Liver Cancer

Research Article

Liver Cancer 2024;13:150–160
DOI: 10.1159/000533857

Received: May 24, 2023
Accepted: August 24, 2023
Published online: October 31, 2023

Impact of Liver Fibrosis Severity on Oncological Prognosis in Hepatocellular Carcinoma

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Keywords
Liver fibrosis · Liver cirrhosis · Hepatocellular carcinoma

Abstract

Introduction: Cirrhosis is deemed to be a contributing factor to the postoperative recurrence of hepatocellular carcinoma (HCC); however, the precise impact of liver fibrosis on both cancer-specific prognoses remains unclear. This investigation sought to elucidate the effect of liver fibrosis severity on the cancer-specific prognosis. ***Methods:*** A total of 524 consecutive patients were included. Recurrence-free survival (RFS) and disease-specific survival (DSS) were compared according to fibrosis stage. Moreover, postoperative outcomes were subjected to analysis in cohorts of patients with F0 and F1–3, as well as in those with F1–3 and F4, who were carefully matched for background factors. ***Results:*** The 5-year RFS exhibited a significantly worse outcome in the F4 group compared to other stages of fibrosis: 5-year RFS – F0 (46.6%), F1–3 (33.1%), and F4 (23.5%), $p = 0.03$ (F0 vs. F1–3) and $p < 0.01$ (F1–3 vs. F4). Additionally, the 5-year DSS also presented a significantly worse prognosis in the F4 group: 5-year DSS – F0 (82.9%), F1–3 (73.6%), and F4 (57.4%), $p = 0.04$ (F0 vs. F1–3) and $p < 0.01$ (F1–3 vs. F4). In multivariate analysis, fibrosis 1, 2, 3, and 4 stage (compared with F0) (HR: 1.70, 1.81, 1.89, and 3.99, 95% confidence interval: 1.10–1.99, 1.39–2.22, 1.41–2.55, and 2.25–5.01, $p = 0.022$, $p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively) was independent risk factor for RFS. After matched analysis, both RFS and DSS exhibited significantly worse prognoses in the presence of more advanced fibrosis. There was a significantly higher incidence of multiple recurrences in the F4 group than the F1–3 group, and a number of recurrences were observed both in the same hepatic segment as the resected side and in the contralateral lobe in F4 group. ***Discussion/Conclusion:*** The hazard and recurrence pattern of HCC signifies that the prognosis could potentially be poor, as the hepatic fibrosis likely owing to a higher hepatocarcinogenic potential, even in the absence of progression to cirrhotic condition. The risk of de novo recurrence may also increase with the progression of this fibrosis.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer with an estimated global prevalence of 782,000 cases in 2012 [1] and a rapidly increasing incidence [2]. The postoperative prognosis for HCC has been improved by advanced management and diagnostic techniques [3]. However, HCC is still associated with high incidences of metastasis and recurrence [4, 5].

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Recurrence after curative hepatectomy is divided into two unique patterns: recurrence derived from remnant micrometastases and de novo recurrence arising owing to carcinogenic potential in the liver injury such as viral infection [6, 7]. Several studies have reported that the incidence of HCC arising from established liver cirrhosis (LC) is 2.5–6.6% [8–10], suggesting that HCC recurrence may be associated with LC. One study reported that the recurrence rate of HCC is significantly higher in patients with LC than in patients with normal liver [11]. However, the prognosis was only based on whether the patient had LC or normal liver [11], while few studies have evaluated the prognosis by classifying liver fibrosis into stages in accordance with the New-Inuyama criteria [12–14].

The aim of this investigation was to scrutinize the cancer-specific consequences in precisely staged patients with hepatic fibrosis. In addition to evaluating the impact of fibrosis on recurrence in the entire cohort, the clinicopathological characteristics of the F1, F2, and F3 groups were compared with those of the F0 and F4 groups to analyze whether the degree of fibrosis was linked to cancer-specific outcomes.

Methods

Patients

Consecutive patients who underwent hepatectomy (n = 735) for HCC at the Department of Surgery, Shinshu University Hospital, between January 2000 and June 2020 were identified. Among these patients, we excluded 150 who underwent non-first hepatectomy, 30 who underwent non-curative resection, 29 with missing medical data, and two who died because of liver failure. Finally, a total of 524 patients were included in this study. The severity of hepatic fibrosis was scored using the New-Inuyama criteria as F0 (no fibrosis), F1 (fibrous portal expansion), F2 (bridging fibrosis), F3 (bridging fibrosis with architectural distortion), and F4 (LC). The patients were divided into five groups based on the fibrosis stage: F0 (n = 67), F1 (n = 70), F2 (n = 124), F3 (n = 95), and F4 (n = 168).

The study was approved by the Ethics Committee of Shinshu University School of Medicine (approval No. 2020-5011) and conducted in accordance with the principles outlined in the Declaration of Helsinki. Because of the retrospective nature of the study and absence of invasive interventions, the requirement for written consent was waived by the review board. Data were collected from the medical records and analyzed retrospectively and anonymously.

Pathological Evaluation

A pathologist assigned the diagnoses, and the ultimate histopathologic determinations were arrived at through a multidisciplinary conference with a consortium of experts. Illustrations of resected liver specimens and their corresponding histological photomicrographs for each stage of fibrosis are displayed in online supplementary Figure S1 (for all online suppl. material, see https://doi.org/10.1159/000533857). Each resection specimen underwent comprehensive evaluation of both hematoxylin-and-eosin-stained and Azan-Mallory-stained slides (a minimum of two slides per case for both staining methods) from non-tumoral regions to establish the fibrosis score according to the New-Inuyama criteria. The pathology findings recorded in accordance with the 7th edition of the American Joint Committee on Cancer [15] were retrospectively collected.

Selection Criteria for Liver Resection

The preoperative management was thoroughly outlined in a previous study [16]. In summary, surgical criteria were established based on the Makuuchi criteria [17], which yield an acceptable approach to hepatectomy through consideration of factors such as the possible extent of liver resection, presence of ascites, serum total bilirubin concentration, and 15-min indocyanine green retention rate (ICGR15). In cases with no ascites and normal serum bilirubin concentration, patients with an ICGR15 of less than 10% were eligible for removal of two-thirds of their non-tumorous liver parenchyma, whereas those with an ICGR15 of 10–19% were eligible for removal of one-third. Couinaud's segmentectomy was recommended for patients with an ICGR15 of 20–29%, while limited resection was recommended for patients with an ICGR15 exceeding 30%.

