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Factors Affecting the Clinical Outcome of Hepatocellular Carcinoma in Elderly Patients: A Retrospective, Multicenter Study

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Abstract

Background: The incidence of hepatocellular carcinoma (HCC) in Japanese elderly patients (ages sixty -five and older) has been on the increase, but the clinical characteristics of patients with HCC have not been well described. The aim of the present study was to evaluate the impact of aging on the clinical characteristics findings and the survival of HCC patients.

Method: A total of 2,370 patients with HCC diagnosed between 1999 and 2011, were recruited for this study. The age of HCC was categorized to four groups; not old: sixty-four and younger, young old: sixty-five to seventy-four, old old: seventy -five to eighty-four, oldest old: eighty -five and older. The significance of clinical parameter was examined for elderly HCC patients using logistic regression analysis.

Result: Multivariate analysis identified sex, body mass index (BMI), alcohol consumption, Child-Pugh grade, etiology of liver disease, alanine aminotransferase (ALT)), α-fetoprotein (AFP) and Tumor-Node-Metastasis (TNM) stage, as independent and significant risk factors for elderly HCC patients. Additionally, the significant risk factors for elderly HCC patients according to four age groups are presented. The ratio of male, BMI, alcohol intake patients, ALT, and AFP decreased significantly from 80%, 23.0, 40%, 50 IU/l and 48.7 ng/ml in not old group to 57%, 21.6, 26%, 28IU/l and 12.8 ng/ml in oldest old group, respectively. The ratio of Child-Pugh grade A and non-hepatitis virus infection increased significantly from 60% and 17% in not old group to 80% and 43% in oldest old group, respectively. When patients were classified according to the TNM stage, patients in the oldest old group with TNM stage I or II had a lower cumulative survival rate than those in the younger three groups.

Conclusion: It appears that eighty -five years and older patients with HCC were poorer prognosis than that younger patients in early stage HCC.

Introduction

Primary liver cancer is the most common primary cancer of the liver, accounting for approximately 6% of all human cancers. It is estimated that half a million cases occur worldwide annually, making primary liver cancer the fifth most common malignancy in men and the ninth in women [1-6]. Hepatocellular Carcinoma (HCC) accounts for 85% to 90% of primary liver cancers [7], and the age-adjusted HCC mortality rate has increased in recent decades in Japan [8]. Similarly, a trend of increasing rates of HCC has been reported in several developed countries of North America, Europe, and Asia [9,10]. HCC often develops in patients with liver cirrhosis caused by hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol consumption, or non-alcoholic fatty liver disease. Of the hepatitis viruses causing HCC, HCV is predominant in Japan [11-14]. However, it has been reported that the number and ratio of both hepatitis B surface antigen (HBsAg)- and HCV antibody (HCVAb)-negative HCC (HCC-nonBC) is steadily increasing in Japan [15,16].

The prognosis for patients with HCC is still poor. Surgical resection and liver transplantation are the standard forms of curative treatment available. Recently, radio-frequency ablation (RFA) and percutaneous ethanol injection (PEI) is also recognized as effective methods to induce complete tumor necrosis for small HCCs [17]. With advances in diagnostic and biomedical technologies, most of the studies have shown that treatment of elderly patients with HCC is as safe and effective as in younger patients, with overall post-treatment survival rate similar to those of younger patients. However, unintentional bias in the selection of patients might have occurred in the above-mentioned studies, with inclusion of patients with good liver function or those without severe concomitant diseases for the aggressive treatment of HCC [18-25].

In this retrospective cohort study, our aim was to characterize elderly patients who were diagnosed consecutively with HCC in a 12-year period (1999-2011) at the centers composing the Nagasaki Association Study of Liver Disease (NASLD) group. The aim of the present study was to evaluate the effect of age on the clinical outcome of HCC patients, including tumor stage, treatment, and survival.

