Survival Analysis of Hepatocellular Carcinoma: A Comparison Between Young Patients and Aged Patients

Xin-Sen Xu, Wei Chen, Run-Chen Miao, Yan-Yan Zhou, Zhi-Xin Wang, Ling-Qiang Zhang, Kai Qu, Qing Pang, Rui-Tao Wang, Chang Liu

Department of Hepatobiliary Surgery, The First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an, Shannxi 710061, China

Abstract

Background: To compare the clinicopathological features and prognosis between younger and aged patients with hepatocellular carcinoma (HCC).

Methods: We analyzed the outcome of 451 HCC patients underwent liver resection, transcatheter arterial chemoembolization and radiofrequency ablation, respectively. Then risk factors for aged and younger patients' survival were evaluated by multivariate analysis, respectively.

Results: The patients who were older than 55 years old were defined as the older group. The overall survival for aged patients was significantly worse than those younger patients. The younger patients had similar liver functional reserve but more aggressive tumor factors than aged patients. Cox regression analysis showed that the elevated levels of aspartate aminotransferase (AST) (Wald $\chi^2 = 3.963$, $P = 0.047$, hazard ratio [HR] =1.453, 95% confidence interval [CI]: 1.006–2.098), lower albumin (Wald $\chi^2 = 12.213$, $P < 0.001$, $HR = 1.982$, 95% CI: 1.351–2.910), tumor size (Wald $\chi^2 = 8.179$, $P = 0.004$, $HR = 1.841$, 95% CI: 1.212–2.797), and higher alpha-fetoprotein level (Wald $\chi^2 = 4.044$, $P = 0.044$, $HR = 1.465$, 95% CI: 1.010–2.126) were independent prognostic factors for aged patients, while only elevated levels of AST (Wald $\chi^2 = 14.491$, $P < 0.001$, $HR = 2.285$, 95% CI: 1.493–3.496) and tumor size (Wald $\chi^2 = 21.662$, $P < 0.001$, $HR = 2.928$, 95% CI: 1.863–4.604) were independent prognostic factors for younger patients.

Conclusions: Age is a risk factor to determine the prognosis of patients with HCC. Aged patients who have good liver functional reserve are still encouraged to receive curative therapy.

Key words: Age; Hepatocellular Carcinoma; Multivariate Analysis; Prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide, with the incidence rising both in Orient and Occident.[1,2] Despite implementation of potentially curative treatments such as liver resection, radiofrequency ablation (RFA), and transcatheter hepatic arterial chemoembolization (TACE), the prognosis is yet generally poor, resulting in 500,000 deaths per year.[3]

Liver resection remains the gold standard for resectable HCC that develops in the setting of normal liver parenchyma. However, most HCC patients have diseased liver and resection is fraught with potential complications.[4] Luckily, the dual blood supply of liver that nontumor parenchyma receives nutrient predominantly from portal vein, while the tumor part mostly by the hepatic artery, has allowed hepatic artery-based therapies such as the TACE to develop over the past 30 years.[5] In addition, RFA is also a curative option for early-stage HCC patients with lesions measuring <3 cm while for larger or paucifocal tumors, ablation might be performed in combination with embolization.[6]

Common sense have persuaded people that younger cancer patients tend to have better long-term outcomes, probably due to the better health conditions and stronger tolerance to curative treatment. However, some studies suggested that younger patients tend to present with advanced stage tumors at the time of diagnosis, thereby indicating a relative poorer prognosis.[7] Thus, the exact prognostic role of aging on HCC patients is yet not very clear.[8] Accordingly, our study performed Kaplan-Meier method and multivariate analysis, attempting to evaluate the exact prognostic role of aging on HCC patients. In addition, we also explored the differences of liver conditions and tumor characteristics between the aged patients and younger patients, aiming to investigate the specific factors affecting the long-term prognosis between different-age patients.

Address for correspondence: Dr. Chang Liu,
Department of Hepatobiliary Surgery, The First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an, Shannxi 710061, China
E-Mail: liuchangdoctor@163.com

METHODS

Patient selection

Prospectively collected data in our unit (First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, China) were reviewed retrospectively. There were altogether 451 HCC patients enrolled in this study, among which, 172 patients underwent liver resection, 191 patients underwent TACE, and 88 patients underwent RFA, with complete follow-up during the 10-year period from April 2002 to August 2012. For this study, we included those patients who met all the following criteria: (1) Patients were diagnosed of only HCC, but with no concomitant intrahepatic cholangiocarcinoma, or any other malignancies, to eliminate the confounding effects from disease etiology; (2) patients had serum liver enzymes (alkaline phosphatase [ALP] and gamma-glutamyltransferase [GGT]) and alpha-fetoprotein (AFP) measured simultaneously at study entry, making the baseline analyses comparable; (3) liver resection, TACE, and radiofrequency were firstly performed on these patients, respectively, without any other pre-treatment of HCC; and (4) patients had a minimum follow-up time of 1 year from the study entry point.

