

# Prognoses, outcomes and clinicopathological characteristics of very elderly patients with hepatocellular carcinoma who underwent hepatectomy

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## Research

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## Abstract

**Background** The aim was to evaluate the prognostic factors, clinicopathological characteristics and surgical outcomes after hepatectomy in very elderly patients with hepatocellular carcinoma (HCC). **Methods** We analyzed 796 patients with HCC from 2000 to 2017. Patients aged 80 years or older were classified into the very elderly group (group VE; n=49), patients younger than 80 years old and aged 65 years or older were classified into the elderly group (group E; n=363), and patients younger than 65 years old were classified into the young group (group Y; n=384). We investigated the prognoses, clinicopathological characteristics and surgical outcomes after hepatectomy. **Results** The number of surgical procedures and outcomes, including morbidities, were not significantly different. Groups VE, E and Y showed similar prognoses in terms of both survival and recurrence. In group VE, PT < 80% and PIVKA-II  $\geq$  400 mAU/ml were unfavorable factors for survival, and PIVKA-II  $\geq$  400 mAU/ml and the presence of portal venous invasion (PVI), hepatic venous invasion, and fibrosis were unfavorable factors for recurrence. In group E, ChE < 180 IU/l, AFP  $\geq$  20 ng/ml, tumor size  $\geq$  10 cm, and the presence of multiple tumors, PVI, and hepatic venous invasion (HVI) were unfavorable factors for survival, and ChE < 180 IU/l, tumor size  $\geq$  10 cm, and the presence of multiple tumors, PVI, and HVI were unfavorable factors for recurrence. In group Y, AFP  $\geq$  20 ng/ml, the presence of multiple tumors, poor differentiation, PVI, HVI, and blood loss  $\geq$  400 ml were unfavorable factors for survival, and PT < 80%, albumin < 3.5 g/dl, AFP  $\geq$  20 ng/ml, tumor size  $\geq$  10 cm, and the presence of multiple tumors, poor differentiation, and PVI were unfavorable factors for recurrence. **Conclusions** Tumor factors might have limited influence on the prognosis of very elderly patients, and liver function reserve might be important for the long-term survival of very elderly patients. Hepatectomy can be performed safely, even in very elderly patients. Hepatectomy should not be avoided in very elderly patients with HCC if the patients have a good general status because these patients have the same prognoses as nonelderly people.

## Background

It is estimated that 18.1 million new cancer cases and 9.6 million cancer deaths occurred in 2018 around the world [1]. Liver cancer is the seventh most frequent type of cancer, with an estimated 841,080 cases per year, and it is the second leading cause of cancer-related death; liver cancer is responsible for approximately 781,631 deaths per year [1]. Hepatocellular carcinoma (HCC) has a poor prognosis and accounts for 70–85% of primary liver cancers [2]. The size of the aging population is increasing worldwide. According to a report by the Ministry of Health, Labour and Welfare, the number of people aged 80 years or older was 10.35 million in 2016, which represented 8.3% of the whole Japanese population at the time [3]. The report also states that the average expected life span of 80-year-old individuals is 8.95 years in men and 11.84 years in women [4].

Curative hepatectomy for HCC is a useful method for achieving long-term survival [5]. Thus, the opportunity to treat very elderly people with HCC with hepatectomy has been increasing. Elderly patients have frequent systemic comorbidities because of deteriorating organ, musculoskeletal and cardiovascular functions due to aging [6]. In terms of gastroenterological surgery, hepatectomy is a highly invasive surgical procedure with a high morbidity rate [7]. Surgeons should consider the balance between advantages and disadvantages of the procedure for elderly patients. In addition, it has been reported that some kinds of cancer show different characteristics and prognoses in aging populations. It is known that lung [8], prostate [9], and thyroid [10] cancers show poorer prognoses in elderly patients than in young patients. In contrast, gastric [11], colorectal [12], and breast [13] cancers show poorer prognoses in young patients than in elderly patients. There have been some reports concerning HCC; however, the conclusions of these reports are controversial [14, 15].

In this study, we evaluated the prognostic factors and clinicopathological characteristics of patients with HCC aged 80 years or older and compared these patients to those younger than 80 years old. We also investigated the surgical outcomes after hepatectomy.

## Methods

### Patients

Between January 2000 and December 2017, 796 consecutive patients with HCC underwent primary liver resection at the Gastroenterological Surgery I Unit of the Hokkaido University Hospital in Sapporo, Japan. We divided the patients into three groups: patients aged 80 years or older were classified into the very elderly group (group VE; n = 49, 6.2%), patients younger than 80 years old and aged 65 years or older into the elderly group (group E; n = 363, 45.6%), and patients younger than 65 years old into the young group (group Y; n = 384, 48.2%). We compared the prognoses in terms of survival and recurrence, clinicopathological characteristics and surgical outcomes after hepatectomy between these groups. We defined HBs-Ag-positive as HBV and HCV-Ab-positive as HCV.

This study was approved by the Hokkaido University Hospital Voluntary Clinical Study Committee (approval 018–0304; 5/Apr/2019) and was performed in accordance with the Helsinki Declaration guidelines.

