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Original Article

Prognostic factors of hepatocellular carcinoma patients treated by transarterial chemoembolization

Jun Xiao[1], Guojian Li[3], Shuhan Lin[2], Ke He[1], Hao Lai[1], Xianwei Mo[1], Jiansi Chen[1], Yuan Lin[1]

[1]Department of Gastrointestinal Surgery, Tumor Hospital of Guangxi Medical University, Nanning 530021, Guangxi Autonomous Region, China; [2]Department of Hepatobiliary Surgery, The 8th Affiliated Hospital of Guangxi Medical University, Guigang 537120, Guangxi Autonomous Region, China; [3]Provincial Departments of Health, Nanning 530021, Guangxi Autonomous Region, China

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Abstract: We aim to investigate the clinical characteristics and prognostic factors of Hepatocellular Carcinoma (HCC) patients treated by transarterial chemoembolization (TACE) in Chinese cohort. A total of 2,493 HCC patients treated by TACE were included in this retrospective study. Patients were divided into the younger group (n=1,877) or the elderly group (n=616) based upon their ages (cut-off value of 60 y/o). Chi-square test or Wilcoxon rank-sum test was used to compare patients' characteristics. Univariate and multivariate analysis were used to determine prognostic factors. When compared with the younger group, the elderly group had lower male/female ratio and family liver disease history ratio, as well as advanced stage or Child-Pugh grade B patients. The median survival time was 8 months and 27 months for the younger and the elderly group, respectively. The 1-, 2-, and 3-year survival rates in the younger group and the elderly group were 31.82%, 12.5%, 6.53%, and 84.66%, 53.28%, 28.39%, respectively. Multivariate analysis showed that HBV infection, AFP value, TNM stage, Child-Pugh class, portal vein tumor thrombus (PVTT) and tumor number were independent prognostic factors for the younger patients; the elderly ones had similar independent prognostic factors except for HBV infection. The elderly group had lower male/female ratio and family history ratio, as well as advanced stage or Child-Pugh grade B patients. The elderly seems to have better prognosis than the younger ones, which is probably related to the fact that the elderly have lower tumor burden and better liver function.

Keywords: Clinical characteristics, hepatocellular carcinoma, prognostic factor, TACE

Introduction

The incidence of hepatocellular carcinoma (HCC) has rapidly increased over the past decade; HCC is the sixth most common cancer in the world [1]. This disease has very clear regional distribution pattern. Epidemiologic study showed that approximately 80% of HCC cases occurred in developing countries, with over half diagnosed in China alone [2]. Three significant etiological factors associated with HCC: which are chronic infection of hepatitis B virus (HBV) and hepatitis C virus (HCV), and chronic alcohol abuse [3]. HBV infection is the most common cause of Chinese HCC patients.

Surgical treatments such as resection and transplantation are the preferential treatment for HCC; however, because of its insidious nature, most of HCC patients are diagnosed at advanced stages. Clinically, only 10% to 20% of HCC patients could be treated by surgical operation [4]. Therefore, most patients are only suitable for palliative treatments, such as radiotherapy, systemic chemotherapy, immunotherapy, transarterial chemoembolization (TACE) and so on. Of these palliative treatments, TACE had demonstrated survival benefit for non-surgical HCC patients [5].

Age is one of the influencing prognosis factors for HCC [6-8]. Some research indicated that the elderly have poor prognosis after TACE treatment due to their have more comorbidities and shorter life expectancy [9, 10]. However, in our clinical practice, we noticed that the prognosis of younger HCC patients may be shorter than that of elderly ones. Under this situation, we

