

Impact of age on the prognosis after liver transplantation for patients with hepatocellular carcinoma: a single-center experience

Pusen Wang^{1,*}
 Chunguang Wang^{1,*}
 Hao Li¹
 Baojie Shi¹
 Jianning Wang²
 Lin Zhong¹

¹Department of General Surgery, Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, ²Department of Urology, Affiliated Qianfoshan Hospital, Shandong University, Jinan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lin Zhong
 Department of General Surgery,
 Shanghai General Hospital, Shanghai
 Jiaotong University School of Medicine,
 100 Haining Road, Hongkou District,
 Shanghai 200080, People's Republic of
 China
 Tel +86 21 6324 0090 ext 3133
 Fax +86 21 6324 2903
 Email zhongl_3284@hotmail.com

Jianning Wang
 Department of Urology, Affiliated
 Qianfoshan Hospital, Shandong
 University, 16766 Jingshi Road, Jinan City
 250014, People's Republic of China
 Tel +86 531 8228 7327
 Email guowz_wps@hotmail.com

Background: Liver transplantation (LT) offers the most effective treatment for hepatocellular carcinoma patients. Various preoperative variables are correlated with survival after LT, but the prognostic role of aging on LT remains controversial.

Methods: Between January 2001 and December 2011, 290 consecutive transplants for patients with hepatocellular carcinoma performed in Shanghai First People's Hospital (People's Republic of China) were analyzed retrospectively. We compared patient characteristics and survival curves between a younger group (less than 49 years, n=135) and an aged group (50 years or older, n=155). We then performed Cox multivariate regression analysis of the risk factors for survival in aged and younger patients.

Results: Younger age was associated with higher alpha-fetoprotein ($P=0.014$), larger tumor size ($P=0.038$), poorer differentiation ($P=0.025$), portal lymph node metastasis ($P=0.001$), and higher recurrence rate ($P=0.038$). Aged patients had significantly longer recurrence-free survival and overall survival ($P=0.020$ and $P=0.014$, respectively); however, there were no significant differences between the younger and aged patients who met the Milan criteria ($P>0.05$). The 1-, 3-, and 5-year recurrence-free survival rates were 59.7%, 44.5%, and 37.3%, respectively, in the younger group, and 67.9%, 55.3%, and 53.8%, respectively, in the aged group. The 1-, 3-, and 5-year overall survival rates were 68.4%, 45.5%, and 38.9%, respectively, in the younger group, and 76.1%, 59.7%, and 53.9%, respectively, in the aged group. Alpha-fetoprotein ≥ 400 ng/mL, microvascular invasion, and tumor size > 5 cm were independent risk factors for prognosis in both groups.

Conclusion: Younger patients in our center tended to present with more aggressive tumors and have a higher risk of recurrence. Our single-center experience suggests that younger patients should be assessed more rigorously before LT, while aged patients should be actively considered for LT after appropriate selection.

Keywords: age, hepatocellular carcinoma, liver transplantation, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer-related deaths worldwide.¹ It is estimated that there were 782,000 liver cancer cases and 746,000 liver cancer-related deaths worldwide in 2012.² Despite various therapeutic options such as liver resection, radiofrequency ablation, and transcatheter hepatic arterial chemoembolization, the prognosis remains generally poor, leading to 500,000 deaths per year.³ The incidence of HCC is increasing rapidly worldwide.^{4,5}

Liver transplantation (LT) remains the most effective treatment for small HCC with chronic liver disease and the best chance for end-stage liver disease.⁶⁻⁸ Sequential development from hepatitis B to liver cirrhosis and HCC is a typical phenomenon

in most Chinese patients.⁹ Fortunately, patients undergoing LT for hepatitis B virus-related cirrhosis have excellent long-term outcomes, with 5-year survival rates of 80%.¹⁰ Various studies confirm that some preoperative variables such as tumor size, number of nodules, vascular invasion, histopathologic grading, and pre-LT serum alpha-fetoprotein (AFP) level are correlated with survival after LT in patients with HCC.^{11–13}

