The Impact of Comorbid Renal Dysfunction in Patients with Hepatocellular Carcinoma on Long-Term Outcomes after Curative Resection

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Abstract

Background:

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. However, the number of patients with chronic kidney disease (CKD) is also on the rise because of the increase in lifestyle-related diseases. To establish a tailored management strategy for HCC patients, we evaluated the impact of comorbid renal dysfunction (RD), as stratified by using the estimated glomerular filtration rate (eGFR), and assessed the oncologic validity of hepatectomy for HCC patients with RD.

Methods:

We enrolled 800 HCC patients who underwent hepatectomy between 1997 and 2015 in our university hospital. We categorized patients into two (RD, eGFR < 60 mL/min/1.73m^2; non-RD, 60 ≤ eGFR) and three groups (severe CKD, eGFR < 30; mild CKD, 30 ≤ eGFR < 60; control, 60 ≤ eGFR) according to renal function as defined by the eGFR. Overall survival (OS) and recurrence-free survival (RFS) were compared among these groups with the log-rank test, and we also analyzed survival by using a propensity score matching (PSM) model for excluding the influence of patient characteristics. The mean of postoperative observation period was 64.7 ± 53.0 months.

Results:

RD patients were significantly older and had lower serum total bilirubin, AST, and ALT levels than those in non-RD patients (P < 0.0001, P < 0.001, < 0.05, and < 0.01, respectively). No patient was introduced to maintenance hemodialysis after surgery. Although the overall postoperative complications rates were similar between RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in RD patients (5.5% vs. 1.8%; P < 0.05, 3.9% vs. 1.8%; P < 0.05, respectively), and postoperative bleeding was the highest in severe CKD group (P < 0.05). Regardless of the degree of comorbid RD, OS and RFS were comparative, even when using PSM between RD and non-RD groups to exclude the influence of patient characteristics, liver function, and other causes of death.

Conclusions:

Comorbid RD had a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management, and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

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Background

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death in many parts of the world and is estimated to be the fourth most common cause of cancer-related death worldwide (1, 2).

Hepatectomy for the treatment of HCC has the highest controllability among local treatments and results in a good survival rate (3, 4). On the other hand, the number of patients with chronic kidney disease (CKD) is also on the rise, and CKD affects 8–16% of the population worldwide, especially in developed countries, and is most commonly attributed to diabetes and/or hypertension (5). Several studies have shown that patients with CKD who underwent any major surgery are at risk because they have more comorbidities, including coagulopathy and systemic atherosclerosis (6–8). Previous reports have shown a relation between preoperative renal dysfunction (RD) and prognosis and postoperative complications in patients with HCC underwent hepatectomy; however, these relations remain controversial (9–11). Moreover, previously, the serum creatine (Cr) value was used as an indicator of renal function, but recently, it has been common to use the estimated glomerular filtration rate (eGFR) to determine the stage of RD because serum Cr is influenced by age, sex, muscle quantify, lifestyle (5). So far, only one study reported the effects of preoperative RD defined by using the eGFR in patients with HCC (12), but little is known about the impact of preoperative RD on the long-term prognosis or postoperative complications, including acute kidney disease (AKI) and the initiation of hemodialysis in HCC patients underwent hepatectomy. In this study, we aimed to evaluate the impact of comorbid RD as stratified by the eGFR and assess the oncologic validity of hepatectomy for HCC patients with RD, such as end-stage renal disease (ESRD) on short and long-term outcomes after the curative resection in patients with HCC.

Methods

Patients

We enrolled 800 HCC patients who underwent hepatectomy between January 1997 and December 2015 at the Gastroenterological Surgery I unit of Hokkaido University Hospital in Sapporo, Japan. Baseline information, including the etiology of chronic liver disease, serum biochemistry, severity of cirrhosis, performance status, and cancer stage, was recorded when the diagnosis was established. This study was conducted with the approval of the Institutional Review Board of Hokkaido University Hospital (No. 016-0354) and was performed in accordance with the Helsinki Declaration guidelines. Informed consent was obtained in the opt-out form on the website of Hokkaido University Hospital.

Diagnosis and definitions

The diagnosis of HCC, disease progression and resectability status were assessed via general statuses, physical findings, serological tests, and imaging studies, including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US). Liver function was assessed with a blood liver function test, the Child-Pugh grade, the estimated indocyanine green retention rate at 15 minutes (ICGR15) (13), and the technetium-99m-galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy index (14). To evaluate the feasibility of hepatectomy in HCC patients with RD, the primary endpoint of the present study was long-term outcomes [median survival time (MST)] after hepatectomy. The secondary endpoint was postoperative complications.

Diagnostic criteria for RD

Preoperative RD was defined by the preoperative eGFR. CKD stage 3a ($45 \leq$ eGFR < 60 mL/min/1.73 m^2) or higher according to KDIGO CKD guideline (15) is reportedly associated with an increase in the risk of various diseases and mortality (16), so the RD group was comprised of patients with an eGFR < 60 mL/min/1.73 m^2, and the non-RD group was comprised of patients with an eGFR ≥ 60. Moreover, we also categorized patients into three groups according to the RD as defined by eGFR (severe CKD, eGFR < 30; mild CKD, $30 \leq$ eGFR < 60; control, $60 \leq$ eGFR) because patients with ESRD who were undergoing dialysis were likely to be at high risk of developing HCC (17).

Treatment and perioperative management of patients with severe CKD

The criteria for hepatectomy were decided regardless of renal function. Surgical procedures were determined according to liver function and the general status, including the extent of disease (18), and were classified as anatomical resection (subsegmentectomy, segmentectomy, bisegmentectomy, and trisegmentectomy) or nonanatomical resection (partial resection). Postoperative complications of class II or higher according to the Clavien-Dindo classification system were recorded (19). Postoperative mortality was defined as death within 90 days after surgery.

All patients were managed pre- and postoperatively according to previous reports (18). In particular, the patients with severe CKD consulted with the nephrology team, and preparations for emergency hemodialysis were made prior to surgery. For six patients in the RD group on maintenance hemodialysis, hemodialysis was scheduled to be performed the day before surgery, postoperative day one, and then three times per week thereafter.

Statistical analysis

Categorical data were compared with chi-square test. Continuous data were compared between RD and non-RD group by the Mann-Whitney *U*-test, and among three groups (severe CKD, mild CKD, and non-RD) by the Kruskal–Wallis test followed by Dunn's multiple comparison test. Overall survival (OS) and recurrence-free survival (RFS) curves were drawn using the Kaplan-Meier method with the generalized log-rank test in all 800 patients and 110 pairs of matched HCC patients selected by using a propensity score matching (PSM) model. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were conducted with JMP 14 software (SAS Institute Inc., Cary, NC, USA) or GraphPad Prism 7 (GraphPad Software, Inc., La Jolla CA, USA).