The fibrosis-4 (Fib-4) index is a noninvasive, simple, and widely used tool to assess liver fibrosis in patients with liver diseases. It is used to estimate the degree of fibrosis (scarring) in the liver without the need for a liver biopsy, which can be an invasive procedure. The Fib-4 index is calculated using the following formula:

$$\text{Fib-4 index} = \left(\text{Age} \times \text{AST}\right) \Big/ \left(\text{Platelet count} \times \sqrt{\text{ALT}}\right)$$

Nevertheless, the utilization of the Fib-4 index did not factor into the determination of the surgical approach. Instead, the decision-making process relied solely upon the ICGR15 values and the extent of resection as detailed earlier.

Postoperative Follow-Up

Adjuvant chemoradiotherapy was not administered in every case. Follow-up appointments were scheduled at 3-month intervals at our outpatient clinic. The serum concentrations of the tumor markers alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) were measured. Ultrasonographic, computed tomography, magnetic resonance imaging, or gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced magnetic resonance imaging scans were conducted every 6 months or as required. Intrahepatic recurrence of HCC was defined as the detection of a newly formed hypervascular hepatic lesion. Specifically, a diagnosis was established by some hepatobiliary surgeons and some independent radiologists using CT/MRI Liver Imaging Reporting and Data System (LI-RADS). Patients with sufficient liver function underwent repeat hepatectomy for intrahepatic HCC recurrence. In cases where liver resection was not possible, medical management was initiated, namely, radiofrequency ablation, percutaneous ethanol injection therapy, transcatheter arterial embolization (TAE), or molecular targeted therapies. If the intra-abdominal or pulmonary metastases were amenable to resection, aggressive surgical intervention was carried out for distant metastasis, whereas molecular targeted therapies were implemented if resection was deemed unfeasible.

Case-Matching

To minimize the potential influence of various factors on HCC recurrence between the F0 and F1–3, F1–3, and F4 groups, a 1-to-1 individual case-matching analysis was performed to control for clinical factors other than underlying liver injury. This analysis was conducted using R statistical software (R Foundation for Statistical Computing) and the optmatch package, which implements the optimal matching method without a caliper. The Mahalanobis distance was used to calculate the dissimilarity between cases. The matching criteria were sex, age, type of surgery, surgical margin, tumor size, number of tumors, microvascular invasion, and preoperative serum AFP and DCP concentrations. After the matching process, the recurrence patterns and temporal changes in recurrence rates were compared and analyzed.

Definitions

Recurrence patterns were characterized as recurrence in the same anatomical segment as the primary tumor site, in a different segment of the ipsilateral liver lobe, in a different segment of the contralateral liver lobe, and in both lobes (multiple). Anatomical segments were classified based on lateral, medial, anterior, and posterior positioning. The left liver lobe was further divided into medial (S1 + S4) and lateral (S2 + S3) areas, and the right lobe into anterior (S5 + S8) and posterior (S6 + S7) regions, in accordance with Couinaud's classification system. In patients with multiple tumors who underwent initial hepatectomy, the site of recurrence was determined based on the largest tumor. Operative mortality was defined as death during the intraoperative period, within 90 days postoperatively, or during hospitalization.

Statistical Analysis

Data are presented as *n* (%) or median (range). The Mann-Whitney U test, χ^2 test, or Fisher's exact test was used for univariate analysis, as appropriate. Recurrence-free survival (RFS) was determined as the time elapsed from the date of surgical resection to the date of recurrence or death due to any cause. Disease-specific survival (DSS) was defined as the time from surgery to death from HCC or the final follow-up. All mortalities apart from HCC, encompassing instances like liver failure, variceal rupture, and the advancement of encephalopathy in cirrhotic patients, were categorized as deaths attributable to other diseases. The hazard ratio (HR) and 95% confidence interval (CI) were calculated using relevant variables. The forward selection method was applied for multivariate analysis with covariates that were identified as significant by univariate analysis, after the elimination of potential confounding factors. $p < 0.05$ was considered statistically significant. The Kaplan-Meier method was used to estimate cumulative survival probabilities, and differences between groups were compared using the log-rank test. Calculate the cumulative hazards: to calculate the cumulative hazards for each time interval, use the following formula:

Cumulative Hazard at Time t = (Number of events at or before time t)/(Number of patients at risk at time t).

The cumulative incidence of recurrence was able to obtain by subtracting the cumulative hazards from 1 at each time point. The cumulative hazards were plotted against time to visualize the risk of recurrence over the follow-up period. Statistical analyses were performed using EZR and GraphPad Prism version 8.2 (GraphPad Software, La Jolla, CA, USA RRID:SCR_002798).

Results

Patient Characteristics

The clinicopathological features and surgical outcomes of the entire patient cohort are summarized in Table 1. *p* values were calculated by comparing F0 with F1–3, and F1–3 with F4. The prevalence of F4 development was significantly higher in females than males ($p < 0.001$). There were significantly fewer cases of F0 among hepatitis C antibody (HCV-Ab)-positive patients than nonviral patients, and the prevalence of HCV-Ab positivity increased as the fibrosis stage progressed. The Fib-4 index significantly increased as the fibrosis stage progressed (F0 vs. F1–3, F1–3 vs. F4, $p < 0.001$). The ICGR15 also significantly increased with the fibrosis stage (F0 vs. F1–3, $p = 0.027$; F1–3 vs. F4, $p < 0.001$). The AFP concentration was comparable between groups, but the DCP concentration was significantly lower in patients with F4 than in those with F0 and F1–3 ($p = 0.016$ and $p < 0.001$, respectively). Although the tumor number was comparable across all fibrosis stages, the tumor size was significantly smaller in the F4 group than in other groups ($p < 0.001$). The operation time and inflow occlusion time were shorter in patients with F4 than in those with F1–3, which led to a significantly greater prevalence of partial resection in the F4 group ($p < 0.001$). Although the incidences of Clavien-Dindo grade III major complications and mortality were comparable between groups, the incidence of post-hepatectomy liver failure was significantly higher in patients with F4 than in those with F1–3.

