

Impact of patient age on outcome after resection for hepatocellular carcinoma

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SUMMARY There is little information on the impact of aging on liver resection of hepatocellular carcinoma (HCC). The aim of study was to evaluate the prognostic impact of the patient's age on the long-term survival after resection of HCC. The postoperative outcomes of the 291 elderly (≥ 70 years) and 340 younger (< 70 years) patients underwent curative liver resection for HCC were analyzed using multivariate and propensity-score matching. Risk score were calculated from the results of Cox regression analysis. The overall survival rate was significantly lower in the elderly group than that in the younger group ($p = 0.01$). Factors related to overall survival were vascular invasion (absent vs. present, HR 2.25; 95% CI 1.52-3.33, $p = 0.0001$), albumin level (< 3.0 vs. ≥ 3.0 g/dl, HR 2.23; 95% CI 1.31-3.79, $p = 0.003$), and number of tumors (solitary vs. multiple, HR 1.68; 95% CI 1.24-2.27, $p = 0.001$). The results of risk-score analysis with a Cox proportional-hazards model indicated that the proportion of poor-risk patients was significantly higher in the elderly than in the younger group. Propensity-score matching analysis yielded 234 pairs of patients. There were no significant differences in baseline profiles or risk scores between the two groups ($p = 0.43$). There were also no significant differences in the overall survival between the two groups ($p = 0.23$). Advanced age does not have a significant impact on the outcomes of patients after resection of HCC.

Keywords elderly, hepatocellular carcinoma, liver resection, propensity score matching analysis, risk scores

1. Introduction

The average age of patients with hepatocellular carcinoma (HCC) is advancing, and the mean ages at diagnosis of HCC are estimated to be 65-69 years in Japan and 63-65 years in Europe and North America (1-3). Age at diagnosis of HCC depends primarily on etiological factors, *i.e.*, hepatitis B (HBV) and C (HCV) virus infections and alcohol abuse, which have different peak ages of exposure (4,5). Although there have been many reports of liver resection in elderly patients with HCC, there have been few large studies of long-term outcomes in such cases (6-15). Moreover, previous studies indicated a wide range of long-term outcomes among elderly patients with HCC following liver resection, and it was suggested that the discrepancy in survival may be attributable to differences in patient backgrounds, including etiologic factors, between groups (6,10,14). However, nearly all previous studies compared patients solely on the basis of whether they were elderly or not, and only a few studies have attempted to adjust for bias associated with other demographic and clinical

characteristics (5,7,8). One of these studies had a small sample size of less than 50 elderly patients after liver resection, and so the statistical power was low (5). One of the remaining two studies defined elderly as age more than 75 years and had a sample size of less than 150 elderly patients after liver resection (7). The other of these studies defined elderly as age more than 55 years, which was the median age of patients in their cohort; however, this cutoff value is too young (8). These two studies investigated patients undergoing liver resection for HCC mainly caused by HBV (7,8).

It has been difficult to identify the specific role of advanced age in the outcome of patients with HCC undergoing liver resection. Even sophisticated multivariate analyses were probably inadequate to clarify whether advanced age itself is a risk factor. Instead of performing a randomized controlled trial, a one-to-one match created by propensity score analysis has been used to overcome bias between two groups (16,17).

The aim of this study was to investigate the impact of advanced age (≥ 70 years) on long-term survival in patients undergoing liver resection for HCC caused

mainly by HCV. Propensity score matching was performed to compare groups of patients who had similar preoperative and operative profiles.

2. Patients and Methods

2.1. Patients

The study population consisted of 631 consecutive patients who had undergone initial curative liver resection for HCC between 2001 and 2012. Clinicopathological data and outcomes after liver resection were prospectively followed up and compared. The patients were divided into two groups according to age at initial diagnosis: 340 patients were < 70 years old (younger group) and 291 patients were \geq 70 years old (elderly group). We defined elderly as \geq 70 years for the following reasons: the majority of previous studies have defined elderly as 70 years or older (5-14), age \geq 70 years is related to systemic complications after liver resection (11), and 70 years old is the lower limit of senescence associated with age-related changes occurring after this age (18).

The study design conformed to the ethical guidelines of the Declaration of Helsinki. This retrospective study was approved by the institutional review board of the Nihon University School of Medicine (approval number: RK-200908-7).

