

Association and interaction between model for end-stage liver disease score and minimally invasive treatment with regard to mortality of patients with hepatitis B virus-associated hepatocellular carcinoma and portal vein tumor thrombi

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Abstract. The development of minimally invasive treatment over the last two decades has had a great impact on hepatitis B virus (HBV)-associated primary liver cancer. The model for end-stage liver disease (MELD) score is the optimal evaluated parameter for mortality in patients with end-stage liver disease. However, the association between MELD score and minimally invasive treatment with regard to the mortality of patients with HBV-associated hepatocellular carcinoma (HCC) with a portal vein tumor thrombus (PVTT) remains unclear. In the present study, a total of 173 patients who had been diagnosed with HBV-associated HCC and PVTT in the Beijing Ditan Hospital (Beijing, China), between January 2012 and January 2015, were screened. Follow-up was performed to observe the survival time and collect information on the demographic characteristics and associated clinical indicators present in the cohort. The patient's age, sex, laboratory parameters and the use of minimally invasive treatment were analyzed with SPSS 20.0 software. Independent risk factors for mortality were screened by Cox regression analysis. Logistic regression indicated that there was an interaction between the MELD score and minimally invasive treatment. In addition, a MELD score ≤ 17.85 was associated with a lower mortality rate subsequent to minimally invasive treatment.

Introduction

Primary liver cancer is the fifth most common malignancy and the second leading cause of cancer-associated mortality worldwide (1). Hepatocellular carcinoma (HCC) accounts for >80% of primary liver cancer cases (2). Patients with chronic hepatitis B virus (CHB) have been reported to frequently progress to cirrhosis and liver failure (3). Furthermore, it has been demonstrated that CHB is associated with the development of HCC. It has been estimated that CHB-associated HCC accounts for >80% of HCC cases in areas with high hepatitis B virus (HBV) incidence (4). HCC is prone to invade the intrahepatic vessels, particularly the portal vein system (4). It has been reported that portal vein tumor thrombus (PVTT) occurs frequently in patients with HCC (5). Patients with HCC and PVTT often present with portal vein hypertension, ascites, tumor dissemination and deterioration of liver function. In addition, poor prognosis and a survive rate of 2-3 months has been reported for these patients when no treatment is received (6). Since radical resection cannot be performed in patients with HCC and PVTT, minimally invasive treatment is widely used for treating patients with HCC and PVTT (7,8). The development of minimally invasive treatments in the past 20 years has greatly improved (9). It has been reported that the most widely used minimally invasive treatments include transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) (10). It has been reported that TACE is the optimal treatment recommended by the European Association for the study of the liver and by the American Association for the study of liver diseases in the HCC management guidelines for patients with intermediate HCC (11). According to the guidelines for the management of HCC, RFA is one of the first-line treatments for patients with Barcelona clinic liver cancer (BCLC)-0 which is in the earliest stages of cancer, and BCLC-A grade (12).

Liver function is one of the important factors that affect tumor prognosis. The model for end-stage liver disease score (MELD), which includes serum creatinine, bilirubin and the

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international normalized prothrombin time ratio, serves as an alternative non-invasive biomarker of liver function (13). In the present study, the associations between liver function and minimally invasive treatment and the survival rate of patients with liver cancer were determined. However, the association between MELD score and minimally invasive treatment requires further investigation. The purpose of the present study was to analyze the demographic characteristics, laboratory indicators and imaging data in patients with HBV-associated HCC and PVTT, and to further examine the effect of MELD score and minimally invasive treatment on the 1-year overall survival rate of the aforementioned patients.

Materials and methods

Patients. A total 173 patients (18 to 80 years old, the median age was 56 years) with HBV-associated primary liver cancer and PVTT were included in the present retrospective study. Samples (n=173) were collected from Beijing Ditan Hospital (Beijing, China) between January 2012 and January 2015. The present study was approved by the Ethics Committee of the Beijing Ditan Hospital, Capital Medical University, in accordance with the Declaration of Helsinki (approval no. 7142081). Written informed consent was obtained from all individual participants included in the present study.