Survival after Hepatic Resection by Fibrosis Stage

The Kaplan-Meier survival plots categorized by fibrosis stage are depicted in Figure 1. While no noteworthy disparity was detected between F0 and F1, F1 and F2, and F2 and F3, F4 exhibited a considerably worse prognosis than F3, F2, F1, and F0. The respective 5-year RFS values for F0–4 were 46.6%, 34.7%, 33.9%, 30.6%, and 23.5% ($p < 0.001$ for F4 vs. F0, F1; $p = 0.007$ for F4 vs. F2; $p = 0.037$ for F4 vs. F3). Moreover, the F4 group had a worse prognosis than the F1–3 group (5-year RFS: 23.5 vs. 33.1%, $p = 0.006$), and F1–3 also had a worse prognosis than F0 (5-year RFS: 33.1 vs. 46.6%, $p = 0.026$). Moreover, the corresponding 5-year DSS values for F0–4 were 82.9%, 68.4%, 72.4%, 65.8%, and 57.4% ($p < 0.001$ for F4 vs. F0, $p = 0.048$ for F4 vs. F1; $p = 0.016$ for F4 vs. F2; $p = 0.042$ for F4 vs. F3). In a similar vein, the F4 cohort displayed a more unfavorable prognosis compared to the F1–3 group (5-year DSS: 57.4 vs. 73.6%, $p = 0.044$), and the F1–3 group also exhibited a poorer prognosis than F0 (5-year DSS: 73.6 vs. 82.9%, $p = 0.001$). The cumulative hazard of recurrence is shown in Figure 2.

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DOI: 10.1159/000533857

Table 1. Clinicopathological features, surgical outcomes, and postoperative short-term outcomes in patients with fibrosis stages 0–4

	Fibrosis stage[a]					*p* value[b]	*p* value[c]
	0 (*n* = 67)	1 (*n* = 70)	2 (*n* = 124)	3 (*n* = 95)	4 (*n* = 168)		
Host-related factors							
Age*, years	71 (41–88)	70 (50–84)	72 (36–89)	71 (16–84)	68 (41–84)	0.964	0.052
Sex ratio (M:F)	57:10	55:15	95:29	78:17	107:61	0.310	<0.001
BMI*, kg/m^2	22.4 (16.0–31.2)	22.1 (14.0–45.2)	22.5 (13.4–28.0)	23.0 (16.4–31.7)	23.0 (16.0–34.7)	0.290	0.153
HBsAg positive	8 (11.9)	9 (12.9)	19 (15.3)	17 (17.9)	37 (22.0)	0.569	0.086
HCV-Ab positive	5 (7.5)	30 (42.9)	69 (55.7)	51 (53.7)	92 (54.8)	<0.001	0.562
Fib-4 index*	1.8 (0.6–5.1)	2.5 (0.7–6.1)	2.6 (0.5–10.7)	3.0 (0.6–14.3)	4.4 (1.1–13.6)	<0.001	<0.001
ICGR15*, %	10 (3–89)	11 (2–26)	12 (3–34)	12 (4–34)	18 (5–48)	0.027	<0.001
AFP*, ng/mL	49 (1–1,868,000)	34 (1–166,130)	30 (1–107,637)	46 (1–540,590)	39 (1–22,550)	0.066	0.862
DCP*, mAU/mL	169 (12–98,400)	164 (10–23,575)	101 (10–255,600)	32 (10–32,608)	30 (1–34,915)	0.016	<0.001
Child-Pugh classification						0.625	0.185
A	66 (98.5)	70 (100.0)	122 (98.4)	90 (94.7)	160 (95.2)		
B	1 (1.5)	0 (0.0)	2 (1.6)	5 (5.3)	8 (4.8)		
Tumor factors							
Tumor size*, cm	5.2 (1.3–16.5)	4.1 (0.9–17.0)	3.2 (0.9–15.0)	3.0 (1.0–12.0)	2.4 (0.5–8.0)	<0.001	<0.001
Tumor number						0.160	0.264
Single	12 (17.9)	10 (14.3)	38 (30.7)	30 (31.6)	37 (22.0)		
Multiple	55 (82.1)	60 (85.7)	86 (69.3)	65 (68.4)	131 (78.0)		
Portal vein invasion	5 (7.5)	1 (1.4)	5 (4.0)	3 (3.2)	3 (1.8)	0.152	0.548
Hepatic vein invasion	5 (7.5)	1 (1.4)	7 (5.7)	2 (2.1)	0 (0.0)	0.171	0.016
Surgical factors							
Operation time*, min	375 (110–846)	361 (145–820)	344 (82–694)	380 (145–990)	322 (100–832)	0.452	0.002
Blood loss*, mL	450 (0–4,000)	420 (10–6,600)	350 (0–5,500)	400 (0–3,250)	300 (0–5,100)	0.189	0.021
Inflow occlusion time*, min	72 (0–270)	61 (0–180)	67 (0–143)	71 (0–247)	51 (0–180)	0.348	<0.001
Intraoperative PRBC	4 (6.0)	5 (7.1)	11 (8.9)	7 (7.4)	13 (7.7)	0.798	0.933
Procedure						0.572	<0.001
Partial resection	21 (31.1)	18 (25.7)	45 (36.3)	39 (41.1)	108 (64.3)		
Anatomical resection	46 (68.9)	52 (74.3)	79 (63.7)	56 (58.9)	60 (35.7)		
Surgical margin*, mm	2 (0–40)	2 (0–44)	3 (0–60)	3 (0–35)	3 (0–40)	0.231	0.989
Postoperative short-term outcomes							
PHLF						0.164	0.019
Grade A	5 (5.1)	6 (6.1)	8 (8.2)	10 (10.2)	21 (21.4)		
Grade B	5 (5.1)	5 (5.1)	6 (6.1)	9 (9.2)	22 (22.4)		
Major complication[d]	13 (19.4)	12 (17.1)	21 (16.9)	19 (20.0)	32 (19.1)	0.861	0.803
Mortality	2 (2.3)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.7)	0.946	0.876
Postoperative hospital stay*, days	17 (7–70)	20 (5–95)	16 (7–105)	16 (5–98)	18 (4–117)	0.835	0.211

HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C antibody; BMI, body mass index; Fib-4, fibrosis-4; ICGR15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin; PRBC, packed red blood cell; PHLF, post-hepatectomy liver failure. *Data are presented as median (range). Other data are presented as *n* (%). [a]According to the New-Inuyama classification. [b]Comparison between fibrosis stages 0 and 1–3. [c]Comparison between fibrosis stages 1–3 and 4. [d]Major complications refer to grade III or IV events according to the Clavien-Dindo classification.