### Hepatectomy

The indications for hepatic resection were as follows: patients with a performance status score between 0 and 2, patients with an American Society of Anesthesiologists (ASA) grade between 1 and 3, patients who were not senile, and patients whose comorbidities were controlled. Patients with or suspected to have ischemic heart disease or cardiac failure were assessed by cardiologists. The type of surgical procedure was usually determined based on the patients' liver function reserve, i.e., according to the results of the indocyanine green retention test at 15 min (ICGR15) [16]. Anatomical resection was performed for patients with an ICGR15 result lower than 25%. Fibrosis was defined as f3, and bridging fibrosis as f4; cirrhosis was defined according to the general rules for the clinical and pathological study of primary liver cancer set by the Liver Cancer Study Group of Japan [17]. Postoperative morbidity was assessed using the validated Clavien–Dindo classification system [18]. Serious complications were categorized as grades III–V and defined as morbidity requiring surgical or radiological intervention.

### Follow-up after hepatectomy

Patients were followed up at 3-month intervals. We have checked physical examination and serological examination including alpha-fetoprotein (AFP) level, protein induced by vitamin K absence-II (PIVKA-II), and liver function. In addition, radiological examinations including contrast-enhanced computed tomography (CT) scans and/or ultrasound sonography (US) or contrast-enhanced magnetic resonance imaging (MRI) were performed.

## Statistical analyses

Differences in characteristic factors were evaluated by the Mann-Whitney U test for continuous variables or the chi-square test for noncontinuous variables. The survival curves according to the Kaplan-Meier method were compared by using the log-rank test. Overall survival (OS) and relapse-free survival (RFS) were evaluated. Prognostic factors were evaluated by these univariate analyses and multivariate analyses with Cox proportional hazard model. We used JMP Pro 14.0.0 for Windows (SAS Institute, Cary, NC) for the statistical analyses.

## Results

### Clinicopathological characteristics and operative variables

We divided the period between 2000 and 2017 and designated the period from 2000 to 2008 as the early period and the period from 2009 to 2017 as the late period. In the early period, group VE included 8 patients (2.1%, 8/390). In contrast, this group had 41 patients (10.1%, 41/406) in the late period.

In this cohort, the median survival time (MST) and five-year OS rate in our 796 study patients were 103 months and 63%, respectively. The median RFS time was 20 months. The median length of hospital stay was 24 (9-386) days. The number of cases with HBV and HCV was 292 and 249, respectively. There were 15 patients with both HBV and HCV. There were 285 cases of NBNC (NonBNonC)-HCC.

The univariate analysis showed that the proportion of patients who were HCV positive, without HBV and HCV (NBNC), was significantly higher in group VE than in group Y (Table 1). In contrast, the proportion of patients who were HBV positive with portal venous invasion (PVI) and liver fibrosis was significantly lower in group VE than in group Y. Cholinesterase (ChE), serum albumin, and AFP levels were significantly lower in group VE than in group Y. The proportion of patients who were HCV positive was significantly higher in group VE than in group E (Table 1). The proportion of patients who were HBV positive and had liver fibrosis was significantly lower in group VE than in group E. Other factors were not different between groups VE and E.

Table 1  
Clinicopathological characteristics of HCC

Characteristics	Group VE (n = 49)	Group E (n = 363)	Group Y (n = 384)	p VE vs.E	p VE vs.Y
Epidemiology	82 (80–92)	71 (65–79)	57 (33–64)	< 0.01	<0.01
Age (y.o)	80(39):20(10)	83(301):17(62)	84(321):16(63)	0.56	0.48
Sex male : female (%)	6 (3)	20 (74)	56 (215)	0.01	<0.01
HBs-Ag positive (%)					
HCV-Ab positive (%)	65 (32)	35 (127)	23 (90)	< 0.01	< 0.01
NBNC (%)	59 (29)	46 (167)	23 (89)	0.08	<0.01
Biochemical Factors					
Child-Pugh Score	5.2 ± 0.5	5.2 ± 0.5	5.2 ± 0.5	0.50	0.38
Platelets (10 <sup>4</sup> /mm <sup>3</sup> )	18.4 ± 6.8	17.5 ± 10.8	17.0 ± 7.6	0.54	0.20
PT (%)	94.8 ± 13.5	92.5 ± 14.0	91.4 ± 13.9	0.28	0.10
ChE (IU/L)	230 ± 68	244 ± 71	262 ± 90	0.22	0.01
Albumin (g/dl)	3.9 ± 0.3	4.0 ± 0.4	4.1 ± 0.5	0.06	0.04
ICGR15 (%)	15.8 ± 8.2	16.7 ± 9.6	15.8 ± 11.5	0.56	0.94
AFP (ng/ml)	5.5 (0-60961)	10.6 (0-378718)	27.5 (1-5986980)	0.05	< 0.01
PIVKA-II (mAU/ml)	198 (10-217422)	181 (8-664680)	207 (2.3-928799)	0.95	0.98
Tumor Factors					
Tumor size (cm)	6.4 ± 3.5	5.7 ± 4.1	6.1 ± 5.2	0.23	0.66
Multiple tumor (%)	31 (15)	35 (128)	38 (144)	0.52	0.34
Differentiation: poor (%)	39 (19)	37 (134)	46 (175)	0.80	0.36
PVI (%)	14 (7)	21 (75)	34 (131)	0.29	<0.01
HVI (%)	14 (7)	11 (41)	14 (52)	0.54	0.88
Fibrosis: f3/f4 (%)	16 (8)	40 (146)	55 (213)	< 0.01	<0.01
VE, very elderly group; E, elderly group; Y, young group; HBs-Ag, HBs-antigen; HCV-Ab, HCV-antibody; NBNC, without HBV and HCV; PT, prothrombin time; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion.					