Age is a complex prognostic factor in HCC and may play a paradoxical role in the prognosis of HCC patients.¹⁴ Chen et al¹⁵ found that male patients below 40 years of age with positive Hepatitis B surface antigen (HBsAg) had the worst survival in the early years because of increased AFP level and poor hepatic function. However, Zhang and Sun¹⁶ demonstrated that younger patients with liver cancer have higher liver cancer-specific survival after liver resection, despite the poorer biological behavior of this carcinoma.¹⁶ The prognostic role of aging on survival following LT remains controversial.^{17–20}

In this study, we evaluated the prognostic role of aging on survival after LT. In addition, we investigated the differences in clinical characteristics between aged and younger patients to explore the specific factors affecting the long-term prognosis between these two groups.

Materials and methods

Patients

A retrospective review of a prospectively maintained database in our institution (Affiliated First People's Hospital, Shanghai Jiao Tong University, Shanghai, People's Republic of China) was conducted. Between January 2001 and December 2011, a total of 314 HCC patients underwent LT; of these, 290 (259 males and 31 females) were included in this study. The median age of patients in our sample was 50 years (range 18–73 years). The mean follow-up time was 36.14 months (range 0.03–146.60 months). A total of 38 HCC patients with portal lymph node metastasis were included in the study. Among these patients, 31 were diagnosed on the basis of pathological specimens after surgery and it was not identified in preoperative evaluation (computed tomography [CT] and positron emission tomography-CT). The other seven of these patients were diagnosed as HCC with portal lymph node metastasis during recipient hepatectomy or by preoperative evaluation (CT and positron emission tomography-CT) and transplantation was performed because these patients met the Milan criteria. All diagnoses were confirmed by histopathologic examination. We excluded patients who had undergone

LT more than once, had living donors or split-liver donors, were diagnosed with other malignancies in addition to HCC, or had missing pathology data.

Data collection

Patient baseline and clinical data, including age, sex, blood type, liver cirrhosis, hepatitis B virus status, hepatitis C virus status, pre-orthotopic liver transplantation (OLT) serum AFP level (stratification according to previous research²¹), Child–Pugh status,²² tumor size, multinodular, microvascular invasion, portal lymph node metastasis, histologic grade (differentiated [well differentiated + moderately differentiated] and poorly differentiated), Milan criteria,²³ HCC recurrence, overall survival (OS), and recurrence-free survival (RFS), were recorded. Patients who were still alive or died from other causes (not HCC) were censored at their date of last visit or date of death. According to a previous study,¹⁹ all recipients were divided into two groups: younger group (<49 years) and aged group (≥ 50 years).

This study was approved by the Institutional Review Board for Liver Transplantation Surgery, Shanghai First People's Hospital, Shanghai, People's Republic of China, under the guidelines of the Ethics Committee of the hospital and in accordance with the Declaration of Helsinki.²⁴ Due to the retrospective nature of the study, informed consent was waived.

Statistical analysis

All statistical analyses were performed using SPSS Version 19.0 statistical software (IBM Corporation, Armonk, NY, USA). Continuous data were expressed as the mean \pm standard deviation or median (range), and discrete variables as frequencies. Categorical variables were compared using the Pearson's χ^2 test or Fisher's exact test, whereas continuous variables were calculated with Student's *t*-test. RFS and OS were assessed by Kaplan–Meier analysis and compared by the log-rank test. We also performed age-stratified survival analysis. Multivariate Cox proportional hazard regression was used to obtain hazard ratios and 95% confidence intervals associated with RFS and OS. The final models were determined by placing all variables with $P < 0.05$ from the univariate analysis into a multivariate Cox regression model and using a forward stepwise variable selection process. Statistical significance was established at the $P < 0.05$ level.

