

Hepatocellular Carcinoma in the Elderly: Clinical Characteristics, Treatment, Survival Analysis in Korean Patients Older than 70 Years

Yun Jung Kim, Byoung Kuk Jang,
Eun Soo Kim, Woo Jin Chung,
Kyung Sik Park, Kwang Bum Cho,
and Jae Seok Hwang

Department of Internal Medicine, Keimyung
University School of Medicine, Daegu, Korea

Received: 10 February 2012
Accepted: 23 July 2012

Address for Correspondence:
Byoung Kuk Jang, MD
Department of Internal Medicine and Institute of
Gastroenterology and Hepatology, Keimyung University School
of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 700-712, Korea
Tel: +82.53-250-7088, Fax: +82.53-250-7088
E-mail: jangha106@dsmc.or.kr

The prevalence of hepatocellular carcinoma (HCC) has increased in recent years. However, HCC remains poorly characterized in elderly patients, and comprehensive data are limited. This study aimed to investigate the clinical characteristics, prognostic features and survival outcome of elderly HCC patients. We retrospectively analyzed 992 HCC patients treated at Dongsan Hospital from January 2003 to December 2007. The patients were divided into two age groups: < 70 yr (n = 813) and ≥ 70 yr (n = 179). Elderly HCC patients, compared to younger patients, had significantly higher incidence of females (31.3% vs 18.9%, $P = 0.001$), hepatitis C-related disease (HCV antibody positivity 26.3% vs 9.2%, $P = 0.001$) and comorbid condition (53.6% vs 32.1%), but lower rates of hepatitis B-related disease (HBs antigen positivity 31.3% vs 69.4%, $P = 0.001$). There were no significant differences in underlying liver function, stage and survival outcomes. Factors significantly influencing the prognosis of HCC were Child-Pugh grade, number of HCC, level of alpha-fetoprotein, presence of metastasis. The survival outcome of older patients with HCC was not different from that of younger patients. There were no differences between groups in independent factors influencing the prognosis of HCC. Therefore, determining the optimal management strategy for elderly HCC patients is important to improve survival and long-term outcomes.

Key Words: Hepatocellular Carcinoma; Elderly; Survival; Prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is an important cause of cancer-related morbidity and mortality in endemic area of hepatitis B virus (HBV) infection including Korea. The prevalence of HCC in Korea has increased in recent years, with an increase in the mean age of patients. The high prevalence of HCC and prolonged life expectancy in the population has led to reconsideration of the treatment strategy in elderly patients, and it is expected that the frequency of treating elderly HCC patients will further increase in the future. However, HCC remains poorly characterized in elderly patients and comprehensive data regarding elderly patients with HCC are limited, even though abundant evidence exists on the significant variance in the prognosis of non-elderly patients with HCC (1). In addition, elderly HCC patients have not been included in many clinical trials to develop standard treatments and there have been only few studies investigating the benefits and risks of treating them (2, 3).

In the present study, we analyzed the clinical characteristics of HCC in elderly patients and compared the prognostic features and survival outcomes between older and younger HCC

patients.

MATERIALS AND METHODS

Patients and study design

We retrospectively analyzed 1,016 patients who were treated of HCC at Keimyung University Dongsan Hospital in Daegu, Korea, from January 2003 to December 2007. Patients who were diagnosed and treated at other institutions before referral to our center were excluded. The diagnosis of HCC was made based on the guidelines proposed by the Korea Liver Cancer Study Group (4). Using these criteria, a patient is diagnosed as HCC if who has one or more risk factors (hepatitis B or C virus infection, and/or cirrhosis) and one of the following: a serum alpha-fetoprotein (AFP) level of > 200 ng/mL and a positive result with at least one of the three typical imaging techniques (triple phase computerized tomography [CT], contrast enhanced dynamic magnetic resonance imaging [MRI] or hepatic angiography); or a serum AFP level of < 200 ng/mL and positive findings for typical HCC with dynamic CT or MRI is indicative of arterial enhancement followed by venous washout in the delayed portal/venous phase.

The patients were divided into two groups according to their age at the time of HCC diagnosis: the younger group (< 70 yr; n = 813) and the older group (\geq 70 yr; n = 179). We compared the clinical characteristics, prognostic features and survival outcomes between the two groups.