A total of 288 (36%) patients died; 237 (82%) were cancer-related deaths. Five (1.7%) patients with controlled HCC had liver failure-related deaths. In total, 1 (0.3%) death was related to the surgical procedure (posthepatectomy liver failure); 46 (16%) were other disease-related deaths.

There were 11 (22%) deaths in group VE, 120 (33%) deaths in group E, and 157 (41%) deaths in group Y. The cause of death and the breakdown among the three groups were as follows (group VE vs. group E vs. group Y): cancer-related: 7 (64%) vs. 92 (77%) vs. 138 (88%) (p = 0.33, 0.02); liver failure not related to cancer: 0 (0%) vs. 3 (3%) vs. 2 (1.3%) (p = 0.59, 0.70); and others: 4 (36%) vs. 27 (23%) vs. 15 (10%) (p = 0.30, < 0.01). Group VE showed significantly fewer cancer-related deaths and more noncancer-related deaths than group Y. Between groups VE and E, there were no significant differences in the cause of death.

Table 2 shows the surgical procedures and outcomes in group VE, group E and group Y. The median operative time in group VE was significantly shorter than that in groups E and Y. There were no significant differences in blood loss or postoperative morbidities.

Table 2  
Surgical procedure and outcomes

	Group VE (n = 49)	Group E (n = 363)	Group Y (n = 384)	p VE vs.E	p VE vs.Y
Surgical procedure	20 (10)	23 (85)	25 (95)	0.63	0.50
Partial hepatectomy (%)	41 (20)	41 (149)	36 (140)	0.97	0.55
Subsegmentectomy or Segmentectomy (%)					
Bisegmentectomy or Trisegmentectomy (%)	39 (19)	36 (129)	39 (149)	0.65	0.99
Operative outcome	400	380	375	0.64	0.50
Median blood loss (ml) (range)	(0-2400)	(0-35820)	(0-20190)		
Median operative time (min) (range)	288 (113–508)	327 (99–911)	312 (78–609)	<0.01	0.01
Morbidity					
Total morbidities (%)	14 (7)	19 (68)	23 (88)	0.44	0.16
Pleural effusion (%)	4 (2)	4 (15)	7 (27)	0.98	0.43
Ascites (%)	4 (2)	3 (12)	5 (19)	0.77	0.79
Postoperative bleeding (%)	2 (1)	2 (7)	4 (17)	0.95	0.43
Bile leakage (%)	8 (4)	7 (26)	6 (22)	0.80	0.49
Hyperbilirubinemia (%)	2 (1)	2 (9)	4 (15)	0.85	0.51
Wound infection (%)	2 (1)	2 (8)	2 (7)	0.94	0.91
Pneumonia (%)	4 (2)	1 (4)	2 (8)	0.10	0.38
Ileus (%)	4 (2)	1 (5)	1 (4)	0.16	0.08
Postoperative stay (days) (range)	22 (14–308)	25 (11–386)	24 (9-176)	0.17	0.43
Mortality					
30-day (%)	0 (0)	0 (0)	0 (0)		
90-day (%)	0 (0)	0 (0)	0.3 (1)		
VE, very elderly group; E, elderly group; Y, young group.					

#### Recurrence site and treatment after recurrence

Regarding recurrence, 24 patients experienced recurrence (49%), with a median recurrence time of 11 months (3–68) in group VE. Of the group E and Y patients, 231 experienced recurrence (64%), with a median recurrence time of 11 months (0.4–111), and 261 experienced recurrence (68%), with a median recurrence time of 9 months (0.2–197), respectively. The initial recurrence sites were not significantly different among the three groups (Table 3). Table 3 also shows the treatment methods used after recurrence. No cases of re-hepatectomy or liver transplantation were performed in group VE. The frequency of treating patients with re-hepatectomy was significantly lower in group VE than in group Y.