Inclusion criteria. Patients with hepatitis B surface antigen-positive primary liver cancer were included in the present study. The pathological diagnostic criteria for primary liver cancer were as follows: Tissue specimens were diagnosed as primary liver cancer by histopathology and cytology, and tissue specimens were acquired from liver lesions or extra-hepatic metastases by biopsy or surgical resection. Clinical diagnostic criteria for primary liver cancer were in accordance with the 'primary liver cancer diagnosis and treatment norms' (14). PVTT was diagnosed on the basis of a filling defect in the portal vein or its branch on contrast-enhanced computed tomography or magnetic resonance imaging.

Exclusion criteria. Patients with the following characteristics were excluded from the present study: i) Hepatitis C, human immunodeficiency virus infection, autoimmune liver disease, genetic metabolic liver disease, drug-induced liver disease and other chronic liver diseases; ii) diseases affecting the heart, lungs, kidneys, brain, blood and other vital organs; iii) severe mental illness; iv) pregnancy and lactation; v) metastatic liver cancer; vi) treatment with radiotherapy or chemotherapy; and vii) incomplete clinical data.

Statistical analysis. Statistical analysis was performed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Mean \pm standard deviation was used to fit the normal distribution. Student's t-test was used to compare continuous variables and the significant differences between two groups (15). In non-normal distribution data, the two groups were compared using the Wilcoxon rank sum test. Frequency represented the count data, which were compared with the χ^2 test. In univariate analyses, the χ^2 test or Fisher exact test were utilized to compare categorical data and the two sample groups (16). Logistic regression analysis was used for multivariate analysis and interaction

between MELD and minimally invasive treatment. In multivariate regression analysis, single factor ($P < 0.05$) was used to calculate the independent risk factors. $P < 0.05$ was considered to indicate a statistically significant difference. Overall survival rates were calculated by the Kaplan-Meier method with the log-rank test applied for comparison. Bonferroni's test was used to correct for the multiple comparisons. Kaplan-Meier survival curves were drawn using GraphPad 5.0 software (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Patients and disease characteristics. Patients and disease characteristics are summarized in Table I. The present study included 173 patients with HBV-associated HCC who received PVTT treatment in the Beijing Ditan Hospital between January 2012 and January 2015 (Fig. 1). Complete follow-up of the patients (n=173) was available until the time of patient mortality or for the following 2 years. Out of the 173 patients participating in the present study, a total of 121 succumbed within a year and 52 survived. The survival rate was 42.98% and the median survival time was 5 months. Baseline characteristics were compared between the survival group and the mortality group. The alanine transaminase, aspartate transaminase, direct bilirubin, glutamyl transferase, alkaline phosphatase and MELD scores were significantly higher in the mortality group ($P < 0.05$), while the cholinesterase and percentage of cluster of differentiation (CD)4⁺/CD8⁺ T cells were significantly lower in the mortality group relative to the survival group ($P < 0.05$). In addition, there was an increased number of patients with α -fetoprotein (AFP) $> 1,000$ ng/ml, HBV-DNA > 500 copies and abdominal effusion in the mortality group compared with that in the survival group ($P < 0.001$, Table I).

Site of tumor thrombus invasion is associated with mortality rate. The association was analyzed between the site of invasion of the tumor thrombus and patient mortality. As indicated in Table II, the highest mortality rate (54.5%) was exhibited in patients where the tumor thrombus had invaded the trunk and the branches of the portal vein, whereas the lowest mortality rate (7.4%) was indicated in patients where the tumor thrombus had only invaded the trunk. Kaplan-Meier survival curves illustrated the survival time of patients with tumor thrombus invasion on a 1-year mortality scale. The tumor thrombus invasion site significantly affected the survival time of patients with HBV-associated HCC ($P = 0.003$; Fig. 2). The patients with a tumor thrombus invasion site only in the trunk of the portal vein experienced a longer survival time ($P = 0.003$; Fig. 2).

Association between minimally invasive treatment and mortality. The effect of minimally invasive treatment for a cancer embolus on patient mortality rate was analyzed. The mortality rates of conservative treatment and minimally invasive treatment were 75.95 and 64.89%, respectively, indicating a significant difference ($P < 0.01$) between the two types of treatment. By comparing different minimally invasive treatment methods, the lowest mortality rate of 52.3% was indicated in patients with the combination treatment of TACE and RFA (Table III). The mortality rate was 75.9% in patients without minimally invasive treatment.

Table I. Baseline characteristics of the study cohort.