Data collection

Patient baseline and clinical data, including age, gender, liver enzymes such as ALP and GGT, serum AFP, hepatitis B virus (HBV) infection, HBV-DNA level, hepatitis C virus (HCV) infection, pretreatment imaging data (tumor size, number, and invasion), and therapy procedure records (liver surgery, TACE, and RFA) were recorded. Other synthetic liver function was also assessed, such as total bilirubin (Tbil), albumin (ALB), and INR, to evaluate the child classification of every patient. Our study complied with the standards of the Declaration of Helsinki, and approval for conducting the study was obtained from the institutional review board.

Liver resection, transcatheter arterial chemoembolization, and radiofrequency ablation

The liver resection techniques principally involved were either anatomical or nonanatomical according to the patients' preoperative liver function and tumor anatomical status. TACE patients underwent a distal super-selective catheterization of the hepatic arteries using a coaxial technique and microcatheters. Then chemolipiodolization was performed using epirubicin 50 mg, and mitomycin 8 mg mixed with 5 ml of lipiodol. As to RFA, it was performed under real-time ultrasound guidance and a needle electrode with a 15-Ga insulated cannula with 10 hook-shaped expandable electrode tines with a diameter of 3.5 cm at expansion. The treatment strategy was carried out in accordance with the American Association for the Study of Liver Diseases practice guideline. Patients who have a single lesion can be offered surgical resection if they are noncirrhotic or have cirrhosis but still have a well-preserved liver function. RFA is safe and effective therapy for patients with early stage HCC, who cannot undergo resection.

TACE is recommended for nonsurgical patients with large/multifocal HCC, who do not have vascular invasion or extrahepatic spread. After treatment, the macroscopic features of the tumor, including size, number of tumors, portal vein invasion, and hepatic vein invasion, were recorded if possible. The following management included symptomatic therapy, if any surgical complications occurred, such as bleeding, infection, or hypoalbuminemia.

Follow-up

After liver resection, TACE or RFA, patients were followed every 3 months in the first year, every 4 months in the second year and every 6 months thereafter. All patients were followed up until their last visit in our hospital or death. Imaging with computed tomography or magnetic resonance imaging was obtained for each patient on every follow-up visit, along with liver function analysis and serum AFP level. Tumor recurrence was diagnosed based on the combined findings of these clinical examinations. Patients who developed recurrence were treated with repeat TACE or further symptomatic therapy.

Statistical analysis

Continuous data were expressed as median value and range, and discrete variables as absolute and relative frequencies. To compare continuous variables, we applied the t test and the one-way ANOVA, whereas discrete variables were compared using the Pearson χ^2 test and Fisher's exact test, as appropriate. Patient survival was assessed according to the Kaplan–Meier method and compared by the log-rank test. After comparing the demographic data between these two groups, we performed age-stratified survival analysis. Multivariate Cox proportional hazard regression was used to obtain hazard ratios and 95% confidence intervals associated with overall survival (OS). The final models were determined by placing all variables with $P < 0.05$ from the univariate analysis into multivariate Cox regression model and using a forward stepwise variable selection process. Statistical analysis was performed using the SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Clinical demographics and follow-up data

The main demographic, clinical, and follow-up data of the 451 study patients are reported in Table 1. Treatment of HCC included hepatic resection in 172 patients (38.1%), TACE in 191 patients (42.4%), and RFA in 88 (19.5%) patients, respectively. Three hundred and sixty-two patients (80.3%) were men and 89 (19.7%) were women. The mean age was 54.1 years (range: 22–82 years). Regarding the viral etiology of liver disease, 340 patients (75.4%) had chronic HBV infection, and 20 patients (4.4%) had chronic HCV infection. Mean follow-up time was 2.1 years (range: 0.1–10.0 years). Altogether, 282 (62.5%) patients died during follow-up. The 1-, 3-, and 5-year OS in this study were 74.1%, 54.4%, and 46.6%, for hepatic resection patients, 40.3%, 24.6%, 14.9% for TACE patients, and 69.3%, 48.1%,

32.9% for RFA patients, respectively [Figure 1a]. The 1-, 3-, and 5-year disease-free survival (DFS) in this study were 63.7%, 46.7%, and 45.1%, for hepatic resection patients, 35.8%, 24.1%, 14.9% for TACE patients, and 63.7%, 40.0%, 23.1% for RFA patients, respectively [Figure 1b]. The mean diameter of the HCC nodule was 6.93 cm, and the mean tumor number was 1.3. Serum AFP levels were within the normal range (20 ng/ml) in 139 patients (30.8%), mildly elevated (21–400 ng/ml) in 148 patients (32.8%), and markedly elevated (>400 ng/ml) in 164 patients (36.4%).