Keywords: Elderly Patients; HCC; Multicenter Study; Prognosis

Patients and Methods

Patients

A total of 2,370 patients, diagnosed with HCC between 1999 and 2011 by the NASLD group, were recruited for this study. The diagnosis of HCC was based on α-fetoprotein (AFP) and/or des-gamma-carboxy prothrombin (DCP) levels; results of imaging techniques such as ultrasonography (USG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Hepatic Angiography (HAG); and/or liver biopsy. The diagnostic criteria included characteristic liver biopsy findings, elevated AFP (≥20 ng/ml) and/or DCP (≥40 ng/ml), and neovascularization on HAG, CT and/or MRI.

The diagnosis of chronic HCV infection was based on the presence of HCVAb (microparticle enzyme immunoassay; Abbott Laboratories) and HCV RNA, as detected by polymerase chain reaction. The diagnosis of chronic HBV infection was based on the presence of HBsAg (enzyme-linked immunosorbent assay; Abbott Laboratories). Serum AFP level was measured by radioimmunoassay (Abbott Laboratories). The history of alcohol intake was noted from medical records; excessive drinking was defined as an average daily consumption of an amount equivalent to 80 g of pure ethanol for a period of more than 10 years, and not excessive drinking was defined as an average daily consumption of an amount equivalent to 1-79 g of pure ethanol for a period of more than 10 years.

Patients were divided into four groups according to age: not old (≤64 years); young old (65-74 years); old old (75-84 years); and oldest old (≥85 years). The stages of aging were defined as per the Japan Geriatrics Society. Logistic regression analysis was performed to evaluate the association between HCC and age, sex, Body Mass Index (BMI), alcohol intake, diabetes mellitus, underlying liver disease, Child-Pugh grade, platelet count, prothrombin time (PT), Albumin (ALB), Total Bilirubin (Bil), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), AFP, DCP, and Tumor Node Metastasis (TNM) stage.

Treatment Modalities

Patients diagnosed with HCC were assessed for surgery on the basis of the extent of lobar involvement and liver function status. The extent of lobar involvement was evaluated by a combination of USG, CT, MRI, and HAG. Patients were considered unfit for resection if they met the following criteria: (1) bilobar involvement, (2) evidence of tumor infiltration into the main portal vein or thrombosis of the vein, (3) evidence of extrahepatic metastases, (4) Child–Pugh grade C cirrhosis, or (5) poor cardiac and respiratory statuses. If the patients were deemed unfit for operation or refused to undergo operation, RFA or PEI therapy was the second choice of treatment offered to such patients with HCCs less than 3 cm in diameter. The remaining patients without main portal vein thrombosis or extrahepatic metastasis were advised to undergo Transcatheter Arterial Chemo- Embolizatio (TACE) irrespective of the size and number of tumors.

After initial treatment, AFP levels and liver function of the patients were assessed every 1 to 3 months, and USG imaging was performed every 3 to 6 months during the follow-up period.

Patients suspected to have HCC recurrence were further evaluated by CT and/or MRI. The assessment of treatment for recurrent HCC was based on lobar involvement and liver function status as described for the initial treatment. RFA or liver transplantation to treat HCC was started at our institution in 2002. Furthermore, none of the subjects in our study received either of these treatments for recurrent HCC during the follow-up period.

Statistical Analysis

The time of survival was measured from the time of the diagnosis of HCC to the time of death or until the time of preparation of the manuscript. The survival rate was analyzed using the Kaplan-Meier method, and the differences between the survival probability curves were tested using the log-rank test. Descriptive summaries of study groups are reported as the median (range) and number (%). Data were analyzed using the Mann-Whitney *U* test for continuous ordinal data, and the chi-square test with Yates' correction and Fisher's exact test were performed for intergroup comparisons to determine the association between two qualitative variables. *P*-values <0.05 were considered statistically significant. Variables achieving statistical significance according to univariate analysis were subsequently included in the multivariate analysis using a logistic regression model and are described as Hazard Ratio (HR) with 95% Confidence Interval (CI). Coefficients were calculated from the linear discriminating function of the variables. Data analysis was performed using SPSS version 16.0 for Windows. We followed the methods of Akahoshi et al. (2010) [26].