Table 1. Patient characteristics

	Younger (n=1,877)	Elderly (n=616)	Value	P
Age				
Mean ± SD	45.63±8.89	67.03±5.38	-	-
Median	47.00 (21-59)	66.00 (60-80)		
Gender				
Female	250 (13.32%)	109 (17.69%)	X^2=7.20	0.007
Male	1,627 (86.68%)	507 (82.31%)		
M-to-F ratio	6.51:1	4.65:1		
Family liver disease history				
Negative	1,426 (75.97%)	567 (92.05%)	X^2=279.01	<0.0001
Positive	451 (24.03%)	49 (7.95%)		
Presence of symptoms				
Negative	1,258 (67.02%)	400 (64.94%)	X^2=0.91	0.341
Positive	619 (32.98%)	216 (35.06%)		
Diagnosed by screening				
Negative	1,624 (85.99%)	549 (89.12%)	X^2=3.97	0.286
Positive	253 (14.01%)	67 (10.88%)		
TNM Stage				
I	114 (6.07%)	27 (4.38%)	X^2=238.74	<0.0001
II	250 (13.32%)	236 (38.31%)		
III	1,154 (61.48%)	337 (54.71%)		
IV	359 (19.13%)	16 (2.60%)		
Tumor number				
Multiple	545 (29.04%)	184 (29.87%)	X^2=0.16	0.693
Single	1,332 (70.96%)	432 (70.13%)		
HBV infection				
Negative	844 (44.97%)	267 (43.34%)	X^2=0.493	0.482
Positive	1,033 (55.03%)	349 (56.66%)		
HCV infection				
Negative	1,858 (98.99%)	610 (99.03%)	X^2=0.01	0.930
Positive	19 (1.01%)	6 (0.97%)		
Child-Pugh class				
A	334 (17.79%)	185 (30.03%)	X^2=42.14	<0.0001
B	1,543 (82.21%)	431 (69.97%)		
PVTT				
Negative	1,340 (71.39%)	420 (68.18%)	X^2=2.30	0.129
Positive	537 (28.61%)	196 (31.82%)		
AFP value (ng/ml)				
<20	694 (36.97%)	234 (37.99%)	X^2=0.668	0.716
20-400	544 (28.98%)	168 (27.27%)		
>400	639 (34.04%)	214 (34.74%)		

Abbreviations: M-to-F ratio=male-to-female ratio; FH=family history; TNM stage=tumor-nodal-metastasis stage; HBV=hepatitis B virus; HCV=hepatitis C virus; C-P class=Child-Pugh class; AFP=alpha-fetoprotein; PVTT=portal vein tumor thrombus.

performed this multicenter retrospective study to investigate the clinical characteristics and prognosis factors of the younger and elderly HCC patients who received transarterial chemoembolization.

Methods

Patient and cohort stratification

This retrospective study was conducted at 20 hospital crossed the Guangxi Autonomous Re-

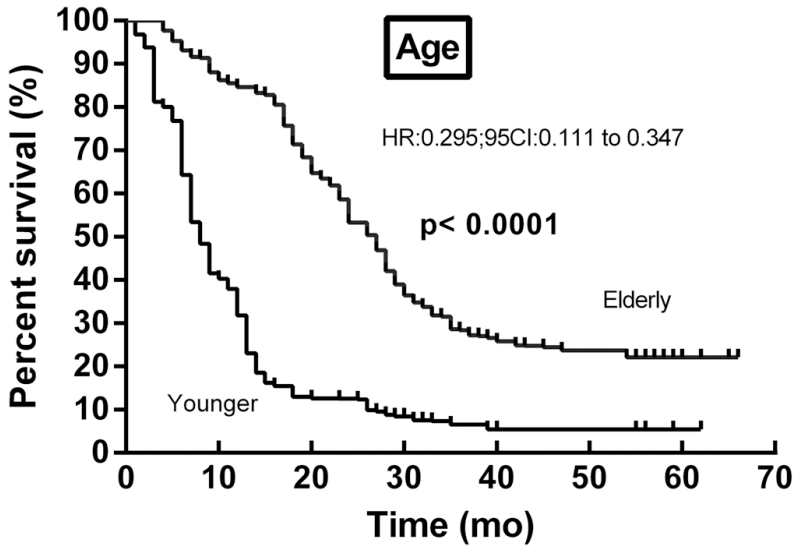

Figure 1. Overall survival rates of the younger (n=1,877) and the elderly patients (n=616) treated by TACE. The 1-, 2-, and 3-year survival rates in the younger group and the elderly group were 31.82%, 12.5%, 6.53%, and 84.66%, 53.28%, 28.39%, respectively. *P*-values were calculated by the log-rank test.

gion (GAR). The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki, and was approved by the ethical committee of the Tumor Hospital of the Guangxi Medical University. Informed consent was waived due to the retrospective nature of the study.

A total of 2,493 consecutive HCC patients were recruited form these hospital from January 2004 to December 2008, the inclusion criteria were: (1) initial treatment is TACE; (2) no extrahepatic metastasis existed; (3) Child-Pugh grade classification not more than C and (4) without serious complications such as cardiovascular disease. The follow up date of these patients was lasted to April 2013.