Survival of aged and younger patients with hepatocellular carcinoma stratified by age

After a median follow-up of 25.2 months, 282 (62.5%) patients died, and 169 (37.5%) patients were still alive for their last visit. Choosing the 55 years old to be the cut-off value of age, the patients were divided into two groups, with 205 (45.5%) patients in the aged group (age > 55 year) and 246 (54.5%) in the younger group (age ≤ 55 year). The OS for aged patients was significantly worse than those younger patients (Log rank χ^2 = 12.979, $P < 0.001$). As to the HCC patients underwent liver resection, Kaplan–Meier curve analysis showed that the OS rates at 1, 3, 5, years were 82.5%, 62.1%, 48.1% in younger patients, and 69.5%, 46.3%, 43.9%, respectively, in aged patients. Likely, with

respect to the HCC patients underwent TACE, the OS rates at 1, 3, 5, years were 53.1%, 33.8%, 19.4% in younger patients, and 32.4%, 13.3%, 9.7%, respectively, in aged patients. Regarding the patients underwent ablation, the OS rates at 1, 3, 5, years were 71.1%, 50.3%, 46.1% in younger patients, and 63.1%, 45.9%, 12.5%, respectively, in aged patients. In sum, the OS rates were better in younger patients with HCC than in the older patients ($P < 0.05$) [Figure 2a-2c]. With respect to the DFS, aged patients also showed poorer prognosis than those younger patients (Log rank χ^2 = 4.229, P = 0.04), as shown in Figure 2d-2f.

Comparison of liver conditions and tumor characteristics between younger and aged patients

In order to explore the underlying factors attributing to the varied prognosis of HCC patients with different age, we compared the features of liver conditions and tumor characteristics of the age-stratified patients. Results showed that although the average level of ALB was a little lower in older patients, there were no statistically significant differences based on P values. Liver conditions such as alanine transaminase (ALT), aspartate aminotransferase (AST), ALB, and Tbil were comparable between the two groups [Table 2]. Furthermore, tumor characteristics such as tumor size and tumor invasion were also comparable. Interestingly, although

Table 1: Patients baseline characteristics

Characteristics	Resection (n = 172)	TACE (n = 191)	Ablation (n = 88)	P
Age (years)	54 ± 11	54 ± 11	55 ± 11	0.47 (F = 0.749)*
Gender (male/female)	139/33	159/32	64/24	0.12 (χ^2 = 4.261)[†]
Child A/B/C	160/12/0	165/25/1	72/15/1	0.08 (χ^2 = 8.492)[†]
HBV (%)	121 (70.3)	148 (77.5)	71 (80.7)	0.13 (χ^2 = 4.137)[†]
HCV (%)	8 (4.7)	6 (3.1)	6 (6.8)	0.38 (χ^2 = 1.953)[†]
Tumor size (cm)	6.9 ± 4.1	7.8 ± 4.0	5.0 ± 3.1	<0.001 (F = 15.404)*
Tumor number	1.3	1.4	1.3	0.24 (F = 1.421)*
Invasion (yes/no)	54/118	95/96	6/82	<0.001 (χ^2 = 50.289)[†]
Follow-up (months)	34.7 ± 2.0	16.5 ± 1.4	25.7 ± 2.1	<0.001 (F = 29.831)*
Death (%)	87 (50.6)	147 (77.0)	48 (54.5)	<0.001 (χ^2 = 29.857)[†]