2.2. Liver resection

The indications for liver resection and the surgical procedures were determined according to a decision tree based on the indocyanine green retention rate at 15 minutes (ICG-R₁₅), the presence or absence of uncontrolled ascites, and the presence or absence of jaundice (19). Other types of organ failure, including ischemic heart disease, were examined, and the decision to operate or not was made after consultation with the attending physician and an anesthesiologist. Age was not an exclusion criterion for liver resection. Performance status was used as a criterion for patient selection. In principle, patients with a performance status of 0-2 were considered candidates for surgery (20).

Anatomical resection of a subsegment, Couinaud's segment, sector, or hemiliver was the preferred surgical procedure (21). All liver resections were performed using the clamp crushing method (22). The total inflow occlusion technique (Pringle's maneuver) was applied in an intermittent manner, with 15 minutes of occlusion alternating with 5 minutes of reperfusion. Postoperative complications were defined and classified according to the modified Clavien-Dindo classification (23).

2.3. Postoperative management

After discharge, all patients were examined for recurrence by dynamic computed tomography every 3

to 4 months. Recurrence was defined as the appearance of a new lesion with radiological features typical of HCC (21). The disease-free survival period was defined as the interval between surgery for HCC and the date of diagnosis of the first recurrence or the last follow-up visit. When recurrence was diagnosed, the candidates for treatments were selected according to the same criteria used to select primary treatment (21).

2.4. Statistical Analysis

The statistical significance of differences between the two groups was assessed using the Mann-Whitney *U* test and the chi-square test for continuous and categorical data, respectively. Standardized differences were also estimated for all variables considered (24). The survival curves of the two groups were compared by the log-rank test. Factors that were significantly related to overall survival on univariate analysis were included in multivariate analysis, performed using a Cox proportional-hazards model. The assumption of proportional hazards was checked by examination of plots of log cumulative hazard for parallelism, and in no case was this assumption materially violated.

To overcome bias due to the different distributions of covariates between the two groups, we performed propensity analysis using logistic regression to create propensity scores for younger and older patients (16,17). To identify the propensity of being elderly, multiple logistic regression analysis was performed using forward stepwise variable selection. The model was then used to provide a one-to-one match between two groups using the nearest-neighbor matching method. Model calibration was assessed using the Hosmer-Lemeshow statistic. We used the standardized difference to measure covariate balance, whereby an absolute standardized difference above 10% on a covariate indicates a meaningful imbalance (24). After matching, the statistical significance of differences between the two groups was assessed using the Wilcoxon signed-rank test and McNemar's test to analyze continuous and categorical data, respectively.

To develop the risk score for poor prognosis and to determine the cutoff value of the risk score, we used the following equation with β regression coefficients that were estimated with the Cox proportional-hazards model: risk score = $X_1\beta_1 + X_2\beta_2 + \dots + X_k\beta_k$ (25). Next, to determine the cutoff value for poor prognosis, the risk score was distributed according to whether the patient died within 1, 3, or 5 years after the operation (26). The most suitable cutoff value was derived from the area under the receiver operating characteristic (ROC) curve (AUC) of the score, based on the highest Youden index, to achieve the highest sensitivity and specificity (27).

All analyses were performed using IBM SPSS Statistics 19 software (IBM SPSS, Tokyo, Japan). In

all analyses, $p < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. Preoperative Characteristics

The elderly group had a lower rate of seropositivity for HBs antigen (4.1%) and of habitual alcohol consumption (24.4%) and a higher rate of seropositivity for HCV antibody (65.9%) than did the younger group (22.6%, 33.8%, and 52.1%; $p = 0.01, 0.01,$ and $0.01,$ respectively). The elderly group had a lower hemoglobin concentration [median, 12.8; range (8.1-

16.6) g/dL], a lower serum albumin level [3.8; range (2.3-4.9) g/dL], and a higher ICG-R₁₅ [13.2; range (3.0-48.5)%] than did the younger group [13.5; range (8.3-17.3) g/dL, 3.9; range (2.4-5.3) g/dL, and 11.4; range (1.3-82.3)%; $p = 0.0001, 0.001,$ and $0.001,$ respectively]. The elderly group had worse renal function as estimated by creatinine clearance (CCr) [79.9; range (29.7-180.1) %] than did the younger group [96.5; range (5.9-281.5) %, $p = 0.0001$]. Although the elderly group had lower blood loss [270; range (5-2725) mL] than did the younger group [322; range (5-3777) mL, $p = 0.03$], there were no significant differences in other perioperative variables between the two groups (Table 1A). Regarding the site of recurrence and cause