Results

Patient characteristics

Patients in the RD group (128 patients, 16.0%) were significantly older ($P < 0.0001$); had a lower prevalence of hepatitis B ($P < 0.001$); had lower serum total bilirubin (T-bil), aspartate aminotransferase (AST), aspartate aminotransferase (ALT), alpha-fetoprotein (AFP), and alpha-fetoprotein isoform, lectin affinity (AFP-L3) levels ($P < 0.001$, < 0.05, < 0.01, < 0.01, and < 0.05, respectively); a higher prevalence of non-hepatitis B virus (HBV) and non-hepatitis C virus (HCV) (NBNC) ($P < 0.001$); and higher serum HbA1c, blood urine nitrogen (BUN), and Cr levels ($P < 0.05$, < 0.0001, and < 0.0001, respectively) than in the non-RD group (Table 1). The preoperative characteristics of severe, mild CKD and non-RD patient groups are also summarized in Table 2. Nineteen patients had severe CKD, including six patients who were received routine preoperative hemodialysis, and 109 patients had mild CKD. Age (73.0, 69.0, and 63.0 years; $P < 0.0001$), female ratio (31.6%, 10.1%, and 18.3%; $P < 0.05$), BUN (38.0 mg/dL, 19.0 mg/dL, and 14.0 mg/dL; $P < 0.0001$), Cr (2.4 mg/dL, 1.0 mg/dL, and 0.7 mg/dL; $P < 0.0001$), and AFP-L3 (21.7%, 0%, and 3.1%; $P < 0.05$) in severe CKD patient group were significantly higher than in other patient groups. On the other hand, serum albumin (3.8 g/dL, 4.1 g/dL, and 4.1 g/dL; $P < 0.01$), T-bil (0.4 mg/dL, 0.7 mg/dL, and 0.8 mg/dL: $P < 0.001$), ALT (21.0 IU/L, 34.0 IU/L, and 40.0 IU/L; $P < 0.05$), and cholinesterase levels (181.0 IU/L, 249.0 IU/L, and 245.0 IU/L, $P < 0.01$) in severe CKD group were significantly lower than in other patients groups. NBNC ratio (31.6%, 47.7%, and 28.5%; $P < 0.001$), and HbA1c (5.5%, 5.9%, and 5.3%; $P < 0.05$) in mild CKD patient group was higher, and HBV ratio (26.3%, 22.0%, and 39.1%; $P < 0.01$) in the severe and mild CKD groups were lower than in non-RD group. The mean follow-up time was 64.7 ± 53.0 months after hepatectomy.

Table 1
Characteristics of patients with and without RD (n, %)

	RD (eGFR < 60)			Non-RD (60 ≤ eGFR)			*P*-value
	n = 128			n = 672			
Age (yeas)	69.5	±	8.6	63.0	±	10.4	**< 0.0001**
Sex							
Male	111 (86.7)			549 (81.7)			0.17
Female	17 (13.3)			123 (18.3)			-
Etiology							
HBV	29 (22.7)			263 (39.1)			**< 0.001**
HCV	41 (32.0)			218 (32.4)			0.93
NBNC	58 (45.3)			191 (28.5)			**< 0.001**
Child-Pugh grade							
A	124 (96.9)			649 (96.6)			0.86
B	4 (3.1)			23 (3.4)			-
Laboratory data							
Plt ($\times 10^4/\mu L$)	16.2	±	6.2	15.5	±	7.3	0.26
PT (%)	94.9	±	13.7	91.7	±	14.7	0.08
Alb (g/dL)	4.0	±	0.4	4.1	±	0.4	0.32
T-bil (mg/dL)	0.7	±	0.3	0.8	±	0.4	**< 0.001**
AST (IU/L)	35.5	±	31.2	43.0	±	43.4	**< 0.05**
ALT (IU/L)	31.5	±	30.0	40.0	±	36.1	**< 0.01**
ChE (IU/L)	238.0	±	89.8	245.0	±	81.3	0.92
ICG15R (%)	14.4	±	7.3	13.6	±	10.6	0.61
HbA1c (%)	5.7	±	1.1	5.3	±	1.1	**< 0.05**

P values were determined by the chi-square test or the Mann-Whitney *U*-test. The bold values represent significant differences (*P*-value < 0.05). RD, renal dysfunction; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV or HCV; Plt, platelet count; PT, prothrombin time; Alb, serum albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ChE, choline esterase; ICGR15, indocyanine green rate at 15 minutes; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein-induced vitamin K absence-II.

	RD (eGFR < 60)		Non-RD (60 ≤ eGFR)		*P*-value
	n = 128		n = 672		
BUN (mg/dL)	20.0	± 10.8	14.0	± 4.0	**< 0.0001**
Cr (mg/dL)	1.1	± 1.6	0.7	± 0.1	**< 0.0001**
AFP (ng/mL)	10.3	(1.4–164321.4)	19.9	(0–5986980)	**< 0.01**
AFP-L3 (%)	0.0	± 23.8	3.1	± 24.4	**< 0.05**
PIVKA-II (mAU/mL)	11385.0	(0–436410)	136.0	(0–664680)	0.68

P values were determined by the chi-square test or the Mann-Whitney *U*-test. The bold values represent significant differences (*P*-value < 0.05). RD, renal dysfunction; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV or HCV; Plt, platelet count; PT, prothrombin time; Alb, serum albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ChE, choline esterase; ICGR15, indocyanine green rate at 15 minutes; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein-induced vitamin K absence-II.

Table 2
Characteristics of patients with severe, mild CKD, and without RD (n, %)

	CKD Stage			*P*-value
	severe	**mild**	**non-RD**	
	(eGFR < 30)	**(30 ≤ eGFR < 60)**	**(60 ≤ eGFR)**	
	n = 19	**n = 109**	**n = 672**	
Age (yeas)	73.0 ± 8.9	69.0 ± 8.6	63.0 ± 10.4	**< 0.0001**
Sex				
Male	13 (68.4)	98 (89.9)	549 (81.7)	**< 0.05**
Female	6 (31.6)	11 (10.1)	123 (18.3)	-
Etiology				
HBV	5 (26.3)	24 (22.0)	263 (39.1)	**< 0.01**
HCV	8 (42.1)	33 (30.3)	218 (32.4)	0.59
NBNC	6 (31.6)	52 (47.7)	191 (28.5)	**< 0.001**
Child-Pugh grade				
A	19 (100.0)	105 (96.3)	649 (96.6)	0.71
B	0 (0.0)	4 (3.7)	23 (3.4)	-
Laboratory data				
Plt ($\times 10^4$/μL)	14.5 ± 5.2	16.3 ± 6.4	15.5 ± 7.3	0.76
PT (%)	94.9 ± 10.1	95.2 ± 14.3	91.7 ± 14.7	0.35
Alb (g/dL)	3.8 ± 0.3	4.1 ± 0.4	4.1 ± 0.4	**< 0.01**
T-bil (mg/dL)	0.4 ± 0.2	0.7 ± 0.3	0.8 ± 0.4	**< 0.001**
AST (IU/L)	27.0 ± 17.4	38.0 ± 32.5	43.0 ± 43.4	0.07

P values were determined by the chi-square test or by the Kruskal–Wallis test followed by Dunn's multiple comparison test. The bold values represent significant differences (*P*-value < 0.05). RD, renal dysfunction; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV or HCV; Plt, platelet count; PT, prothrombin time; Alb, serum albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ChE, choline esterase; ICGR15, indocyanine green rate at 15 minutes; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein-induced vitamin K absence-II.

