The ratio of preoperative alpha-fetoprotein level to total tumor volume as a prognostic factor of hepatocellular carcinoma after liver transplantation

Tao Jiang, PhD, Xiao-shi Zhang, MD[ID], Fei Pan, MD, Shao-cheng Lyu, PhD, Jing Wang, PhD, Meng-xiu Huang, MD, Qiang He, PhD, Ren Lang, PhD*

Abstract

To evaluate the effect of preoperative serum alpha-fetoprotein(AFP) level to total tumor volume (TTV) ratio as a prognostic marker on predicting the tumor recurrence and overall survival time of patients with hepatocellular carcinoma (HCC) after liver transplantation.

One-hundred eight patients with HCC who underwent liver transplantation in Beijing Chaoyang Hospital from April 2013 to October 2017 were studied. Divided into AFP/TTV≤2 group and AFP/TTV>2 group by the best cut-off score calculated by receiver operation characteristic curve, the clinical and pathological data of the patients in two groups were compared to explore the relationship between AFP/TTV and tumor recurrence together with the prognosis of HCC patients after liver transplantation. Risk factors of early tumor recurrence and poor prognosis of HCC in patients after liver transplantation were studied by multivariate regression analysis. Kaplan-Meier survival analysis was used to compare the tumor-free survival and overall survival between the two groups of patients.

In 108 patients, 47 patients have AFP/TTV≤2 while 61 patients have AFP/TTV>2. Patients in AFP/TTV≤2 group have longer tumor-free survival time and overall survival time compared with patients in AFP/TTV>2 group. The age, total bilirubin level, serum AFP level, TTV, portal vein tumor thrombus and AFP/TTV (all $P < .05$) of patient with HCC are closely related to poor prognosis after liver transplantation. Multivariate regression analysis showed that have portal vein tumor thrombus (hazard ratio [HR]=2.345, $P < .05$), TTV≥65.5 cm^3 (HR=2.701, $P < .05$) and AFP/TTV>2 (HR=4.624, $P < .05$) are independent risk factors for poor prognosis of patients with HCC after liver transplantation while TTV≥65.5 cm^3 (HR=2.451, $P < .05$) and AFP/TTV>2 (HR=4.257, $P < 0.05$) were independent risk factors for tumor recurrence at the same time.

The tumor recurrence and the prognosis of patients with HCC after liver transplantation is affected by many factors. AFP/TTV ratio has important predictive value for the tumor recurrence and the prognosis of patients with HCC after liver transplantation. AFP/TTV>2 is an independent risk factor for both early tumor recurrence and poor prognosis of patients with HCC after liver transplantation.

Abbreviations: AFP = alpha-fetoprotein, DFS = disease-free survival, HCC = hepatocellular carcinoma, OS = overall survival, TBil = total bilirubin, TTV = total tumor volume.

Keywords: alpha-fetoprotein, hepatocellular carcinoma, liver transplantation, prognosis, total tumor volume

---

1. Introduction

Hepatocellular carcinoma (HCC), whose morbidity ranks fifth while mortality ranks fourth with a rapidly rising trend in the world, has become one of the most common malignant tumor.[1,2] It has been suggested that surgical resection and liver transplantation are main treatments for HCC recently. In terms of the indications for liver transplantation, Milan criteria, namely, individual tumor with the diameter less than 5 cm or no more than three tumors with the diameter less than 3 cm without extrahepatic metastasis or major vascular invasion, is widely recognized all over the world[3] Number of studies have shown that the prognosis of HCC patients within Milan criteria with liver transplantation is better than those who suffered hepatectomy.[3–5] With the accumulation of clinical experience, scholars successively put forward the University of California San Francisco criteria, Hangzhou criteria, Fudan criteria, etc. to extend the Milan criteria. Clinical studies have demonstrated that HCC patients who meet any of the above criteria can obtain a satisfactory survival rate after liver transplantation.[6–8] But, however, tumor recurrence is still the main factor leading the poor prognosis of HCC patients after liver transplantation, so early prediction of high-risk factors of tumor recurrence would become a key point of preventing and treating it, which may improve the prognosis of patients with HCC who suffered liver transplantation.

Alpha-fetoprotein (AFP), as a specific tumor marker, plays an important role in diagnosing HCC[9] Despite that, AFP can be used to assess the severity of tumor burden and as an indicator of the prognosis after different treatments. It has been confirmed that using AFP in the prognostic scoring system is beneficial to increase the accuracy of prediction.[9,10] Total tumor volume (TTV), as another indicator of tumor burden, also has great significance in predicting the prognosis of patients with HCC.[11–14] Combined each other, the specific ratio of AFP to TTV reflects the number of cells which can synthesize AFP in a unit volume of tumor tissue, which would be a better index to predict the prognosis of HCC patients. Therefore, in this study, we found the risk-factors which cause poor prognosis and discovered the relationship between the ratio of AFP level to TTV and the prognosis of patients with HCC after liver transplantation.

2. Methods

2.1. Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Chaoyang Hospital (No.2019-D.-305). The participants provided written informed consent to participate in this study.