Table 1A. Clinical and operative variables

Items	All patients, $n = 631$	younger, $n = 340$	elderly, $n = 291$	p -value
Clinical variable				
Age	69 (36-85)	63 (36-69)	74 (70-85)	0.00001
Gender	Male	276 (81.2%)	206 (70.8%)	0.01
Hepatitis type				
HBV, positive	Present	77 (22.6%)	12 (4.1%)	0.01
HCV, positive	Present	177 (52.1%)	191 (65.9%)	0.01
Alcohol	Present	115 (33.8%)	71 (24.4%)	0.01
Child-Pugh classification				
	A	327 (96.2%)	282 (96.9%)	0.62
	B+C	13 (3.8%)	9 (3.1%)	
Hemoglobin (g/dL) ^d	13.1 (8.1-17.3)	13.5 (8.3-17.3)	12.8 (8.1-16.6)	0.00001
Platelets (10 ³ /μL) ^d	14.2 (2.6-68.6)	14.3 (2.6-68.6)	14.0 (3.2-44.3)	1.00
Total protein (g/dL) ^d	7.1 (5.0-8.9)	7.2 (5.6-8.9)	7.0 (5.0-8.8)	0.04
Albumin (g/dL) ^d	3.8 (2.3-5.3)	3.9 (2.4-5.3)	3.8 (2.3-4.9)	0.0001
Total bilirubin (mg/dL) ^d	0.6 (0.2-3.4)	0.6 (0.2-2.0)	0.6 (0.3-3.4)	0.78
AST (IU/L) ^d	41 (12-295)	41 (12-295)	41 (13-265)	0.81
ALT (IU/L) ^d	37 (5-296)	40 (5-253)	35 (7-296)	0.07
Prothrombin time (%) ^d	98 (53-100)	97 (62-100)	99 (53-100)	0.36
ICG-R ₁₅ ^{a,d}	12.3 (1.3-82.3)	11.4 (1.3-82.3)	13.2 (3.0-48.5)	0.001
α-fetoprotein (ng/mL) ^d	12.3 (0.6-91725)	19.1 (0.8-91725)	14.1 (0.6-24275)	0.16
CCr ^{b,d}	88.9 (5.9-281.5)	96.5 (5.9-281.5)	79.9 (29.7-180.1)	0.00001
Operative variable				
Tumor size	32 (7-205)	31 (7-205)	32 (9-180)	0.38
Number of tumors	Solitary	281 (82.6%)	231 (79.4%)	0.30
Vascular invasion	Present	36 (10.6%)	43 (14.8%)	0.11
Anatomical resection	Present	125 (36.8%)	100 (34.4%)	0.53
Major hepatic resection	Present	19 (5.6%)	17 (5.8%)	0.89
UICC stage ^c	1, 2	306 (90.0%)	267 (91.8%)	0.45
	3	34 (10.0%)	24 (8.2%)	
Blood loss ^d	301 (5-3777)	322 (5-3777)	270 (5-2725)	0.03
Clamp time ^d	75 (0-860)	76 (11-860)	72 (0-222)	0.07
Operative time ^d	330 (120-1590)	339 (130-1590)	318 (120-803)	0.06
Differentiation	Mod, well	305 (89.7%)	258 (88.7%)	0.03
	Poor	35 (10.3%)	33 (11.3%)	
Complications	0-II	260 (76.5%)	226 (77.7%)	0.72
	III-V	80 (23.5%)	65 (22.3%)	

^aICG15: indocyanine green retention rate at 15 minutes; ^bCCr: Creatinine clearance; ^cInternational Union Against Cancer (UICC) TNM staging classification; ^dMedian (range)

Table 1B. Site of recurrence and cause of death

Variable	All patients	younger	elderly	p -value
Site of recurrence				
	$n = 370$	$n = 199$	$n = 171$	0.67
Intrahepatic	331 (89.5%)	180 (90.50%)	151 (88.3%)	
Extrahepatic	27 (7.3%)	14 (7.0%)	13 (7.6%)	
Intra- and Extrahepatic	12 (3.2%)	5 (2.50%)	7 (4.1%)	
Cause of death				
	$n = 223$	$n = 113$	$n = 110$	0.83
Hepatocellular carcinoma	183 (82.1%)	91 (80.50%)	92 (83.6%)	
Liver failure	10 (4.5%)	6 (5.30%)	4 (3.6%)	
Other carcinoma	8 (3.6%)	5 (4.40%)	3 (2.7%)	
Other	22 (9.9%)	11 (9.70%)	11 (10.0%)	