The patients were stratified by age and divided into two cohorts by age (<60 years and ≥60 years). All HCC patients were diagnosed by histopathological findings, arterial hypervascularization on contrast-enhanced Computed Tomography (CT) or magnetic resonance imaging (MRI) with a serum α-fetoprotein (AFP) value over 400 ng/mL [11, 12].

TACE procedure

All 20 hospitals followed the same TACE protocol. Briefly, Seldinger's method was used to insert a catheter through the femoral artery. Angiography of the celiac and superior mesenteric arteries was routinely performed to determine the tumor blood supply, distribution of hepatic arteries, and collateral circulation routes [13]. The tumor's primary artery was selected for catheter placement. Patients were given a standard drug regimen of emulsified Pirambicin (THP, 40-60 mg), cis-platinum (DDP, 20-60 mg) and lipiodol (5-40 mL) through the hepatic artery.

Follow-up and examination

CT scanning was performed 4 weeks after treatment, and every 2 months thereafter for the next 2 years. Liver function tests and serum AFP tests were performed at each follow-up time. Residual viable tumor tissue was considered present upon the first CT assessment at 4 weeks after treatment if enhancement areas were seen within the tumor at either the arterial or the portal venous phase. MRI was performed if CT results were unclear on whether residual viable tumor tissue was present.

Statistical analysis

Patient characteristics were summarized by mean ± SD, median and range of continuous variables, and percentages for categorical variables. Chi-square test or Wilcoxon rank sum test was used to compare patient characteristics between the two groups. Overall survival (OS) is defined as the interval between the date of HCC diagnosis and the date of death due to any cause. Kaplan-Meier method was used to estimate survival distribution of OS. Significant prognosis variables determined by a univariate analysis were subjected to a multivariate analysis using a Cox proportional hazard regression model.

P-values less than 0.05 were considered to be statistically significant (two-tailed). Statistical analyses were carried out by SPSS software package (version13.0; SPSS Inc., Chicago, IL, USA).

Table 2. Prognostic Factors Determined by the Univariate Analysis in the younger HCC Patients treated by TACE

Variables	No.	Survivals (%)			HR	*P* value
		1-yr	2-yr	3-yr		
Gender						
Female	250	32.40	14.40	8.80	reference	
Male	1,627	28.03	11.00	5.04	1.153 (1.036-1.335)	0.022
Family history						
Negative	1,426	31.98	12.97	7.01	reference	
Positive	451	29.93	11.97	5.99	0.982 (0.8811-1.088)	0.719
Smoking						
Negative	820	31.95	13.05	8.05	reference	
Positive	1,057	29.99	11.92	5.89	1.250 (1.190-1.426)	<0.0001
Drinking						
Negative	803	32.41	13.43	7.74	reference	
Positive	1,074	30.09	12.07	6.16	1.225 (1.162-1.393)	<0.0001
HBV infection						
Negative	844	27.84	7.43	1.25	reference	
Positive	1,033	34.26	15.30	9.68	0.602 (0.469-0.571)	<0.0001
HCV infection						
Negative	1,858	31.71	12.44	6.83	reference	
Positive	19	36.84	15.79	10.53	1.286 (0.899-1.425)	0.671
AFP value (ng/ml)						
<20	694	79.71	53.78	22.48	reference	
20-400	544	40.45	36.43	12.13	1.190 (1.068-1.325)	<0.0001
>400	639	20.28	7.01	1.03	2.448 (2.173-2.758)	<0.0001
TNM Stage						
I	114	98.41	81.60	70.87	reference	
II	250	76.93	57.21	28.41	1.077 (1.060-1.098)	<0.0001
III	1,154	27.14	11.57	5.73	1.133 (1.106-1.167)	<0.0001
IV	359	21.73	5.07	1.13	1.280 (1.229-1.341)	<0.0001
Child-Pugh class						
A	334	57.91	23.12	14.12	reference	
B	1,543	31.17	10.97	4.73	1.347 (1.240-1.539)	<0.0001
PVTT						
Negative	1,340	40.17	14.43	6.53	reference	
Positive	537	20.51	7.11	0	3.259 (3.200-4.561)	<0.0001
Tumor number						
Single	545	51.17	32.14	6.53	reference	
Multiple	1,332	26.94	6.47	0	2.285 (3.299-4.245)	<0.0001

Abbreviations: HBV=hepatitis B virus; HCV=hepatitis C virus; TNM stage=tumor-nodal-metastasis stage; AFP=alpha-fetoprotein; PVTT=portal vein tumor thrombus.