2.1.1. Patients enrolled. We collected and retrospectively analyzed the information of patients who suffered liver transplantation because of HCC in the department of Hepatobiliary and Pancreaticosplenic Surgery, Beijing ChaoYang Hospital, Capital Medical University from April, 2013 to October, 2017. All the transplantation surgery came from donors who had died. The process of screening for included patients in this study was showed as Figure 1. All the included patients were treated in department of Hepatobiliary and Pancreaticosplenic Surgery, Beijing ChaoYang Hospital within the above period and the tumor of whom meets at least one of the liver transplant recipient selection criteria including Milan criteria, University of California San Francisco criteria, Hangzhou criteria and Fudan criteria. All these patients were

confirmed to have HCC by postoperative pathology after liver transplantation. Patients with distant tumor metastasis and suffered other treatments were excluded. Patient who had suffered hepatectomy or other tumor-related treatment before their admission was excluded. Patients who died during the perioperative period because of non-tumor factors or lost of follow up was excluded. There were totally 108 patients included in this study.

2.1.2. General clinical data. The age, gender, preoperative albumin, transaminase, total bilirubin, hepatitis B surface antigen, hepatitis C antibody, AFP index, operation time, and intraoperative blood loss of the patients above were recorded. Tumor number and tumor differentiation index were provided by postoperative pathology report. Due to the shape of hepatocellular tumor was more inclined to an approximate sphere, the diameter of the tumor was measured according to the postoperative CT or MRI. If there were more than one tumor, add the radius of each tumor as the total tumor radius. TTV was calculated by the following formula: TTV $(cm^3)= 4/3 \times 3.14 \times$ total tumor radius $(cm)^3$.[13,15] A receiver operation characteristic(ROC) curve was constructed based on the ratio of AFP to TTV. Showed as Figure 2, the optimal cut-off value was determined to be 2.01 [area under curve(AUC), 0.733, $95\%CI$:0.638-0.828, $P < .05$]. Refered to the cut-off value, all the patients were divided into AFP/TTV≤2 group and AFP/TTV>2 group. There were a total of 47 patients in AFP/TTV≤2 group and 61 patients in AFP/TTV>2 group.

2.1.3. Follow-up strategy. To obtain the postoperative survival status, all the patients were followed up regularly from the day they suffered surgery to May 1, 2020. Blood routine, biochemistry, serum AFP level, abdominal ultrasound and CT scan were checked weekly within the first month after liver transplantation. Examinations above were rechecked every 2 weeks within 3 months after surgery and rechecked monthly until a year after operation. After that, patients were reviewed every 2 months. Ultrasound and CT provided the diagnostic basis of tumor recurrence. All the patients included in this study have complete follow-up data while the median follow-up time was 35.5 months.

2.1.4. Statistical analysis. All data were analyzed with SPSS (version 22.0, IBM SPSS Inc.). Chi-square test or Fisher exact test was used for classification data. Measurement data conforming to the normal distribution were expressed by mean ± standard deviation while those who conformed to the non-normal distribution were expressed by median (interquartile range). Normally distributed data was analyzed by t test and non-normally distributed data was analyzed by *Wilcoxon* rank sum test. Kaplan-Meier survival analysis was used to compare the differences of survival time between the two groups and *COX* regression model was used for multiple-factor analysis. A value of $P < .05$ was considered as statistically significant difference. All the results were repeated three times.