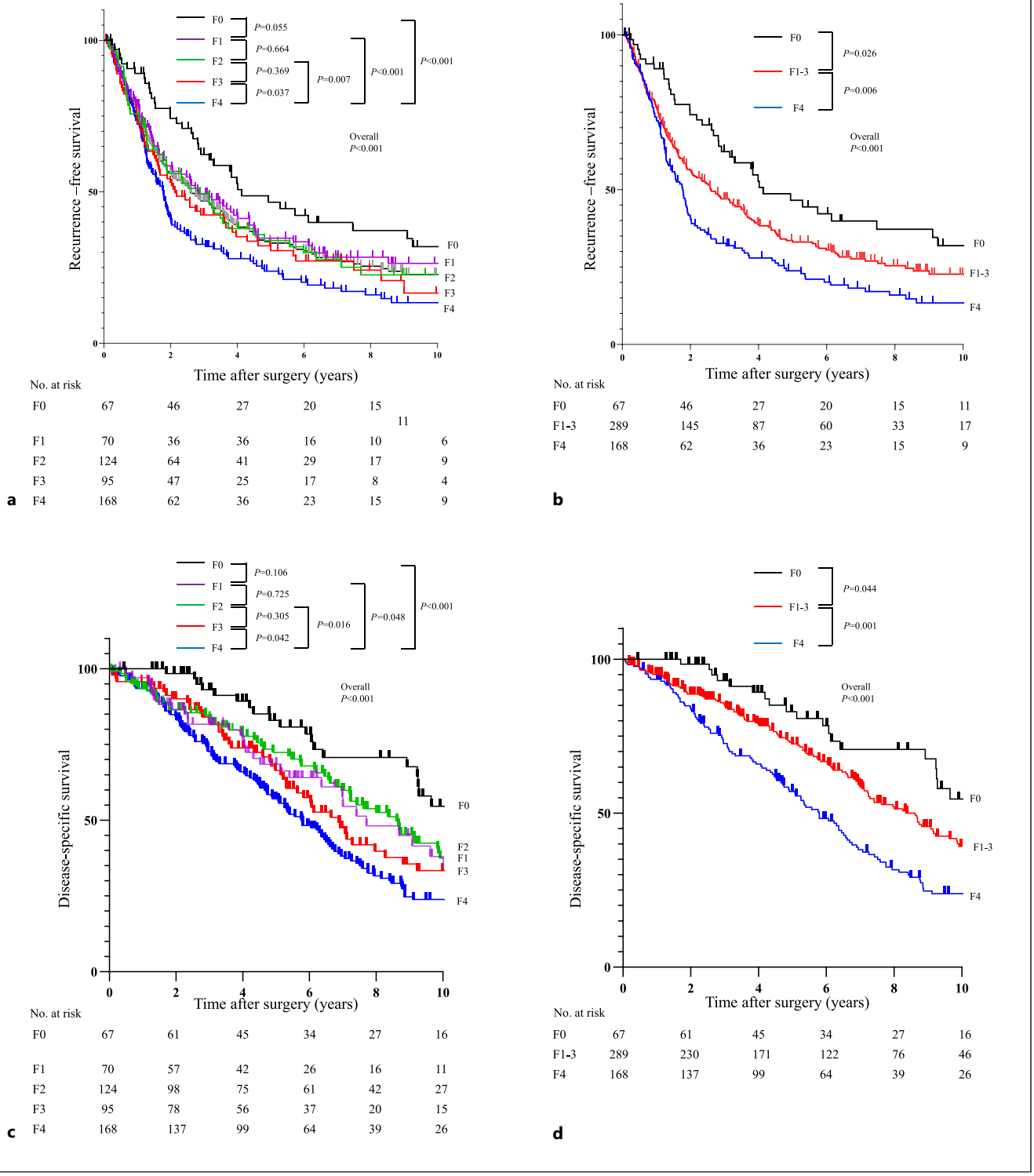

Fig. 1. Kaplan-Meier survival analysis for RFS and DSS in accordance with the New-Inuyama fibrosis stage in patients with HCC. Survival curves were constructed using the Kaplan-Meier method and compared using a log-rank test. **a** RFS curve stratified by individual fibrosis stage. **b** RFS curve stratified by fibrosis stages 0, 1–3, and 4. **c** Disease-free survival curve stratified by individual fibrosis stage. **d** DSS curve stratified by fibrosis stages 0, 1–3, and 4.

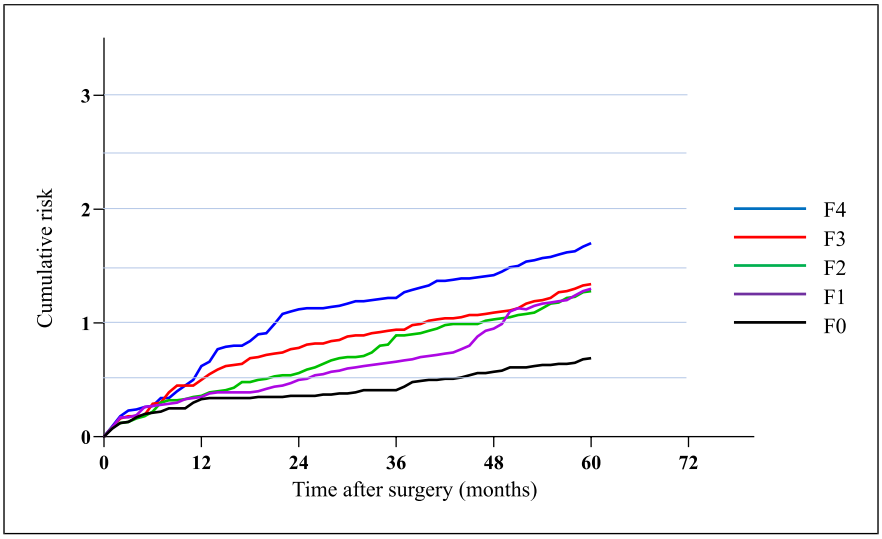

Fig. 2. Cumulative hazard of recurrence according to the fibrosis stage.