Results

Patient Characteristics at Enrollment

We diagnosed 2,370 patients with HCC during the study period. Patient characteristics at the time of diagnosis of HCC are presented in Table 1. We assigned 716 (30%) patients to the not-old group, 881 (37%) to the young-old group, 704 (30%) to the old-old group, and 69 (3%) to the oldest-old group.

Overall, the median survival of all 2,370 patients was 5.6 years. The cumulative survival rate was 54% at the 5th year.

Characteristics		(Range) (%)
Number	2,370	
Age (years)	71	13-96
Sex		
Male	1,605	68
Female	765	32
Alcohol consumption		
Excessive	200	8
not excessive	552	22
No consumption	1,648	70
DM (unknown patients: 39)		
(+)	681	29
(-)	1,650	70
BMI (kg/m^2)	22.7	13.0-45.3
Hepatitis virus		
HBV	426	18
HCV	1,337	56
B+C	23	1
NBNC	584	25
Underlying liver disease (unknown patients: 113)		
Chronic hepatitis	745	31
Cirrhosis	1,512	64
Child-Pugh Grade (unknown patients: 81)		
A	1,618	68
B	542	23
C	129	5
TNM stage		
I	571	24
II	951	40
III	533	22
IVa	210	9
IVb	105	4
Therapy		
Surgical resection	417	18
RFA and/or PEIT	603	25
TACE and/or TAI	1,079	45
Chemotherapy	54	2
LDLT	10	1
BSC	207	9
Plt (10^3/ml)	120	8-980
ALT (IU / L)	43	4-19679
Bil (mg/dl)	0.9	0.2-30.1
Alb (g/dl)	3.7	1.4-7.2
PT (%)	83	7-134
AFP (ng/ml)	24	1-2,920,000

(unknown patients: 71)		
<20	1,090	46
20-199	627	26
≥200	582	25
DCP (mAU/ml)	96	2-2,650,000
(unknown patients: 133)		
<40	814	34
40-199	490	21
≥200	933	39
Observation period (years)	1.7	0.1-10.2

DM - Diabetes Mellitus
BMI - Body Mass Index
HBV - Hepatitis B Virus
HCV - Hepatitis C Virus
NBNC - Non-Hepatitis Virus
TNM - Tumor-Node-Metastasis
RFA - Radio- Frequency Ablation
PEI - Percutaneous Ethanol Injection
TACE - Trans catheter Arterial Chemo- Embolization
TAI - Trans catheter Arterial Infusion
LDLT - Living Donor Liver Transplant
BSC - Best Supportive Care
Plt - Platelet
ALT - Alanine Aminotransferase
Bil - Total Bilirubin
Alb - Albumin
PT - Prothrombin Time
AFP - α-fetoprotein
DCP - Des-Gamma-Carboxy Prothrombin

Table 1: Demographic and clinical characteristics of the 2,370 patients with hepatocellular carcinoma.

Univariate and Multivariate Analyses of the Factors Associated with HCC in the Elderly

Univariate and multivariate analyses were performed to identify the independent factors associated with HCC in elderly patients (Table 2). In the univariate analysis, the following 13 significant factors were identified: sex, BMI, alcohol intake, underlying liver disease, Child-Pugh grade, hepatitis virus, platelet count, PT, Bil, ALT, AFP, DCP, and TNM stage. Subsequent multivariate analysis identified sex (female, HR 2.20), BMI (≥25 kg/m^2, HR 0.35), alcohol intake (not excessive drinker, HR 0.64; excessive drinker, HR 0.36), Child-Pugh grade (B, HR 0.68; C, HR 0.32), etiology of liver disease (HCV, HR 9.12; HBV and HCV, HR 4.32; non-hepatitis virus infection, HR 11.28), ALT (>46 IU/l, HR 0.53), AFP (≥200 ng/ml, HR 0.53), and TNM stage (II, HR 1.65) as independent significant risk factors for HCC in elderly patients (Table 3).