*Analysis of variance; [†]Chi-square test. HBV: Hepatitis B virus; HCV: Hepatitis C virus; TACE: Transcatheter arterial chemoembolization.
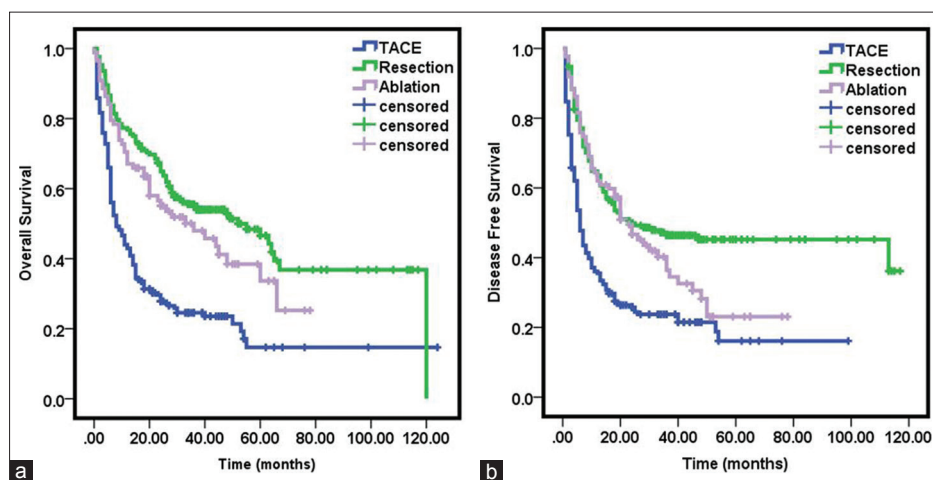

Figure 1: Kaplan–Meier curves of overall survival (a) and disease-free survival (b) for the whole 451 hepatocellular carcinoma patients enrolled in this study, who underwent liver resection, transcatheter arterial chemoembolization, or ablation.
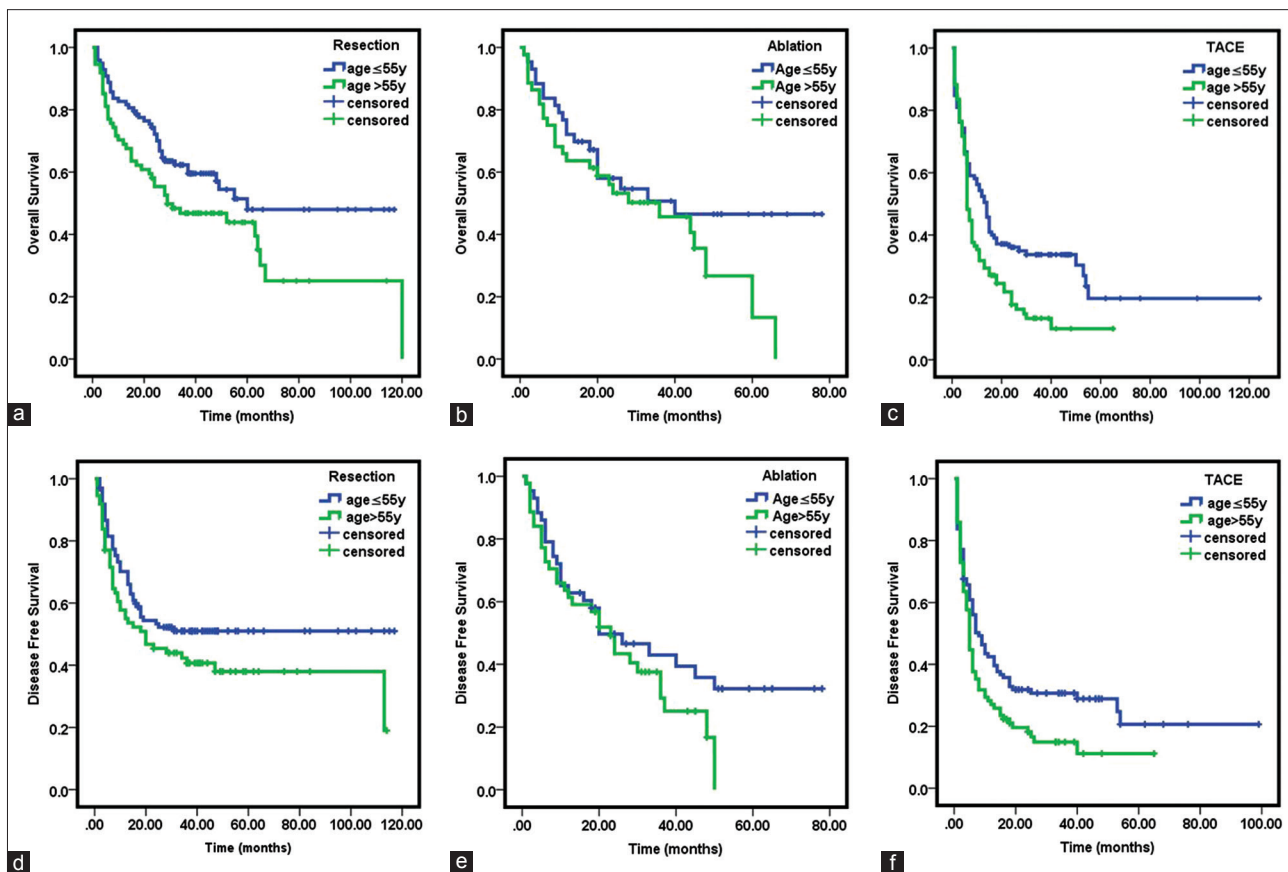
Figure 2: Impact of age on the overall survival and disease-free survival of hepatocellular carcinoma patients following surgical resection (a and d), ablation (b and e) and transcatheter arterial chemoembolization (c and f), respectively, as classified by the cut-off value of age.