Results

Clinical demographics and follow-up data

The main demographic and clinical data of the 290 patients are listed in Table 1. The aged group had a significantly

Table 1 Patient characteristics by age group

Variables	Age group		P-value
	<50 years (n=135)	≥50 years (n=155)	
Sex (male/female)	125/10	134/21	0.091
Blood type (A/B/AB/O)	49/15/32/39	52/17/49/37	0.481
Liver cirrhosis (%)	117 (86.7)	145 (93.5)	0.048
HBV (%)	123 (91.1)	146 (94.2)	0.312
HCV (%)	1 (0.7)	1 (0.6)	1.000
AFP level (<400 ng/mL, ≥400 ng/mL)	81/54	114/41	0.014
Multinodular (%)	55 (40.7)	72 (46.5)	0.328
Tumor size (≤5 cm, >5 cm)	70/65	99/56	0.038
Histologic grade (differentiated/undifferentiated)	104/31	135/20	0.025
Child–Pugh status (A/B/C)	74/47/14	74/62/19	0.484
Microvascular invasion (%)	37 (27.4)	29 (18.7)	0.078
Portal lymph node metastasis (%)	27 (20)	11 (7.1)	0.001
Milan criteria (in/out)	48/87	54/101	0.903
HCC recurrence (%)	65 (48.1)	56 (36.1)	0.038
Number of deaths (%)	75 (55.6)	68 (43.9)	–

Abbreviations: AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

higher percentage of liver cirrhosis ($P=0.048$). Interestingly, there were more patients with AFP ≥ 400 ng/mL in the younger group (40.0% vs 26.5%, $P=0.014$). Moreover, the percentages of patients with tumor size >5 cm ($P=0.038$), poor differentiation ($P=0.025$), and portal lymph node metastasis ($P=0.001$) were all higher in the younger group. The mean follow-up time was 36.14 months (range 0.03–146.60 months). A total of 147 (50.7%) patients died during follow-up. The proportions of HCC recurrence and death were higher in the younger group (48.1% vs 36.1% and 55.6% vs 43.9%, respectively).

Kaplan–Meier survival analysis

Kaplan–Meier survival curves were generated in combination with log-rank tests to compare RFS and OS across the age groups. There were significant differences in RFS and OS between these two groups ($P=0.020$ and $P=0.014$, respectively; Figures 1 and 2). RFS and OS were remarkably higher in the aged group. The 1-, 3-, and 5-year RFS rates were 59.7%, 44.5%, and 37.3%, respectively, in the younger group and 67.9%, 55.3%, and 53.8%, respectively, in the aged group. Similarly, the 1-, 3-, and 5-year OS rates were 68.4%, 45.5%, and 38.9%, respectively, in the younger group and 76.1%, 59.7%, and 53.9%, respectively, in the aged group.

To investigate further, patients were assessed according to the Milan criteria. Among the 290 patients, 102 (35.2%) met these criteria, with 48 (47.1%) in the younger group and 54 (52.9%) in the aged group. However, among these selected patients, there were no statistically significant differences in

both RFS and OS between two groups ($P=0.303$ and $P=0.263$, respectively; Figures 3 and 4).

Multivariate Cox regression analysis of factors associated with RFS and OS stratified by age

Univariate and multivariate models were used to identify factors associated with RFS and OS for younger and aged HCC patients. All variables with $P<0.05$ in the univariate