3. Results

3.1. Clinical data analysis

AFP/TTV among the 108 patients was 2.63(0.46,11.05). All the patients were grouping by whether AFP/TTV was less than or equal to 2, which was the approximate value of the cut-off value. Totally 47 patients were classified into AFP/TTV≤2 group while
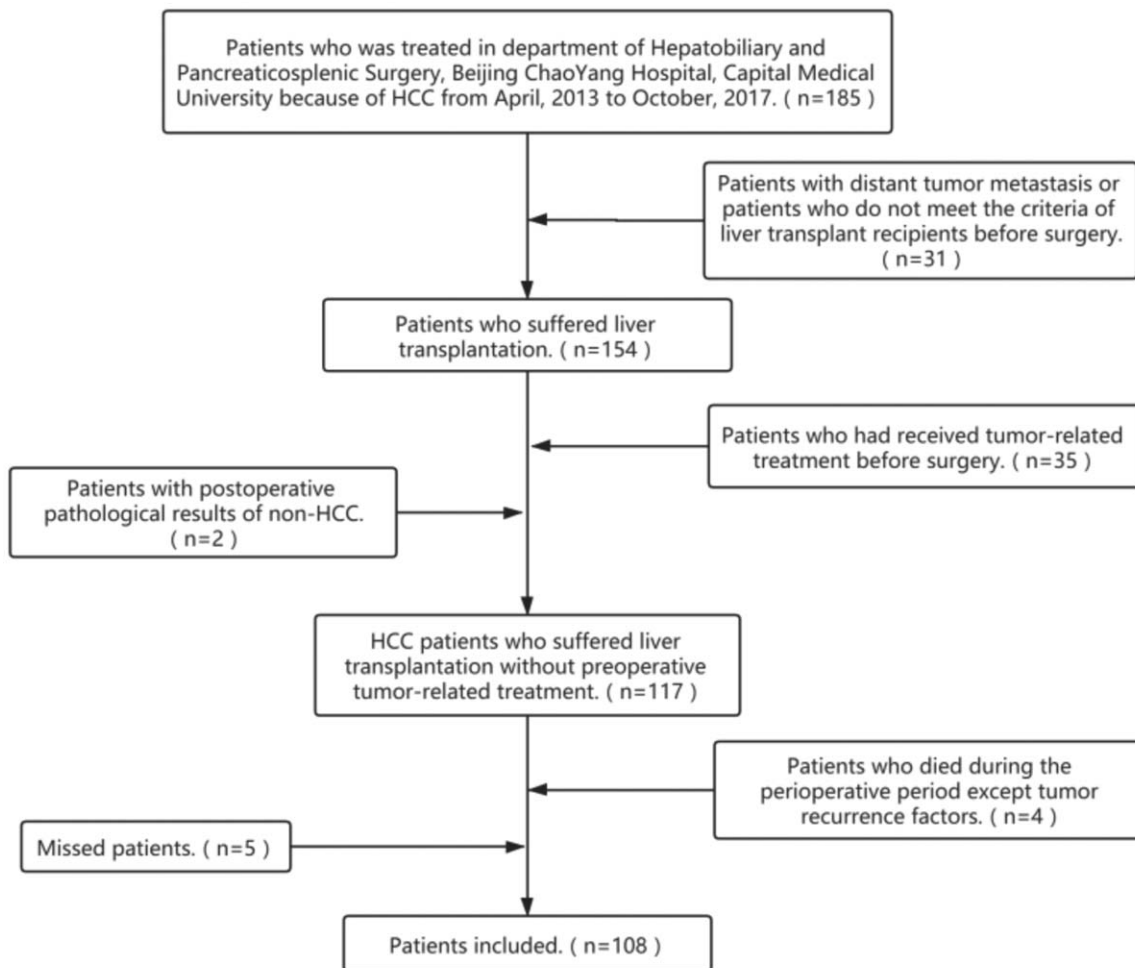
Figure 1. Process of screening for included patients for this study. HCC = hepatocellular carcinoma.
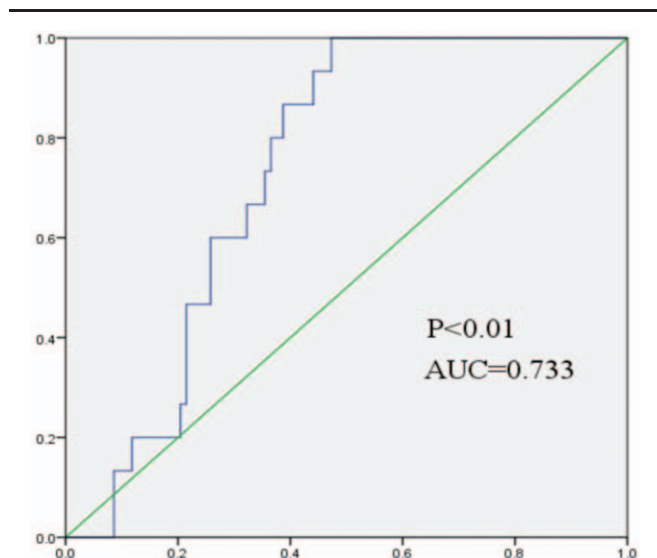
Figure 2. Receiver operation characteristic curve of AFP/TTV. AFP = alpha-fetoprotein, AUC = area under curve, TTV = total tumor volume.

61 patients were classified into AFP/TTV>2 group. Comparison of basic information, preoperative laboratory index, surgical related data and postoperative pathological data between the two groups was showed in Table 1.

The age of the patients in two groups were (51.6 ± 8.9) year old and (53.3 ± 8.2) year old respectively. Patients over 60 years old were considered as elderly patients. From the analysis we can see, compared the basic information of the two groups, there was no significant difference in whether the patient is male, advanced aged, with underlying diseases, with Child-Pugh A/B grade, with HBsAg positive or with HCV antibody positive. As for laboratory tests, patients in AFP/TTV≤2 group had an albumin level of 34.7(31.3,40.2) ng/L, aspartate aminotransferase level of 51.0(31.0,96.5) U/L, alanine aminotransferase level of 42.0 (29.0,85.5) U/L and total bilirubin (TBil) level of 22.3(15.2,47.0) μmol/L. The above indicators of patients in AFP/TTV>2 group were 35.1(31.1,39.9) g/L, 44.0(34.5,65.5) U/L, 32.0(22.0,48.5) U/L and 25.3(15.8,43.5) μmol/L. Distinguished the patients according to whether their index of the aspects above was within normal range, there was no significant difference between the two groups. The preoperative serum AFP level of the two groups were 10.7(4.7,34.0) ng/ml and 105.0(27.1,1324.0) ng/ml, which has significant statistical difference ($P < .001$). Data of surgical

Table 1

Correlation between the factors and clinicopathologic characteristics in HCC (n = 108).