	CKD Stage									P-value
	severe			mild			non-RD			
	(eGFR < 30)			(30 ≤ eGFR < 60)			(60 ≤ eGFR)			
	n = 19			n = 109			n = 672			
ALT (IU/L)	21.0	±	19.0	34.0	±	30.9	40.0	±	36.1	**< 0.05**
ChE (IU/L)	181.0	±	68.1	249.0	±	90.0	245.0	±	81.3	**< 0.01**
ICG15R (%)	10.5	±	6.2	15.3	±	7.3	13.6	±	10.6	0.18
HbA1c (%)	5.5	±	1.0	5.9	±	1.1	5.3	±	1.1	**< 0.05**
BUN (mg/dL)	38.0	±	15.8	19.0	±	5.2	14.0	±	4.0	**< 0.0001**
Cr (mg/dL)	2.4	±	3.2	1.0	±	0.2	0.7	±	0.1	**< 0.0001**
AFP (ng/mL)	51.5	(2.1–164321.4)		6.5	(1.4–37525.5)		19.9	(0–5986980)		0.61
AFP-L3 (%)	21.7	±	30.6	0.0	±	21.6	3.1	±	24.4	**< 0.05**
PIVKA-II (mAU/mL)	1309.0	(10–167600)		105.0	(0–436410)		136.0	(0–664680)		0.93

P values were determined by the chi-square test or by the Kruskal–Wallis test followed by Dunn's multiple comparison test. The bold values represent significant differences (*P*-value < 0.05). RD, renal dysfunction; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV or HCV; Plt, platelet count; PT, prothrombin time; Alb, serum albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ChE, choline esterase; ICGR15, indocyanine green rate at 15 minutes; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein-induced vitamin K absence-II.

Intraoperative Variables And Tumor Characteristics

As listed in Table 3, the proportion of curability A or B was significantly higher in RD patients than in non-RD patients (91.4% vs. 83.8%; $P < 0.05$). Those of vascular invasion and advanced fibrosis (F stage 3 and 4) were significantly lower in RD patients than in non-RD patients (8.6% vs. 21.6%; $P < 0.001$, 32.0% vs. 53.2%; $P < 0.0001$, respectively). The intraoperative variables and other tumor characteristics of severe, mild CKD and non-RD groups were also almost comparable for all groups. In this analysis, curability of severe and mild CKD group patients was higher than that of non-RD group patients ($P < 0.05$), on the other hand, the proportion of vascular invasion and advanced fibrosis in patients with severe and mild CKD were significantly lower than that of non-RD group patients ($P < 0.01$, and < 0.001, respectively).

Resected liver weight (365 g, 222 g, and 252 g, $P = 0.24$) in severe CKD patient group tends to higher than in other patient groups, although the difference was not statistically significant (Table 4).

Table 3
Intraoperative parameters in patients with and without RD (n, %)

	CKD Stage						***P*-value**
	RD (eGFR < 60)			**non-RD (60 ≤ eGFR)**			
	n = 128			**n = 672**			
Intraoperative variables							
Operative time (min)	323.0	±	125.0	329.0	±	108.0	0.70
Blood loss (mL)	380.0	±	3230.1	425.0	±	1577.3	0.42
Procedure of resection							
Anatomical resection	99 (77.3)			498 (74.1)			0.44
Non-anatomical resection	29 (22.7)			174 (25.9)			-
Resected liver weight (g)	239.0	±	459.3	252.0	±	630.0	0.57
Curability							
A + B	117 (91.4)			563 (83.8)			**< 0.05**
C	11 (8.6)			109 (16.2)			-
Tumor characteristics							
Tumor size (cm)	4.5	±	3.9	4.4	±	4.6	0.85
Tumor number	1.0	±	1.7	1.0	±	2.8	0.55
pStage							
I	8 (6.3)			53 (7.9)			0.11
II	62 (48.4)			272 (40.5)			-
III	40 (31.3)			207 (30.8)			-
IV	18 (14.1)			140 (20.8)			-
Pathological grade							
well	24 (18.7)			95 (14.1)			0.29

P values were determined by the chi-square test or the Mann-Whitney U-test. The bold values represent significant differences (P-value < 0.05). The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. Liver Cancer Study Group of Japan, 6th edition ‡ Liver fibrosis was graded and staged according to the New Inuyama classification system37 as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).

	CKD Stage		*P*-value
	RD (eGFR < 60)	**non-RD (60 ≤ eGFR)**	
	n = 128	**n = 672**	
mod-por	104 (81.3)	577 (85.9)	-
Vascular invasion			
yes	11 (8.6)	145 (21.6)	**< 0.001**
no	117 (91.4)	527 (78.4)	-
Liver fibrosis score			
0–1	44 (34.4)	143 (21.2)	**< 0.0001**
2	43 (33.6)	172 (25.6)	-
3	22 (17.2)	149 (22.2)	-
4	19 (14.8)	208 (31.0)	-

P values were determined by the chi-square test or the Mann-Whitney U-test. The bold values represent significant differences (P-value < 0.05). The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. Liver Cancer Study Group of Japan, 6th edition ‡ Liver fibrosis was graded and staged according to the New Inuyama classification system37 as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).

Table 4
Intraoperative parameters in patients with severe, mild CKD, and without RD (n, %)

	CKD Stage			*P*-value
	severe	**mild**	**non-RD**	
	(eGFR < 30)	**(30 ≤ eGFR < 60)**	**(60 ≤ eGFR)**	
	n = 19	**n = 109**	**n = 672**	
Intraoperative variables				
Operative time (min)	311.0 ± 112.0	331.0 ± 127.0	329.0 ± 108.0	0.52
Blood loss (mL)	389.0 ± 1254.1	380.0 ± 3464.9	425.0 ± 1577.3	0.64
Procedure of resection				
Anatomical resection	13 (68.4)	86 (78.9)	498 (74.1)	0.46
Non-anatomical resection	6 (31.6)	23 (21.1)	174 (25.9)	-
Resected liver weight (g)	365.0 ± 388.5	222.0 ± 471.3	252.0 ± 630.0	0.24
Curability				
A + B	19 (100.0)	98 (89.9)	563 (83.8)	**< 0.05**
C	0 (0.0)	11 (10.1)	109 (16.2)	-
Tumor characteristics				
Tumor size (cm)	5.8 ± 4.0	4.5 ± 3.8	4.4 ± 4.6	0.41
Tumor number	1.0 ± 2.1	1.0 ± 1.6	1.0 ± 2.8	0.44
pStage□				

P values were determined by the chi-square test or by the Kruskal–Wallis test followed by Dunn's multiple comparison test. The bold values represent significant differences (P-value < 0.05). The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. □ Liver Cancer Study Group of Japan, 6th edition ‡ Liver fibrosis was graded and staged according to the New Inuyama classification system37 as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).