Results

Demographic data of recruited patients

A total of 2,493 HCC patients were recruited in this study. Of those peoples, 1,877 patients <60 years old (median age of 47 years, the younger group), and another 616 patients ≥60 years old (median age of 66 years, the elderly group). Patient demographic data are summarized in **Table 1**. The male (M) to female (F) ratio was 4.65:1 in the elderly and 6.51:1 in the younger group. The family history of liver disease ratio of HCC was significantly higher in the

Table 3. Prognostic Factors Determined by the Univariate Analysis in the elderly HCC Patients treated by TACE

Variables	No.	Survivals (%)			HR	*P* value
		1-yr	2-yr	3-yr		
Gender						
Female	109	86.74	55.43	30.17	reference	
Male	507	83.61	52.14	26.89	0.944 (0.737-1.161)	0.559
Family history						
Negative	567	85.34	54.47	29.91	reference	
Positive	49	83.42	52.19	26.31	1.040 (0.759-1.463)	0.783
Smoking						
Negative	215	85.97	55.21	30.14	reference	
Positive	401	83.46	52.76	27.24	0.964 (0.793-1.137)	0.634
Drinking						
Negative	213	85.98	55.23	30.17	reference	
Positive	403	83.41	52.70	27.23	0.977 (0.809-1.158)	0.766
HBV infection						
Negative	267	85.24	55.31	31.72	reference	
Positive	349	83.01	51.70	23.34	1.193 (1.088-1.530)	0.015
HCV infection						
Negative	610	84.48	53.17	28.01	reference	
Positive	6	100	66.67	33.33	1.012 (0.952-1.151)	0.821
AFP value (ng/ml)						
<20	234	78.14	54.83	34.81	reference	
20-400	168	29.57	15.79	7.89	1.481 (1.384-1.603)	<0.0001
>400	214	21.94	10.31	0	1.248 (0.988-1.575)	<0.0001
TNM Stage						
I	27	97.17	80.27	72.17	reference	
II	236	67.39	58.43	27.17	1.122 (1.071-1.209)	<0.0001
III	337	17.18	10.46	5.73	1.182 (1.102-1.324)	<0.0001
IV	16	11.03	3.07	0	1.925 (0.761-1.124)	<0.0001
Child-Pugh class						
A	185	89.16	57.81	46.14	reference	
B	431	79.13	43.29	13.12	2.473(2.160-3.033)	<0.0001
PVTT						
Negative	420	86.96	56.39	33.86	reference	
Positive	196	81.24	47.21	15.95	1.202 (1.130-1.606)	<0.0001
Tumor number						
Single	184	89.14	55.71	37.19	reference	
Multiple	432	78.32	48.12	21.94	1.434 (1.506-2.192)	<0.0001

Abbreviations: HBV=hepatitis B virus; HCV=hepatitis C virus; TNM stage=tumor-nodal-metastasis stage; AFP=alpha-fetoprotein; PVTT=portal vein tumor thrombus.

younger group than the elderly group (24.03% versus 7.95%, p<0.0001).

According to the TNM classification system, there were 6.07% of stage I, 13.32% of stage II, 61.48% of stage III, and 19.13% of stage IV patients in the younger group, corresponding data of the elderly group were 4.38%, 38.31%, 54.71%, and 2.60%, respectively (p<0.0001). There was more Child-Pugh grade B patients in the younger group than the elderly group (82.21% versus 69.97%, p<0.0001). There was no significant difference in the following variables: Presence of symptoms, Diagnosed by

screening, Tumor number, HBV and HCV infection, PVTT, and AFP value (p>0.05).

Overall survival and prognostic factors

The median survival time was 8 months (95% CI, 2-62 months) for the younger group and 27 months (95% CI, 4-66 months) for the elderly group. The 1-, 2-, and 3-year survival rate of the younger group was 31.82%, 12.5%, and 6.53%, respectively, with the related data of the elderly group was 84.66%, 53.28%, and 28.39%. **Figure 1** shows the overall survival curves of the two groups, which had significant difference (p<0.0001).