Variable		AFP/TTV ≤ 2	AFP/TTV > 2	P value
		(n = 47)	(n = 61)	
Gender	male	44 (93.6)	54 (88.5)	.365
	female	3 (6.4)	7 (11.5)	
Age	< 60	38 (80.9)	48 (78.7)	.374
	≥ 60	9 (19.1)	13 (21.3)	
Underlying diseases	yes	10 (21.3)	15 (24.5)	.685
	no	37 (78.7)	46 (75.5)	
Child-Pugh grade	A/B	45 (95.7)	59 (96.7)	.790
	C	2 (4.3)	2 (3.3)	
HBsAg	(−)	6 (12.8)	9 (14.8)	.767
	(+)	41 (87.2)	52 (85.2)	
Anti-HCV	(−)	46 (97.9)	59 (96.7)	.718
	(+)	1 (2.1)	2 (3.3)	
ALB (g/L)	≥ 40	11 (23.4)	12 (19.7)	.639
	< 40	36 (76.6)	49 (80.3)	
AST (U/L)	≤ 40	16 (34.0)	23 (37.7)	.694
	> 40	31 (66.0)	38 (62.3)	
ALT (U/L)	≤ 40	24 (51.1)	39 (63.9)	.178
	> 40	23 (48.9)	22 (36.1)	
TBil (μmol/L)	≤ 21	20 (42.6)	20 (32.8)	.297
	> 21	27 (57.4)	41 (67.2)	
AFP (ng/ml)	≤ 100	43 (91.5)	26 (42.6)	<.001
	> 100	4 (8.5)	35 (57.4)	
Operation time (h)	≤ 10	29 (61.7)	37 (60.7)	.911
	> 10	18 (38.3)	24 (39.3)	
Intraoperative blood loss (ml)	≤ 1000	29 (61.7)	35 (57.4)	.650
	> 1000	18 (38.3)	26 (42.6)	
Intraoperative blood transfusion	(+)	24 (51.1)	36 (59.0)	.409
	(−)	23 (48.9)	25 (41.0)	
The number of tumor	single	26 (55.3)	27 (44.3)	.255
	multiple	21 (44.7)	34 (55.7)	
Tumor differentiation	high/moderate	42 (89.4)	58 (95.1)	.260
	low	5 (10.6)	3 (4.9)	
TTV (cm^3)	≤ 65.5	26 (55.3)	40 (65.6)	.279
	> 65.5	21 (44.7)	21 (34.4)	
Cancer embolus in portal vein	(+)	4 (8.5)	16 (29.2)	.019
	(−)	43 (91.5)	45 (70.8)	

*ALB = albumin; AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBil = total bilirubin; TTV = total tumor volume.

information showed that the average operation time of the two groups was (9.27 ± 2.08) hours and (9.39 ± 2.09) hours while the intraoperative blood loss was 800(600, 1500) ml and 800(500, 1500) ml. No statistical difference was found in the above two aspects together with whether there was intraoperative blood transfusion. Differences in tumor numbers and tumor differentiation had negative statistical significance, but there was statistical difference in whether the patient had cancer embolus in the portal vein (P = .019). TTV between the patients of the two groups were 57.9(22.4, 179.5) cm^3 and 14.1(2.6, 113.0) cm^3, which had negative statistical difference.

3.2. Survival analysis

108 patients with HCC were regularly followed up for 1 to 81 months after liver transplantation with a median follow-up time of 35.5 months. The overall survival (OS) is from the day of liver transplantation to the date of death of the patient or till the endpoint of the follow-up. The disease-free survival (DFS) is from the day of liver transplantation to the date when the patient was diagnosed with tumor recurrence through CT, MR, etc. or till the endpoint of the follow-up. Tumor recurrence time and survival

time were recorded in order to calculate OS and DFS of the two groups of patients. Up to May 1st, 2020, a total of 29 of the 108 patients had tumor recurrence, with the recurrence rate of 26.9%, including 6 cases in the AFP/TTV ≤ 2 group (12.8%) and 23 cases in the AFP/TTV > 2 group (37.7%). The Kaplan-Meier survival curves of OS and DFS are showed as Figure 3 and Figure 4. From the result we can see, both OS and DFS have significant difference between patients in AFP/TTV ≤ 2 group and AFP/TTV > 2 group.