Methods

Data were collected to evaluate the clinical characteristics of the patients. Data recorded for each patient included sex, age, viral hepatitis B surface antigen (HBs Ag), viral hepatitis C antibody (HCV Ab), AFP values, size and number of tumors, Child-Pugh (C-P) grade, presence or absence of portal vein tumor thrombosis (PVTT), comorbid condition, performance status by Eastern Cooperative Oncology Group (ECOG) (5), initial therapy and survival. Level of AFP was measured at the time of the initial diagnosis of HCC. The AFP level was divided into two categories: < 400 ng/mL and > 400 ng/mL. The C-P scoring system (6) was used for evaluation of the functional status of the liver. Medical imaging was based on dynamic contrast CT. According to the maximal tumor diameter, HCCs were classified as tumor diameter < 3 cm or > 3 cm. HCCs were also divided into solitary and multiple tumors. The extent of HCC was assessed using the Tumor-Node-Metastasis (TNM) staging system (7) and the Barcelona Clinic Liver Cancer (BCLC) staging system (8). To evaluate the types of initial treatment, treatment modality was subdivided into six types: 1) transarterial chemoembolization (TACE); 2) local ablation therapy such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA); 3) local chemotherapy, such as hepatic arterial infusion therapy (HAIT) and concurrent chemoradiotherapy (CCRT); 4) surgical resection; 5) systemic chemotherapy and 6) palliative treatment. If the patient was untreated, the initial treatment modality was regarded as palliative therapy. Treatment related morbidity was defined as any complication within 30 days of treatment and treatment related mortality was defined as death from a complication within 30 days of treatment in this present study. Survival and mortality, including cause of death, were investigated by examination of the final medical record. A survival census was performed on 31 July 2011. Survival was defined as the interval between the date of HCC diagnosis and either the date of liver-related death or the last follow-up to July 31, 2011. We investigated the cause of death in both groups and separated patients with extrahepatic disease (cardiopulmonary diseases, malignancies in other organ, etc.) from patients with diseases related to the liver (cancer progression, hepatic failure, complication of liver cirrhosis like variceal bleeding and hepatorenal syndrome, etc.).

Statistical analyses

Data management and statistical analyses were performed with SPSS software version 18.0 (SPSS, Chicago, IL, USA). Means and

proportions were calculated for categorical variables. Categorical variables were compared between the two groups using the chi-square test. The Student's t-test was used for comparison of continuous variables, as appropriate. Prognostic indicators of survival were defined by uni- and multivariate analyses. Univariate analysis was performed to identify parameters predicting survival by computing the survival curves, according to the Kaplan-Meier method, and then comparing them using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard regression model, to evaluate the independent factors predictive of patients' survival. A *P* value < 0.05 was considered as statistically significant.

Ethics statement

This study protocol was approved by the institutional review board of Keimyung University Dongsan Hospital (IRB No.11-180). Informed consent was waived by the board.

RESULTS

Clinical characteristics of patients

Of the 1,016 patients reviewed, 24 patients who were firstly diagnosed and treated at other institutions were excluded. Of the 992 patients enrolled, 179 (18.0%) patients were aged 70 yr or older. The median age in this older group was 74.0 yr (range 70-91 yr) (Table 1), compared to 57.0 yr (range 30-69 yr) in the younger group. The percentage of female patients was higher in the older group than that in the younger group (31.3% vs 18.9%, *P* = 0.001). The percentage of patients with HCV infection, as determined by HCV Ab positivity, was also higher in the older group than that in the younger group (26.3% vs 9.2%, respectively; *P* = 0.001). The percentages of comorbid conditions were higher in the older group than those in the younger group (53.6% vs 32.1%, *P* = 0.001). In contrast, the percentage of patients with HBV infection, as evident by HBs Ag positivity, was lower in the older group than that in the younger group (31.3% vs 69.4%, *P* = 0.001). There were no significant differences between the two groups with regard to liver cirrhosis, C-P grade, serum AFP values, TNM stage, BCLC stage, size and number of tumors and presence of PVTT or metastasis, performance status.

Comparison of treatment modalities

Overall, approximately 83.7% of our investigated patients underwent not palliative treatment, regardless of age. There were significantly lower rates of treatment in the older group, compared to the younger group (73.7% vs 86%, *P* = 0.001). TACE accounted for the majority of treatments and were similarly performed in both groups (48.0% vs 53.8%, *P* = 0.193). The older group received exclusively palliative treatment in 26.3% of the cases, compared to only 14.0% in the younger group (*P* = 0.001). Only eight (4.5%) older patients underwent surgical resection,

compared to 12.5% in the younger group ($P = 0.001$). Local chemotherapy tended to be less performed in older group (2.8% vs 7.1%, $P = 0.020$) and local ablative therapy tended to be more performed in older group (17.3% vs 11.1%, $P = 0.024$).