Table 2: Comparison of liver conditions and tumor characteristics of HCC patients stratified by age

Characteristics	Aged (n = 205)	Young (n = 246)	P
Age, (years)	63 ± 6	46 ± 7	<0.001 (t = 29.027)*
Gender (male/female)	168/37	194/52	0.48 (χ^2 = 0.674)†
HBV (%)	134 (65.4)	206 (83.7)	<0.001 (χ^2 = 20.346)†
HCV (%)	16 (7.8)	4 (1.6)	0.002 (χ^2 = 10.073)†
Liver conditions			
Child A/B/C	176/28/1	221/24/1	0.43 (χ^2 = 1.695)†
ALT (U/L)	68 ± 10	73 ± 6	0.72 (t = −0.362)*
AST (U/L)	83 ± 10	82 ± 6	0.85 (t = 0.192)*
ALB (g/L)	32 ± 0.4	34 ± 0.4	0.68 (t = −0.408)*
Tbil (g/L)	27 ± 4	24 ± 1	0.35 (t = 0.929)*
Tumor characteristics			
Tumor size (cm)	6.8 ± 0.3	7.0 ± 0.3	0.46 (t = −0.732)*
Tumor number	1.4	1.3	0.04 (Z = −0.257)‡
Invasion (yes/no)	116/89	129/117	0.39 (χ^2 = 0.775)†
AFP level (ng/ml)	3628 ± 899	10147 ± 1698	0.001 (t = −3.202)*

*t-test; †Chi-square test; ‡Mann–Whitney test. HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALB: Albumin; Tbil: Total bilirubin; AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma.

the average tumor number in aged patients were a little more than younger patients, the aggressiveness marker like AFP was significantly higher in younger patients (10,147 vs.

3628 ng/ml, $t = −3.202$, $P < 0.001$) [Table 2]. With this respect, we have to speculate that regardless of the higher cancer aggressiveness of younger patients, the better health conditions and stronger tolerance to curative treatment might both contribute to the better overall prognosis in younger patients that age might be an independent factor in predicting the overall prognosis of HCC patients.

As age might be strongly correlated with B or C hepatitis, we also evaluated the differences of HBV or HCV between the younger and aged patients. As shown in Table 2, compared with the older patients, younger patients tend to have a higher percentage of HBV infection (83.7% vs. 65.4%, $\chi^2 = 20.346$, $P < 0.001$), which is consistent with the higher cancer aggressiveness of younger patients. However, with respect to the HCV, the infection rate was a little lower in the younger patients (1.6% vs. 7.8%, $\chi^2 = 10.073$, $P = 0.002$), probably due to the low infection rate of HCV in China.

Relationship between age, liver function, and tumor characteristics

When taking a deeper look at the relationship between age, liver function, and tumor characteristics, we found that age was associated with less aggressive tumor (lower AFP level). As shown in Figure 3, no obvious correlation was found between age and ALB level ($r = −0.078$, $P = 0.097$), or between age and Tbil level ($r = −0.012$, $P = 0.801$). However,
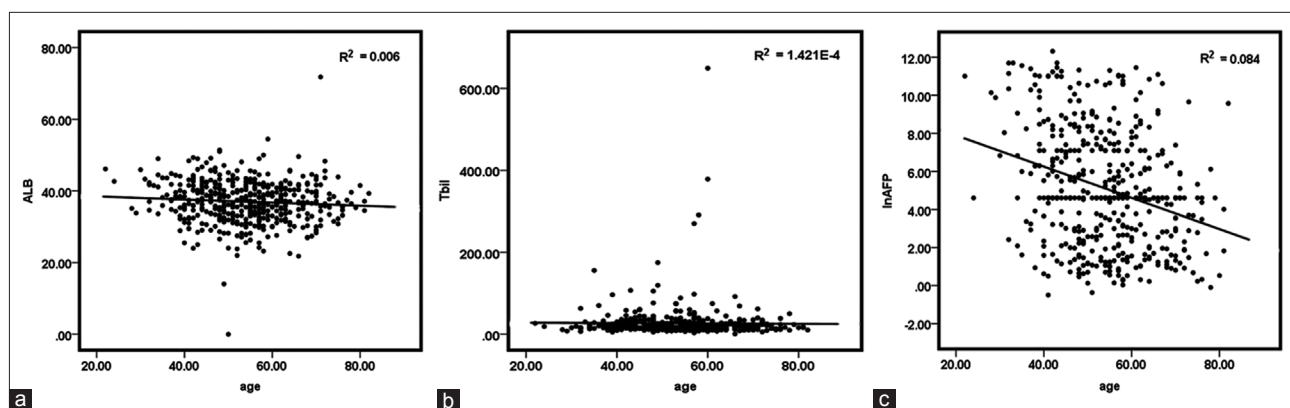
Figure 3: Relationship between age, liver function, and tumor characteristics. Correlation analysis was made between age and different factors, such as albumin (a), total bilirubin (b), and alpha-fetoprotein (c).