3.3. Risk factors analysis

In order to find out the risk factors which would cause early tumor recurrence and poor prognosis of patients with HCC after liver transplantation, basic information, preoperative laboratory index, surgical related data and postoperative pathological data were analyzed using Kaplan-Meier survival analysis. Factors that affecting OS and DFS of the patients were analyzed separately and the results were showed as Table 2 and Table 3. It uncovered that patients who was over 60 years old ($\chi^2 = 3.91$, $P < .05$), with preoperative TBil over 21 μmol/L ($\chi^2 = 9.93$, $P < .05$), with preoperative serum AFP over 100 ng/ml ($\chi^2 = 9.34$, $P < .05$), with
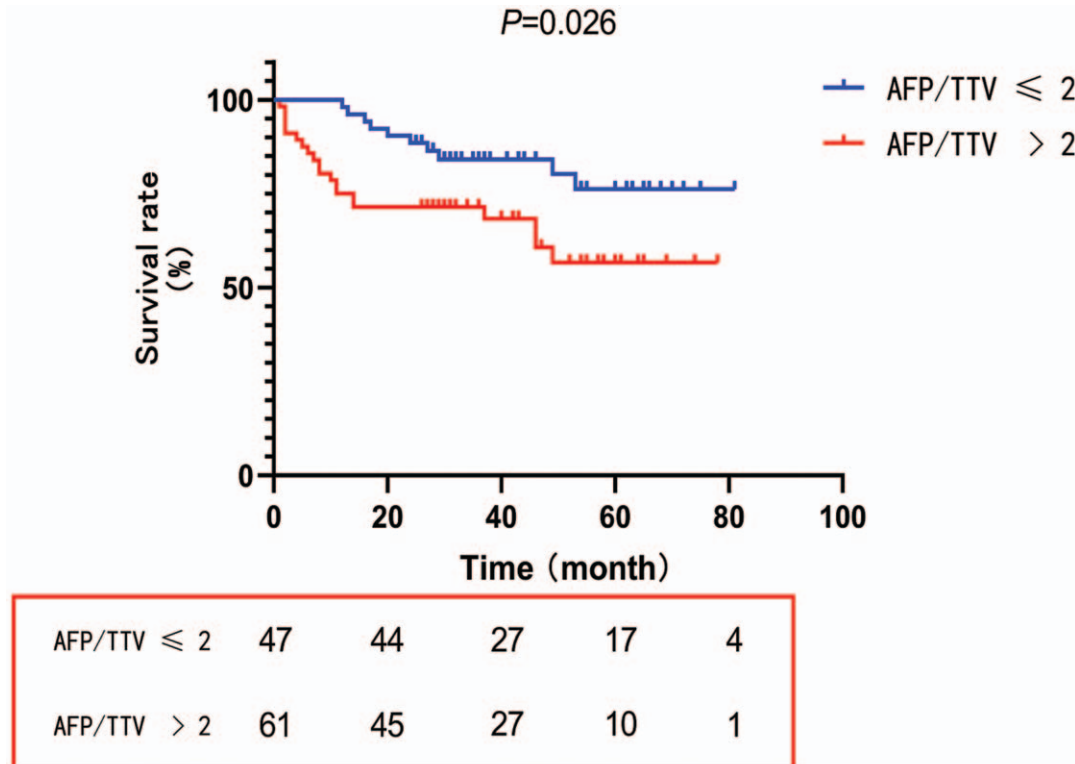
Figure 3. Kaplan-Meier survival curve for overall survival in patients with AFP/TTV≤2 and AFP/TTV>2. AFP = alpha-fetoprotein, TTV = total tumor volume.
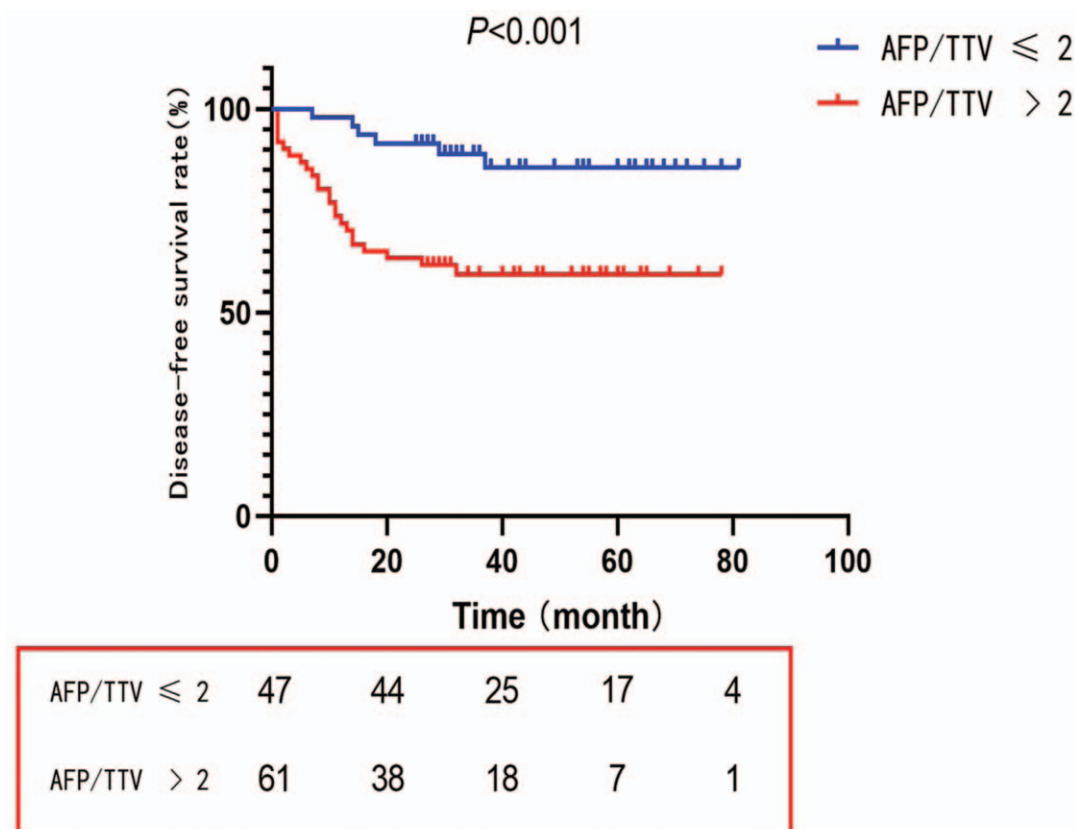
Figure 4. Kaplan-Meier survival curve for disease-free survival in patients with AFP/TTV≤2 and AFP/TTV>2. AFP = alpha-fetoprotein, TTV = total tumor volume.

Table 2

Univariate analyses of prognostic factors in HCC patients after LT (n = 108).

Variable		1 yr OS(%)	3 yr OS (%)	5 yr OS(%)	P
Age	<60	95.5	90.9	86.4	.048
	≥60	89.5	81.4	76.7	
Gender	male	89.8	81.6	77.6	.780
	female	90.0	83.1	75.9	
Underlying diseases	(+)	88.0	80.0	72.0	.574
	(−)	89.2	81.9	77.1	
Child-Pugh grade	A/B	91.3	84.6	80.8	.284
	C	90.0	80.0	80.0	
ALB(g/L)	≥40	92.6	85.2	81.5	.256
	<40	90.1	82.7	77.8	
AST(U/L)	≤40	92.1	84.2	76.3	.364
	>40	87.1	80.0	75.7	
ALT(U/L)	≤40	91.8	85.0	76.1	.488
	>40	87.0	82.5	75.5	
TBil(μmol/L)	≤21	93.5	89.1	86.4	.002
	>21	88.7	79.0	72.6	
AFP(ng/ml)	≤100	94.1	83.8	80.9	.002
	>100	80.0	75.0	67.5	
Operation time(h)	≤10	90.9	81.8	77.9	.319
	>10	87.1	80.6	74.2	
Intraoperative blood loss(ml)	≤1000	93.2	83.6	78.1	.367
	>1000	82.9	77.1	76.8	
Intraoperative blood transfusion	(+)	93.5	84.8	73.9	.537
	(−)	87.1	79.0	77.4	
The number of tumor	single	90.6	83.0	81.1	.067
	multiple	89.1	81.8	74.5	
Tumor differentiation	high/moderate	93.2	87.5	84.1	.060
	low	85.0	70.0	65.0	
TTV(cm³)	≤65.5	92.4	86.4	83.3	.007
	>65.5	90.0	71.4	66.7	
Cancer embolus in portal vein	(+)	75.0	70.0	60.0	.002
	(−)	92.0	83.0	78.4	
AFP/TTV	≤2	100.0	93.6	89.4	.001
	>2	83.6	75.4	70.5	