After analysis, there were 11 potential prognostic factors affecting survivals, univariate analysis revealed that gender, smoking, drinking, HBV infection, AFP value, TNM stage, Child-Pugh class, PVTT and tumor number were significant prognostic factors for the younger group (**Table 2**); Meanwhile, HBV infection, AFP value, TNM stage, Child-Pugh class, PVTT and tumor number were significant prognostic factors for the elderly group (**Table 3**). Multivariate analysis showed that HBV infection, AFP value, TNM stage, Child-Pugh class, PVTT, and tumor number were independent prognostic factors (p<0.05) for the younger patients, among those factors, PVTT had the highest HR of 3.684 (**Table 4** and **Figure 2**). As for the elderly peoples, AFP value, TNM stage, Child-Pugh class, PVTT and tumor number were five independent prognostic factors (p<0.05); Of them, the TNM stage IV had the highest HR of 2.603 (**Table 4** and **Figure 2**).

Discussion

There were few literatures regarding the treatment outcome of elderly HCC patients, in particularly to those patients treated by TACE. Previous studies used different cut-offs such as 60, 65, 70 and 75 years to define the elderly [14-20]. However, because the life expectancy of the Chinese peoples is shorter than that of the western countries, in current study, we use the WHO standard to define the elderly [21].

Our results demonstrate that the elderly and younger HCC patients differed in several features. Firstly, a higher proportion of female patients constituted in the elderly HCC patients, which is consistent with a recent epidemiological survey performed by the NCI [22]. Although the mechanism was unclear, it was possible related to the behavioral risk factors of younger males, as well as alcohol abuse. In addition, data showed the ratio of family liver disease history (FH) of HCC was 24.03% in the younger group and 7.95% in the elderly group (p=0.000), this supports the view that a FH of HCC might have a potential genetic susceptibility, or share similar living habits [23]. Thirdly, among the elderly, the proportion of early stage was higher (stage I and II was 42.69% in the elderly versus 19.37% in the younger). In addition, the ratio of Child-Pugh A of the elderly was higher than the younger (30.03% versus 17.79%, P<0.001). In another word, these elderly patients have a lower tumor TNM stage and better liver function. The result was similar with a 20-year multi center experience from Italy [15], but conflicts with previous reports describing no significant differences with respect to younger patients [9, 10].

As these studies did not report the circumstances leading to HCC diagnosis, a different proportion of cancers disclosed at a subclinical stage could explain the discrepancy. Besides, the definition of the elderly, the sample sizes, and different level of health investment might be another selection bias.

In spite of the increased chance of renal or vascular complications, or the potential of liver function deterioration, the elderly populations had a significant longer overall survival rate than the younger (P<0.0001). Opposite to the previous studies, which indicated that the elderly had a poorer survival outcome [16] or had comparable efficacy as compared with the younger [24, 25]. We speculate that these inconsistency may contribute to the definition of the elderly, the sample size, and different tumor stage and a better liver function.

For the younger HCC patients, the variables associated with survival were: gender, smoking, drinking, HBV infection, AFP value, TNM stage, Child-Pugh class, PVTT, and tumor number (P<0.05). When taken into multivariate analysis, HBV infection (HR: 0.645), AFP value (>400 ng/ml, HR: 1.764), TNM stage IV (HR: 1.586), Child-Pugh class (HR: 1.639), and PVTT (HR: 3.684) were strong factors associated with survival (p<0.0001) of the younger. A previous study [16] indicated that a serious liver

Table 4. Independent prognostic factors determined by the Multiple Cox regression analysis

	Younger (HR, 95% CI)	Elderly (HR, 95% CI)
HBV infection		
Negative	reference	reference
Positive	0.645 (0.580-0.718), p<0.0001	0.910 (0.745-1.111), p=0.355
AFP value (ng/ml)		
<20	reference	reference
20-400	1.173 (1.034-1.332), p=0.013	1.305 (1.144-1.488), p=0.038
>400	1.764 (1.547-2.012), p<0.0001	1.413 (1.044-1.912), p=0.025
TNM Stage		
I	reference	reference
II	1.190 (1.145-1.249), p=0.015	1.160 (0.906-1.260), p=0.125
III	1.320 (1.246-1.417), p=0.011	1.475 (1.284-1.766), p=0.002
IV	1.586 (1.505-1.631), p<0.0001	2.603 (1.690-3.011), p<0.0001
Child-Pugh class		
A	reference	reference
B	1.639 (1.562-1.726), p<0.0001	1.434 (1.193-1.973), p=0.001
PVTT		
Negative	reference	reference
Positive	3.684 (3.087-4.397), p<0.0001	1.541 (1.041-2.281), p=0.031
Tumor number		
Single	reference	reference
Multiple	1.193 (1.012-1.408), p=0.036	1.426 (1.387-1.679), p=0.002

Abbreviations: HBV=hepatitis B virus; TNM stage=tumor-nodal-metastasis stage; AFP=alpha-fetoprotein; PVTT=portal vein tumor thrombus.