Parameters		Hazard ratio	95% CI	P value
Sex	Female	2.39	1.94-2.94	<0.001
BMI (kg/m^2)	≥25	0.81	0.66-0.99	0.036
Alcohol consumption	No consumption	1	---	---
	Moderate	0.56	0.46-0.69	<0.001
	Excessive	0.5	0.37-0.68	<0.001
Diabetes mellitus	+	1.12	0.92-1.36	0.27
Underlying liver disease	Cirrhosis	0.82	0.67-0.99	0.041
Child-Pugh grade	A	1	---	---
	B	0.66	0.57-0.82	<0.001
	C	0.26	0.18-0.38	<0.001
Hepatitis virus	HBV	1	---	---
	HCV	8.52	6.67-10.88	<0.001
	HBV+HCV	3.03	1.29-7.08	0.011
	NBNC	8.91	6.70-11.88	<0.001
Platelet (10^3/μL)	<120	0.8	0.67-0.96	0.016
ALT (IU/l)	≥46	0.61	0.51-0.73	<0.001
PT (%)	≥83	0.63	0.53-0.725	<0.001
Bil (mg/dl)	≥0.9	0.65	0.55-0.78	<0.001
Alb (g/dl)	<3.7	1.02	0.85-1.22	0.818
AFP (ng/ml)	<20	1	---	---
	20-199	0.77	0.62-0.96	0.021
	≥200	0.47	0.38-0.58	<0.001
DCP (mAU/ml)	<40	1	---	---
	40-199	0.91	0.71-1.16	0.439
	≥200	0.74	0.61-0.91	0.005

TNM stage	I	1	---	---
	II	1.41	1.11-1.77	0.004
	III	1.07	0.82-1.38	0.621
	IVa	0.51	0.37-0.70	<0.001
	IVb	0.39	0.26-0.60	<0.001

CI - Confidence Interval
BMI - Body Mass Index
HBV - Hepatitis B Virus
HCV - Hepatitis C Virus
NBNC - Non-Hepatitis Virus
TNM - Tumor-Node-Metastasis
ALT - Alanine Amino Transferase
Bil - Total Bilirubin
Alb - Albumin
PT - Prothrombin Time
AFP - α-fetoprotein
DCP - Des-Gamma-Carboxy Prothrombin

Table 2: Univariate analysis of the factors associated with hepatocellular carcinoma in elderly patients.

Parameters		Hazard ratio	95% CI	P value
Sex	Female	2.2	1.65-2.93	<0.001
BMI (kg/m^2)	≥25	0.35	0.59-0.98	0.035
Alcohol consumption	No consumption	1	---	---
	Moderate	0.64	0.48-0.85	0.002
	Excessive	0.36	0.23-0.55	<0.001
Underlying liver disease	Cirrhosis	1.23	0.91-1.65	0.173
Hepatitis virus	HBV	1	---	---
	HCV	9.12	6.69-12.39	<0.001
	HBV+HCV	4.32	1.55-12.06	0.005
	NBNC	11.28	7.73-16.47	<0.001
Platelet (10^3/μL)	<120	0.79	0.60-1.05	0.1
ALT (IU/l)	>46	0.53	0.42-0.68	<0.001
PT (%)	<83	0.89	0.67-1.17	0.401
Bil (mg/dl)	>0.9	1.01	0.78-1.30	0.945
AFP (ng/ml)	<20	1	---	---
	20-199	0.79	0.60-1.05	0.103
	≥200	0.53	0.39-0.74	<0.001
DCP (mAU/ml)	<40	1	---	---
	40-199	1.01	0.74-1.38	0.943
	≥200	1.34	0.98-1.83	0.07
TNM stage	I	1	---	---
	II	1.65	1.21-2.24	0.001
	III	1.37	0.96-1.95	0.087
	IVa	0.91	0.91-2.57	0.153
	IVb	0.73	0.38-1.41	0.351

CI - Confidence Interval
BMI - Body Mass Index
HBV - Hepatitis B Virus
HCV - Hepatitis C Virus
NBNC - Non-Hepatitis Virus
TNM - Tumor-Node-Metastasis
ALT - Alanine Aminotransferase
Bil - Total Bilirubin
AFP - α-fetoprotein
DCP - Des-Gamma-Carboxy Prothrombin

Table 3: Multivariate analysis of the factors associated with hepatocellular carcinoma in elderly patients.