Comparison of treatment-related mortality and complication between the two groups

There was no significant difference in the treatment mortality rates between older group (2.8%) and younger group (1.6%). There was also no significant difference in the treatment-related complications between the two groups. The most common complication in both groups was hepatic failure (2.6% for older group vs 2.8% for younger group). In the same respective order with respect to subject group, other treatment-related complications included gastrointestinal bleeding (1.1% vs 1.1%), liver abscess (1.7% vs 1.1%), rupture of HCC (1.1% vs 0.9%) and acute pancreatitis (0% vs 0.4%).

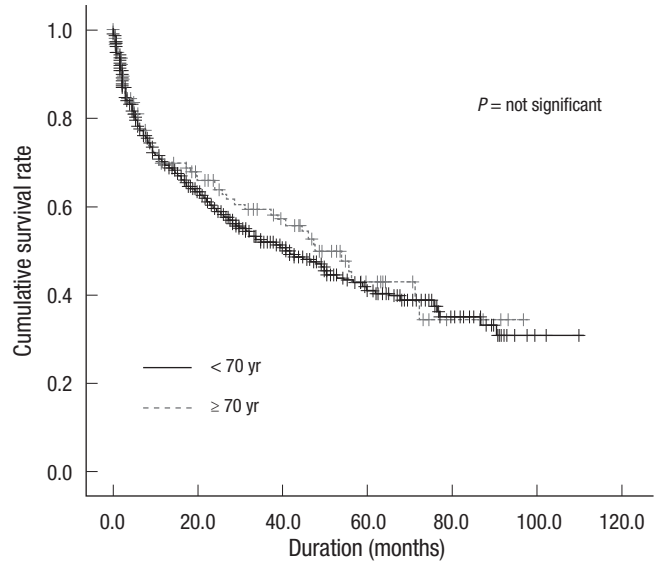


Fig. 1. Accumulated survival between old (≥ 70 yr) and young (< 70 yr) HCC patients. HCC, hepatocellular carcinoma.

Table 1. Characteristics of old and young HCC patients

Variables	Old (age ≥ 70 yr) (n = 179)	Young (age < 70 yr) (n = 813)	P value	Variables	Old (age ≥ 70 yr) (n = 179)	Young (age < 70 yr) (n = 813)	P value
Median age (yr, range)	74.0 (70-91)	57.0 (30-69)	< 0.001	BCLC stage			0.126
Male/Female, No (%)	123/56 (68.7/31.3)	659/154 (81.1/18.9)	< 0.001	Very early stage	6 (3.4)	60 (7.4)	
HCC cause, No (%)			< 0.001	Early stage	27 (15.1)	101 (12.4)	
HBV	56 (31.3)	564 (69.4)		Intermediate stage	13 (7.3)	44 (5.4)	
HCV	47 (26.3)	75 (9.2)		Advanced stage	119 (66.5)	518 (63.7)	
Alcohol	29 (16.2)	103 (12.7)		End stage	14 (7.8)	90 (11.1)	
Unknown	47 (26.3)	66 (8.1)		PVTT, No (%)			0.086
HBV/HCV	0 (0)	5 (0.6)		Positive	43 (24.0)	248 (30.5)	
Virus marker				Negative	136 (76.0)	565 (69.5)	
HBsAg(+)/HBsAg(-)	58/118	587/204	< 0.001	Metastasis			0.73
HBeAg(+)/HBeAg(-)	15/69	173/329	0.004	Positive	24 (13.4)	120 (14.8)	
HCVAb(+)/HCVAb(-)	49/110	77/557	< 0.001	Negative	155 (86.6)	693 (85.2)	
Liver cirrhosis, No (%)			0.198	Comorbid condition, No (%)			
Positive	132 (73.7)	637 (78.4)		Hypertension	50 (27.9)	124 (15.3)	< 0.001
Negative	47 (26.3)	176 (21.6)		Cardiovascular disease	17 (9.5)	16 (2.0)	< 0.001
C-P grade, No (%)			0.508	Respiratory disease	16 (8.9)	39 (4.8)	0.045
A	101 (56.4)	435 (53.5)		Diabetes mellitus	43 (24.0)	128 (15.7)	0.012
B, C	78 (43.6)	378 (46.5)		Cerebrovascular disease	10 (5.6)	16 (2.0)	0.016
AFP, No (%)			0.155	Chronic renal failure	3 (1.7)	12 (1.5)	0.742
< 400 ng/dL	125 (75.8)	519 (69.9)		Other malignancy	10 (5.6)	21 (2.6)	0.054
≥ 400 ng/dL	40 (24.2)	224 (30.1)		Performance status, No (%)			0.192
Diameter of HCC, No (%)			0.359	0	49 (27.4)	249 (30.6)	
≤ 3 cm	70 (39.1)	349 (42.9)		1	60 (33.5)	314 (38.6)	
> 3 cm	109 (60.9)	464 (57.1)		2	43 (24.0)	165 (20.3)	
Number of HCC, No (%)			0.056	3	21 (11.7)	71 (8.7)	
Solitary	87 (48.6)	461 (56.7)		4	6 (3.4)	14 (1.7)	
Non-solitary	92 (51.4)	352 (43.3)		Survival			0.469
TNM stage			0.646	1-yr	44.7	51.8	
I	20 (11.2)	93 (11.4)		3-yr	27.9	26.0	
II	61 (34.1)	323 (39.7)		5-yr	8.9	10.8	
III	60 (33.5)	239 (29.4)					
IVA	31 (17.3)	131 (16.1)					
IVB	7 (3.9)	27 (3.3)					

HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HCV Ab, hepatitis C antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; C-P grade, Child-Pugh grade; AFP, alpha-fetoprotein; TNM, Tumor-Node-Metastasis; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis.

Comparison of survival rates between the two groups

During the mean follow-up period of 21.6 ± 1.8 months (range, 0.3-96.8 months) in the older group and 23.2 ± 0.9 months (range, 0.3-109.8 months) in the younger group, a total of 138 (13.9%) patients were still alive on 30 June 2011.

No statistically significant difference was found in the survival outcomes between the two groups. The mean survival was 51.3 months (95% CI, 43.5-59.0) in the older group, compared with 52.8 months (95% CI, 48.7-56.8) in the younger group ($P = 0.469$) (Fig. 1). The overall survival rate at 1-, 3- and 5-yr, in the older and younger groups was 44.7%, 27.9%, and 8.9% vs 51.8%,

26.0%, and 10.8%, respectively. There was no significant difference in survival outcome between the two groups, when adjusted for stage of disease (Table 2). There was no significant difference in survival outcome according to age in terms of treatment (Fig. 2) and types of treatment (Table 3). However, there was a significant difference in survival outcome depending on treatment between the older and younger groups (Fig. 3).

Factors related to survival

Both univariate and multivariate analyses were employed to identify factors closely related to survival in the older group. In