Table 3  
Initial recurrence patterns and treatment for recurrence

	Group VE (n = 49)	Group E (n = 363)	Group Y (n = 384)	p VE vs.E	p VE vs.Y
Recurrence cases (%)	49 (24)	64 (231)	68 (261)	0.04	< 0.01
Median recurrence duration (months) (range)	11 (3–68)	11 (0.4–111)	9 (0.2–197)	0.98	0.39
Recurrence site	(n = 24)	(n = 231)	(n = 261)		
Liver (%)	75 (18)	83 (192)	82 (213)	0.32	0.42
Lung (%)	33 (8)	18 (41)	29 (75)	0.06	0.63
Adrenal glands (%)	8 (2)	2 (5)	5 (14)	0.07	0.54
Bone (%)	13 (3)	11 (25)	10 (27)	0.80	0.74
Treatment for recurrence	(n = 24)	(n = 231)	(n = 261)		
Re-hepatectomy (%)	0 (0)	6 (15)	46 (119)	0.19	< 0.01
Liver transplantation (%)	0 (0)	0 (0)	3 (8)	-	0.38
RFA/MCT (%)	33 (8)	25 (57)	18 (46)	0.35	0.06
TACE (%)	63 (15)	52 (121)	47 (122)	0.34	0.13
Resection of metastases (%)	13 (3)	3 (7)	5 (13)	0.02	0.12
Systemic chemotherapy including molecular target drug (%)	17 (4)	23 (53)	33 (85)	0.48	0.10
Radiation (%)	17 (4)	12 (27)	16 (43)	0.47	0.98
VE, very elderly group; E, elderly group; Y, young group; RFA, radiofrequency ablation; MCT, microwave coagulation therapy; transcatheter arterial chemoembolization.					

Prognostic factors of elderly patients with HCC

The five-year OS rate of group VE was 62%, and the rates of group E and group Y were 65% and 62%, respectively ( $p = 0.86$ ). The median RFS times of groups VE, E and Y were 22 months, 21 months and 17 months, respectively ( $p = 0.65$ ). Both the OS and RFS rates were not significantly different among the three groups (Fig. 1).

Table 4a presents the factors related to OS and RFS in group VE. The multivariate analysis indicated that a PT < 80% and PIVKA-II  $\geq 400$  mAU/ml were unfavorable factors for OS and that PIVKA-II  $\geq 400$  mAU/ml and the presence of PVI, hepatic venous invasion (HVI), and fibrosis were unfavorable factors for RFS in group VE. Table 4b presents the factors related to OS and RFS in group E. The multivariate analysis indicated that ChE < 180 IU/l, AFP  $\geq 20$  ng/ml, tumor size  $\geq 10$  cm, and the presence of multiple tumors, PVI, and HVI were unfavorable factors for OS and that ChE < 180 IU/l, tumor size  $\geq 10$  cm, and the presence of multiple tumors, PVI and HVI were unfavorable factors for RFS in group E. Table 4c presents the factors related to OS and RFS in group Y. The multivariate analysis indicated that AFP  $\geq 20$  ng/ml, the presence of multiple tumors, poor differentiation, PVI and HVI, and operative blood loss  $\geq 400$  ml were unfavorable factors for OS and that a prothrombin time (PT) < 80%, albumin < 3.5 g/dl, AFP  $\geq 20$  ng/ml, tumor size  $\geq 10$  cm, and the presence of multiple tumors, poor differentiation, and PVI were unfavorable factors for RFS in group Y.

Future remnant liver rates in pretty elderly patients who underwent hepatectomy

We evaluated the future remnant liver rate (FRLR) in group VE. The patients with an FRLR  $\geq 50\%$  showed significantly more favorable survival than the patients with an FRLR < 50% ( $p = 0.03$ ). On the other hand, there was no significant difference in recurrence between the patients with an FRLR  $\geq 50\%$  and FRLR < 50% (Fig. 2). Furthermore, there were no significant differences in survival between the patients with an FRLR  $\geq 50\%$  and FRLR < 50% in groups E and Y ( $p = 0.63, 0.42$ ; Table 4b and c).

Table 4a. Prognostic factors for survival and recurrence of very elderly patients

Characteristics	Overall Survival		Relapse-free survival	
	Univariate ( <i>p</i> )	Multivariate ( <i>p</i> ) (hazard ratio) (95% CI)	Univariate ( <i>p</i> )	Multivariate ( <i>p</i> ) (hazard ratio) (95% CI)
<b>Epidemiology</b>				
Sex Male	0.64		0.29	
HBs-Ag positive	0.24		0.09	
HCV-Ab positive	0.28		0.94	
NBNC	0.07		0.63	
<b>Biochemical Factors</b>				
Platelets < 100,000 /mm <sup>3</sup>	0.50		0.42	
PT < 80 %	< 0.01	0.02 (8.109) (1.227-53.587)	0.57	
ChE < 180 IU/l	0.01	0.35 (2.021) (0.447-9.127)	0.70	
Albumin < 3.5 g/dl	0.24		0.43	
ICGR15 ≥ 15 %	0.06		0.77	
AFP ≥ 20 ng/ml	0.11		<0.01	0.85 (0.911) (0.339-2.444)
PIVKA-II ≥ 400 mAU/ml	<0.01	0.03 (9.838) (1.220-79.309)	0.01	0.02 (4.038) (1.147-14.211)
<b>Tumor Factors</b>				
Tumor size ≥ 10 cm	0.03	0.65 (0.707) (0.157-3.189)	<0.01	0.27 (0.424) (0.089-2.006)
Tumor Number Multiple	0.93		0.04	0.20 (2.115) (0.672-6.657)
Macroscopic type Except simple nodular	0.42		0.03	0.05 (2.646) (0.982-7.127)
<b>Histological Factors</b>				
Differentiation poor	0.35		0.02	0.45 (1.440) (0.552-3.757)
PVI	0.75		0.01	0.01 (4.580) (1.342-15.629)
HVI	0.24		0.02	<0.01 (7.393) (1.923-28.424)
Fibrosis	0.57		0.02	0.01 (3.483) (1.258-9.644)
<b>Surgical Factors</b>				
FRLR < 50 %	0.03	0.81 (1.204) (0.245-5.911)	0.17	
Non-anatomical resection	0.80		0.99	
Blood loss ≥ 400 ml	< 0.01	0.18 (5.000) (0.470-53.111)	0.77	