Comparison of Clinical Characteristics between the Four Age Groups

The significant risk factors for HCC in elderly patients according age are presented in Table 4. Male gender, BMI, alcohol intake, ALT, and AFP decreased significantly from 80%, 23.0 kg/m^2, 40%, 50 IU/ml and 48.7 ng/ml in the not-old group to 57%, 21.6 kg/m^2, 26%, 28 IU/l and 12.8 ng/ml in the oldest-old group, respectively ($P < 0.05$). Child-Pugh grade and non-hepatitis virus infection increased significantly from 60% and 17% in the not-old group to 80% and 43% in the oldest-old group, respectively ($P < 0.05$).

Parameters	Not old (<65 years)	Young old (65-74 years)	Old old (75-84 years)	Oldest old (≥85 years)	Total
All patient	716	881	704	69	2,370
Sex (%)		*	*	*	
Male	572 (80)	565 (64)	428 (61)	40 (57)	1,605 (68)
Female	144 (20)	316 (36)	276 (39)	29 (43)	765 (32)
BMI (kg/m2)	23.0(13.0-45.3)	23.0 (15.4-43.3)	22.0 (14.6-36.9)*	21.6 (14.6-36.9)*	22.7 (13.0-45.3)
Alcohol consumption (%)		*	*	***	
No consumption	431 (60)	607 (69)	559 (79)	51 (74)	1,648 (70)
Moderate drinking	202 (28)	191 (22)	112 (16)	17 (25)	522 (22)
Excessive drinking	83 (12)	83 (9)	33 (5)	1 (1)	200 (8)
Child-Pugh grade (%)		*	*	***	
A	430 (60)	611 (69)	522 (74)	55 (80)	1,618 (68)
B	192 (27)	201 (23)	136 (19)	13 (19)	542 (23)
C	75 (10)	36 (4)	17 (2)	1 (1)	129 (5)
Unknown	19 (3)	33 (4)	29 (5)	0 (0)	81 (4)
Hepatitis virus (%)		*	*	*	
HBV	298 (42)	89 (10)	35 (5)	4 (6)	426 (18)
HCV	287 (40)	563 (64)	452 (64)	35 (51)	1,337 (56)
HBV+HCV	10 (1)	6 (1)	7 (1)	0 (0)	23 (1)
NBNC	121 (17)	223 (25)	210 (30)	30 (43)	584 (25)
ALT (IU/l) (range)	50 (8-781)	43 (6-1,802)*	39 (4-19,679)*	28 (9-295)*	43 (4-19,679)
AFP (ng/ml) (range)	48.7 (1-2,920,000)	21.9 (1-963,300)*	16.1 (1-2,710,000)*	12.8 (1-119,720)**	24 (1-2,920,000)
TNM stage (%)		*	**		
I	176 (25)	236 (27)	149 (21)	10 (17)	571 (24)
II	229 (31)	359 (41)	330 (47)	33 (55)	951 (40)
III	157 (22)	189 (21)	166 (24)	21 (35)	533 (22)
IVa	149 (21)	65 (7)	44 (6)	3 (5)	210 (9)
IVb	10 (1)	32 (4)	15 (2)	2 (3)	105 (4)
* $p < 0.001$ versus not old; ** $p < 0.01$ versus not old; *** $p < 0.05$ versus not old					
BMI - Body Mass Index HBV - Hepatitis B Virus HCV - Hepatitis C Virus NBNC - Non-Hepatitis Virus TNM - Tumor-Node-Metastasis ALT - Alanine Amino Transferase Bil - Total Bilirubin AFP - α-fetoprotein					

Table 4: Comparison of the clinical characteristics of hepatocellular carcinoma patients per age group.

Treatments of each group according to age and TNM stage are listed in Table 5. The percentage of patients treated with supportive care alone in TNM stage I or II was significantly higher in the oldest-old group than in the other groups ($P < 0.001$), and higher in patients with TNM stage III or IV than in patients with TNM stage I or II for each age group.