a negative correlation of age and AFP level ($r = −0.268$, $P < 0.001$) were demonstrated. As AFP to some extent represents the malignancy of the tumor, younger patients thus tend to present with the more aggressive tumors. On the other hand, although we failed to demonstrate the negative correlation between age and liver function, it is not difficult to comprehend that liver functional reserve, in other words, the tolerance to curative treatment like liver surgery, was not able to be completely evaluated by merely current liver conditions. Younger patients indeed have a better liver functional reserve and stronger tolerance to different treatments. Further evaluations are still needed to confirm this issue.

Factors associated with overall survival stratified by age

Our cox regression analyses for determining the risk factors associated with poor OS for aged and younger HCC patients are shown in Tables 3 and 4, respectively.

For aged patients, an AST level of greater than 40 U/L, a serum ALB level of 4 g/dl or less, an AFP level of greater than 200 ng/ml, and a tumor size of greater than 5 cm were the independent risk factors associated with mortality by cox regression analysis [Table 3].

For younger patients, an AST level of greater than 40 U/L and a tumor size of greater than 5 cm were associated with a poor prognosis [Table 4].

Both younger and aged patients shared similar risk factors in OS that both tumor factors and liver conditions were crucial in determining a prognosis irrespective of age.

Discussion

The present study analyzed the outcomes of different age groups of patients with HCC, who underwent liver resection, TACE or RFA. In our cohort, younger patients were superior to the aged ones, associated with a better OS.

The prognostic role of aging on patients with HCC has been widely discussed.[9,10] There are still some controversies regarding whether age influences the survival of HCC patients. Trevisani *et al.* reported that both the HCC patients

with age below 50 years and over 50 years shared the similar long-term prognosis.[11] Likely, Furuta *et al.* and Lam *et al.* found that there was no significant difference between the younger HCC patients and the older ones in terms of OS.[12,13] However, Kim *et al.* found that young HCC patients tend to have a poor prognosis owing to advanced tumor stage, irrespective of the well-preserved liver function and curative treatment.[14] With respect to our result, we found that the younger HCC patients shared the similar liver conditions with the older ones, and in terms of tumor characteristics, the AFP level in the younger group was significantly higher (10147 vs. 3628 ng/ml, $t = −3.202$, $P < 0.001$), indicating the more aggressiveness of the tumors in young patients. However, irrespective of the aggressiveness of the tumor state, younger patients still tend to have a better prognosis, probably due to the better health conditions and stronger tolerance to curative treatment.

The conflicting data with respect to the age influences on HCC prognosis might be due to the heterogeneity among these studies. Trevisani *et al.*[11] used 50 years as the cut-off age for young HCC, while Furuta *et al.*[12] Lam *et al.*[13] and Kim *et al.*[14] defined young patients as <45 years old, 40 years old and 30 years old, respectively. As to our study, we chose the 55 years old to be the cut-off age value because it was supposed to be the risk factors of HCC mortality in many studies.[15,16] We also included the HCC patients underwent liver resection, TACE and RFA in total, to eliminate the discrepancies of different curative therapies on the age impact of HCC.

In the present study, contradictory to the better prognosis, younger patients tend to present with more aggressive tumors. We speculate that the carcinogenesis might be different between these groups, which would eventually result in the varied prognosis.[17] Furthermore, the younger patients might also have a delayed diagnosis due to unawareness and lack of surveillance, which is also another reason.[18]

We performed cox regression analysis to clarify the true independent factors for the prognosis of the younger and aged patients with HCC, respectively. According to the results of the cox regression analysis in the present study,