Table 2. Univariate analysis of clinical variables

Variables	No.	Overall survival rate (%)			p-value
		1 yr	3 yr	5 yr	
Age					0.01
< 70	340	92.8	76.0	61.8	
≥ 70	291	89.1	72.9	52.9	
Platelet count (10 ⁴ /μL)					0.03
< 15	353	91.4	74.7	54.6	
≥ 15	278	90.8	74.4	62.2	
Albumin (g/dL)					0.004
< 3.0	30	72.7	53.4	40.7	
≥ 3.0	601	92.1	75.6	58.7	
Total bilirubin (g/dL)					0.31
< 1.0	549	91.5	74.7	59.2	
≥ 1.0	82	88.8	74.2	48.9	
AST (IU/L)					0.0001
< 35	250	94.3	82.0	67.0	
≥ 35	381	89.0	69.8	52.0	
α-fetoprotein (ng/mL)					0.001
< 20	336	95.7	79.6	63.9	
≥ 20	295	85.9	68.9	51.1	
ICG-R ₁₅ ^a					0.04
< 15	391	92.7	76.1	61.0	
≥ 15	240	88.5	72.1	51.8	
CCr ^b (%)					0.04
< 70	144	88.0	68.1	49.6	
≥ 70	487	92.0	76.4	60.2	
Tumor size					0.01
< 5cm	490	93.3	77.5	60.4	
≥ 5cm	141	83.5	64.2	49.3	
Number of tumors					0.001
Solitary	512	92.4	77.1	62.2	
Multiple	119	85.6	64.4	41.3	
Vascular invasion					0.001
Absent	552	93.0	76.4	59.6	
Present	79	78.2	61.2	43.4	

^aICG15: indocyanine green retention rate at 15 minutes; ^bCCr: Creatinine clearance.

of death after liver resection, there were no significant differences between the two groups ($p = 0.67$ and 0.83 , respectively; Table 1B).

3.2. Survival Outcomes

There was no significant difference in recurrence-free survival between the two groups ($p = 0.24$; supplementary Figure S1A). Overall survival rates in the elderly group at 1, 3, and 5 years were 89.1% [95% confidence interval (CI), 84.9 to 92.2], 72.9% [95% CI, 66.8 to 78.3], and 52.9% [95% CI, 45.1 to 60.5], respectively, whereas those in the younger group were 92.8% [95% CI, 89.5 to 95.2], 76.0% [95% CI, 70.6 to 80.7], and 61.8% [95% CI, 55.1 to 68.0], respectively (Table 2). The overall survival was significantly shorter in the elderly group than in the younger group ($p = 0.01$; Figure 1A).

3.3. Multivariate Analysis

Multivariate analysis with a Cox proportional-hazards model showed that macroscopic vascular invasion

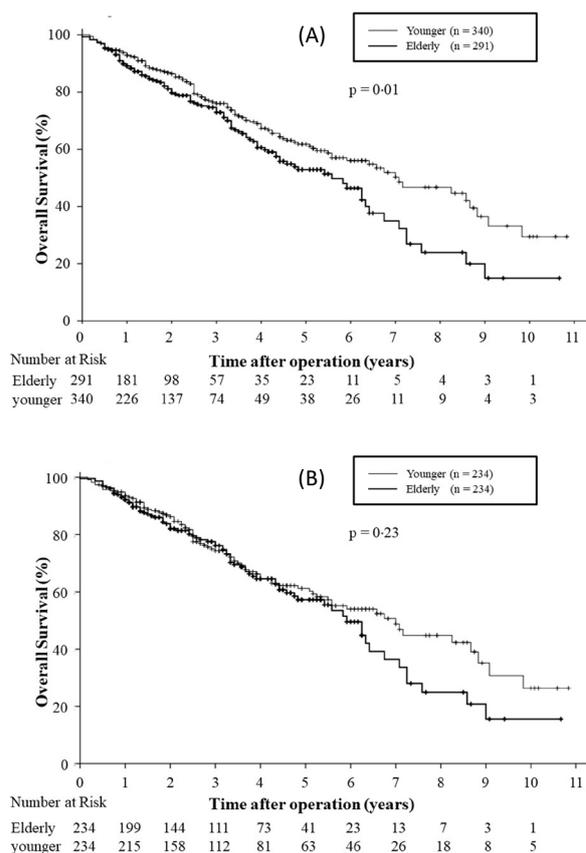


Figure 1. (A) Cumulative overall survival in patients with hepatocellular carcinoma stratified by age. The younger group had a higher overall survival rate than the elderly group ($p = 0.01$). (B) Cumulative overall survival in patients with hepatocellular carcinoma by propensity score matching analysis. There were no significant differences between the two groups ($p = 0.23$).