Prognostic Factors for RFS in the Entire Patient Cohort

The results of the multivariate analysis using the Cox proportional hazard model for predictors of RFS in patients who underwent hepatectomy for HCC are presented in Table 2. We ranked fibrosis stages and calculated the hazard risk of RFS at each stage. Specifically, we analyzed the hazard risk of F0 relative to F1, F2, F3, and F4. Among the 13 significant predictors of RFS identified by univariate analysis, multivariate analysis revealed that the independent poor prognostic factors were male sex (HR: 1.67, 95% CI: 1.29–2.17, $p < 0.01$), AFP concentration >100 ng/mL (HR: 1.36, 95% CI: 1.08–1.72, $p = 0.008$), multiple tumors (HR: 1.48, 95% CI: 1.17–1.88, $p = 0.001$), tumor size >3 cm (HR: 1.52, 95% CI: 1.16–2.00, $p = 0.002$), portal vein invasion (HR: 2.32, 95% CI: 1.25–4.32, $p = 0.008$), hepatic vein invasion (HR: 2.68, 95% CI: 1.42–5.04, $p = 0.002$), partial resection (HR: 1.26, 95% CI: 1.01–1.57, $p = 0.041$), and fibrosis 1, 2, 3, and 4 stage (compared with F0) (HR: 1.70, 1.81, 1.89, and 3.99, 95% CI: 1.10–1.99, 1.39–2.22, 1.41–2.55, and 2.25–5.01, $p = 0.022$, $p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively).

Case-Matched Analysis

The clinicopathological features of the case-matched population, 62 patients with F0 and 62 with F1–3, and 122 patients with F1–3 and 122 with F4, are presented in online supplementary Table S1. While the HCV-Ab positive, DCP, and tumor size were similar between the matched F0 and F1–3 groups, the Fib-4 index was dissimilar. Likewise, in F1–3 and F4 groups, while the BMI, background liver factors, and surgical factors were similar between the matched F4 and F1–3 groups, the Fib-4 index, ICGR15, and incidence of postoperative liver failure were dissimilar. Standardized difference is shown in online supplementary Figure 2S.

The intrahepatic recurrence patterns are presented in Table 3. During the follow-up period, the total tumor recurrence rate was significantly higher in the F1–3 group than F0 (66.1 vs. 46.8%, $p = 0.029$), and F4 group than the F1–3 group (75.4 vs. 54.9%, $p < 0.001$). No significant differences were observed in other factors such as size of recurrent tumor, multiplicity, and location of recurrence between the F0 and F1–3 groups. Extrahepatic recurrence was more common in F1–3 (9.8 vs. 1.6%), while intrahepatic recurrence was more common in F4 (45.1 vs. 73.8%). Although the recurrent tumor size was similar, the proportion of patients with multiple recurrence tumors was greater in the F4 group than the F1–3 group (23.6 vs. 53.3%, $p = 0.004$). The recurrence rate by site differed significantly between the F4 and F1–3 groups ($p < 0.001$) for recurrence in the same segment (54.5 vs. 14.4%), unilateral hemiliver ipsilateral lobe (23.6 vs. 16.7%), contralateral lobe (7.3 vs. 36.7%), and bilateral lobes (14.5 vs. 32.2%).

Table 4 presents the initial treatments for tumor recurrence. The treatment significantly differed between both groups. The F0 group had a higher rate of liver resection compared with the F1–3 group (hepatectomy: 62.1 vs. 24.4%, $p < 0.001$). Likewise, the F4 group had a lower rate of liver resection and a higher rate of TAE compared with the F1–3 group (hepatectomy: 8.8 vs. 32.8%, $p = 0.006$; TAE: 49.5 vs. 19.4%, $p < 0.001$).

Figure 3 shows the RFS and DSS in the two matched cohorts. Comparing F0 and F1–3 according to RFS, the

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DOI: 10.1159/000533857

Table 2. Factors associated with poor RFS in the total patient cohort

	RFS					
	univariate			multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex (male)	1.43	1.11–1.83	0.005	1.67	1.29–2.17	<0.001
Age >70 years	1.21	0.99–1.50	0.063	–		
BMI >22 kg/m^2	0.95	0.77–1.17	0.641	–		
HBsAg positive	0.90	0.68–1.18	0.453	–		
HCV-Ab positive	1.16	0.95–1.43	0.146	–		
AFP >100 ng/mL	1.49	1.20–1.85	<0.001	1.36	1.08–1.72	0.008
DCP >40 mAU/mL	1.40	1.14–1.72	0.002	1.26	0.99–1.59	0.057
Tumor number (multiple)	1.76	1.40–2.22	<0.001	1.48	1.17–1.88	0.001
Tumor size >3 cm	1.50	1.18–1.90	<0.001	1.52	1.16–2.00	0.002
Portal vein invasion (yes)	2.51	1.49–4.21	<0.001	2.32	1.25–4.32	0.008
Hepatic vein invasion (yes)	2.87	1.68–4.91	<0.001	2.68	1.42–5.04	0.002
Fibrosis stage[a]						
0 versus 1	1.34	1.02–1.98	0.039	1.70	1.10–1.99	0.022
0 versus 2	1.53	1.12–2.20	0.018	1.81	1.39–2.22	0.008
0 versus 3	1.55	1.19–2.41	0.011	1.89	1.41–2.55	<0.001
0 versus 4	2.31	2.20–4.98	<0.001	3.99	2.25–5.01	<0.001
Partial resection	1.34	1.09–1.65	0.006	1.26	1.01–1.57	0.041
Surgical margin <2 mm	1.15	0.90–1.47	0.255	–		
Major complication[b]	1.43	1.11–1.85	0.006	1.24	0.95–1.62	0.119

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C antibody; AFP, α-fetoprotein; DCP, des-gamma-carboxy prothrombin. [a]According to the New-Inuyama classification. [b]Major complications refer to grade III or IV events according to the Clavien-Dindo classification.