	CKD Stage			*P*-value
	severe	**mild**	**non-RD**	
	(eGFR < 30)	**(30 ≤ eGFR < 60)**	**(60 ≤ eGFR)**	
	n = 19	**n = 109**	**n = 672**	
I	1 (5.3)	7 (6.4)	53 (7.9)	0.45
II	8 (42.1)	54 (49.5)	272 (40.5)	-
III	7 (36.8)	33 (30.3)	207 (30.8)	-
IV	3 (15.8)	15 (13.8)	140 (20.8)	-
Pathological grade				
well	2 (10.5)	22 (20.2)	95 (14.1)	0.84
mod-por	17 (89.5)	87 (79.8)	577 (85.9)	-
Vascular invasion[]				
yes	2 (10.5)	9 (8.3)	145 (21.6)	**< 0.01**
no	17 (89.5)	100 (91.7)	527 (78.4)	-
Liver fibrosis score[‡]				
0–1	7 (36.8)	37 (34.0)	143 (21.2)	**< 0.001**
2	8 (42.1)	35 (32.1)	172 (25.6)	-
3	3 (15.8)	19 (17.4)	149 (22.2)	-
4	1 (5.3)	18 (16.5)	208 (31.0)	-

P values were determined by the chi-square test or by the Kruskal–Wallis test followed by Dunn's multiple comparison test. The bold values represent significant differences (P-value < 0.05). The liver fibrosis score was assessed by expert pathologists using a noncancerous lesion from the resected specimen. [] Liver Cancer Study Group of Japan, 6th edition ‡ Liver fibrosis was graded and staged according to the New Inuyama classification system37 as follows: F1 (periportal expansion), F2 (porto-portal septa), F3 (porto-central linkage or bridging fibrosis), and F4 (cirrhosis).

Postoperative Complications

Although the overall postoperative complications rates were similar between RD and non-RD patients, the proportions of postoperative bleeding and surgical site infection were significantly higher in RD patients (5.5% vs. 1.8%; $P < 0.05$, 3.9% vs. 1.8%; $P < 0.05$, respectively) (Table 5). In comparison between patients with severe CKD and those with mild CKD, there was no difference of postoperative complications. Postoperative complications were also not significant different among three groups, except for bleeding that were higher than in severe CKD group ($P < 0.05$) (Table 6). Regarding these bleeding complications, three RD patients (2.3%) and eight non-RD patients (1.2%) required reoperation to control postoperative bleeding. There were no complications of ascites, pleural effusion, liver failure, or surgical site infection in six patients who required maintenance hemodialysis before surgery. The duration of postoperative hospital stay was not significantly different among three groups (16.0, 16.0, and 16.0 days; $P = 0.92$). There was no mortality during hospitalization in severe CKD group, but one patient each in the mild CKD and non-RD groups died during hospitalization. In the mild CKD group, one patient died due to postoperative gastrointestinal perforation and an intraabdominal abscess. In the non-RD group, one patient died due to postoperative liver failure.

Table 5
Postoperative complications in patients with and without RD (n, %)

	CKD Stage		***P*-value**
	RD (eGFR < 60)	**non-RD (60 ≦ eGFR)**	
	n = 128	**n = 672**	
All complications	33 (25.8)	169 (25.1)	0.96
Major complication (Grade ≧ 2)	20 (15.6)	112 (16.7)	0.91
Bile leakage	12 (9.8)	44 (6.5)	0.33
Ascites	6 (4.7)	27 (4.0)	0.90
Pleural effusion	4 (3.1)	37 (5.5)	0.41
Pneumonia	6 (5.3)	12 (1.8)	0.70
Bleeding	7 (5.5)	12 (1.8)	**< 0.05**
Liver failure	1 (0.8)	9 (1.3)	0.55
Surgical site infection	5 (3.9)	12 (1.8)	**< 0.05**
Duration of postoperative hospital stay (day)	16.0 ± 14.5	16.0 ± 19.3	0.17
Died during hospitalization	1* (0.8)	1** (0.1)	0.96

P values were determined by the chi-square test or the Mann-Whitney U-test. The bold values represent significant differences (P-value < 0.05). One patient in the RD group died due to postoperative gastrointestinal perforation and an intraabdominal abscess (*), and one patient in the non-RD group died due to postoperative liver failure (**).

Table 6
Postoperative complications in patients with severe, mild CKD, and without RD (n, %)

	CKD Stage			P-value
	severe	**mild**	**non-RD**	
	(eGFR < 30)	**(30 ≤ eGFR < 60)**	**(60 ≤ eGFR)**	
	n = 19	**n = 109**	**n = 672**	
All complications	5 (26.3)	28 (25.7)	169 (25.1)	0.99
Major complication (Grade ≥ 2)	3 (15.8)	17 (15.6)	112 (16.7)	0.98
Bile leakage	2 (10.5)	10 (9.2)	44 (6.5)	0.40
Ascites	2 (10.5)	4 (3.7)	27 (4.0)	0.45
Pleural effusion	0 (0.0)	4 (3.7)	37 (5.5)	0.68
Pneumonia	1 (5.3)	5 (4.6)	12 (1.8)	0.84
Bleeding	2 (10.5)	5 (4.6)	12 (1.8)	**< 0.05**
Liver failure	0 (0.0)	1 (0.9)	9 (1.3)	0.55
Surgical site infection	0 (0.0)	5 (4.6)	12 (1.8)	0.07
Duration of postoperative hospital stay (day)	16.0 ± 15.3	16.0 ± 14.4	16.0 ± 9.3	0.92
Died during hospitalization	0 (0.0)	1* (0.9)	1** (0.1)	0.96

P values were determined by the chi-square test or by the Kruskal–Wallis test followed by Dunn's multiple comparison test. The bold values represent significant differences (P-value < 0.05). One patient in the RD group died due to postoperative gastrointestinal perforation and an intraabdominal abscess (*), and one patient in the non-RD group died due to postoperative liver failure (**).

Impact Of Hepatectomy On Postoperative Rd

We compared eGFR values before and one month after hepatectomy in patients with CKD stage 4 or 5 according to KDIGO CKD guideline (15) who didn't receive maintenance hemodialysis (n = 13) (Fig. 1). The eGFR values did not decrease after the operation, and furthermore, no patient received maintenance hemodialysis after hepatectomy.