PT, prothrombin time; ChE, cholinesterase; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion; FRLR, future remnant liver rates.

**Table 4b. Prognostic factors for survival and recurrence of elderly patients**

Characteristics	Overall Survival		Relapse-free survival	
	Univariate ( <i>p</i> )	Multivariate ( <i>p</i> ) (hazard ratio) (95% CI)	Univariate ( <i>p</i> )	Multivariate ( <i>p</i> ) (hazard ratio) (95% CI)
<b>Epidemiology</b>				
Sex Male	0.62		0.66	
HBs-Ag positive	0.27		0.70	
HCV-Ab positive	0.90		0.75	
NBNC	0.12		0.63	
<b>Biochemical Factors</b>				
Platelets < 100,000 /mm <sup>3</sup>	0.93		0.35	
PT < 80 %	0.17		0.04	0.40 (1.163) (0.813-1.665)
ChE < 180 IU/l	< 0.01	< 0.01 (2.530) (1.684-3.800)	< 0.01	< 0.01 (1.578) (1.125-2.214)
Albumin < 3.5 g/dl	< 0.01	0.58 (1.163) (0.679-1.992)	< 0.01	0.29 (1.282) (0.802-2.050)
ICGR15 ≥ 15 %	0.56		0.18	
AFP ≥ 20 ng/ml	< 0.01	0.03 (1.553) (1.041-2.315)	< 0.01	0.55 (1.095) (0.811-1.480)
PIVKA-II ≥ 400 mAU/ml	< 0.01	0.63 (0.905) (0.596-1.373)	< 0.01	0.94 (0.989) (0.732-1.337)
<b>Tumor Factors</b>				
Tumor size ≥ 10 cm	< 0.01	0.01 (1.922) (1.128-3.274)	< 0.01	0.01 (1.654) (1.102-2.484)
Tumor Number Multiple	< 0.01	0.02 (1.559) (1.049-2.316)	< 0.01	< 0.01 (2.223) (1.679-2.943)
Macroscopic type Except simple nodular	0.11		< 0.01	0.13 (1.249) (0.931-1.675)
<b>Histological Factors</b>				
Differentiation Poor	< 0.01	0.40 (1.179) (0.797-1.744)	0.01	0.78 (0.959) (0.707-1.300)
PVI	< 0.01	< 0.01 (2.653) (1.674-4.206)	< 0.01	0.03 (1.460) (1.027-2.078)
HVI	< 0.01	0.02 (1.889) (1.066-3.346)	< 0.01	< 0.01 (1.980) (1.284-3.053)
Fibrosis	0.42		0.60	
<b>Surgical Factors</b>				
FRLR ≥ 50 %	0.63		0.83	
Non-anatomical resection	0.20		0.06	
Blood loss ≥ 400 ml	0.02	0.97 (1.005) (0.674-1.500)	0.04	0.91 (1.014) (0.772-1.333)

PT, prothrombin time; ChE, cholinesterase; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion; FRLR, future remnant liver rates.