	Not old (<65 years)	Young old (65-74 years)	Old old (75-84 years)	Oldest old (≥85 years)	Total
TNM stage I or II					
Total	405	595	479	43	1,522
Surgical resection	103 (25)	119 (20)	90 (19)	2 (5)	314 (21)
Liver transplantation	6 (1)	2 (0)	0	0	8(1)
RFA and/or PEIT	139 (34)	235 (39)	170 (35)	12 (28)	556 (37)
TACE and/or TAI	142 (35)	220 (37)	165 (34)	18 (42)	545 (36)
Chemotherapy	0	2 (0)	0	1 (2)	3 (0)
Supportive care	15 (4)	17 (3)	24 (5)	10 (23)	66 (4)
TNM stage III or IV					
Total	311	286	225	26	848
		*	*	***	
Surgical resection	39 (13)	31 (11)	31 (14)	2 (8)	103 (12)
Liver transplantation	1 (0)	1 (0)	0	0	2 (0)
RFA and/or PEIT	10 (3)	21 (7)	15 (7)	1 (4)	47 (6)
TACE and/or TAI	166 (53)	186 (65)	137 (61)	15 (58)	504 (59)
Chemotherapy	32 (10)	8 (2)	4 (2)	0	44 (5)
Supportive care	63 (20)	39 (14)	38 (17)	8 (31)	148 (18)

TNM - Tumor-Node-Metastasis
RFA - Radio-Frequency Ablation
PEI - Percutaneous Ethanol Injection
TACE - Trans Catheter Arterial Chemo- Embolization
TAI - Trans Catheter Arterial Infusion

Table 5: Treatment for hepatocellular carcinoma according to age and Tumor Node Metastasis (TNM) stage.

Patients in the oldest-old group with TNM stage I or II had a significantly lower cumulative survival rate than those in the younger three groups. In patients with TNM stage III or IV, the cumulative survival rate was not different among the four age groups (Figure 1).

Figure 1

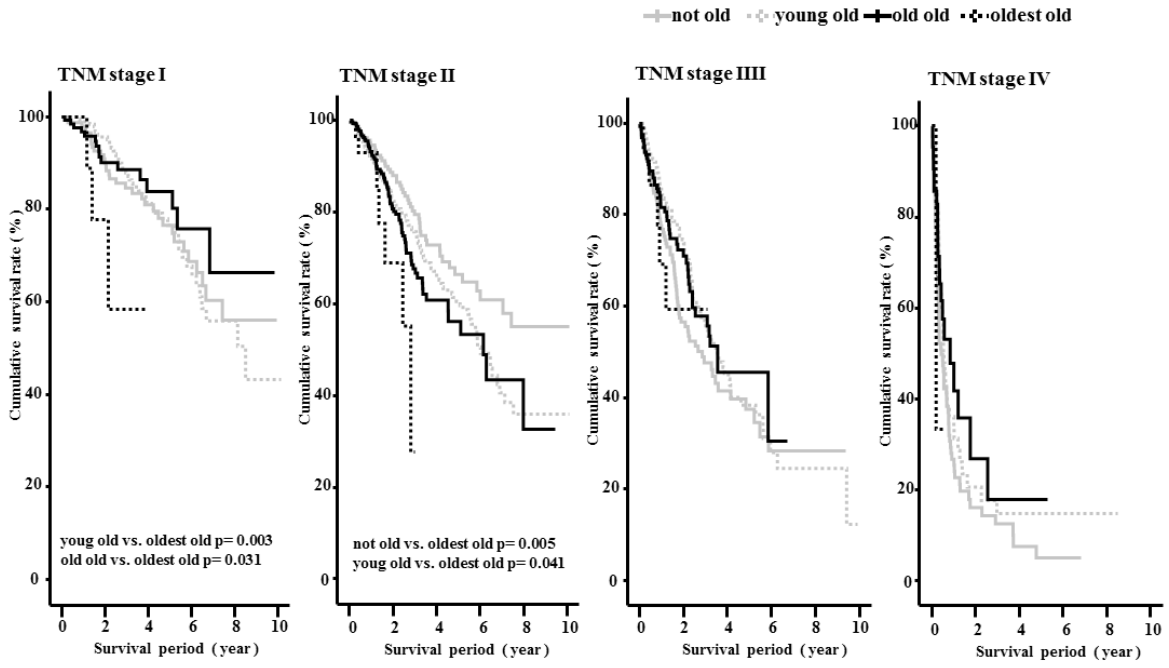

Figure 1: Cumulative survival rate for hepatocellular carcinoma (HCC) according to Tumor Node Metastasis (TNM) stage.