Variables	Survival group (n=52)	Mortality group (n=121)	P-value
Age, years	53.560±1.960	54.780±1.479	0.859
Sex, n (%)			
Male	42 (29.000)	103 (79.000)	0.503
Female	10	18	
Alcohol consumption, n	19	52	0.410
WBC, x10 ⁹ /l	4.500 (2.000, 7.000)	5.000 (3.500, 7.000)	0.100
HGB, g/l	109.00±7.499	119.332±3.745	0.900
PLT, x10 ⁹ /l	118.75±17.009	122.457±9.356	0.440
NLR	3.150 (2.278, 5.237)	3.404 (2.293, 4.986)	0.210
ALT, U/l	35.500(15.500, 51.750)	45.000 (32.000, 62.000)	0.004 ^a
AST, U/l	40.000 (23.750, 51.750)	85.000 (50.000, 168.000)	<0.001 ^a
DBIL, μmol/l	8.000 (5.000, 13.500)	11.00 (7.000, 25.000)	0.010 ^a
GGT, U/l	107.000 (58.000, 235.250)	148.000 (95.500, 271.500)	<0.001 ^a
ALP, U/l	134.188±12.234	167.530±11.367	<0.001 ^a
CHE, U/l	4426.938±606.710	3855.385±224.471	0.039 ^a
ALB, g/l	33.000 (29.250, 37.750)	34.000 (30.000, 40.500)	0.687
Cr, μmol/l	69.500 (52.250, 76.500)	63.000 (55.000, 73.000)	0.284
PTA, %	70.000 (57.750, 76.750)	75.000 (66.000, 81.500)	0.650
CD4 ⁺ /CD8 ⁺ , %	2.500 (2.000, 3.000)	2.000 (1.000, 2.000)	0.007 ^a
AFP (>1,000 ng/ml), n (%)	9 (12.676)	62 (87.324)	<0.001 ^a
HBV DNA (>500 copies/l), n (%)	9 (14.754)	52 (85.246)	<0.001 ^a
Treatment method, n (%)			0.010 ^a
Minimally invasive	33 (63.462)	61 (50.413)	
Conservative	19 (36.538)	60 (49.587)	
MELD score, n (%)			
≤17.85	30 (37.975)	49 (62.025)	0.037 ^a
>17.85	22 (23.404)	72 (76.595)	
Complication, n (%)			
Abdominal effusion	27 (23.894)	86 (76.106)	0.030 ^a
Abdominal infection	12 (22.222)	42 (77.778)	0.150

^aStatistically significant. WBC, white blood cell; HGB, hemoglobin; PLT, platelet count; NLR, neutrophil lymphocyte rate; ALT, alanine transaminase; AST, aspartate transaminase; DBIL, direct bilirubin; GGT, glutamyl transferase; ALP, alkaline phosphatase; CHE, cholinesterase; ALB, albumin; Cr, creatinine; PTA, prothrombin activity; HBV, hepatitis B virus; CD, cluster of differentiation; AFP, α-fetoprotein; MELD, model for end-stage liver disease. Student's t-test was used to compare normal distribution data. In non-normal distribution data, the two groups were compared using the Wilcoxon rank sum test (Mann-Whitney U test). Frequency represented the count data, which were analysed by the χ^2 test (Pearson χ^2 test). Normal distribution is represented by mean ± standard deviation and non-normal distribution is represented by median (upper quartile and lower quartile).

A Kaplan-Meier curve for 1-year mortality was used to compare the survival times among patients with conservative treatment and patients with different types of minimally invasive treatment. Results indicated that the patients with minimally invasive treatment exhibited a significantly longer survival time compared with patients with conservative treatment (P=0.007; Fig. 3A). Furthermore, the minimally invasive treatments were further divided into the TACE, RFA, combined TACE and RFA, and conservative treatment groups. It was indicated that the minimally invasive treatment of TACE plus RFA exerted the best survival time of patients with HBV-associated HCC in all group (P=0.005; Fig. 3B).

Multivariate analysis. The Kaplan-Meier curve for 1-year mortality was used to compare the survival time between patients with AFP >1,000 ng/ml and AFP ≤1,000 ng/ml, and between patients with HBV-DNA >500 copies/l and HBV-DNA ≤500 copies/l. As indicated in Fig. 4A, in patients with AFP ≤1,000 ng/ml refer to a significantly higher survival rate compared with patients with AFP >1,000 ng/ml (P<0.001). In addition, patients with HBV-DNA ≤500 copies/l refer to a significantly higher survival rate compared with patients with HBV-DNA >500 copies/l (P=0.001) (Fig. 4B).