**Table 4c. Prognostic factors for survival and recurrence of young patients**

Characteristics	Overall Survival		Relapse-free survival	
	Univariate ( <i>p</i> )	Multivariate ( <i>p</i> ) (hazard ratio) (95% CI)	Univariate ( <i>p</i> )	Multivariate ( <i>p</i> ) (hazard ratio) (95% CI)
<b>Epidemiology</b>				
Sex Male	0.42		0.26	
HBs-Ag positive	0.73		0.13	
HCV-Ab positive	0.19		0.78	
NBNC	0.38		0.13	
<b>Biochemical Factors</b>				
Platelets < 100,000 /mm <sup>3</sup>	0.84		0.34	
PT < 80 %	0.03	0.27 (1.261) (0.833-1.908)	< 0.01	0.01 (1.449) (1.063-1.974)
ChE < 180 IU/l	< 0.01	0.13 (1.416) (0.901-2.225)	< 0.01	0.79 (0.954) (0.666-1.366)
Albumin < 3.5 g/dl	< 0.01	0.47 (1.215) (0.711-2.076)	< 0.01	< 0.01 (1.834) (1.213-2.774)
ICGR15 ≥ 15 %	0.94		0.09	
AFP ≥ 20 ng/ml	< 0.01	< 0.01 (1.769) (1.242-2.520)	< 0.01	0.02 (1.344) (1.029-1.755)
PIVKA-II ≥ 400 mAU/ml	< 0.01	0.83 (1.045) (0.691-1.580)	< 0.01	0.88 (0.977) (0.715-1.333)
<b>Tumor Factors</b>				
Tumor size ≥ 10 cm	< 0.01	0.78 (0.932) (0.570-1.526)	< 0.01	0.01 (1.637) (1.122-2.388)
Tumor Number Multiple	< 0.01	< 0.01 (1.674) (1.194-2.346)	< 0.01	< 0.01 (1.704) (1.307-2.222)
Macroscopic type Except simple nodular	< 0.01	0.52 (0.880) (0.593-1.306)	< 0.01	0.72 (0.947) (0.704-1.274)
<b>Histological Factors</b>				
Differentiation Poor	< 0.01	< 0.01 (1.818) (1.270-2.601)	< 0.01	0.01 (1.419) (1.070-1.884)
PVI	< 0.01	< 0.01 (1.904) (1.290-2.808)	< 0.01	0.02 (1.467) (1.061-2.028)
HVI	< 0.01	0.02 (1.718) (1.080-2.735)	< 0.01	0.66 (1.089) (0.734-1.615)
Fibrosis	0.18		0.05	
<b>Surgical Factors</b>				
FRLR ≥ 50 %	0.42		0.49	
Non-anatomical resection	0.79		0.89	
Blood loss ≥ 400 ml	< 0.01	0.01 (1.604) (1.108-2.323)	< 0.01	0.15 (1.218) (0.927-1.601)

PT, prothrombin time; ChE, cholinesterase; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion; FRLR, future remnant liver rates.

## Discussion

Our present study indicated that the number of patients in group VE increased in the late period (2009–2017) and that there was a higher proportion of patients with HCV and patients without HBV and HCV.

The incidence of PVI and fibrosis was lower in group VE than in group Y. The number of surgical procedures was not significantly different between groups. Group VE showed significantly fewer cancer-related deaths and more noncancer-related deaths than group Y. The surgical outcomes and morbidities of group

VE were almost the same as those of the other two groups. These three groups showed similar OS and RFS results. Regarding the prognostic factors, tumor factors such as tumor size and tumor number had a smaller influence on the prognosis of patients in group VE than on that of patients in groups E and Y.

According to the nationwide survey of HCC patients in Japan, the rate of nonviral HCC was 32.5% in 2015 [19]. In this study, the rate in group VE was 59%. This rate was high. Previous studies have reported that the number of elderly patients with HCC is increasing [20] and that elderly patients have higher rates of HCV or NBNC than nonelderly patients [14, 15, 20, 21], which is consistent with our results. HCV infections generally occur in adulthood, in contrast to HBV infections, which are generally acquired through mother-child transmission [22]. The reason why there are more elderly NBNC-HCC patients is thought to be because non-alcoholic fatty liver disease and non-alcoholic steatohepatitis-related HCC with metabolic syndromes are more likely to occur in elderly patients than in young patients [23, 24]. Regarding liver function, elderly patients tend to develop HCC without cirrhosis or liver fibrosis [21]. Paradis et al. reported that HCC patients with metabolic syndromes showed less significant fibrosis than those without metabolic syndromes [23]. Tokushige et al. reported that cryptogenic HCC patients aged 80 years or older tended to develop HCC without cirrhosis [25]. Regarding oncological features, some reports have shown a higher frequency of tumor encapsulation and lower vascular invasion in elderly patients than in young patients [26, 27]. These results were consistent with our results. Katsuta et al. reported an age-related upregulation of the androgen and phosphatidylinositol 3-kinase pathways in tumor tissue and a downregulation of fibrosis-related pathways in noncancerous liver tissue [28]. Thus, compared to those of HCC in young patients, the characteristics of HCC in elderly patients could be somewhat different, such as a slightly lower degree of malignancy and relatively better liver function. In this study, prognostic factors such as tumor size and tumor number had less influence on the prognoses of patients in group VE than on those of patients in groups E and Y. This result might be explained by these biological differences. The liver function reserve might be more important in group VE than in group E or Y. Interestingly, the patients with an FRLR  $\geq$  50% showed significantly more favorable survival than the patients with an FRLR  $<$  50% in group VE according to the univariate analysis. Furthermore, there were no significant differences in recurrence. During hepatectomy for very elderly patients, surgeons might have to make a maximum effort to preserve the remnant liver as much as possible.

The prognoses of pretty elderly patients with HCC are under investigation. Many reports have claimed that the prognoses after hepatectomy are not different between elderly patients and nonelderly patients [15, 20, 26]. Oishi et al. reviewed 23 papers and reported that the 5-year OS rates after hepatectomy in elderly HCC patients ranged from 26–75.9%, whereas those in young patients ranged from 31.4–68%. Tsukioka et al. reported that in the early stage, patients with HCC aged 80 years or older had a poorer prognosis than nonelderly patients with HCC, although there were no differences in all stages; additionally, their study included not only hepatectomy but also other treatments [14]. Huang et al. reported that elderly patients had a better 5-year OS rate than younger patients (43.2% and 31.4%, respectively) [27]. In this study, the OS and RFS rates of very elderly patients were not different from those of elderly or young patients.