Survival And Recurrence After Hepatectomy For Hcc

The median survival time (MST) was 70.6 months in RD patients and 72.4 months in non-RD patients (*P* = 0.524). The one-, 3-, 5-, and 10-year OS rates were 87.3%, 74.0%, 60.2%, and 20.6% in RD patients and 89.9%, 74.1%, 64.6%, and 23.1% in non-RD patients, respectively (Fig. 2A). Moreover, the MST was 40.8 months in the severe CKD group, 70.9 months in the mild CKD group and 72.4 months in the non-RD group (*P* = 0.605). The one-, 3-, 5-, and 10-year OS rates were 78.2%, 64.5%, 48.4%, and 9.7% in the severe CKD group, 89.0%, 75.5%, 62.2%, and 22.5% in the mild CKD group and 89.9%, 74.1%, 64.6%, and 23.1% in the non-RD group, respectively (Fig. 2B). The median RFS time was 46.2 months in RD patients and 27.4 months in non-RD patients (*P* = 0.464) (Fig. 2C). The median RFS time was 17.0 months in the severe CKD group, 47.5 months in the mild CKD group and 27.4 months in the non-RD group (*P* = 0.762) (Fig. 2D).

OS and RFS between RD and non-RD groups after PSM

Regarding patient characteristics, RD patients were significantly older, associated with lower proportion of HBV and higher proportion of NBNC, and had lower serum T-bil, AST, ALT, and higher serum HbA1c levels than non-RD patients. Therefore, we examined the impact of preoperative RD on OS and RFS rates, excluding the influence of these factors, by using a propensity model. A total of 110 pairs of matched HCC patients undergoing hepatectomy were selected in this model (Sup Table 1). The comparison of OS and RFS rates between matched patients with RD and non-RD showed no significant difference (*P* = 0.343, *P* = 0.314, respectively) (Fig. 3). In addition, considering the influence of liver function or other causes of death, we also analyzed survival in patients with Child-Pugh grade A disease and in those who died from cancer-related causes. The OS rate was similar between RD and non-RD patients with Child-Pugh grade A disease (*P* = 0.489, Fig. 4) and in those who died from cancer-related causes (*P* = 0.993, Fig. 5).

Prognostic Factor Analysis In Hcc Patients With Rd

Table 7 shows the prognostic factors for OS and RFS in HCC patients with RD in this cohort. In RD patients, the multivariate analysis showed that the presence of multiple tumors was an independent factor for both OS and RFS (OS: hazard ratio [HR] 2.44, 95% confidence interval [CI] 1.04–5.75, *P* = 0.040, RFS: HR 3.77, 95% CI 1.61–8.97, *P* = 0.002).

Table 7
Prognostic factors for OS and RFS in HCC patients with RD

Variable	Overall survival			Recurrence-free survival		
	Univariate	Multivariate analysis		Univariate	Multivariate analysis	
RD patients	*P* value	HR (95% CI)	*P* value	*P* value	HR (95% CI)	*P* value
Age > 60 years	**0.029**	3.85 (0.81–22.53)	0.092	**0.045**	0.98 (0.26–4.76)	0.978
Male	0.371			0.122		
HBV+	0.995			0.947		
HCV+	0.899			0.889		
NBNC	0.898			0.849		
Child-Pugh grade B	0.44			0.919		
Plt < 13.8	0.598			0.257		
PT < 80	0.706			0.858		
Alb < 4.0	0.32			0.376		
T-bil > 1.2	0.772			0.95		
AST > 38	0.534			0.223		
ALT > 44	0.16			0.421		
ChE < 168	**0.0048**	1.06 (0.31–3.15)	0.921	**0.002**	2.21 (0.17–1.35)	0.147
ICGR15 > 15	0.8			0.176		
HbA1c > 5.6	0.145			0.823		
AFP > 10	0.068			**0.002**	0.79 (0.29–2.03)	0.634

RD, renal dysfunction; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV or HCV; Plt, platelet counts; PT, prothrombin time; Alb, serum albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ChE, choline esterase; ICGR15, indocyanine green rate at 15 minutes; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein-induced vitamin K absence-II; Ave, average; mod, moderately differentiated; por, poorly differentiated; Vp, portal vein invasion; Vv, hepatic vein invasion. The bold values represent significant differences (P-value < 0.05).

Variable	Overall survival			Recurrence-free survival		
AFP-L3 > 10	**< 0.0001**	2.57 (0.99–6.70)	0.051	**0.003**	2.22 (0.87–5.98)	0.095
PIVKA-II > 40	**0.009**	2.57 (0.64–11.50)	0.186	0.067		
Operative time > Ave	0.868			0.916		
Blood loss > Ave	0.28			0.533		
Anatomical resection	0.833			0.391		
Resected liver weight > Ave	**0.007**	0.99 (0.37–2.66)	0.978	0.137		
Tumor size > Ave	**0.006**	1.06 (0.33–3.30)	0.918	**0.015**	1.86 (0.63–5.40)	0.258
Tumor number > 1	**0.002**	**2.44 (1.04–5.75)**	**0.04**	**< 0.0001**	**3.77 (1.61–8.97)**	**0.002**
Pathological grade (mod-por)	0.505			0.337		
Vascular invasion (Vp+, Vv+)	**< 0.0001**	1.88 (0.61–5.14)	0.26	**0.002**	1.89 (0.70–4.60)	0.198
Liver fibrosis score 3, 4	0.278			0.186		

RD, renal dysfunction; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV or HCV; Plt, platelet counts; PT, prothrombin time; Alb, serum albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ChE, choline esterase; ICGR15, indocyanine green rate at 15 minutes; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein-induced vitamin K absence-II; Ave, average; mod, moderately differentiated; por, poorly differentiated; Vp, portal vein invasion; Vv, hepatic vein invasion. The bold values represent significant differences (P-value < 0.05).

Discussion

We revealed here that the prognoses for survival and recurrence in HCC patients with and without RD who underwent curative hepatectomy were similar, even if patients had severe CKD. This finding indicated that comorbid RD had a negligible impact on the prognosis of HCC patients who undergo curative hepatectomy. However, preoperative RD affected on some kinds of postoperative complications, such as postoperative bleeding and surgical site infection.

It has been reported that progressive CKD is associated with adverse clinical outcomes, including ESRD, cardiovascular disease, and increased mortality (20, 21). The prognosis of HCC patients with RD might be

affected by these comorbidities. In addition, Toyoda et al. reported that the survival rate of patients who required dialysis was significantly lower than that of non-dialysis controls (17). In our study, there was no significant difference in both OS and RFS between patients with and without RD, even if patients had severe CKD. Moreover, because there were some differences in patient characteristics such as age, etiology, liver function, and HbA1c levels between patients with and without RD, we also performed PSM. The OS and RFS rates were comparable between patients with and without RD after PSM. These results indicated that curative hepatectomy might be effective for the long-term prognosis of HCC patients, regardless of the presence of concomitant RD.