Table 3. Recurrence pattern in patients with intrahepatic recurrence of HCC among matched pairs

Factors	Fibrosis stage[a]				*p* value[b]	*p* value[c]
	0 (*n* = 62)	1–3 (*n* = 62)	1–3 (*n* = 122)	4 (*n* = 122)		
All recurrence	29 (46.8)	41 (66.1)	67 (54.9)	92 (75.4)	0.029	<0.001
Extrahepatic recurrence	9 (14.5)	9 (14.5)	12 (9.8)	2 (1.6)		
Intrahepatic recurrence	20 (32.3)	32 (51.6)	55 (45.1)	90 (73.8)		
Recurrent tumor size, cm	1.9 (0.7–5.0)	1.5 (0.1–9.1)	1.5 (0.4–10.0)	1.5 (0.2–5.1)	0.659	0.915
Recurrent tumor number					0.353	0.005
Single	15 (75.0)	16 (50.0)	42 (76.4)	42 (46.7)		
Multiple	5 (25.0)	16 (50.0)	13 (23.6)	48 (53.3)		
Site of recurrence					0.782	0.001
Same segment Unilateral hemiliver	6 (30.0)	9 (28.9)	30 (54.5)	13 (14.4)		
Ipsilateral	6 (30.0)	7 (21.9)	13 (23.6)	15 (16.7)		
Contralateral	7 (35.0)	12 (37.5)	4 (7.3)	33 (36.7)		
Bilateral (multiple)	1 (5.0)	4 (12.5)	8 (14.5)	29 (32.2)		

Data are presented as *n* (%) or median (range). [a]According to the New-Inuyama classification. [b]Comparison between fibrosis stages 0 and 1–3. [c]Comparison between fibrosis stages 1–3 and 4.

F0 group had a significantly better prognosis than the F1–3 group (5-year RFS: 74.9 vs. 40.6%, $p = 0.003$). Likewise, in the DSS, the F0 group had a significantly better prognosis (5-year DSS: 83.2 vs. 62.9%, $p = 0.042$). In the other cohort, in terms of RFS, the F4 group had a significantly worse prognosis than the F1–3 group (5-year

Table 4. Initial treatment for patients with recurrent HCC in the case-matched cohort

Factors	Fibrosis stage[a] (recurrence, *n*)				*p* value[b]	*p* value[b]
	0 (*n* = 29)	1–3 (*n* = 41)	1–3 (*n* = 67)	4 (*n* = 92)		
Treatment for recurrence					0.021	0.001
Hepatectomy (including resection for extrahepatic)	18 (62.1)	10 (24.4)	22 (32.8)	8 (8.8)		
TAE	5 (17.2)	19 (46.3)	13 (19.4)	45 (49.5)		
RFA	3 (10.2)	8 (19.5)	12 (17.9)	23 (24.3)		
PEIT	0 (0.0)	1 (2.4)	5 (7.5)	1 (1.1)		
Molecular target drug	2 (6.9)	2 (4.9)	7 (10.5)	4 (4.3)		
BSC	1 (3.4)	1 (2.4)	8 (11.9)	11 (12.0)		

Data are presented as *n* (%). TAE, transcatheter arterial embolization; RFA, radiofrequency ablation; PEIT, percutaneous ethanol injection therapy; BSC, best supportive care. [a]According to the New-Inuyama classification. [b]Comparison between fibrosis stages 0 and 1–3. [c]Comparison between fibrosis stages 1–3 and 4.