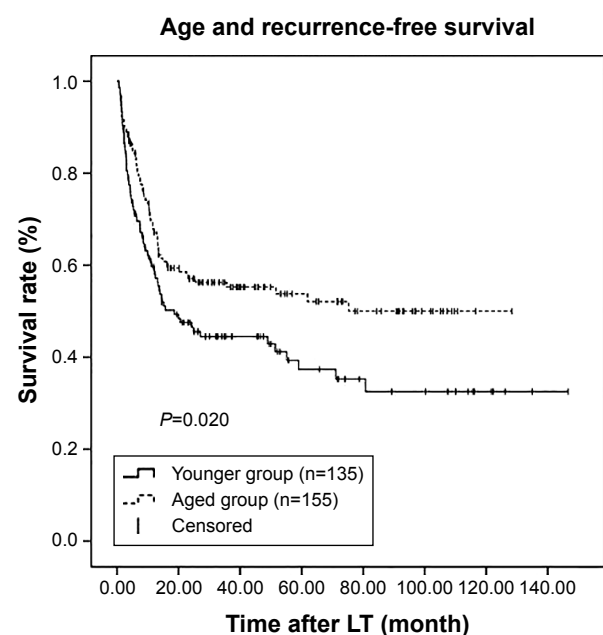


Figure 1 Kaplan–Meier survival estimates of RFS between the younger and aged groups.

Abbreviations: LT, liver transplantation; RFS, recurrence-free survival.

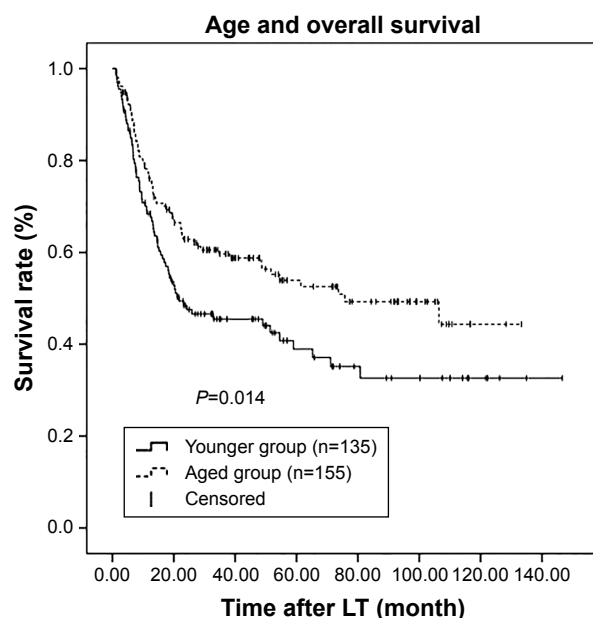


Figure 2 Kaplan–Meier survival estimates of OS between the younger and aged groups. **Abbreviations:** LT, liver transplantation; OS, overall survival.

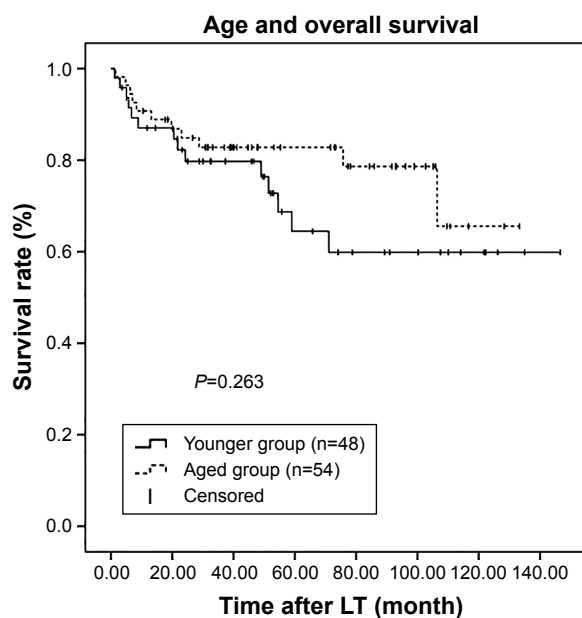


Figure 4 OS of younger patients and aged patients who met the Milan criteria. **Abbreviations:** LT, liver transplantation; OS, overall survival.

analysis (data not shown) were included in the multivariate Cox regression model. To avoid collinearity, the forward stepwise variable selection process was performed.