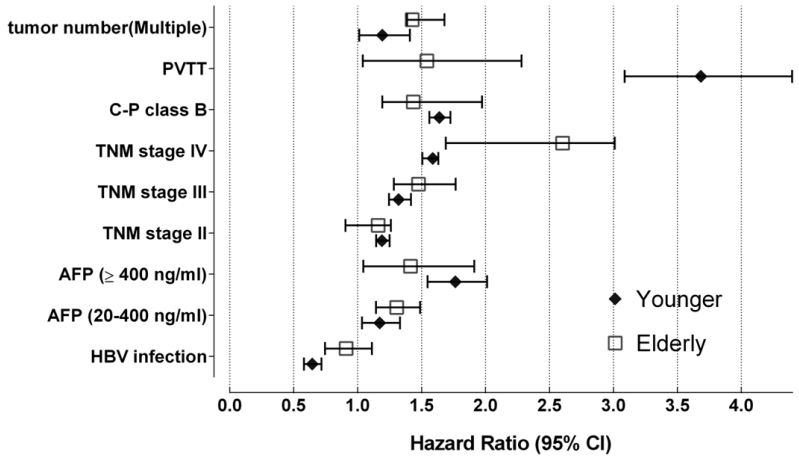

Figure 2. Independent prognostic factors determined by the Multiple Cox regression analysis. Multivariate analysis showed that HBV infection, AFP value, TNM stage, Child-Pugh class, PVTT and tumor number were independent prognostic factors for the younger patients; among which PVTT had the highest HR of 3.684. AFP value, TNM stage, Child-Pugh class, PVTT and tumor number were independent prognostic factors for the elderly peoples; among which TNM stage IV had the highest HR of 2.603.

function, tumor burden, and TACE treated outcome of the elderly patients were poorer than young patients. In our study, only stage IV (HR: 2.603) was the strong factors associated with prognosis of the elderly (p< 0.0001). Our results indicate that a worse liver function was not the main factors affecting the outcome of elderly patients who received TACE treatment. HBV infection was an prognostic factor for the younger (p<0.05). However, it was not an independent prognostic factor for the senior (P>0.05). Although the mechanism was obscure, we speculate that the younger HCC patients had a faster disease progress, a higher degree of malignancy, and the progress of the disease might be not carcinogenesis with traditionally pathway, that is HBV infection firstly lead to liver cirrhosis, and then develop to liver cancer.

Potential risk of ischemic liver damage may be existed in patients with PVTT [26], liver injury is one of most common adverse effect related to TACE. Yamada et al [26] performed TACE in 9 patients with obstruction in the main portal vein, five patients died of hepatic insufficiency within 1 mo after TACE. Autopsy demonstrated that 3 patients died of hepatic insufficiency, extensive necrosis of tumor tissue, and surrounding liver parenchyma was observed [26]. Based on result above, some clinician indicated that TACE was contraindicated in patients with PVTT. However, others argued that TACE might be safely performed in patients with PVTT if they have good hepatic reserve and collateral circulation around the portal trunk [27, 28]. Our data shows that the younger and elderly HCC patients had equal rate of PVTT ($p=0.129$); however, PVTT was a much stronger risk factor for the younger than the elderly (HR: 3.684 versus 1.541), which suggesting that PVTT might be a reason of explaining why the younger patients had poorer survival than the elderly ones.

Although the relationship between AFP and HCC was unclear, it is still a most useful tumor marker for screening HCC patients since discovered. Besides, serum AFP could also be used as a prognostic indicator for HCC [29]. HCC patients with a high AFP concentration (>400 ng/mL) tend to have greater tumor size, higher rate of portal vein thrombosis and lower median survival rate [30, 31]. In our study, AFP value was an independent risk factor for both groups; however, the HR of AFP value (>400 ng/mL) for the younger patients is 1.764 and 1.413 for the elderly, suggesting AFP value (>400 ng/mL) is relative high risks factor for the younger patients.