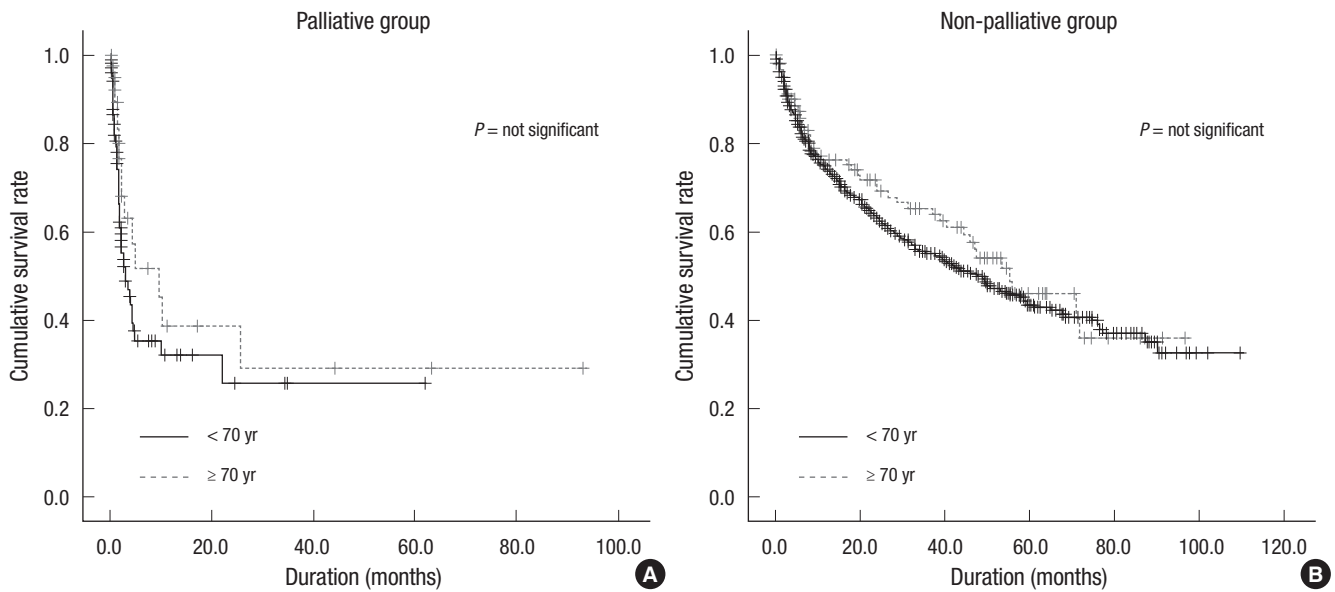


Fig. 2. Comparison of overall survival between old (≥ 70 yr) and young (< 70 yr) HCC patients according to age in terms of treatment (A) Palliative group. (B) Non-palliative group). HCC, hepatocellular carcinoma.

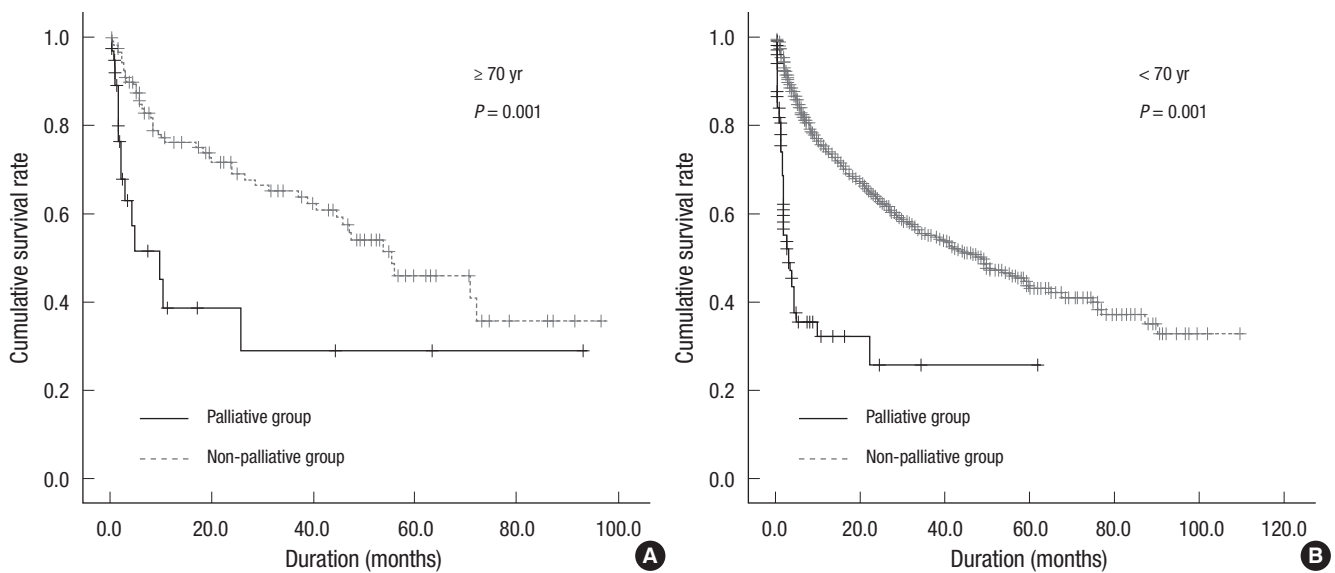


Fig. 3. Comparison of overall survival between old (≥ 70 yr) and young (< 70 yr) HCC patients depending on whether treatment (A, old [≥ 70 yr] group; B, young [< 70 yr] group). HCC, hepatocellular carcinoma.

the univariate Cox regression analysis, the variables associated with survival in the older group included C-P class, TNM stage, BCLC stage, level of AFP, diameter and number of tumors, presence of metastasis and performance of status (Table 4). In the multivariate analysis, C-P class, number of tumors, level of AFP

and presence of metastasis were independent factors associated with survival in older group (Table 5). In the multivariate analysis in younger group, C-P class ($P = 0.001$), BCLC stage ($P = 0.002$), level of AFP ($P < 0.001$), diameter and number of tumors ($P =$