*ALB = albumin; AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LT = liver transplantation; TBil = total bilirubin; TTV = total tumor volume.

Table 3

Early and late HCC recurrence with risk factors for 5 years HCC recurrence (n = 108).

Variable		1 yr DFS(%)	3 yr DFS(%)	5 yr DFS (%)	P
Age	<60	95.5	90.9	86.4	.038
	≥60	89.5	81.4	77.9	
Gender	male	90.8	82.7	79.6	.782
	female	80.0	80.0	80.0	
Underlying diseases	(+)	88.0	80.0	72.0	.675
	(−)	89.2	80.7	79.5	
Child-Pugh grade	A/B	91.3	84.6	81.7	.251
	C	90.0	80.0	80.0	
ALB(g/L)	≥40	92.6	81.5	81.5	.237
	<40	90.1	82.7	79.0	
AST(U/L)	≤40	89.5	78.9	78.9	.398
	>40	88.6	81.4	77.1	
ALT(U/L)	≤40	90.0	82.5	80.0	.514
	>40	89.7	83.8	79.4	
TBil(μmol/L)	≤21	93.5	89.1	86.4	.001
	>21	88.7	77.4	72.6	
AFP(ng/ml)	≤100	94.1	85.1	83.6	.003
	>100	82.5	75.0	70.0	
Operation time(h)	≤10	92.2	83.1	79.2	.239
	>10	83.9	80.6	74.2	
Intraoperative blood loss(ml)	≤1000	91.8	82.2	78.1	.419
	>1000	82.9	77.1	76.8	
Intraoperative blood transfusion	(+)	93.5	84.8	78.3	.558
	(−)	87.1	79.0	77.4	
The number of tumor	single	90.6	83.0	81.1	.110
	multiple	89.1	80.0	74.5	
Tumor differentiation	high/moderate	93.2	86.4	84.1	.074
	low	85.0	70.0	65.0	
TTV(cm³)	≤65.5	93.9	89.4	87.9	.009
	>65.5	81.0	69.0	64.3	
Cancer embolus in portal vein	(+)	75.0	70.0	60.0	.005
	(−)	90.9	81.8	78.4	
AFP/TTV	≤2	100.0	91.5	89.4	<.001
	>2	83.6	75.4	72.1	

*ALB = albumin; AFP = alpha-fetoprotein; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBil = total bilirubin; TTV = total tumor volume.

TTV over 65.5 cm³ ($\chi^2 = 7.26$, $P < .05$), had cancer embolus in portal vein ($\chi^2 = 9.59$, $P < .05$) and AFP/TTV>2 ($\chi^2 = 14.42$, $P < .05$) had significant poorer prognosis while other factors have no obvious correlation. There were similar results about DFS, which showed that patients who was over 60 years old ($\chi^2 = 4.29$, $P < .05$), with preoperative TBil over 21 μmol/L ($\chi^2 = 10.73$, $P < .05$), with preoperative serum AFP over 100ng/ml ($\chi^2 = 8.94$, $P < .05$), with TTV over 65.5 cm³ ($\chi^2 = 6.82$, $P < .05$), had cancer embolus in portal vein ($\chi^2 = 7.77$, $P < .05$) and AFP/TTV>2 ($\chi^2 = 13.39$, $P < .05$) had significant earlier tumor recurrence.

Risk factors with statistical differences mentioned above were incorporated in the multiple-factor analysis using the COX regression model. Displayed in Table 4, it showed that had cancer

Table 4

Multivariate analyses of prognostic factors in HCC patients after LT (n = 108).

Variable	OS		DFS	
	HR(95% CI)	P value	HR(95% CI)	P value
Age	0.462 (0.106–2.020)	.305	0.260 (0.098–1.874)	.260
Total Bilirubin	2.485 (0.911–6.783)	.075	2.726 (1.002–7.417)	.051
AFP	1.087 (0.442–2.672)	.856	1.138 (0.467–2.773)	.776
Cancer embolus in portal vein	2.345 (1.012–5.432)	.047	1.793 (0.786–4.093)	.165
TTV	2.701 (1.111–6.570)	.028	2.451 (1.017–5.906)	.046
AFP/TTV	4.624 (1.629–13.123)	.004	4.257 (1.506–12.032)	.006

*AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma TTV = total tumor volume.

embolus in portal vein (HR = 2.345, $P < .05$), with TTV≥65.5 cm³ (HR = 2.701, $P < .05$) and with AFP/TTV>2 (HR = 4.624, $P < .05$) were independent risk factors for poor prognosis of HCC patients after liver transplantation. As for tumor recurrence, Table 4 showed that with TTV≥65.5 cm³ (HR = 2.451, $P < .05$) and with AFP/TTV>2 (HR = 4.257, $P < .05$) were independent risk factors for early HCC recurrence after liver transplantation while other factors had no significant difference.