HCC screening and surveillance in a well-defined risk population are important at early stage. The American Association of the Study of Liver Diseases (AASLD) also recommends HCC screening with interval ultrasounds in at-risk patients with chronic HBV, including Asian females over 50 years old, Asian males over 40 years old, all cirrhotic patients, and those with a family history of HCC [32]. Recently, updated guidelines recommend every 6 months [12, 32]. Nevertheless, only 14.01% younger and 10.88% elderly patients could be detected. It showed a deficient screening system in this area, which might be related to resource limitations of the safety net healthcare system, lower socioeconomic status, and health conscious of the public.

Our study included a comparatively large number of HCC patients. However, there were also some limitations. Firstly, a selection bias might be existed; regardless the fact that data was collected from 20 medical institutions crossed the GAR area. Secondly, this is a retrospective study and only limited HCC-related factors were analyzed. Thirdly, we analyzed the treatment results based on initial treatment because most patients with HCC were treated with various treatment modalities.

In conclusion, the elderly HCC patients seems to have a better prognosis than the youngers after TACE treatment, which is probably related to the different impacts resulted from PVTT and AFP value, as well as the fact that the elderly have lower tumor burden and better liver function.

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Disclosure of conflict of interest

None.

Address correspondence to: Yuan Lin, Department of Gastrointestinal Surgery, Tumor Hospital of Guangxi Medical University, Nanning 530021, Guangxi Autonomous Region, China. Tel: (86)-771-5330708; Fax: (86)-771-5312000; E-mail: yuan-77lin@163.com

References

[1] Llovet JM, Pena CE, Lathia CD, Shan M, Meinhardt G, Bruix J; SHARP Investigators Study Group. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012; 18: 2290-2300.

[2] El-Serag HB and Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-2576.

[3] Purohit V, Rapaka R, Kwon OS and Song BJ. Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma. Life Sci 2013; 92: 3-9.

[4] Hashimoto T, Minagawa M, Aoki T, Hasegawa K, Sano K, Imamura H, Sugawara Y, Makuuchi M and Kokudo N. Caval invasion by liver tumor is limited. J Am Coll Surg 2008; 207: 383-392.
[5] Kang JY, Choi MS, Kim SJ, Kil JS, Lee JH, Koh KC, Paik SW and Yoo BC. Long-term outcome of preoperative transarterial chemoembolization and hepatic resection in patients with hepatocellular carcinoma. Korean J Hepatol 2010; 16: 383-388.
[6] Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, Everson GT, Lindsay KL, Lee WM, Bonkovsky HL, Dienstag JL, Ghany MG, Morishima C, Goodman ZD; HALT-C Trial Group. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009; 136: 138-148.
[7] Sarbah SA, Gramlich T, Younoszai A, Osmack P, Goormastic M, Grosso L, Cooper JN, Di Bisceglie A, Seneca R and Younossi ZM. Risk factors for hepatocellular carcinoma in patients with cirrhosis. Dig Dis Sci 2004; 49: 850-853.
[8] N'Kontchou G, Paries J, Htar MT, Ganne-Carrie N, Costentin L, Grando-Lemaire V, Trinchet JC and Beaugrand M. Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis. Clin Gastroenterol Hepatol 2006; 4: 1062-1068.
[9] Collier JD, Curless R, Bassendine MF and James OF. Clinical features and prognosis of hepatocellular carcinoma in Britain in relation to age. Age Ageing 1994; 23: 22-27.
[10] Tsukioka G, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, Abe T, Toyoda M, Katakai K, Kojima A, Yamazaki Y, Otsuka T, Matsuzaki Y, Makita F, Kanda D, Horiuchi K, Hamada T, Kaneko M, Suzuki H and Mori M. Hepatocellular carcinoma in extremely elderly patients: an analysis of clinical characteristics, prognosis and patient survival. World J Gastroenterol 2006; 12: 48-53.
[11] Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35: 421-430.
[12] Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236.
[13] Kimura S, Okazaki M, Higashihara H, Nozaki Y, Haruno M, Urakawa H, Koura S, Shinagawa Y and Nonokuma M. Analysis of the origin of the right inferior phrenic artery in 178 patients with hepatocellular carcinoma treated by chemoembolization via the right inferior phrenic artery. Acta Radiol 2007; 48: 728-733.
[14] Yau T, Yao TJ, Chan P, Epstein RJ, Ng KK, Chok SH, Cheung TT, Fan ST and Poon RT. The outcomes of elderly patients with hepatocellular carcinoma treated with transarterial chemoembolization. Cancer 2009; 115: 5507-5515.
[15] Mirici-Cappa F, Gramenzi A, Santi V, Zambruni A, Di Micoli A, Frigerio M, Maraldi F, Di Nolfo MA, Del Poggio P, Benvegnu L, Rapaccini G, Farinati F, Zoli M, Borzio F, Giannini EG, Caturelli E, Bernardi M, Trevisani F; Italian Liver Cancer Group. Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: a 20-year multicentre experience. Gut 2010; 59: 387-396.
[16] Biselli M, Forti P, Mucci F, Foschi FG, Marsigli L, Caputo F, Ravaglia G, Bernardi M and Stefanini GF. Chemoembolization versus chemotherapy in elderly patients with unresectable hepatocellular carcinoma and contrast uptake as prognostic factor. J Gerontol A Biol Sci Med Sci 1997; 52: M305-309.
[17] Ikeda M, Okada S, Yamamoto S, Sato T, Ueno H, Okusaka T, Kuriyama H, Takayasu K, Furukawa H and Iwata R. Prognostic factors in patients with hepatocellular carcinoma treated by transcatheter arterial embolization. Jpn J Clin Oncol 2002; 32: 455-460.
[18] Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131: 461-469.
[19] Lee SH, Choi HC, Jeong SH, Lee KH, Chung JI, Park YS, Hwang JH, Kim JW, Kim N, Lee DH, Yoon CJ and Kang SG. Hepatocellular carcinoma in older adults: clinical features, treatments, and survival. J Am Geriatr Soc 2011; 59: 241-250.
[20] Olivo M, Valenza F, Buccellato A, Scala L, Virdone R, Sciarrino E, Di Piazza S, Marrone C, Orlando A, Fusco G, Madonia S and Cottone M. Transcatheter arterial chemoembolisation for hepatocellular carcinoma in cirrhosis: survival rate and prognostic factors. Dig Liver Dis 2010; 42: 515-519.
[21] Brubaker TH and Powers EA. The stereotype of "old". A review and alternative approach. J Gerontol 1976; 31: 441-447.
[22] Altekruse SF, McGlynn KA and Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009; 27: 1485-1491.
[23] Loomba R, Liu J, Yang HI, Lee MH, Lu SN, Wang LY, Iloeje UH, You SL, Brenner D, Chen CJ; RE-