Hepatic resection is the main therapeutic method for HCC, even in elderly patients. However, hepatectomy is a highly invasive surgical procedure with a high morbidity rate [7]. Therefore, the indications for hepatectomy in elderly patients with HCC represent an important consideration because these patients frequently have systemic comorbidities and low activities of daily living. Most previous studies have shown that the morbidity rates after hepatectomy are not significantly different between elderly and nonelderly patients. These studies reported that the morbidities after hepatectomy in elderly patients ranged from 9–58% [27, 29, 30]. However, Ferrero et al. showed that elderly patients aged 70 years had lower complication rates after hepatectomy than young patients (23.4% vs. 42.4%), particularly in terms of liver failure (1.6% vs. 12.9%) [31]. The authors considered that this result was due to elderly patients undergoing more meticulous patient selection and less aggressive surgery than young patients. Kondo et al. reported that only the incidence of pneumonia after hepatectomy was significantly higher in elderly patients than in young patients, although the total complication rate and the rates of other complications were not different between the groups [32]. In our study, these rates were not significantly different. Recent technological developments for hepatectomy and perioperative management have resulted in decreased mortality rates [7]. Hepatectomy should not be avoided in very elderly patients with HCC if the patients have a good general status. In our institute, we have empirically confirmed that cognitive function was well maintained and that patients were walking on their own at the outpatient consultation for the selection of elderly patients receiving hepatectomy.

Regarding treatment after recurrence, re-hepatectomy was not performed in group VE in this cohort. This strategy was considered to be due to the conservative patient selection. However, laparoscopic surgery might be a useful tool for re-hepatectomy in very elderly patients.

The limitations of the study are as follows. First, the number of patients aged 80 years or older was small ( $n = 49$ ). Second, elderly patients had a possibility of selection bias when they were referred from internal medicine.

## Conclusions

Tumor factors may have less influence on the prognoses of very elderly patients with HCC than on those of patients younger than 80 years old, and the liver function reserve might be important for the long-term survival of these elderly patients. Hepatectomy can be safely performed, even in very elderly patients, by performing a close evaluation. Hepatectomy should not be avoided in very elderly patients with HCC if the patients have a good general status because these elderly patients with HCC have the same prognoses as nonelderly people with HCC.

## Abbreviations

HCC:Hepatocellular carcinoma; HBs-Ag:HBs-antigen; HCV-Ab:HCV-antibody; ASA:American Society of Anesthesiologists; ICGR15:Indocyanine green retention test at 15 min; AFP:Alpha-fetoprotein; PIVKA-II:Protein induced by vitamin K absence-II; US:Ultrasound sonography; CT:Computed tomography; MRI:Magnetic resonance imaging; OS:Overall survival; RFS:Relapse-free survival; MST:Median survival time; NBNC:NonBNonC; PVI:Portal venous invasion; TACE:Transarterial chemoembolization; PT:Prothrombin time; HVI:Hepatic venous invasion; ChE:Cholinesterase; FRLR:Future remnant liver rates.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Hokkaido University Hospital Voluntary Clinical Study Committee and was performed in accordance with the Helsinki Declaration guidelines.

#### Consent for publication

Not applicable

#### Availability of data and materials

Not applicable

#### Competing interests

The authors declare that they have no competing interests.

#### Funding

Not applicable

#### Authors' contributions

SS and TK conceived the study concept and design, were involved with patient care and drafted the manuscript and literature review. TO, AN, YA, YS, HK, and AT were involved with the formation of the study concept and design, patient care and drafting of the manuscript and literature review. All authors have read and approved the final version of the manuscript.