4. Discussion

Studies have shown that the secretion of AFP may be directly related to cell proliferation and tumor activity, so serum AFP levels may be closely related to tumor invasion ability[15–17] Some scholars believe that AFP>100ng/ml is closely related to the recurrence of HCC while some other scholars pointed out that the recurrence rate of HCC would significantly increase when AFP>400ng/ml in their research.[17,18] TTV, as another indicator of tumor burden, also affects the tumor recurrence rate and the prognosis of HCC patients. Lee, et al. confirmed that when TTV≥40 cm³, the recurrence rate of HCC increased dramatically while Zakaria, et al pointed out that TTV≥65.5 cm³ was a risk factor of HCC recurrence in their research.[19,20] Through calculation, TTV of 65.5 cm³ is approximately equal to tumor diameter of 5 cm, which is the boundary of the diameter of large liver cancer. So we believe that TTV≥65.5 cm³ would be an appropriate grouping basis. In addition, relevant studies in different countries have confirmed that multiple tumors, low degree of tumor differentiation, with vascular invasion and tumor thrombosis and the poor international normalized ratio (INR) are high risk factors for HCC recurrence.[16,21–23] Preoperative liver function status (Child-Pugh score) of HCC patients was considered to have no statistically significant effect on postoperative tumor recurrence and prognosis.[24]

High preoperative serum AFP level was considered to be a high risk factor for tumor recurrence after surgery while tumor recurrence after liver cancer liver transplantation is the main reason causing the poor prognosis of HCC patients. However, with further research, some scholars believe that the accuracy and effectiveness of using AFP alone to predict HCC recurrence are controversial.[14,25] In this regard, studies have suggested that AFP/TTV is more precise in predicting HCC recurrence compared with simply using AFP as a basis[26] Scholars believe that AFP/TTV>1.5 was an independent risk factor for HCC recurrence.[19] In Zakaria's research, AFP/TTV>2 was one of the independent risk factors for HCC recurrence after hepatectomy through multiple-factor analysis.[20] In this study, the included patients were divided into two groups by AFP/TTV≤2 or AFP/TTV>2 and the effects on tumor recurrence and overall prognosis of HCC patients after liver transplantation were studied.

In this study, the results of single factor analysis suggested that patients who was over 60 years old, with TBil>21umol/L, with portal vein tumor thrombus, with AFP>100ng/ml, with TTV>65.5 cm³ and with AFP/TTV>2 are the risk factors for early tumor recurrence together with poor prognosis of patients with HCC after liver transplantation. The results above are basically consistent with those of domestic and foreign studies. It is worth mentioning that in this study, single factor analysis showed that the number of tumors and the degree of differentiation had no significant statistical significance for

either OS or DFS of patients with HCC after liver transplantation. The reason why may be as the following two aspects. First, as a retrospective study with the 108 patients included, this study may have statistically bias due to insufficient sample size. This would be improved by counting more patients during the further research. The second reason may be that the patients included in this study were all suffered liver transplantation, but relatively speaking, most of the patients who were included in both domestic and abroad studies were suffered hepatectomy. As is known to all that most patients with HCC have a basis of cirrhosis on which the tumor may develop rapidly. Simple hepatectomy only removes the primary tumor instead of solving the cirrhosis. Residual hepatic tissue with cirrhosis is still easy to form tumors, which increased the recurrence rate of HCC. In addition, HCC often has intrahepatic metastasis through the portal venous system first, which means that hepatectomy may leave small tumor lesions in liver tissue remaining. Multiple and poorly differentiated tumors are more invasive and are more prone to have microsatellite nodules, which increasing the risk of tumor recurrence and causing the poor prognosis after hepatectomy in patients with HCC. In contrast, liver transplantation cures liver cirrhosis in patients with HCC and removes the entire diseased liver at the same time, which ensures that there is no residual microsatellite focus in the liver. It can also explain in a sense why multiple and poorly differentiated tumors can become a high risk factor for tumor recurrence after hepatectomy but there is no significant statistical significance in HCC patients who suffered liver transplantation in this experiment. In this study, AFP/TTV>2, TTV>65.5 cm³, and had portal vein tumor thrombosis are independent risk factors that lead to poor prognosis in patients with liver cancer after liver transplantation in multivariate analysis while AFP/TTV>2 and TTV>65.5 cm³ are independent risk factors of tumor recurrence. High AFP levels no longer have statistical significance in either tumor recurrence or overall survival of HCC patients after liver transplantation through multiple-factor analysis. This further illustrates that AFP/TTV has stronger specificity and more obvious value in predicting tumor recurrence and prognosis of HCC patients after liver transplantation than using AFP alone. AFP/TTV can be used as a screening index, which can help us to provide preventive measures to patients with high risk of tumor recurrence after liver transplantation. The impact of AFP/TTV on the longer-term prognosis of HCC patients who suffered liver transplantation will still require longer follow-up and further research.

5. Conclusion

To sum up, the prognosis of patients with liver cancer after liver transplantation is affected by many factors. AFP/TTV ratio has important predictive value for the prognosis of patients with HCC after liver transplantation. AFP/TTV>2 is an independent risk factor for poor prognosis of patients with HCC after liver transplantation.