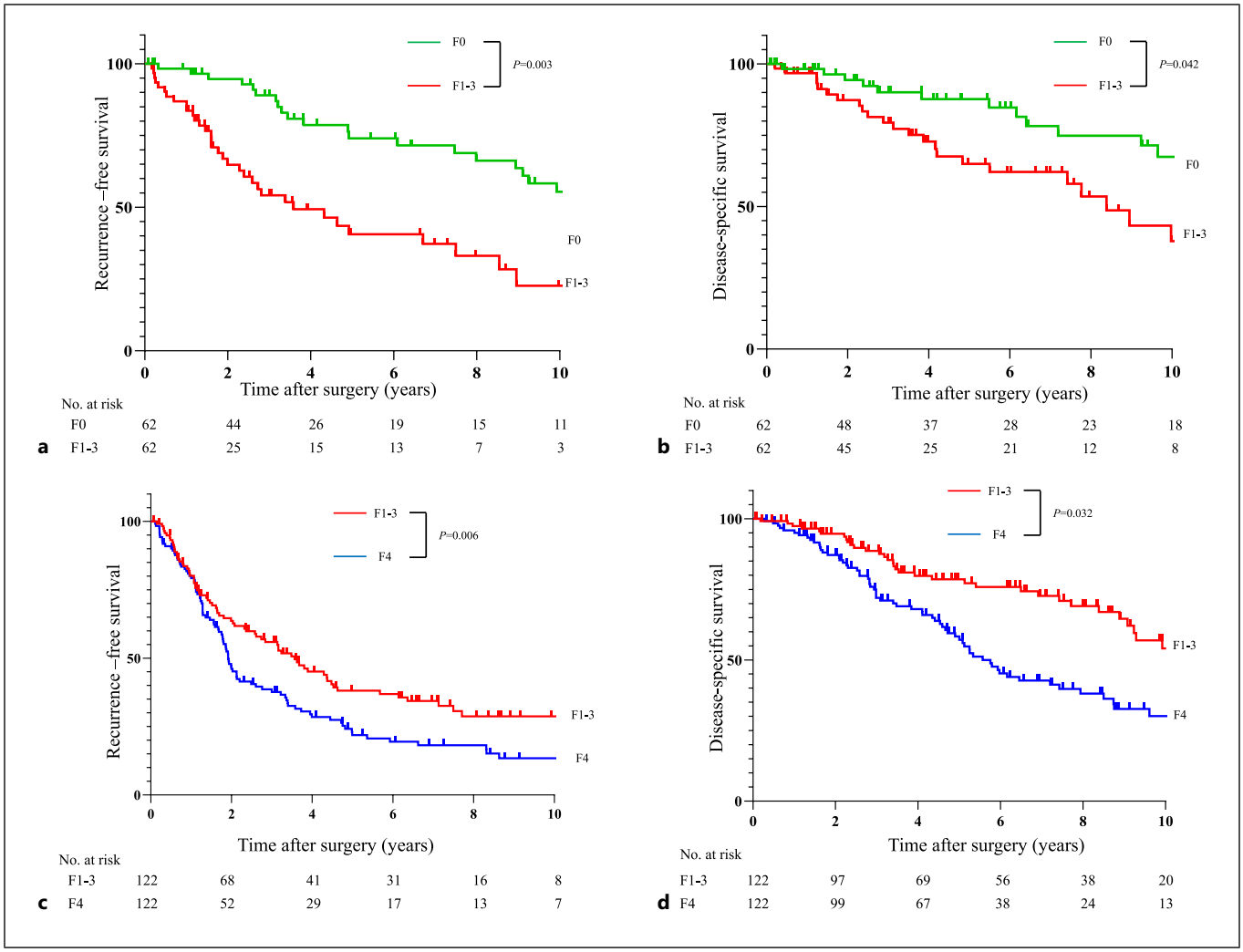

Fig. 3. Kaplan-Meier survival curves for RFS and DSS subdivided by fibrosis stage in the case-matched cohort. **a** RFS curve stratified by fibrosis stage 0 or 1–3. **b** DSS curve stratified by fibrosis stage 0 or 1–3. **c** RFS curve stratified by fibrosis stage 1–3 or 4. **d** DSS curve stratified by fibrosis stage 1–3 or 4.

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DOI: 10.1159/000533857

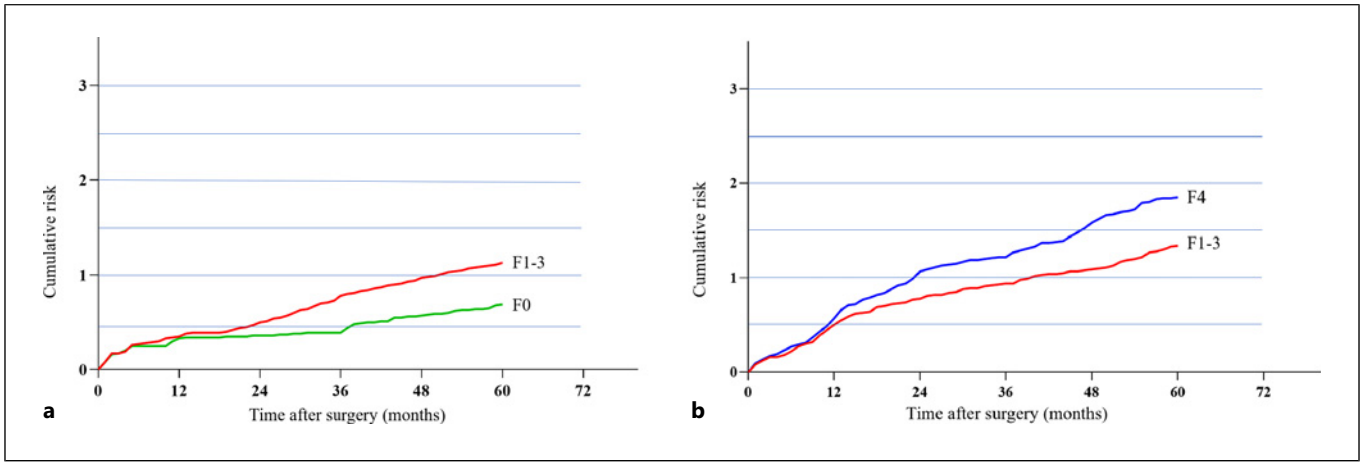

Fig. 4. Difference of cumulative risk of recurrence. **a** Fibrosis stage 0 and 1–3. **b** Fibrosis stage 1–3 and 4.

RFS: 21.9 vs. 38.2%, $p = 0.006$). Similarly, regarding the DSS, the F4 group had a significantly worse prognosis than the F1–3 group (5-year DSS: 56.2 vs. 78.4%, $p = 0.032$). The postoperative cumulative risk is presented in Figure 4. The cumulative recurrence risk in F1–3 and F4 was subsequently elevated when compared to F0 and F1–3, respectively.

Discussion

This study aimed to investigate whether liver fibrosis affects cancer-specific outcomes. In the entire cohort, patients with F0 exhibited a significantly better prognosis than those with F4, as per previous reports [11]. Additionally, patients with F1–3 demonstrated significantly worse outcomes regarding oncological survival compared with those with F0, and F4 demonstrated significantly worse outcomes compared with those with F1–3. This observation was corroborated by the findings of a ranked multivariate analysis, indicating that the likelihood of recurrence escalates as the fibrosis stage advances. Nearly congruent findings were derived for both DSS and RFS, affirming that the oncologic prognosis deteriorates as fibrosis advances. This observation remained consistent with the cumulative hazard of recurrence linked to each fibrosis stage. Furthermore, in an analysis that matched clinical backgrounds, F1–3 was associated with a higher overall recurrence rate than F0, showing an increased risk of recurrence in the F1–3 group, as confirmed by cumulative risk analysis. Likewise, F4 was associated with a higher overall recurrence rate than F1–3, showing an increased risk of recurrence in the F4 group after the initial postoperative year. These results indicate a poor oncologic prognosis in surgical resection as liver fibrosis progresses.