Using multivariate logistic regression analyses (Table IV), the independent risk factors of mortality of HBV-associated HCC with PVTT were HBV-DNA >500 copies/l, (P=0.013;

Table II. Baseline distribution of tumor thrombus.

Location	Survival group (n=52)	Mortality group (n=121)	P-value
Trunk + branch, n (%)	19 (36.538)	66 (54.545)	0.001 ^a
Branch, n (%)	20 (38.462)	46 (38.017)	
Trunk, n (%)	13 (25.000)	9 (7.438)	

^aStatistically significant. analysed by the χ^2 test (Pearson χ^2 test).

Table III. Minimally invasive treatment of baseline distribution.

Treatment	Survival group (n=52)	Mortality group (n=121)	P-value
TACE + RFA, n (%)	21 (40.385)	23 (19.008)	0.016 ^a
TACE, n (%)	12 (23.077)	33 (27.273)	
RFA, n (%)	0 (0.000)	5 (4.132)	
None, n (%)	19 (36.538)	60 (51.240)	

^aStatistically significant. TACE, transarterial chemoembolization; RFA, radiofrequency ablation. Analysed by the χ^2 test (Pearson χ^2 test).

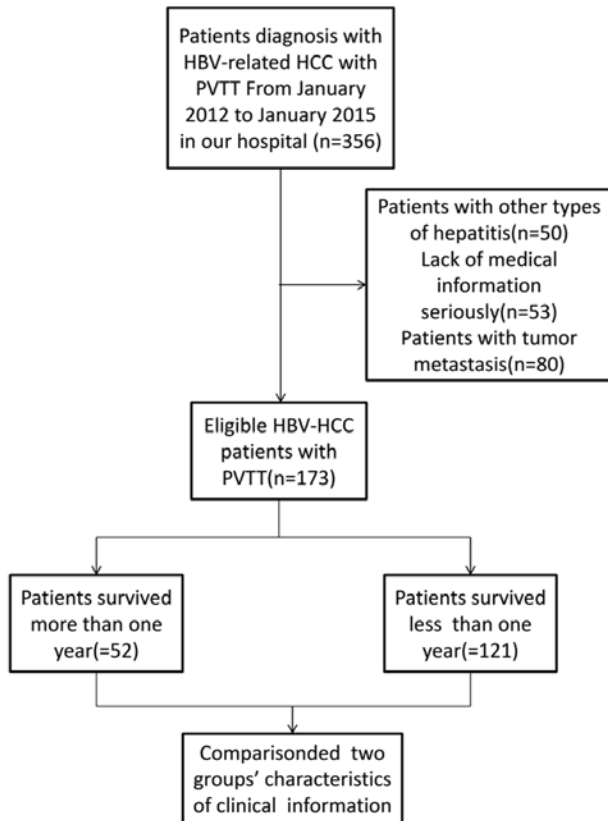


Figure 1. Flow chart of the included patients. HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; HBV, hepatitis B virus.

odds ratio, 4.582) and AFP >1,000 ng/ml (P=0.012; odds ratio, 2.167). Furthermore, the interaction between MELD score and minimally invasive treatment was indicated (P=0.021; odds ratio, 2.167; 95% confidence interval, 1.124-4.177) in Table IV.

In order to verify the interaction between the treatment and the MELD score, the mean survival times of patients with minimally invasive treatments or conservative therapy were analyzed when the MELD score was different (Table V). The cut-off value of the MELD score (17.85) was obtained by using Jorden index. The present study also indicated the survival curves of different types of treatment for different MELD scores (Fig. 5A and B). The results indicated that patients with minimally invasive treatment had a longer survival time compared with patients with conservative treatment (Table V). The patients in the minimally invasive treatment group with a MELD score ≤ 17.85 , experienced a significantly longer survival time compared with that of patients with a MELD