Table 3: Cox regression analysis of factors associated with poor overall survival of aged HCC patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Male (1)	1.329 (0.836–2.113)	0.229		
Female (0)				
HBV				
Yes (1)	0.932 (0.663–1.310)	0.684		
No (0)				
HCV				
Yes (1)	0.563 (0.276–1.149)	0.115		
No (0)				
Cirrhosis				
Yes (1)	0.947 (0.671–1.335)	0.755		
No (0)				
ALT				
>40 U/L (1)	1.455 (1.047–2.021)	0.025	1.020 (0.687–1.516)	0.920
≤40 U/L (0)				
AST				
>40 U/L (1)	1.891 (1.325–2.700)	<0.001	1.453 (1.006–2.098)	0.047
≤40 U/L (0)				
Alb				
≤4 g/dl (1)	2.114 (1.449–3.082)	<0.001	1.982 (1.351–2.910)	<0.001
>4 g/dl (0)				
Tbil				
>20 µmol/L (1)	0.992 (0.713–1.380)	0.962		
≤20 µmol/L (0)				
AFP				
≥400 ng/ml (1)	1.710 (1.200–2.436)	0.003	1.465 (1.010–2.126)	0.044
<400 ng/ml (0)				
Size				
≥5 cm (1)	2.320 (1.553–3.464)	<0.001	1.841 (1.212–2.797)	0.004
<5 cm (0)				
Number				
>1 (1)	1.269 (0.889–1.811)	0.189		
=1 (0)				
Invasion				
Yes (1)	0.782 (0.561–1.089)	0.146		
No (0)				

HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALB: Albumin; Tbil: Total bilirubin; AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma; *CI*: Confidence interval; *HR*: Hazard ratio.

the risk factors associated with OS are similar between the two groups. For aged HCC patients, the higher AST level and lower ALB level (liver functional reserve), the higher AFP level, and larger tumor size (tumor characteristics) were the independent risk factors associated with OS. Similarly, for younger patients, the higher AST level (liver functional reserve) and larger tumor size (tumor characteristics) were also associated with a poor prognosis. Both younger and aged patients shared similar risk factors in OS that both tumor factors and liver conditions were crucial in determining a prognosis irrespective of age.

Nevertheless, in our cohort, the lower ALB level was only associated with the prognosis of older patients that it is not an independent risk factor of OS in the younger patients. It is plausible that younger patients usually have better health conditions and stronger tolerance to curative treatment, indicating the less importance of ALB level in determining the patient prognosis in young patients.[19] On the other hand, higher AFP level was only associated with the prognosis of older patients that it is not an independent risk factor of OS in the younger patients. Although the average level of AFP in young patients was significantly higher than the aged patients, indicating the more aggressiveness of the tumor, it is still not an independent risk factor for the young patients. We could only speculate that some other factors besides tumor characteristics would affect the serum levels of AFP, making it less accurate in predicting the prognosis of young patients with HCC.[20] Furthermore, younger patients were more likely to receive a more aggressive resection in spite of the advanced tumor stage and the more aggressiveness of the tumor, therefore, the effect of AFP level on prognosis is

Table 4: Cox regression analysis of factors associated with poor overall survival of young HCC patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Male (1)	1.060 (0.699–1.607)	0.784		
Female (0)				
HBV				
Yes (1)	1.584 (0.939–2.670)	0.084		
No (0)				
HCV				
Yes (1)	1.340 (0.426–4.218)	0.617		
No (0)				
Cirrhosis				
Yes (1)	1.416 (1.009–1.987)	0.044	1.382 (0.979–1.952)	0.051
No (0)				
ALT				
>40 U/L (1)	0.961 (0.682–1.355)	0.820		
≤40 U/L (0)				
AST				
>40 U/L (1)	2.616 (1.713–3.994)	<0.001	2.285 (1.493–3.496)	<0.001
≤40 U/L (0)				
Alb				
>4 g/dl (1)	1.663 (1.156–2.393)	0.006	1.370 (0.943–1.989)	0.113
≤4 g/dl (0)				
Tbil				
>20 μmol/L (1)	1.272 (0.903–1.792)	0.168		
≤20 μmol/L (0)				
AFP				
≥400 ng/ml (1)	1.623 (1.157–2.278)	0.005	1.164 (0.815–1.662)	0.504
<400 ng/ml (0)				
Size				
≥5 cm (1)	3.261 (2.080–5.115)	<0.001	2.928 (1.863–4.604)	<0.001
<5 cm (0)				
Number				
>1 (1)	1.576 (1.076–2.326)	0.022	1.375 (0.920–2.056)	0.159
=1 (0)				
Invasion				
Yes (1)	0.893 (0.636–1.253)	0.511		
No (0)				

HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALB: Albumin; Tbil: Total bilirubin; AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma; *CI*: Confidence interval; *HR*: Hazard ratio.

not so obvious if the patients could receive complete curative treatment owing to well-preserved liver function.[18]