RD also has been reported to be a risk factor for the development of massive ascites, pleural effusion, respiratory failure, and acute renal failure in patients after hepatectomy (10, 11). Our study showed the proportion of patients who experienced these complications were similar between patients with and without RD. The following reasons might explain these results. First, the low frequencies of ascites and pleural effusion. Second, we might perform hepatectomy in RD patients whose liver function was better because serum T-bil, AST, and ALT levels were lower in RD patients than in non-RD patients. Regarding acute renal failure, the eGFR values did not decrease after liver resection, and furthermore, no patient with stage 4 or 5 disease and not on hemodialysis was treated after hepatectomy; instead, they were given appropriate perioperative care. Some reports also showed that blood loss was higher in RD patients than in non-RD patients (10), but the amounts of blood loss were similar between RD and non-RD patients in our study. On the other hand, the rate of postoperative bleeding was significantly higher in RD patients. Regarding higher proportion of postoperative bleeding in RD patients, especially in those with severe CKD, some degree of coagulopathy and tissue weakness (22) in patients with CKD might influence this complication. Surgical site infection also might be related to the immune dysfunction of CKD patients (23). Therefore, we should make sure blood stanching with attention before closing abdomen.

In the present study, the proportion of postoperative surgical site infections was also higher in RD patients than in non-RD patients, so more careful postoperative management is needed in RD patients. In addition to curative liver resection, hepatectomy requires careful follow-up of patients. As demonstrated in the univariate and multivariate analyses, RD patients with multiple tumors tend to have a poor prognosis. We might have to carefully monitor and perform additional treatments for patients with multiple tumors. Meanwhile, from an oncological point of view, some reports have shown an increased risk of various cancers in patients with severe CKD, especially those on dialysis (24–26). The incidences of various cancers, including kidney, bladder, and thyroid cancers, other endocrine tumors, and multiple myeloma, are higher in ESRD patients than in non-ESRD patients (27, 28). Patients required dialysis are likely to be at risk of HCC, and patients with ESRD may be at high risk of developing HCC (17).

There are some limitations to this study. First, the liver function of RD patients was better than that of non-RD patients because physicians might consider and exclude RD patients who had severe liver function. Second, the number of HCC patients with RD, especially those with severe CKD who underwent hepatectomy, was rather small; therefore, we couldn’t investigate to re-hepatectomy for patients with RD

who experienced HCC recurrence. Third, this study is retrospective study. Additional studies on larger cohorts of HCC patients with RD are required to reveal the pathogenesis of HCC and RD.

In conclusion, we revealed that comorbid RD has a negligible impact on the prognosis of HCC patients who underwent curative hepatectomy with appropriate perioperative management and close attention to severe CKD is necessary to prevent postoperative bleeding and surgical site infection.

Abbreviations

^{99m}Tc-GSA, the technetium-99m-galactosyl human serum albumin

AFP, alpha-fetoprotein

AFP-L3, alpha-fetoprotein isoform, lectin affinity

AKI, acute kidney disease

ALT, aspartate aminotransferase

AST, aspartate aminotransferase

BUN, blood urine nitrogen

CI, confidence interval

CKD, chronic kidney disease

CT, computed tomography

Cr, serum creatine

ESRD, end-stage renal disease

HBV, hepatitis B virus

HCC, hepatocellular carcinoma

HCV, hepatitis C virus

HR, hazard ratio

ICGR15, the estimated indocyanine green retention rate at 15 minutes

MRI, magnetic resonance imaging

MST, median survival time

NBNC, non-hepatitis B virus and non-hepatitis C virus

OS, overall survival

RD, renal dysfunction

RFS, recurrence-free survival

T-bil, total bilirubin

US, ultrasonography

eGFR, the estimated glomerular filtration rate

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of Hokkaido University Hospital (No. 016-0354). Individual consent for this retrospective analysis was waived.

Consent for publication

Not applicable.

Availability of data and materials

We cannot share the data collected for our study to others because of the confidentiality rules of our hospital.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

(I) Conception and design: Y Sakamoto, S Shimada, T Kamiyama; (II) Administrative support: None; (III) Provision of study materials or patients: T Kamiyama, H Kamachi, A Taketomi; (IV) Collection and

assembly of data: Y Sakamoto, S Shimada, K Sugiyama, Y Asahi, A Nagatsu, T Orimo, T Kakisaka; (V) Data analysis and interpretation: Y Sakamoto, S Shimada, T Kamiyama; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Figures

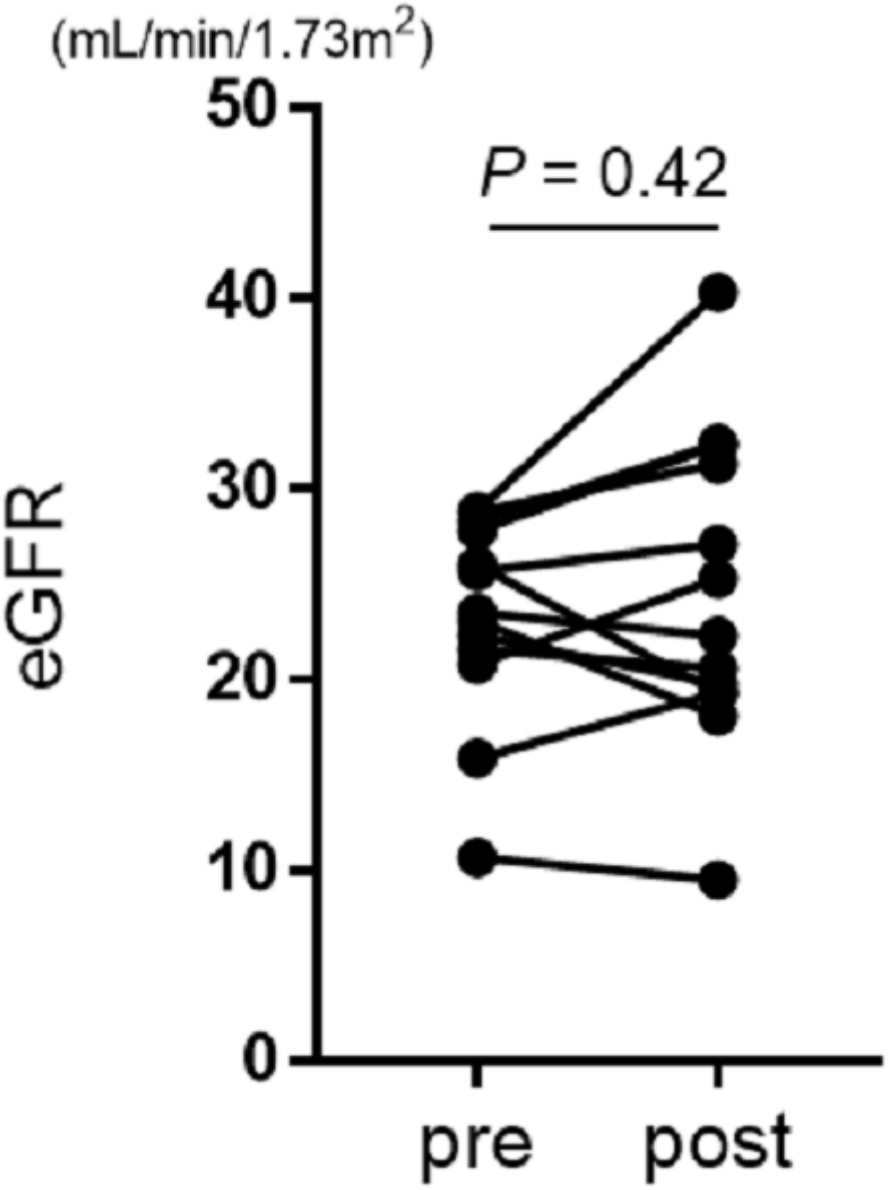

Figure 1

Comparison of the eGFR before and after hepatocellular carcinoma resection in patients with stage 4 or 5 CKD In patients with stage 4 or 5 CKD who didn`t require maintenance hemodialysis, the eGFR values did not decrease after the operation (n=13). Furthermore, no patient was introduced to maintenance hemodialysis after the operation. The eGFR values were measured before and one month after hepatectomy. CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate.