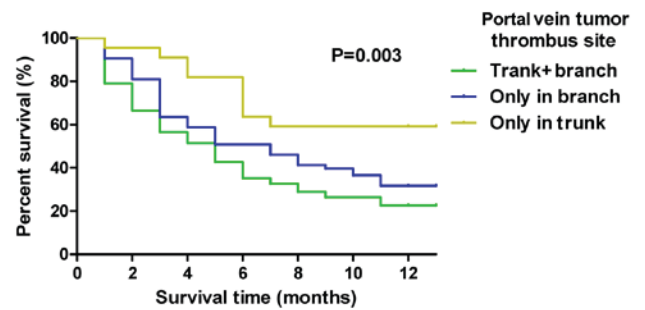


Figure 2. Site of invasion of the tumor thrombus was associated with overall survival rate. Kaplan-Meier curve compared the probability of survival between the portal vein sites of invasion, namely the trunk and branches, of the tumor thrombus.

score >17.85 (Table V; Fig. 5A and B). In addition, the survival time of patients receiving different types of minimally invasive treatments, in addition to having different MELD scores, was analyzed (Table VI). Results indicated that the patients with a MELD score ≤ 17.85 experienced a significantly longer survival time for all types of minimally invasive treatments.

Discussion

Liver cancer is prone to metastasis and confers a poor prognosis (17). Portal vein invasion is common in HCC with intrahepatic metastasis, and is one of the leading causes for tumor recurrence and tumor-associated mortality subsequent to surgery (16). A retrospective study of 601 patients indicated that PVTT significantly affected the survival rate of patients independently (18). However, there have been few studies on prognostic models of HCC with PVTT. The purpose of the present study was to identify independent risk factors for HBV-associated HCC and to establish a predictive model. It was indicated that minimally invasive treatment is the optimal treatment choice for patients with HCC and PVTT plus a low MELD score in comparison to patients with a high MELD score (threshold value, 17.85).

Previous studies have demonstrated the effect of PVTT on patient prognosis. It was reported that patients with HBV-associated HCC and PVTT experienced a low median survival time of 2-4 months (19,20). A recent study conducted by Kokudo *et al* (21) indicated that the median survival time of patients in the liver resection group was 1.77 years longer than

Table IV. Logistic regression analysis of significant variables.

Variables	B	OR	95% CI	P-value
HBV DNA, copies/l		Reference		
≤500				
>500	1.522	4.582	1.377-15.242	0.013
AFP, ng/ml		Reference		
≤1,000				
>1,000	1.598	4.945	1.420-17.223	0.012
MELD score* minimally invasive treatment		Reference		
	0.773	2.167	1.124-4.177	0.021

HBV, hepatitis B virus; AFP, α -fetoprotein; CI, confidence interval; MELD, model for end-stage liver disease; OR, odds ratio*; interacted with. Logistic regression analysis.

Table V. Survival time (months) of patients with minimally invasive and conservative treatment and different MELD scores.

MELD score	Minimally invasive	Conservative	P-value
≤17.85	8.652±0.645	6.273±0.863	0.012
>17.85	6.714±0.565	4.739±0.690	

MELD, model for end-stage liver disease. Analysed by the χ^2 test (Pearson χ^2 test).

that of patients in the non-liver resection group and 0.88 years longer than that of patients in the non-liver resection group in a propensity score-matched cohort. In addition, a survival benefit of chemoembolization plus iodine-125 seed implantation has been reported in unresectable HBV-associated HCC with PVTT (22,23). In the present study, it was indicated that the median survival time was 5 months in patients with HBV-associated HCC and PVTT. The median survival time was significantly longer compared with results reported in previous studies (19,20), suggesting that improvements in treatment methods may have increased patient survival time. In the present study, AFP levels were significantly associated with a poor prognosis in patients with HCC. Since AFP levels have been reported to reflect tumor progression, this marker is frequently measured during patient treatment (24). In previous studies, AFP response had been reported as a predictive factor for radiological response, recurrence and survival in early and advanced HCC cases (25-28). Consistent with previous studies, the present study indicated that AFP >1,000 ng/ml was one of the independent risk factors for survival time of patients with HBV-associated HCC and PVTT. The copies of HBV-DNA represent viral load, which are risk factors for the development of cirrhosis and HCC. The copies of HBV-DNA have also been indicated to be associated with a poor prognosis in patients with HCC (29,30). The present study demonstrated that patients with HBV-DNA >500 copies/l experienced a shorter survival time compared with patients with HBV-DNA ≤500 copies/l. The aforementioned result was consistent with previous studies (20,30).