VEAL–HBV Study Group. Synergistic Effects of Family History of Hepatocellular Carcinoma and Hepatitis B Virus Infection on Risk for Incident Hepatocellular Carcinoma. Clin Gastroenterol Hepatol 2013; 11: 1636-45, e1-3.

[24] Hoshida Y, Ikeda K, Saito S, Kobayashi M, Suzuki Y, Tsubota A, Koida I, Arase Y, Murashima N, Chayama K and Kumada H. [The efficacy and prognosis of transcatheter chemoembolization for hepatocellular carcinoma in the elderly]. Nihon Shokakibyo Gakkai Zasshi 1999; 96: 142-146.

[25] Poon RT, Fan ST, Lo CM, Liu CL, Ngan H, Ng IO and Wong J. Hepatocellular carcinoma in the elderly: results of surgical and nonsurgical management. Am J Gastroenterol 1999; 94: 2460-2466.

[26] Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K and Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 1983; 148: 397-401.

[27] Georgiades CS, Hong K, D'Angelo M and Geschwind JF. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. J Vasc Interv Radiol 2005; 16: 1653-1659.

[28] Chung JW, Park JH, Han JK, Choi BI and Han MC. Hepatocellular carcinoma and portal vein invasion: results of treatment with transcatheter oily chemoembolization. AJR Am J Roentgenol 1995; 165: 315-321.

[29] Tan CK, Law NM, Ng HS and Machin D. Simple clinical prognostic model for hepatocellular carcinoma in developing countries and its validation. J Clin Oncol 2003; 21: 2294-2298.

[30] Tangkijvanich P, Anukulkarnkusol N, Suwangool P, Lertmaharit S, Hanvivatvong O, Kullavanijaya P and Poovorawan Y. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. J Clin Gastroenterol 2000; 31: 302-308.

[31] Fujioka M, Nakashima Y, Nakashima O and Kojiro M. Immunohistologic study on the expressions of alpha-fetoprotein and protein induced by vitamin K absence or antagonist II in surgically resected small hepatocellular carcinoma. Hepatology 2001; 34: 1128-1134.

[32] Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.