(present vs. absent, hazard ratio (HR) 2.25; 95% CI 1.52-3.33, $p = 0.0001$), albumin level (< 3.0 vs. ≥ 3.0 g/dL, HR 2.23; 95% CI 1.31-3.79, $p = 0.003$), number of tumors (multiple vs. solitary, HR 1.68; 95% CI 1.24-2.27, $p = 0.001$), and platelet count (< 15 vs. ≥ 15 × 10⁴/μL, HR 1.46; 95% CI 1.11-1.93, $p = 0.01$) were independent risk factors for overall survival (Table 3).

3.4. Preoperative Characteristics of the Matched Series

Propensity score matching analysis yielded 234 pairs of patients. There were no significant differences in baseline profiles (Table 4).

3.5. Survival Outcomes of the Matched Series

There were no significant differences in recurrence-free survival between the two groups ($p = 0.42$; supplementary Figure S1B). Overall survival rates in the elderly group at 1, 3, and 5 years were 92.1% [95% CI, 87.8 to 95.0], 76.1% [95% CI, 69.4 to 81.8], and 57.3% [95% CI, 48.7 to 65.4], respectively, whereas those in the younger group were 93.5% [95% CI, 89.6

Table 3. Multivariate logistic-regression analysis

Variable	Hazard ratio	95% confidence interval	p-value	Regression coefficients
Vascular invasion: Present vs. Absent	2.25	1.52 - 3.33	0.0001	0.81
Albumin (g/dL): < 3.0 vs. ≥ 3.0	2.23	1.31 - 3.79	0.003	0.80
Number of tumors: Multiple vs. Solitary	1.68	1.24 - 2.27	0.001	0.52
Platelet count (g/dL): < 15 vs. ≥ 15	1.46	1.11 - 1.93	0.01	0.38

Table 4. Clinical and operative variables after propensity match

Items	All patients, n = 468	younger, n = 234	elderly, n = 234	p-value
Clinical variable				
Age	69 (36-85)	64 (36-69)	73 (70-85)	0.00001
Gender	Male	177 (75.6%)	166 (70.9%)	0.25
Hepatitis type				
HBV, positive	Present	11 (4.7%)	11 (4.7%)	1.0
HCV, positive	Present	155 (66.2%)	159 (67.9%)	0.69
Alcohol	Present	60 (25.6%)	58 (24.8%)	0.83
Child-Pugh classification				
A	223 (95.3%)	223 (95.3%)	228 (97.4%)	0.22
B+C	11 (4.7%)	6 (2.6%)	6 (2.6%)	
Hemoglobin (g/dL) ^d	13.0 (8.1-17.3)	13.0 (8.3-17.3)	12.9 (8.1-16.6)	0.03
Platelets (10 ⁴ /μL) ^d	14.0 (2.6-68.6)	14.0 (2.6-68.6)	13.8 (3.2-38.7)	0.85
Total protein (g/dL) ^d	7.1 (5.0-8.9)	7.2 (5.6-8.9)	7.1 (5.0-8.8)	0.06
Albumin (g/dL) ^d	3.8 (2.4-5.3)	3.9 (2.4-5.3)	3.8 (2.6-4.9)	0.06
Total bilirubin (mg/dL) ^d	0.6 (0.2-3.4)	0.6 (0.2-2.0)	0.6 (0.3-3.4)	0.73
AST (IU/L) ^d	40 (12-295)	41 (12-295)	40 (13-265)	0.3
ALT (IU/L) ^d	37 (5-296)	40 (5-253)	35 (10-296)	0.06
Prothrombin time (%) ^d	97 (53-100)	96 (62-100)	99 (53-100)	0.21
ICG-R ₁₅ ^{a,d}	12.8 (1.3-82.3)	12.0 (1.3-82.3)	13.2 (3.0-48.5)	0.05
α-fetoprotein (ng/mL) ^d	15.2 (0.6-60340)	20.7 (0.8-60340)	12.9 (0.6-24275)	0.03
Ccr ^{b,d}	87.9 (5.9-281.5)	92.0 (5.9-281.5)	82.1 (29.7-180.1)	0.06
Operative variable				
Tumor size	31 (7-205)	31 (7-205)	30 (9-180)	0.69
Number of tumors	Solitary	178 (76.1%)	173 (73.9%)	0.59
Vascular invasion	Present	28 (12.0%)	26 (11.1%)	0.77
Anatomical resection	Present	84 (35.9%)	83 (35.5%)	0.92
Major hepatic resection	Present	10 (4.3%)	15 (6.4%)	0.3
UICC stage^c				
1, 2	217 (92.7%)	217 (92.7%)	217 (92.7%)	1.0
3	17 (7.3%)	17 (7.3%)	17 (7.3%)	1.0
Blood loss ^d	285 (5-3378)	320 (10-3378)	252 (5-2725)	0.02
Clamp time ^d	73 (0-860)	76 (13-860)	71 (0-221)	0.2
Operative time ^d	326 (130-1590)	338 (130-1590)	314 (139-803)	0.1
Differentiation				
Mod, well	214 (91.5%)	214 (91.5%)	206 (88.0%)	0.22
Poor	20 (8.5%)	20 (8.5%)	28 (12.0%)	
Complications				
0-II	174 (74.4%)	174 (74.4%)	183 (78.2%)	0.33
III-V	60 (25.6%)	60 (25.6%)	51 (21.8%)	