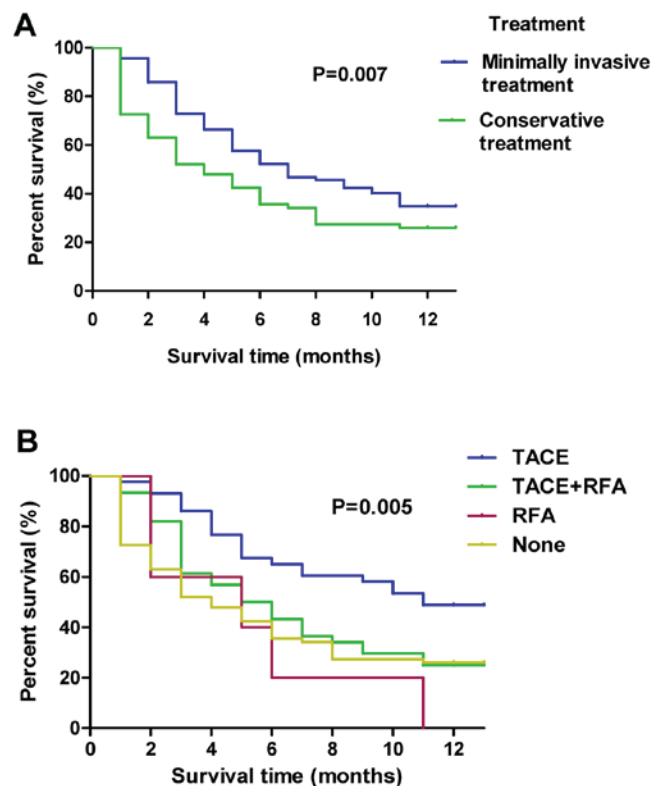


Figure 3. A comparison of overall survival rate following minimally invasive or conservative treatment. (A) A comparison of the survival probability between the minimally invasive and conservative treatment groups. (B) A comparison of the survival probability among the different minimally invasive treatments, including TACE and RFA. TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

Hirooka *et al* (31) indicated that the cumulative survival rates at 6, 12 and 24 months were 100, 89.7 and 78.8%, respectively, with the combined treatment of TACE and RFA and that the median survival time was 953 days. For patients treated only with TACE, the cumulative survival rates at 6, 12 and 24 months were 84.9, 56.1 and 16.9%, respectively, and the median survival time was 352 days. In the present study, it was demonstrated that the combination of TACE and RFA significantly increased the survival time in patients with HCC.

Table VI. Survival time (months) of patients with different minimally invasive treatments and different MELD scores.

Treatment	MELD score ≤17.85	MELD score >17.85	P-value
TACE + RFA	9.680±0.815	8.000±1.094	0.008
TACE	7.667±1.051	5.977±0.817	
RFA	6.000±2.646	4.000±2.000	
None	6.273±0.863	4.739±0.690	

MELD, model for end-stage liver disease; TACE, transarterial chemoembolization; RFA, radiofrequency ablation. Analysed by the χ^2 test (Pearson χ^2 test).