For RFS of the younger group, AFP ≥ 400 ng/mL, microvascular invasion, and tumor size >5 cm were independent risk factors, while microvascular invasion and tumor size >5 cm were independent risk factors for OS (Table 2). For both RFS and OS of the aged group,

AFP ≥ 400 ng/mL, microvascular invasion, and tumor size >5 cm were independent risk factors (Table 3).

Discussion

The correlation between recipient age and clinical prognosis of HCC patients after LT remains controversial. In this single-center study, we evaluated the outcomes of patients in different age groups. Interestingly, our results demonstrated that the aged group was associated with better RFS and OS.

Recipient age as a prognostic factor for survival after LT has been studied for many years. Some studies indicated positive relationships,^{20,25,26} while others yielded contradictory findings.^{19,27} These discrepancies may be due to the different age cut-off values and inclusion criteria applied in these studies as well as center-specific disparities in patient selection, operative techniques, and postoperative management.

A recent study conducted by Kim et al¹⁹ with data obtained from the United Network for Organ Sharing Registry (10,238 patients) demonstrated that age in appropriately selected patients did not predict the success of LT in providing a long-term durable cure for HCC, and there were no significant differences in outcomes between patients aged 35–49 years and those aged 50–64 years. Similar patient selection criteria and age cut-off values were used in the present study, with six (2%) patients who were 65 years or older; however, our results led to a different conclusion. These conflicting outcomes arose from the fact that all HCC

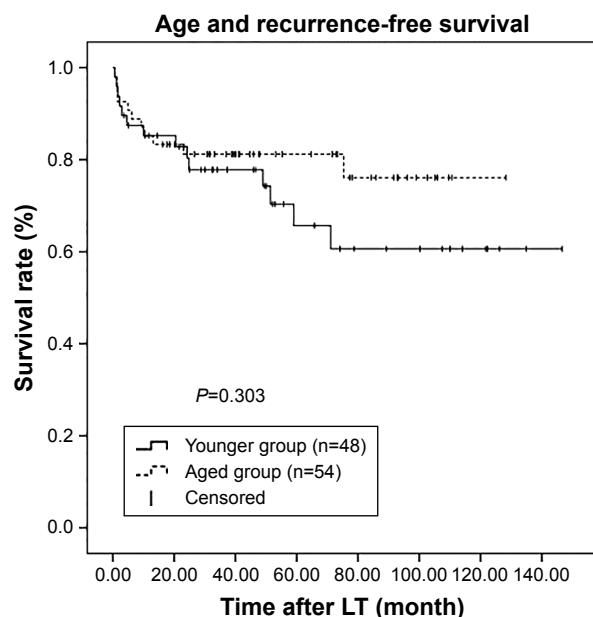


Figure 3 RFS of younger patients and aged patients who met the Milan criteria. **Abbreviations:** LT, liver transplantation; RFS, recurrence-free survival.

Table 2 Multivariate analysis of factors associated with RFS and OS in younger group

	Hazard ratio (95% CI)	P-value
RFS		
AFP level (0=<400 ng/mL, I= \geq 400 ng/mL)	1.709 (1.034–2.825)	0.036
Microvascular invasion (0= negative, I= positive)	1.955 (1.125–3.399)	0.017
Tumor size (0= \leq 5 cm, I= $>$ 5 cm)	3.286 (1.947–5.545)	<0.001
OS		
Microvascular invasion (0= negative, I= positive)	2.448 (1.470–4.079)	0.001
Tumor size (0= \leq 5 cm, I= $>$ 5 cm)	3.138 (1.868–5.269)	<0.001

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; OS, overall survival; RFS, recurrence-free survival.

patients included in the study reported by Kim et al met the Milan criteria.²³ However, when we analyzed the data of selected patients who met the Milan criteria, we found no significant difference in the outcomes of the two groups, which is consistent with the results of the study reported by Kim et al. Nevertheless, our results were consistent with those reported by Wai et al¹⁸ from a study of HCC patients aged less than 50 years, which was the same cut-off age applied in the present study. According to their experience, younger age (<50 years) was related to high risk of recurrence (62% vs 9%, $P<0.001$), and was an independent factor associated with poor RFS.