^aICG15: indocyanine green retention rate at 15 minutes; ^bCcr: Creatinine clearance; ^cInternational Union Against Cancer (UICC) TNM staging classification; ^dMedian (range)

Table 5. Rate of high-risk patients before and after propensity matched analysis

Whole study	All patients, n = 631	Younger, n = 340	Elderly, n = 291	p-value
Risk score < 0.45	418 (66.2%)	241 (70.9%)	177 (60.8%)	
Risk score ≥ 0.45	213 (33.8%)	99 (29.1%)	114 (39.2%)	0.01
After propensity matching analysis				
Risk score < 0.45	316 (67.5%)	162 (69.2%)	154 (65.8%)	0.43
Risk score ≥ 0.45	152 (32.5%)	72(30.8%)	80 (34.2%)	

Risk score = 0.81 X (with vascular invasion) + 0.80 X (albumin level less than 3.0 g/dL) + 0.52 X (multiple nodules) + 0.38 X (platelet count less than 15 × 10⁴/μL).

to 96.1], 74.3% [95% CI, 67.5 to 80.1], and 61.2% [95% CI, 53.3 to 68.6], respectively. There was no significant difference in overall survival between the two groups (*p* = 0.23) (Figure 1B).

3.6. Calculation and Determination of Cutoff Value of Risk Score

Risk scores for individual patients were calculated by combining their four prognostic values with the regression coefficients from the results of analysis with the Cox proportional-hazards model (Table 3), *i.e.*, risk score = 0.81 X (with vascular invasion) + 0.80 X (albumin level < 3.0 g/dL) + 0.52 X (multiple nodules) + 0.38 X (platelet count < 15 × 10⁴/μL). The ROC curve

indicated that the optimal cutoff value of risk score was 0.45, and the AUC was 0.74 (95% CI: 0.67-0.81, $p = 0.000001$). Although the elderly group had a higher proportion of high-risk patients (39.2%) than the younger group (29.1%; $p = 0.01$), after propensity analysis, the proportion of high-risk patients in the elderly group (34.2%) was comparable to that in the younger group (30.8%; $p = 0.43$) (Table 4).

3.7. Survival Outcomes of patients with high and low risk score.

The overall survival and recurrence-free survival were significantly shorter in the patients with high-risk than in the low-risk score ($p = 0.000000004$ and 0.000001 , respectively; supplementary Figure S2A and B).

4. Discussion

We showed that elderly patients with HCC who underwent liver resection had a lower overall survival rate than younger patients; however, after matching, the overall survival rates were similar in both groups. Thus, our results showed no impact of advanced age on the outcome of patients after resection of HCC. Furthermore, we examined why elderly patients with HCC who underwent liver resection had a lower overall survival rate than younger patients, and poor outcomes in the elderly group were probably attributable to the higher proportion of "high-risk patients" who had either vascular invasion, lower albumin level, or multiple nodules in the elderly group.