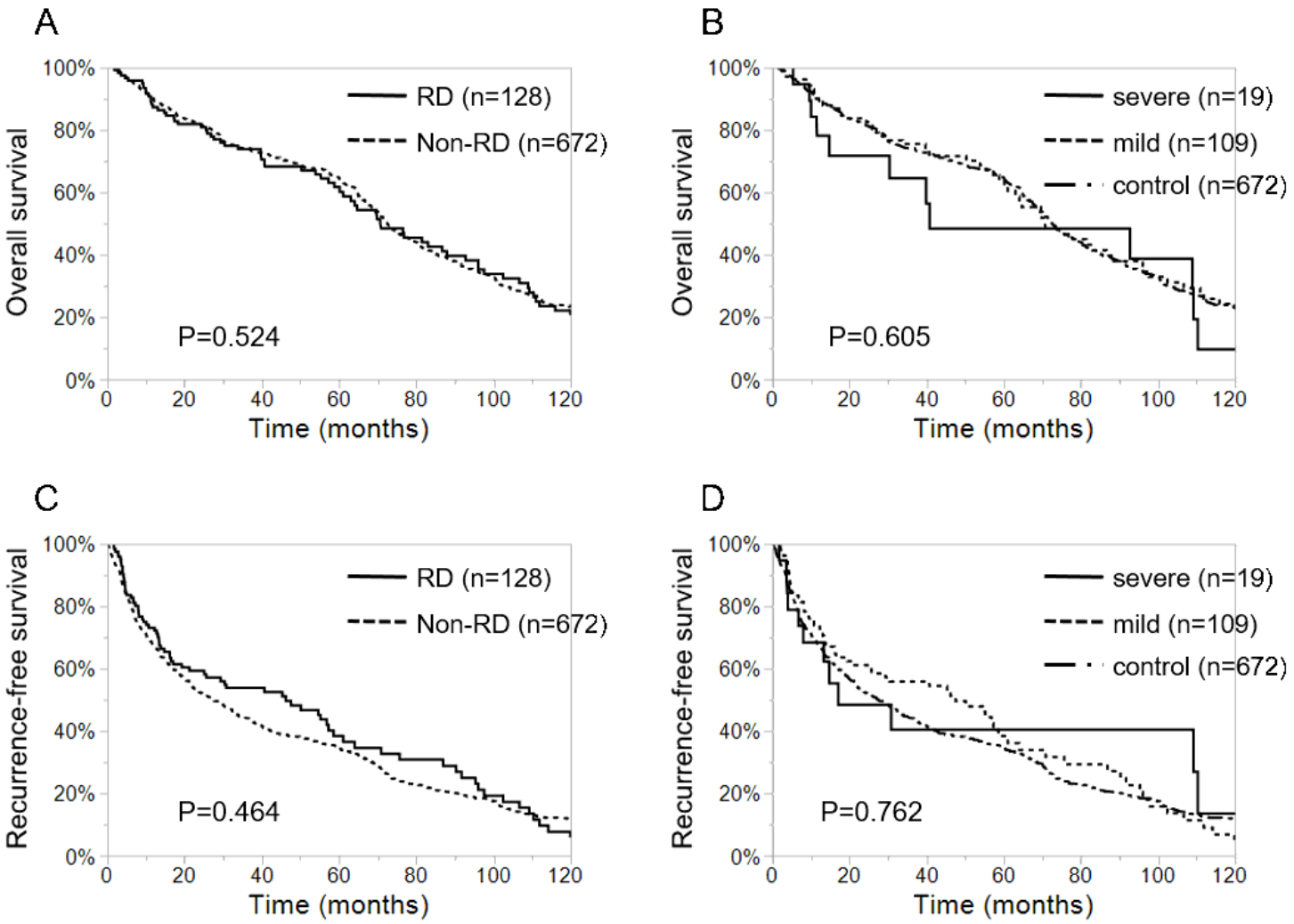

Figure 2

Overall survival and recurrence-free survival rates of patients with or without RD Overall survival (OS) and recurrence-free survival (RFS) among the groups. (A) OS was similar between the RD and non-RD groups (P = 0.524). (B) OS was also similar among the severe, mild, and control groups (P = 0.605). (C) RFS was similar between the RD and non-RD groups (P = 0.464). (D) RFS was also similar among the severe, mild, and control groups (P = 0.762).