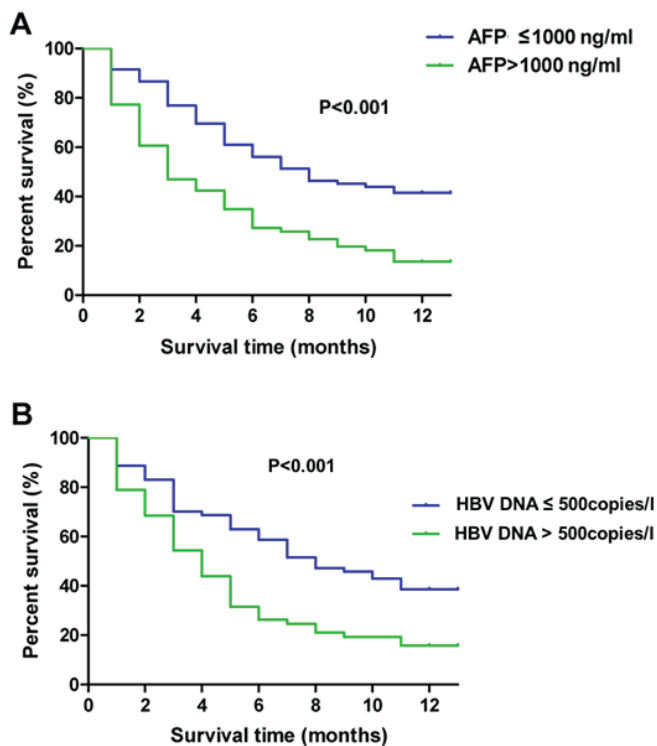


Figure 4. Associations among AFP, HBV DNA and overall survival. (A) A comparison of the survival probability between patients with AFP ≤1,000 ng/ml and AFP >1,000 ng/ml. (B) A comparison of the survival probability between patients with HBV DNA ≤500 copies/l and HBV DNA >500 copies/l. AFP, α -fetoprotein; HBV, hepatitis B virus.

The MELD scoring system has been widely used to assess the prognosis of liver function and liver-associated diseases (13). The cut-off value of the MELD score (17.85) was obtained by using Jorden index (<https://www.scalelive.com/youden-index.html>). The results of the present study indicated that a MELD score ≤17.85 in patients with HCC and PVTT displayed a better prognosis compared with a MELD score >17.85. Furthermore, patient prognosis became worse as MELD score increased. The aforementioned result was consistent with previous studies (32,33). In addition, the present study also indicated an interaction between MELD score and minimally invasive treatment, suggesting that minimally invasive treatment may improve the prognosis in patients with a MELD

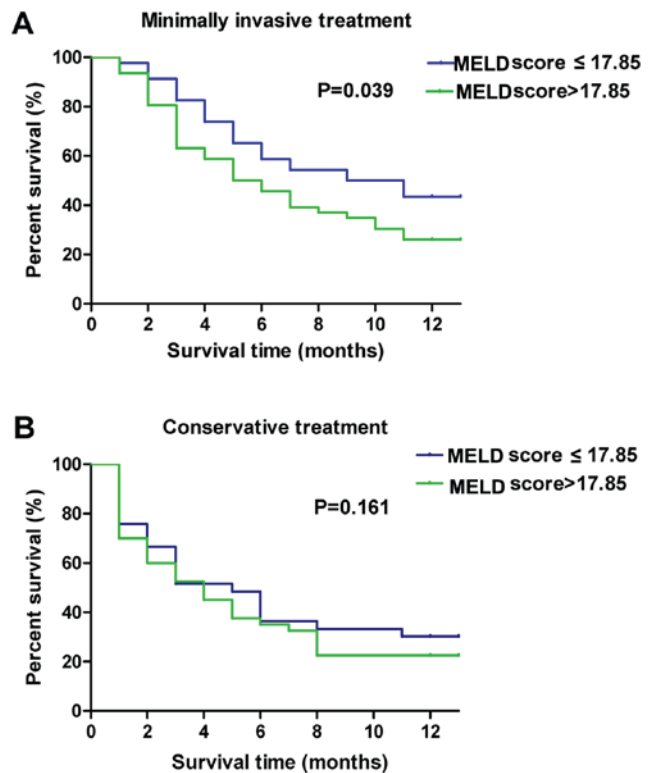


Figure 5. Survival curves of minimally invasive and conservative treatments for different MELD grades. Kaplan-Meier method compared the probability of survival between patients with a MELD score ≤17.85 and a MELD score >17.85 in minimally invasive and conservative treatment groups. MELD, model for end-stage liver disease.

score ≤17.85. However, minimally invasive treatment did not improve the prognosis in patients with a meld score >17.85.

In conclusion, the present study provided a theoretical basis for the treatment of patients with HCC and PVTT. However, the number of samples in the present study was limited and therefore, further investigation is required to expand the sample size, verifying the present study results.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZYY and XLL designed the study; YLZ, XLL and MGL collected and analyzed the data; MGL and XLL wrote the manuscript; XLL acquired, analysed and interpreted the data; XHW and ZBD provided patients' data; YYJ, XLL and ZYY were responsible for the interpretation of data and revision. ZYY and XLL approved the final version.

Ethics approval and consent to participate

The study was approved by the ethics committee of Beijing Ditan Hospital, Capital Medical University. Written informed consent was obtained from each patient.

Patient consent for publication

Written informed consent was obtained from each patient. Information that could identify individual participants during or after data collection was not accessible.

Competing interests

The authors declare that they have no competing interests.

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