To our knowledge, even after propensity matching and reduction of the number of patients, our study group of 234 elderly patients after liver resection represents one of the largest contemporary series of elderly patients undergoing liver resection for HCC reported to date. Therefore, our results represent useful information for the management of HCC in this subgroup of patients.

We performed propensity analysis to adjust for age-related differences in the background characteristics of the younger and elderly groups, and the overall survival rates were comparable in the two groups. This finding suggests that differences in background characteristics between the groups led to the observed difference in survival. Only three previous studies used propensity score matching analysis to investigate the relation between the age and outcomes of patients with HCC after liver resection (5,7,8). One of these studies performed in Italy showed the overall survival rate as one of several treatment results, and therefore the relation between the age and outcomes of HCC patients after liver resection was not discussed sufficiently in this paper. Although this study defined elderly as 70 years or older as in our study, the cohort consisted of less than 50 patients. The study showed that overall survival rates were similar in elderly and younger patients after propensity matching,

consistent with our results regarding long-term survival (5). In the other two studies performed in Taiwan, HBV was the main cause of HCC (61.0% and 63.4%) (7,8). In one of the two studies, the overall survival rate was also shown as one of several treatment results, and therefore the relation between age and outcomes of HCC patients after liver resection was not discussed sufficiently in this paper. Although this study defined elderly as 75 years or older, the cohort consisted of only 118 patients (7). The remaining study defined elderly as 55 years or older, based on the median age of patients in their cohort (8). The results showed that the younger group had better liver functional reserve but more aggressive tumor factors than the elderly group. In our study, we defined elderly as 70 years or older, and liver functional reserve and tumor factors were comparable in the two groups in contrast to the study from Taiwan. The differences between this study and our study may be ascribed to the differences in patients according to whether HCC is associated with underlying HBV or HCV. These two studies performed in Taiwan showed that the elderly group had a lower overall survival rate than the younger group before matching; consistent with our results, however, the overall survival rates were similar in the two groups after matching (7,8). HCV is currently the main cause of HCC in Japan and Southern Europe, accounting for 70% of cases (3,4). In the present study, HCV was the main cause of HCC in the younger group (52.1%) as well as in the elderly group (65.9%). Therefore, our results may be most applicable to countries in which a high proportion of HCC is caused by HCV infection.

Although there were no significant differences between the two groups in assumed prognostic factors, such as tumor size, vascular invasion, and the number of tumors, the overall survival rate was significantly lower in the elderly group than the younger group. Furthermore, the site of recurrence, the cause of death, and the recurrence-free survival were also similar in the two groups. Therefore, we could not determine why the elderly patients had poorer outcomes. To investigate what background characteristics negatively affected outcomes in the elderly group, we defined and calculated risk scores from the results of Cox regression analysis, and the optimal cutoff value of the risk score, calculated by ROC analysis, was 0.45. As the β regression coefficient of the platelet count was 0.38 and lower than the optimal cutoff value, the platelet count could be excluded from the risk score, and all three other variables had β regression coefficients of 0.45 or higher. According to the equation used to calculate our risk score, patients who had either vascular invasion, lower albumin level, or multiple nodules were defined as "high-risk patients". Among these variables, vascular invasion and multiple nodules are common prognostic factors for poor survival in patients with HCC after liver resection (18,28,29). Hypoalbuminemia is common in the elderly (12,18), and previous studies indicated that the incidences of vascular

invasion and hypoalbuminemia were significantly higher in elderly than younger patients with HCC (12,13). In our study, although the albumin level was lower in the elderly group (median, 3.8 g/dL; range, 2.3-4.9 g/dL) than in the younger group (3.9 g/dL; 2.4-5.3 g/dL; $p = 0.0001$), there were no significant differences between the two groups in vascular invasion or the number of tumors ($p = 0.11$ and $p = 0.30$, respectively); therefore, these three variables seem to be unrelated to aging. However, the proportions of high-risk patients were significantly higher in the elderly group than in the younger group. After propensity matching, the effects of the high-risk factors were apparently cancelled by other factors, and overall survival was comparable in both groups. Taken together, these findings indicated that the poor outcomes in the elderly group were not due to advanced age itself, but were probably attributable to the higher proportion of high-risk patients who had either vascular invasion, lower albumin level, or multiple nodules in the elderly group.

Although we used a cutoff age of 70 years or older to define elderly patients, there was no apparent impact of patient age on long-term outcome after liver resection for HCC mainly caused by HCV. Our results suggest that surgeons should not hesitate to perform liver resection because of advanced age in patients with HCC.