Aged patients had better prognosis in this study. One explanation for this may be that the younger patients tend to have more advanced disease, as indicated by the greater proportion with AFP \geq 400 ng/mL, tumor size $>$ 5 cm, poor differentiation, and portal lymph node metastasis. This speculation has been confirmed in previous studies.^{14,16}

Additionally, another interesting observation from our study is that there were more noncirrhotic HCC patients in the younger group. Beard et al²⁸ found higher risk pathologic features and an increased incidence of recurrence among noncirrhotic patients compared with cirrhotic patients. Similarly, younger age was associated with higher risk of recurrence in our study (48.1% vs 36.1%). In Asian countries, religion, culture, politics, and economy have a huge impact on organ allocation so that various patients with unresectable HCC which exceeded the Milan criteria are treated with LT, especially younger patients.²⁹ Consequently, there is a greater proportion of more severe HCC patients in the younger age group. Another explanation for the more favorable outcomes observed in the aged group lies in the more rigorous assessment of factors such as liver functional reserve and tolerance to surgery in older patients compared to younger patients.

However, age was not identified as an independent risk factor in the multivariate analysis conducted in our study

Table 3 Multivariate analysis of factors associated with RFS and OS in aged group

	Hazard ratio (95% CI)	P-value
RFS		
AFP level (0=<400 ng/mL, I= \geq 400 ng/mL)	2.039 (1.233–3.373)	0.006
Microvascular invasion (0= negative, I= positive)	4.871 (2.876–8.251)	<0.001
Tumor size (0= \leq 5 cm, I= $>$ 5 cm)	2.698 (1.646–4.422)	<0.001
OS		
AFP level (0=<400 ng/mL, I= \geq 400 ng/mL)	2.086 (1.255–3.469)	0.005
Microvascular invasion (0= negative, I= positive)	4.802 (2.855–8.076)	0.001
Tumor size (0= \leq 5 cm, I= $>$ 5 cm)	2.906 (1.769–4.773)	<0.001

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; OS, overall survival; RFS, recurrence-free survival.

(data not shown). Although Kim et al¹⁹ presented positive results from their multivariate analysis, some crucial data such as AFP level and tumor features were not included in the Cox regression model. Nevertheless, Wai et al¹⁸ demonstrated that younger age <50 years was an independent risk factor in a cohort of 77 HCC patients, with 86% exceeding the University of California, San Francisco criteria.²³ Compared with their study, we had a larger sample size, and our sample was a consecutive cohort. We conclude that age itself is not an independent risk factor but that the influence of age is associated with liver cirrhosis, AFP level, tumor size, histologic grade, and portal lymph node metastasis. In multivariate analysis stratified by age, both the younger and aged groups shared similar independent risk factors for RFS and OS: AFP level ≥ 400 ng/mL, microvascular invasion, and tumor size >5 cm, which is consistent with previous studies.^{11,18,30}

Inevitably, this analysis, similar to other studies, is limited because the patients in the two groups are not totally comparable in that preoperative assessment is likely to be more rigorous in older patients. An additional limitation is the extended period over which patients were selected for inclusion in the study. With advances in surgical techniques, improved management after surgery, and better immunosuppressive therapy, the clinical outcomes were improved over the period selection, resulting in heterogeneity among these patients.

In conclusion, our study showed that age ≥ 50 years was associated with longer RFS and OS compared with younger patients, but was not an independent risk factor. Younger patients in our center tended to present with more aggressive tumors and have a higher risk of recurrence. Our single-center experience suggests that younger patients should be assessed more rigorously before LT, while aged patients should be actively considered for LT after appropriate selection.

Disclosure

The authors report no conflicts of interest in this work.

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