Table 2. Comparison of overall survival in old and young HCC patients according to stage

Treatment	Survival, months, mean (95% CI)		P value
	Old (≥ 70 yr) (n = 179)	Young (< 70 yr) (n = 813)	
BCLC			
Very early stage	63.0 (45.8-80.3)	76.4 (68.9-83.8)	0.36
Early stage	72.5 (56.6-88.4)	68.2 (60.6-75.8)	0.72
Intermediate stage	32.3 (22.7-45.9)	67.1 (52.8-81.5)	0.26
Advanced stage	46.8 (37.5-56.2)	42.4 (37.6-47.3)	0.14
End stage	23.3 (7.6-39.1)	27.8 (19.8-35.8)	0.19
TNM			
I	70.9 (53.1-88.6)	68.6 (58.9-78.2)	0.55
II	55.7 (44.3-67.2)	57.7 (52.6-62.8)	0.97
III	44.4 (32.6-56.1)	43.5 (36.1-50.9)	0.16
IVA	13.5 (3.3-23.8)	22.7 (15.2-30.3)	0.27
IVB	35.7 (20.5-50.9)	28.1 (17.1-39.2)	0.58

HCC, hepatocellular carcinoma; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; TNM, Tumor-Node-Metastasis.

Table 3. Comparison of overall survival in old and young HCC patients according to types of treatment

Treatment	Survival, months, mean (95% CI)		P value
	Old (≥ 70 yr) (n = 179)	Young (< 70 yr) (n = 813)	
TACE	55.4 (44.0-66.8)	52.4 (46.9-57.8)	0.22
Local ablative therapy PEIT/RFA	53.2 (42.5-63.9)	66.0 (56.1-76.0)	0.50
Local chemotherapy HAIC/CCRT	47.9 (22.2-73.7)	13.2 (8.0-18.4)	0.079
Operation	42.5 (13.2-71.8)	68.4 (60.6-76.3)	0.139
Systemic chemotherapy	6.2 (5.3-7.2)	14.3 (5.6-23.0)	0.954
Palliative therapy	32.0 (12.8-51.2)	18.9 (11.2-26.6)	0.130

HCC, hepatocellular carcinoma; CI, confidence interval; TACE, transarterial chemoembolization; PEIT, percutaneous ethanol injection treatment; RFA, radiofrequency ablation; HAIC, hepatic arterial infusion chemotherapy; CCRT, concurrent chemoradiotherapy.

Table 5. Prognostic significance of their survival in patients with HCC according to multivariate analysis using Cox proportional hazards regression with older HCC patients

Variables	Death, hazard ratio (95% CI)	P value
C-P grade*		
B vs A	0.89 (0.49-1.61)	0.71
C vs A	3.72 (1.55-8.91)	0.003
Diameter of HCC		
> 3 cm vs ≤ 3 cm	1.61 (0.93-2.81)	0.09
Number of HCC*		
Non-solitary vs solitary	1.77 (1.02-3.07)	0.04
AFP*		
≥ 400 vs < 400	2.28 (1.26-4.10)	0.006
Metastasis*		
Positive vs negative	0.42 (0.17-0.99)	0.047

*Significant variables in multivariate analysis. HCC, hepatocellular carcinoma; CI, confidence interval; C-P grade, Child-Pugh grade; AFP, alpha-fetoprotein.

Table 4. Univariate Cox regression analysis of variables associated with survival in old HCC patients