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Supplementary Figures

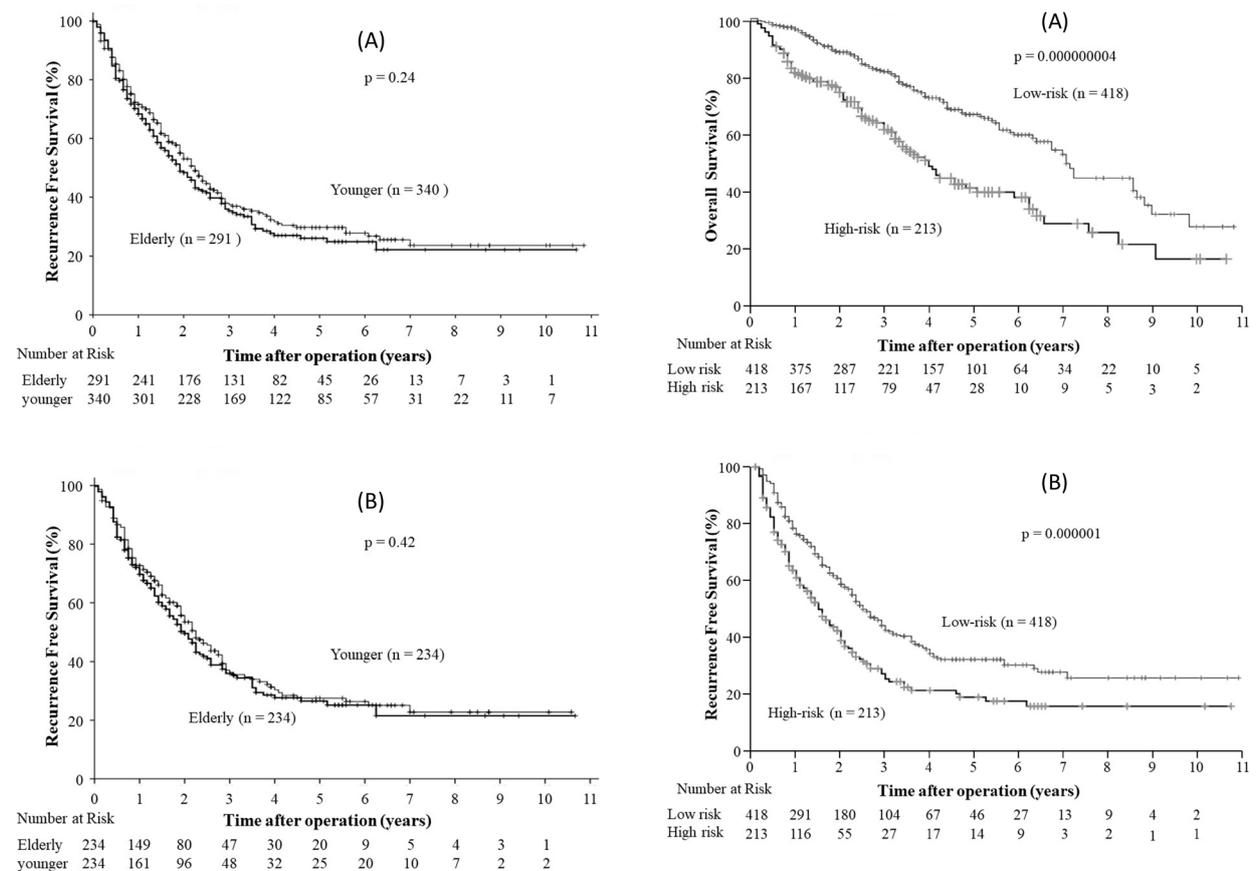


Figure S1. (A) Cumulative recurrence-free survival in patients with hepatocellular carcinoma stratified by age. There were no significant differences between the two groups ($p = 0.24$). (B) Cumulative recurrence-free survival in patients with hepatocellular carcinoma by propensity score matching analysis. There were no significant differences between the two groups ($p = 0.42$).

Figure S2. (A) Cumulative overall survival in patients with hepatocellular carcinoma stratified by risk score. The patients with low-risk had a higher overall survival rate than the low-risk score ($p = 0.000000004$). (B) Cumulative recurrence-free in patients with hepatocellular carcinoma stratified by risk score. The patients with low-risk had a higher recurrence-free rate than the low-risk score ($p = 0.0000001$).