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## Figures

Fig. 1

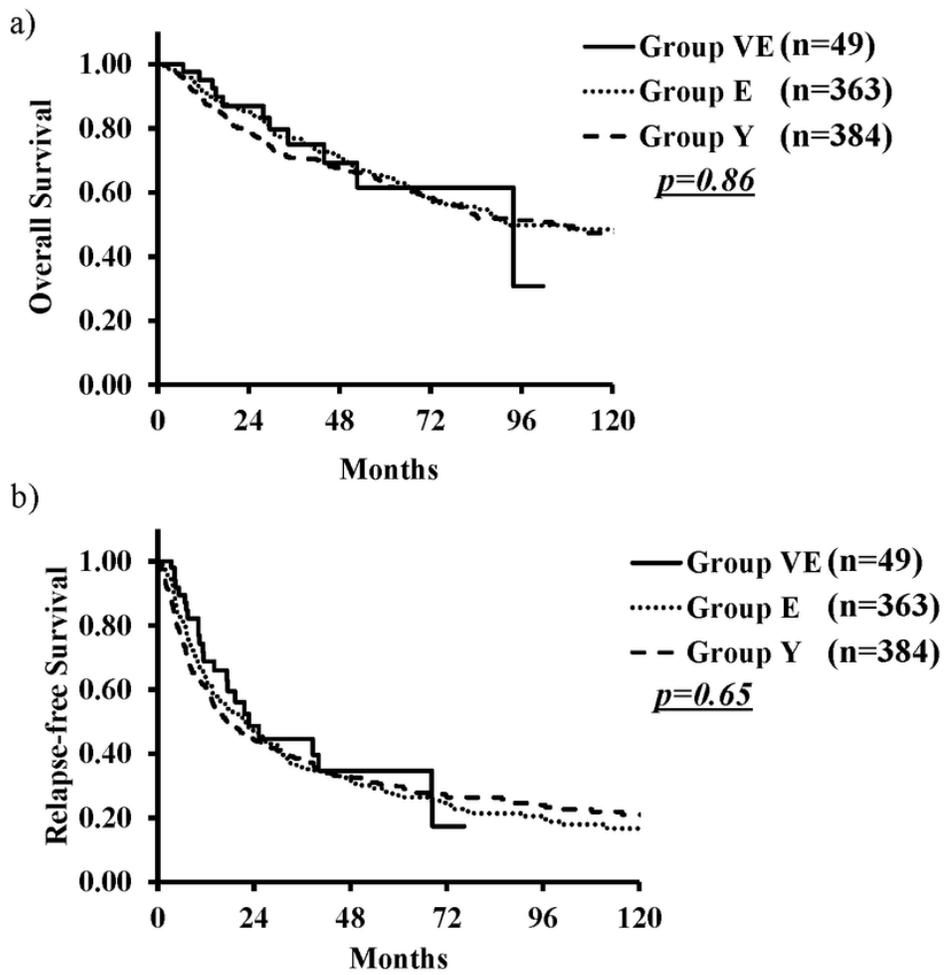


Figure 1  
(a) Overall survival curves for patients with HCC among the VE group, E group and Y group. (b) Relapse-free survival curves for patients with HCC among the VE group, E group and Y group.

Fig. 2

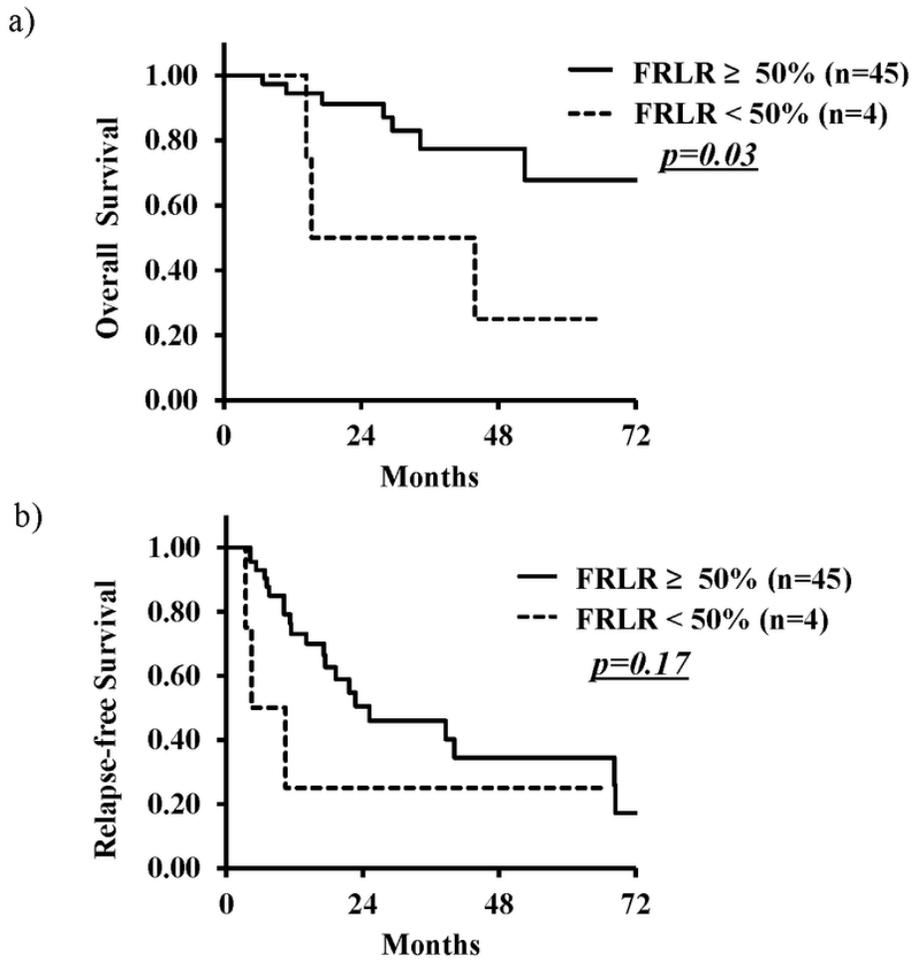


Figure 2

(a) Overall survival curves in group VE between the patients with an FRLR  $\geq$  50% and FRLR < 50%. (b) Relapse-free survival curves in group VE between the patients with an FRLR  $\geq$  50% and FRLR < 50%.