Variables	No. of patients	Survival months, mean	1-/3-/5-yr survival, %	P value
Overall	179	51.3 (43.5-59.0)	44.7/27.9/8.9	
Sex				
Male	123	49.7 (40.9-58.4)	44.7/26.8/9.7	0.969
Female	56	53.0 (39.4-66.6)	44.6/30.4/7.1	
Etiology				
HBV	56	59.5 (46.1-72.9)	48.2/23.2/7.1	0.489
HCV	47	49.4 (35.2-63.6)	40.4/31.9/10.6	
Alcohol	29	46.4 (31.6-61.1)	44.8/20.7/6.9	
Unknown	47	45.0 (32.2-57.8)	44.7/34.0/10.6	
Liver cirrhosis				
Positive	132	50.3 (40.6-59.9)	40.9/22.0/8.3	0.602
Negative	47	53.7 (41.3-66.0)	55.3/44.7/10.6	
C-P grade				
A	101	52.7 (43.6-61.9)	51.5/30.7/10.9	< 0.001
B	64	52.4 (38.9-65.9)	42.2/28.1/7.8	
C	14	21.2 (6.5-35.9)	0	
AFP				
< 400 ng/dL	125	56.1 (47.5-64.8)	55.2/34.4/10.4	< 0.001
≥ 400 ng/dL	40	27.4 (14.4-40.4)	17.5/12.5/7.5	
Diameter of HCC				
≤ 3 cm	70	60.1 (49.3-71.0)	65.7/41.4/12.9	0.010
> 3 cm	109	43.6 (33.5-53.7)	31.2/19.3/6.4	
Number of HCC				
Solitary	87	62.4 (51.9-72.9)	49.4/34.5/13.8	0.002
Non-solitary	92	39.3 (29.3-49.4)	40.2/21.7/4.3	
TNM stage				
I	20	70.9 (53.1-88.6)	80/55/15	< 0.001
II	61	55.7 (44.3-67.2)	54.1/34.4/16.4	
III	60	44.4 (32.6-56.1)	48.3/26.7/5	
IVA	31	13.5 (3.3-23.8)	3.2/0/0	
IVB	7	35.7 (20.5-50.9)	14.3/0/0	
IVC	0	0	0	
BCLC stage				
Very early stage	6	63.0 (45.8-80.3)	66.7/66.7/50	< 0.001
Early stage	27	72.5 (56.6-88.4)	66.7/48.1/14.8	
Intermediate stage	13	34.3 (22.7-45.9)	61.5/46.2/0	
Advanced stage	119	46.8 (37.5-56.2)	39.5/23.5/7.6	
End stage	14	23.3 (7.6-39.1)	0	
PVTT				
Positive	43	31.3 (18.5-44.1)	13.9/9.3/4.7	0.071
Negative	136	53.4 (45.1-61.7)	54.4/33.8/10.3	
Metastasis				
Positive	24	17.1 (5.6-28.7)	33.3/0/0	0.002
Negative	155	53.4 (45.5-61.4)	50.9/31.6/10.3	
Performance status				
0	49	68.2 (55.8-80.5)	67.3/44.9/14.3	0.002
1	60	46.8 (36.3-57.3)	56.7/38.3/10	
2	43	31.7 (20.2-43.3)	20.9/6.9/2.3	
3	21	32.6 (12.1-53.0)	9.5/4.8/4.8	
4	6	22.2 (0-45.8)	33.3/33.3/16.7	
Comorbidity				
Positive	96	55.8 (45.6-66.0)	51.0/35.4/8.3	0.141
Negative	83	44.5 (33.3-55.7)	37.3/19.3/9.6	

HCC, hepatocellular carcinoma; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; C-P grade, Child-Pugh grade; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombosis.

0.013), presence of metastasis ($P = 0.004$) and PVTT ($P < 0.001$) were significantly associated with survival.

Causes of death between the two groups

We investigated the cause of death in both groups and separated patients with not liver related mortality (cardiopulmonary diseases, malignancies in other organs, etc.) from patients with liver related mortality (cancer progression, hepatic failure, complication of liver cirrhosis like variceal bleeding and hepatorenal syndrome, etc.). Non-liver related mortality was higher in elderly patients than that in the younger patients (20.3% vs 9.6%, $P = 0.018$).

DISCUSSION

There is a worldwide trend toward increased age in patients diagnosed with HCC (9, 10). The concept of "elderly" has become more difficult to define. The World Health Organization has not determined a standard age for the definition of an elderly population, and has recently stated that persons aged over 60 yr could be considered as an aged population (11). However, this criterion cannot be applied to all societies. Aging of the population has progressed more rapidly in South Korea than in any other country. According to a report of Statistics Korea in 2010, the country has already become an aging society as the rate of population aged over 70 yr was 8.2% and the average life expectancy has reached about 80.55 yr. Therefore, we used the cut-off value of 70 yr to divide the patients into the older and younger groups to clarify the characteristics of HCC in older patients. We believe that this allows for more reasonable and meaningful comparison with other previous studies (12-14).