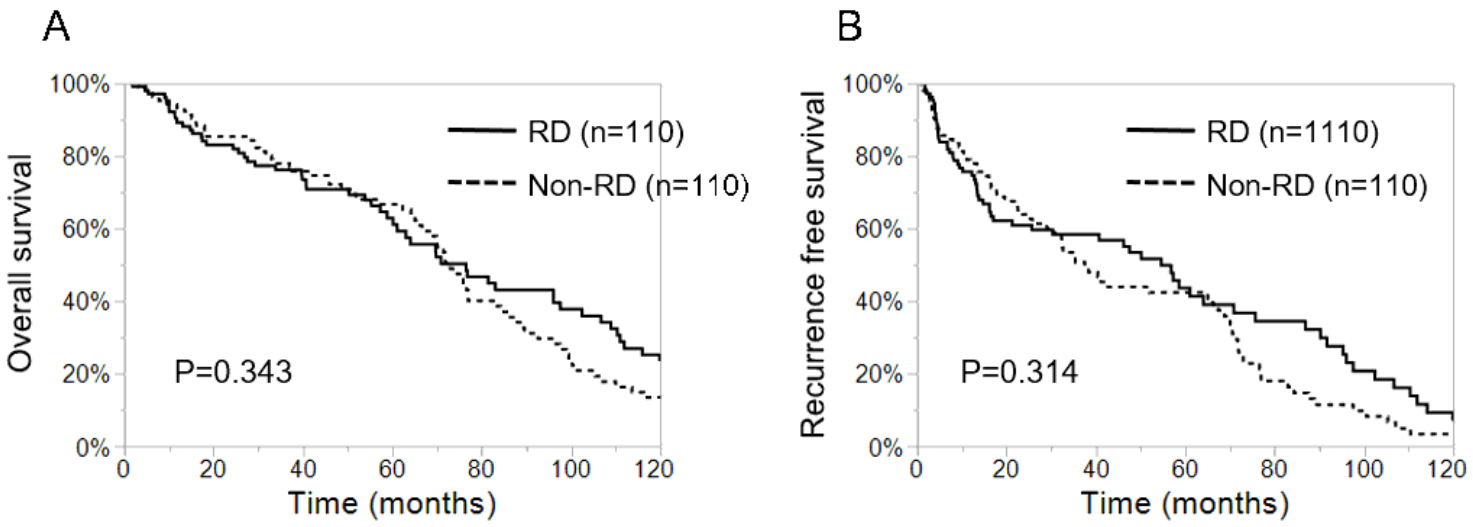

Figure 3

Overall survival and recurrence-free survival rates of patients with RD after propensity score matching After propensity score matching, (A) the median survival time (MST) was 76.5 months in patients with RD and 73.0 months in patients without RD, so overall survival was similar between the RD and non-RD groups (P = 0.343). (B) Recurrence-free survival also did not differ significantly between the RD and non-RD groups after propensity score matching (P = 0.314).

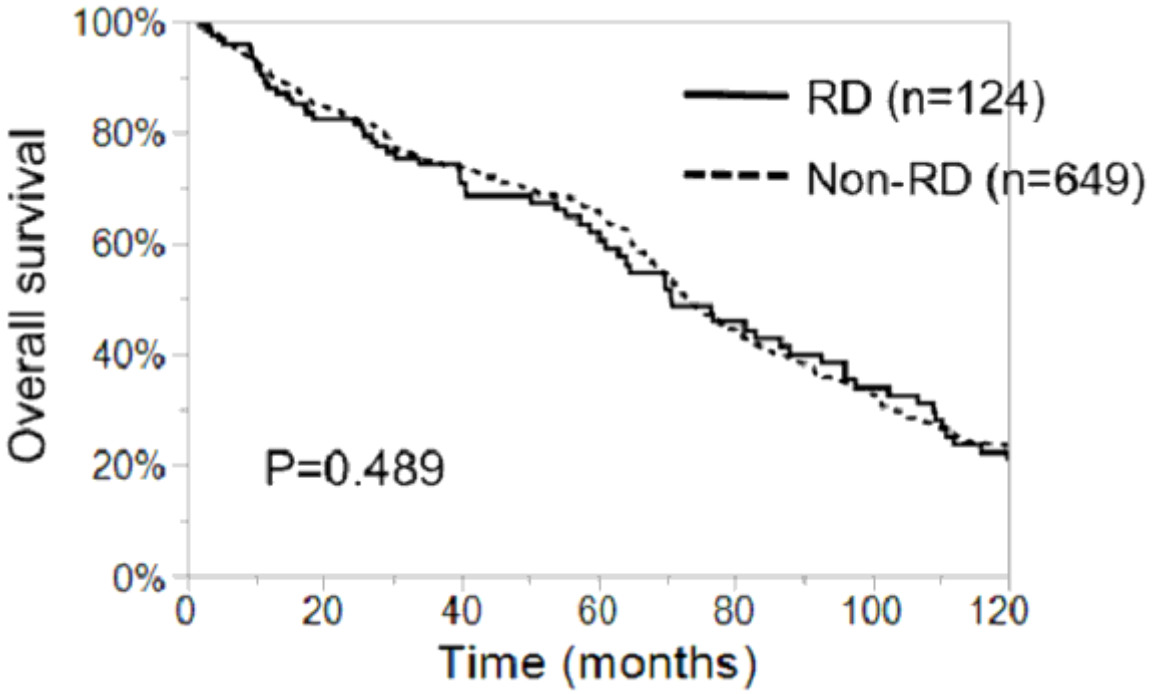

Figure 4

Overall survival rates of patients with RD and Child-Pugh grade A disease Overall survival rate was similar between RD (n=124) and non-RD (n=649) HCC patients with Child-Pugh grade A disease (P = 0.489).

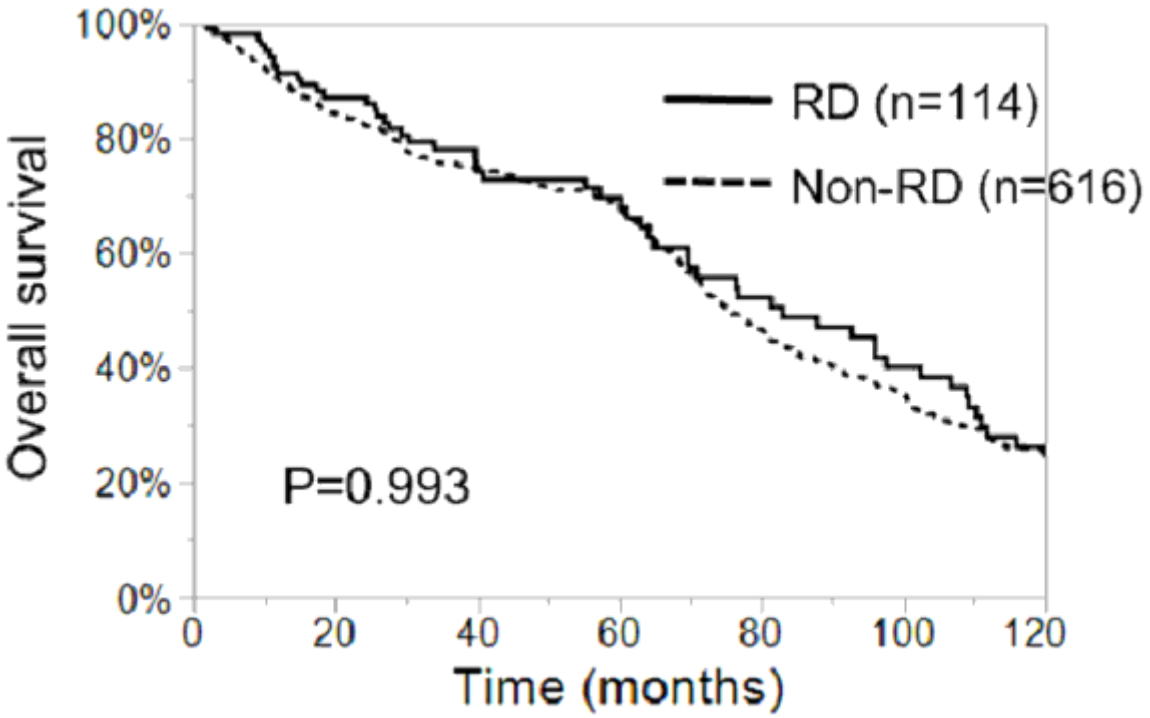

Figure 5

Overall survival rates of patients with RD who died from only HCC Overall survival rate was similar between RD (n=114) and non-RD (n=616) HCC patients who died from only HCC (P = 0.993).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable.docx