No characteristic pattern differences were observed with respect to recurrence form and other aspects of F0 and F1–3; however, a distinctive feature of recurrence was the significantly increased incidence of multiple recurrences in patients with F4 during follow-up. In theory, recurrences arising from residual micrometastases occur when there is already residual disease along the portal region at the time of resection and tend to occur relatively early postoperatively, either at or near the resection site (e.g., intrahepatic micrometastases within the tumor-bearing portal region) or because of the oncogenicity in liver injury [6, 7, 9]. Contralateral recurrence, which is defined as intrahepatic recurrence away from the primary tumor, is considered a typical pattern of de novo recurrence [18, 19]. Initially, it was anticipated that recurrence would be more prevalent in the vicinity of the resection site in F4, where liver function is impaired, because of bias in the selection of surgical technique (i.e., partial resection is often chosen). However, the results revealed numerous cases of recurrence in the contralateral lobe or in both lobes. This may be because our department opts for anatomic resection whenever feasible in accordance with the Makuuchi criteria, which may have influenced the present results. The present study demonstrates that postoperative recurrence in patients with LC is more frequently due to de novo recurrence rather than micrometastases resulting from the high carcinogenicity of the liver. This is similar to the findings of Sasaki et al. [11] who evaluated a cohort adjusted

for tumor factors through case-matching analysis. However, although they reported more single recurrences in F4, there may have been differences in the choice of procedure and follow-up methods.

There are only a few studies concentrating on hepatic fibrosis and postoperative recurrence, and only one report by Sasaki et al. [11] has investigated the underlying factors comprehensively. In our investigation, patients with cirrhosis demonstrated a lower likelihood of experiencing postoperative extrahepatic recurrence. This outcome bears resemblance to a previous report and aligns with our own findings. Furthermore, in our research, all extrahepatic metastases in F4 patients were observed within 12 months following surgery. The rate of intrahepatic recurrence remained relatively constant throughout the follow-up period, which concurs with prior studies. This consistency supports the hypothesis that de novo recurrence is attributed to the high carcinogenic potential of the underlying liver. However, given that this study did not assess the molecular biology of postoperative recurrence related to fibrosis or tumor angiogenesis, there remains an opportunity for further investigation into the reasons behind this discrepancy. Moreover, it is imperative to acknowledge the potential predisposition toward bias within the F4 cohort, where a diminished occurrence of extrahepatic recurrences may be attributed to the unfeasibility of extended postoperative surveillance, owing to the occurrence of early postoperative relapses.

Internationally, the Ishak staging system is widely used to assess liver fibrosis in chronic liver disease because of its precision in histologic assessment of liver fibrosis. Unlike other staging systems, such as the Scheuer system which only has four stages, the Ishak system defines more stages of fibrosis, ranging from 0 to 6 [20]. In Japan, the New-Inuyama classification is used to evaluate chronic hepatitis and liver fibrosis. A notable revelation in the current investigation was the deterioration of RFS and DSS with the advancement of the fibrosis stage across the entire patient cohort until complete cirrhosis establishment. While previous studies have examined the association of liver fibrosis with poor prognosis following surgical resection [21–23], our findings support the significance of fibrosis staging in predicting the prognosis.

In the present study, the therapeutic options for recurrence were observed to be restricted by liver fibrosis. It is not surprising that patients with LC were less inclined to opt for rehepatectomy as a treatment for recurrence owing to their diminished hepatic function. Nevertheless, the efficacy of rehepatectomy in HCC has been established in numerous studies [24, 25]. Therefore, it is desirable to either prevent liver fibrosis from progressing or to revert the liver fibrosis back to its original state. In the former case, treatment with nucleoside or nucleotide analogues, interferons, and direct-acting antivirals has decreased the incidence of HBV and HCV hepatitis, which are the leading causes of HCC. In the latter, it has been reported that hexa-histidine-tagged recombinant human cytoglobin has potential antifibrotic clinical applications [26].

The present study had some limitations, including the retrospective study design. Retrospective studies rely on previously collected patient data, which can lead to selection bias. Patients selected for study inclusion may differ systematically from those who are excluded, which can impact the generalizability of the findings. For example, if patients with more severe liver fibrosis are more likely to be referred to a specific hospital or clinic, then a retrospective study that relies on data from that hospital or clinic may overestimate the association between liver fibrosis and recurrence rates. Another limitation is that we could not identify the advantages of clinically distinguishing F1, F2, and F3 because we had to use the grouping of F0 versus F1–3, and F1–3 versus F4 to perform a case-matched analysis. However, this would probably not change the observation that LC or fibrosis is associated with poor outcome. Despite these limitations, our results may lead to more effective treatment algorithms for patients with HCC and may assist in optimal selection of patients for liver resection.

In conclusion, the present study revealed that the cancer-specific outcomes vary depending upon the severity of fibrosis. The RFS was significantly poorer in the F1-3 group than F0 group, and F4 group than the F1–3 group, and de novo carcinogenesis was significantly more frequent in the F4 group than the F1–3 group. Prophylactic treatment of viral hepatitis, as well as innovative interventions targeted at the fibrotic process, is anticipated to diminish the likelihood of HCC recurrence.

Acknowledgment

We thank Kelly Zammit, BVSc, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Statement of Ethics

The study was approved by the Ethics Committee of Shinshu University School of Medicine (approval No. 2020-5011) and conducted in accordance with the principles outlined in the Declaration of Helsinki. Because of the retrospective nature of the study and absence of invasive interventions, the requirement for written consent was waived by the review board. Data were collected from the medical records and analyzed retrospectively and anonymously.

Conflict of Interest Statement

None declared.

Funding Sources

No funding was received for this work.

Author Contributions

K.Y., A.S., K.K., T.N., K.H., H.H., K.U., A.K., and Y.S. were involved in study design and data interpretation. K.Y., K.H., H.H., K.U., and A.K. were responsible for collecting the data needed for the analysis. K.Y. and A.S. were involved in the drafting of the manuscript and data analysis. Y.S. was involved in the study supervision. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

Data Availability Statement

Data cannot be shared publicly because of the necessity to protect personal information. However, they are available from the Shinshu Institutional Data Access/Ethics Committee (contact via shinhp@shinshu-u.ac.jp) for researchers who meet the criteria for access to confidential data. The data underlying the results presented in the study are available from Shinshu University (shinhp@shinshu-u.ac.jp). Further inquiry can be directed to the corresponding author.

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