The present study has clarified the clinical features of older HCC patients compared with younger HCC patients. Older patients showed lower rates of HBV-related disease and higher incidence of HCV-related disease and female gender, compared to those of younger patients. The incidence of hepatitis-associated etiology and the peak age at disease onset vary according to geographic barriers (15). In the present study, we found age-related difference in the HBs Ag carrier rate, with significant lower incidence in the elderly group. This finding is compatible with results from several previous studies (12, 16). In East Asia, including Korea, patients with HBV-related HCC, predominantly transmitted via perinatal infection, are diagnosed at a younger age than Western patients with HCV-related HCC (17). This could suggest that the mechanisms for carcinogenesis might be different, depending on the etiology and age distribution at HCC diagnosis (15). HBV-related HCC is more aggressive than HCV-related HCC (18), whereas HCV-related HCC may cause gradual progression from cirrhosis over the course of two to three decades (19). Thus, HCV-related HCC and HBV-related HCC differ not only in origin, but also in the clinical course of disease

progression (20). Establishing a specific strategy for the treatment of elderly patients with HCC is more useful than the strategy usually followed in younger patients.

The present study found no significant difference in the overall survival between older and younger HCC patients. In addition, there was no significant difference in the survival outcome according to age in terms of treatment, only a significant difference of survival outcome depending on whether treatment both two groups. Several previous reports support our results. One study (1) investigated the optimal treatment in elderly patients with HCC and reported that advanced stage of HCC, but not advanced age, influenced the survival rate in elderly patients. A Spanish study (21) reported that advanced age seemed to be a prognostic factor of poor survival of HCC, but was not significant when analyzed by treatment subgroups ($P = 0.344$). In other words, patient age was not an independent factor related to survival. Our data echo this view. Furthermore, patients of the same age can show individual differences reflecting the degree of physical aging. Therefore, elderly HCC patients should be classified into patients fitting the standard treatment (i.e., those who can benefit from treatment) and frail patients fitting the modified treatment (i.e., those who are expected to suffer from either severe complications or side effects following the standard treatments), after assessing their functional age through comprehensive geriatric assessment (CGA). CGA has been widely used to evaluate the actual functional age of elderly patients. CGA assesses a subject's condition with various items, including functional status, comorbid medical condition, cognition, psychological state and nutritional status. In studies using CGA, the survival rate of elderly cancer patients with functional impairment was lower, and those with associated disease recorded increased mortality rates (22-24). However, in the present study, we did not collect sufficient data required to evaluate CGA. Further studies are needed to compare the clinical outcome for management of HCC according to functional age evaluated by CGA.

Regarding the initial treatment, the older group received exclusively palliative treatment in 26.3% of the cases, compared to only 14.0% in the younger group ($P = 0.001$). In addition, only eight (4.5%) elderly patients underwent surgical resection, compared to 12.5% in the younger group ($P = 0.001$). This suggests that the older group received less intensive/invasive types of treatment although there were no differences between groups in independent factors influencing the prognosis of HCC. It could be interpreted that many elderly patients did not meet the criteria for invasive treatment due to other associated conditions and/or they might be given up active treatment due to social convention or cultural background specific for advanced age (1, 13). Presently, however, elderly patients did not show different survival rates compared to the younger patients. In multivariate analysis, C-P class, number of HCC, and presence of metastasis

are significant prognostic factor like those of younger patients. These results mean that even though elderly patients have more comorbid condition than younger patients, prognosis is only depend on baseline liver function, tumor factor, and whether treatment or not. Another study (25) also reported that elderly patients undergoing treatment did not show different survival rate compared to younger patients, and survival rate depended solely on whether treatment was initiated.

This present study included a relatively large number of HCC patients and a long follow-up period. However, there were also some limitations. First, a selection bias might be present because data was collected from a single center. Second, we used a retrospective design. Therefore, many patients were lost follow up and we could not collect enough data to evaluate exact functional age of elderly patients. Also we could not determine whether comorbid conditions of elderly patients had influence on their treatment decision or not. Third, we analyzed the treatment results based on initial treatment because most patients with HCC were treated various treatment modalities.

In conclusion, the survival outcome of elderly patients with HCC is not different from that of younger patients. In addition, there are not differences between the two groups in independent factors influencing the prognosis of HCC, such as underlying liver function and tumor stage. Advanced age by itself does not have an adverse effect on survival. Therefore, evaluation of basal liver function and HCC itself as well as general status evaluation for older patients by CGA is necessary to determine the optimal management strategy for elderly HCC patients to improve survival and long-term outcomes.

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