In sum, we provide a comprehensive analysis of age-related clinicopathologic features and prognoses from a series of HCC patients underwent different therapies with an adequate follow-up period at a single medical center. In our cohort, the younger patients with HCC had more advanced tumor factors than did the older patients with HCC, but with similar liver function. If tumors could be detected early and if curative therapy is performed early, long-term survival can be expected in the younger patients owing to better liver functional reserve. With respect to those aged patients with HCC, who have a good liver functional reserve, they are still encouraged to receive curative treatment, which would probably imply a better long-time prognosis.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
3. Maluccio M, Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. CA Cancer J Clin 2012;62:394-9.
4. Thomas MB, Zhu AX. Hepatocellular carcinoma: The need for progress. J Clin Oncol 2005;23:2892-9.
5. Dufour JF, Bargellini I, De Maria N, De Simone P, Goulis I, Marinho RT. Intermediate hepatocellular carcinoma: Current treatments and future perspectives. Ann Oncol 2013;24 Suppl 2:ii24-9.
6. Yan K, Chen MH, Yang W, Wang YB, Gao W, Hao CY, *et al.* Radiofrequency ablation of hepatocellular carcinoma: Long-term outcome and prognostic factors. Eur J Radiol 2008;67:336-47.
7. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: A systematic review of 72 studies. Liver Int 2009;29:502-10.

8. Chen CH, Chang TT, Cheng KS, Su WW, Yang SS, Lin HH, *et al.* Do young hepatocellular carcinoma patients have worse prognosis? The paradox of age as a prognostic factor in the survival of hepatocellular carcinoma patients. Liver Int 2006;26:766-73.

9. Fan HL, Hsieh CB, Chang WC, Huang SH, Chan DC, Yu JC, *et al.* Advanced age is not a contraindication for liver resection in cases of large hepatocellular carcinoma. Eur J Surg Oncol 2014;40:214-9.

10. Faber W, Stockmann M, Schirmer C, Möllerarnd A, Denecke T, Bahra M, *et al.* Significant impact of patient age on outcome after liver resection for HCC in cirrhosis. Eur J Surg Oncol 2014;40:208-13.

11. Trevisani F, D'Intino PE, Grazi GL, Caraceni P, Gasbarrini A, Colantoni A, *et al.* Clinical and pathologic features of hepatocellular carcinoma in young and older Italian patients. Cancer 1996;77:2223-32.

12. Furuta T, Kanematsu T, Matsumata T, Shirabe K, Yamagata M, Utsunomiya T, *et al.* Clinicopathologic features of hepatocellular carcinoma in young patients. Cancer 1990;66:2395-8.

13. Lam CM, Chan AO, Ho P, Ng IO, Lo CM, Liu CL, *et al.* Different presentation of hepatitis B-related hepatocellular carcinoma in a cohort of 1863 young and old patients-Implications for screening. Aliment Pharmacol Ther 2004;19:771-7.

14. Kim JH, Choi MS, Lee H, Kim do Y, Lee JH, Koh KC, *et al.* Clinical features and prognosis of hepatocellular carcinoma in young patients from a hepatitis B-endemic area. J Gastroenterol Hepatol 2006;21:588-94.

15. Ikeda K, Arase Y, Saitoh S, Kobayashi M, Someya T, Hosaka T, *et al.* Prediction model of hepatocarcinogenesis for patients with hepatitis C virus-related cirrhosis. Validation with internal and external cohorts. J Hepatol 2006;44:1089-97.

16. Peng SY, Chen WJ, Lai PL, Jeng YM, Sheu JC, Hsu HC. High alpha-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: Significance of hepatitis virus infection, age, p53 and beta-catenin mutations. Int J Cancer 2004;112:44-50.

17. Namieno T, Kawata A, Sato N, Kondo Y, Uchino J. Age-related, different clinicopathologic features of hepatocellular carcinoma patients. Ann Surg 1995;221:308-14.

18. Su CW, Lei HJ, Chau GY, Hung HH, Wu JC, Hsia CY, *et al.* The effect of age on the long-term prognosis of patients with hepatocellular carcinoma after resection surgery: A propensity score matching analysis. Arch Surg 2012;147:137-44.

19. Fujishima T, Ishikawa T, Shiratori Y, Kanda M, Tateishi R, Akamatsu M, *et al.* Age-related comparison of the profiles of patients with hepatocellular carcinoma. Hepatogastroenterology 2006;53:913-8.

20. Gopal P, Yopp AC, Waljee AK, Chiang J, Nehra M, Kandunoori P, *et al*. Factors that affect accuracy of α-fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12:870-7.