Discussion

The number of elderly patients with HCC has increased over the past few years in Japan, and recent studies have reported the characteristics and prognosis of HCC in this population [15,16,27,28]. Our present study added information to the existing literature and identified a number of independent factors associated with HCC in the elderly. According to the government of Japan, an elderly person is an individual over 65 years, which is the cut-off age we used in this study.

In this study, however, the most interesting findings were made in oldest-old patients (aged 85 years or older). We found that female gender, Child–Pugh grade A, and non-hepatitis virus infection were more frequent in oldest-old HCC patients than in younger patients, and that BMI and ALT were lower in oldest-old HCC patients than in younger patients. These findings suggest that elderly patients had better hepatic reserve capacity than younger patients, which is in agreement with previous reports [24,25,28,29]. However, the survival outcome of oldest-old patients was worse than that of younger patients with early-stage HCC. In other words, patients aged 85 years or older may have poorer prognosis than younger patients with early-stage HCC. Suda et al. [28] analyzed 740 patients with HCC, including 38 patients treated with supportive care alone. They stressed that aging was an adverse factor affecting overall survival of patients with HCC, but when the survival benefit was evaluated on the basis of percent survival to life expectancy, the therapeutic approach should not be restricted due to patient age [31]. Interestingly, the percentage of early-stage HCC patients treated with supportive care alone was significantly higher in the oldest-old group than in the other groups. Hori et al. [28] reported that advanced age was a negative prognostic factor in patients with HCC due to the tendency for frequent use of conservative treatment rather than RFA or surgical treatment. The prognosis of elderly patients may be worse than younger patients, especially in patients with preserved hepatic reserve capacity or earlier stage of HCC, because in such patients RFA or surgical treatment is as effective as in younger patients.

When discussing the treatment and survival outcomes of elderly patients with HCC, clinicians should be aware of the following limitations. There may be an unintentional selection bias, because we tend to select elderly patients with a good performance status, which may favor comparable outcomes to those of younger patients. In fact, in the current study, there

was difference in the population of patients treated with surgical treatment or RFA between the oldest old group and younger groups. Several investigators showed that elderly patients with HCC had a worse survival outcome compared with younger patients due to the tendency for them to receive less aggressive and non-curative treatment [32].

This study is associated with some other limitations. First, it was a retrospective, multicenter study. Therefore, the possibility of unintentional selection bias in selection of patients could not be fully excluded. Second, the therapeutic effects of the second and third line of treatment for HCC were not evaluated as prognostic factors in this patient population.

In conclusion, oldest-old patients had milder underlying liver damage. However, the survival outcome of oldest-old patients was worse than that of younger patients in TNM stage I or II. Early-stage HCC patients aged 85 years and older have poorer prognosis than their younger counterparts.

Acknowledgment

We were presented this study at The American Association for the Study of Liver Diseases (AASLD) The Liver Meeting 2014 and The 6th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2015). Author and corresponding author are employed in Hideaki Masuzaki of the Nagasaki University Hospital.

Data Availability

The clinical data used to support the findings of this study are restricted by the Ethics Committee of Medical Research, Nagasaki University Hospital in order to protect patient privacy. Data are available from corresponding author for researchers who meet the criteria for access to confidential data.

Conflict of Interest

The following people have nothing to disclose: Takehiro Matsumoto, Naota Taura, Tatsuki Ichikawa, Hisamitsu Miyaaki, Eisuke Ozawa, Masaya Shigeno, Yuji Kato, Takashi Goto, Noboru Kinoshita, Nobuyoshi Fukushima, Kazuo Ohba, Hiroshi Yatsuhashi, and Kazuhiko Nakao.

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