Author contributions

Conceptualization: Tao Jiang, Xiao-shi Zhang.
Data curation: Shao-cheng Lyu, Jing Wang, Xiao-shi Zhang.
Formal analysis: Fei Pan, Meng-xiu Huang, Tao Jiang.
Funding acquisition: Ren Lang.
Investigation: Tao Jiang, Xiao-shi Zhang.

Supervision: Ren Lang, Qiang He.
Writing – original draft: Tao Jiang, Xiaoshi Zhang.
Writing – review & editing: Ren Lang, Qiang He.

References

[1] Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:238–55.
[2] Yang JD, Hainaut P, Gores GJ, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019;16:589–604.
[3] Umberto B, Miriam I, Gian LA, et al. Superiority of transplantation versus resection for the treatment of small hepatocellular carcinoma. Transpl Int 2008;21:247–54.
[4] Bigourdan J, Jaeck D, Meyer N, et al. Small hepatocellular carcinoma in Child A cirrhotic patients: hepatic resection versus transplantation. Liver Transpl 2003;9:513–20.
[5] Bellavance EC, Lumpkins KM, Mentha G, et al. Surgical management of early-stage hepatocellular carcinoma: resection or transplantation? J Gastrointest Surg 2008;12:1699–708.
[6] Abdelfattah MR, Elsiesy H, Al-Manea H, Broering DC. Liver transplantation for hepatocellular carcinoma within the Milan criteria versus the University of California San Francisco criteria. Eur J Gastroenterol Hepatol 2018;30:398–403.
[7] Qu Z, Ling Q, Gwiasda J, et al. Hangzhou criteria are more accurate than Milan criteria in predicting long-term survival after liver transplantation for HCC in Germany. Langenbecks Arch Surg 2018;403:643–54.
[8] Gao T, Xia Q, Qiu DK, et al. Comparison of survival and tumor recurrence rates in patients undergoing liver transplantation for hepatitis b-related hepatocellular carcinoma using milan, Shanghai Fudan and Hangzhou criteria. J Dig Dis 2013;14:552–8.
[9] Debruyne EN, Delanghe JR. Diagnosing and monitoring hepatocellular carcinoma with alpha-fetoprotein: new aspects and applications. Clinica Chimica Acta 2008;395:19–26.
[10] Tyson GL, Duan Z, Kramer JR, Davila JA, Richardson PA, El-Serag HB. Level of fetoprotein predicts mortality among patients with hepatitis C–related hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:989–94.
[11] Chan MY, She WH, Dai WC, et al. Prognostic value of preoperative alpha-fetoprotein (AFP) level in patients receiving curative hepatectomy-an analysis of 1182 patients in Hong Kong. Transl Gastroenterol Hepatol 2019;4:52.
[12] Aziz AM, Zakaria H, Ayoub I, Soliman HE, Osman M. The safety and adequacy of liver resection for large hepatocellular carcinoma: a retrospective single institute study. Saudi Surg J 2016;4:20–8.
[13] Toso C, Trotter J, Wei A, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. Liver Transpl 2008;14:1107–15.
[14] Lee Y, Hsia C, Hsu C, Huang YH, Lin HC, Huo TI. Total tumor volume is a better marker of tumor burden in hepatocellular carcinoma defined by the milan criteria. World J Surg 2013;37:1348–55.
[15] Hsu CY, Huang YH, Hsia CY, et al. A new prognostic model for hepatocellular carcinoma based on total tumor volume: the Taipei Integrated Scoring System. J Hepatol 2010;53:108–17.
[16] Saito R, Amemiya H, Hosomura N, et al. Prognostic factors for post-recurrent survival in hepatocellular carcinoma after curative resection. Anticancer Res 2019;39:3033–8.
[17] Sharma Y, Weaver MJ, Ludwig DR, et al. Serum alpha-fetoprotein level per total tumor volume as a predictor of recurrence of hepatocellular carcinoma after resection. Surgery 2018;163:1002–7.
[18] Shirabe K, Takenaka K, Gion T, et al. Significance of alpha-fetoprotein levels for detection of early recurrence of hepatocellular carcinoma after hepatic resection. J Surg Oncol 1997;64:143–6.
[19] Lee Y, Hsu C, Huang Y, et al. Alfa fetoprotein-to-total tumor volume ratio predicts post-operative tumor recurrence in hepatocellular carcinoma. J Gastrointest Surg 2013;17:730–8.
[20] Zakaria HM, Mohamed A, Omar H, et al. Alpha-fetoprotein level to total tumor volume as a predictor of hepatocellular carcinoma recurrence after resection. A retrospective cohort study. Ann Med Surg 2020;54:109–13.
[21] Wu J, Huang Y, Chau G, et al. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. J Hepatol 2009;51:890–7.
[22] Yoh T, Seo S, Taura K, et al. Surgery for Recurrent Hepatocellular Carcinoma: Achieving Long-term Survival. Ann Surg 2021;273:792–9.
[23] Hu JK, Li XM, Zhang F, et al. Progression in influential factors of hepatocelluar carcinoma recurrence. Chin J Hepatobiliary Surg 2018;24:644–8.
[24] Lin GZ, Dai TX, Liu RQ, et al. Effect of different liver function Child-Pugh classification on clinical prognosis of hepatocellular carcinoma recipients after liver transplantation. Organ Transpl 2019;10:308–12.
[25] Li M, Zhao H, Bi X, et al. Total tumor volume predicts survival following liver resection in patients with hepatocellular carcinoma. Tumor Biology 2016;37:9301–10.
[26] Toso C, Meeberg G, Hernandez-Alejandro R, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: a prospective validation. Hepatology 2015;62:158–65.