
25. Kelly SG, Wu K, Tassiopoulos K, Erlandson KM, Koletar SL, Palella FJ. Frailty is an independent risk factor for mortality, cardiovascular disease, bone disease, and diabetes among aging adults with human immunodeficiency virus. Clin Infect Dis. 2019;69(8):1370–6.
26. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017;66(2):564–74.
27. Nakano Y, Hirata Y, Shimogawara T, Yamada T, Mihara K, Nishiyama R, et al. Frailty is a useful predictive marker of postoperative complications after pancreaticoduodenectomy. World J Surg Oncol. 2020;18(1):194.
28. Simcock R, Wright J. Beyond performance status. Clin Oncol (R Coll Radiol). 2020;32(9):553–61.
29. Marcos-Pérez D, Sánchez-Flores M, Maseda A, Lorenzo-López L, Millán-Calenti JC, Gostner JM, et al. Frailty in older adults is associated with plasma concentrations of inflammatory mediators but not with lymphocyte subpopulations. Front Immunol. 2018;9:1056.
30. Lu Y, Tan CT, Nyunt MS, Mok EW, Camous X, Kared H, et al. Inflammatory and immune markers associated with physical frailty syndrome: findings from Singapore longitudinal aging studies. Oncotarget. 2016;7(20):28783–95.

31. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton frail scale. Age Ageing. 2006;35(5):526–9.
32. Kim SW, Han HS, Jung HW, Kim KI, Hwang DW, Kang SB, et al. Multidimensional frailty score for the prediction of postoperative mortality risk. JAMA Surg. 2014;149(7):633–40.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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