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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Prognosis Nomogram for Hepatocellular Carcinoma Patients with Portal Vein Invasion Undergoing Transarterial Chemoembolization Plus Sorafenib Treatment: A Retrospective Multicentre Study

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Abstract

Objectives To explore the outcomes of combined transarterial chemoembolization (TACE) with sorafenib in hepatocellular carcinoma (HCC) patients with portal vein tumour thrombus (PVTT) and to establish a prognostic prediction nomogram to differentiate target patients and stratify risk.

Materials and Methods This multicentre, retrospective study consisted of 185 consecutive treatment-naïve patients with HCC and PVTT treated with TACE plus sorafenib from three institutions between January 1st, 2012 and December 31st, 2017. The primary outcome measurement of the study was overall survival (OS). The type of PVTT was classified by the Liver Cancer Study Group of Japan. The prognostic nomogram was established based on the predictors and was performed with interval validation.

Results The median OS of the Vp1-3 and Vp4 groups was 12.4 months (11.7–18.9) and 8.5 months (7.6–11.2) ($P = 0.00098$), respectively, and there was a significant difference in the median OS between the Vp1-2 and Vp3 subgroups (16.4 months (12.2–27.9) vs. 10.9 months (8.4–18.1), $P = 0.041$). The multivariate Cox regression analysis suggested that tumour size, albumin-bilirubin grade, and PVTT type were independent prognostic factors. The C-index value of the nomogram based on these predictors in the entire cohort was 0.731 (0.628–0.833).

Conclusions After the combined therapy of TACE and sorafenib, advanced HCC patients with segmental or subsegmental PVTT showed better survival than those with main PVTT. The nomogram can be applied to identify advanced HCC patients with PVTT who may benefit most from the combination treatment and be helpful for making decision in clinical practice.

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Keywords Hepatocellular carcinoma · Portal vein tumour thrombus · Transarterial chemoembolization · Sorafenib · Prognosis

Abbreviations

HCC	Hepatocellular carcinoma
BCLC	Barcelona clinic liver cancer
TACE	Transarterial chemoembolization
cTACE	Conventional transarterial chemoembolization
OS	Overall survival
PFS	Progression-free survival
PVTT	Portal vein tumour thrombus
IRBs	Institutional review boards
EASL	European association for the study of the liver
AASLD	American association for the study of liver diseases
CT	Computed tomography
CECT	Contrast-enhanced computed tomography
ECOG	Eastern cooperative oncology group
VEGF	Vascular endothelial growth factor
PDGFR	Platelet-derived growth factor receptor
LCSGJ	Liver cancer study group of Japan
MRI	Magnetic resonance imaging
ALBI	Albumin-bilirubin
CTP	Child-turcotte-pugh
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
TTP	Time to progression
TTR	Tumour response rate
CTCAE	Common terminology criteria of adverse events
C-index	Concordance index
mRECIST	Modified response evaluation criteria in solid tumors
AEs	Adverse events
CI	Confidence interval

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumours and fourth most prevalent cause of cancer-related death [1]. Portal vein tumour thrombus (PVTT) has been found to occur in approximately 30–50% of patients at the time that hepatocellular carcinoma (HCC) is first diagnosed [2]. The presence of PVTT is considered as being indicative of advanced HCC, and the median overall survival (OS) is 2.7–4 months if untreated [3]. Systematic therapy, such as sorafenib, is recommended by the Barcelona Clinic Liver Cancer (BCLC) staging system based on the results of two-phase III randomized controlled trials, but the subgroup analyses demonstrated that the survival benefit to the patients with PVTT/extrahepatic metastasis was modest compared to the placebo [4–8]. The first-rank treatment for HCC patients with PVTT remains controversial [9].

Transarterial chemoembolization (TACE) is the standard therapeutic option for intermediate stage HCC [10]. Most studies show that TACE can be performed safely and improve survival in advanced HCC patients with PVTT, even those with the main trunk of the portal vein involved [11–13]. However, one limitation of TACE is that TACE induces central anoxia and peripheral hypoxia, leading to upregulation of hypoxia inducible factor-1 which, in turn, upregulates vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR) and increases tumour angiogenesis [14–16]. To improve efficacy in HCC patients with PVTT undergoing TACE, combining sorafenib with TACE may decrease angiogenesis after the administration of TACE [17–19]. Some studies have shown that in HCC patients with PVTT, sorafenib combined with TACE offered manageable safety and was observed to prolong survival [20–22]. Zhu reported that combination treatment of TACE and sorafenib improved survival in patients with HCC and PVTT in the segmental or subsegmental portal vein branches [23]. However, the STAH trial suggested that the combination therapy increased survival in patients with severe vascular invasion [24]. Thus, the role of such combination therapy in patients with HCC and different types of PVTT has not been determined.

The aim of this multicentre study is to explore the outcomes of combined TACE and sorafenib in patients with HCC and PVTT and to establish a prognostic prediction nomogram to differentiate target patients and stratify risk.

Materials and Methods

Patient Criteria

This multicentre, retrospective study consisted of consecutive treatment-naïve patients with HCC and PVTT treated with cTACE plus sorafenib from 3 institutions between January 1st, 2012 and December 31st, 2017. The study was endorsed by the Institutional Review Boards (IRBs) at all 3 participating centres, and the requirement for informed consent was waived owing to its retrospective nature. The study complied with the Declaration of Helsinki. HCC was diagnosed by non-invasive criteria used by the European

Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) [25, 26]. As determined by three-phase dynamic computed tomography (CT), the presence of PVTT was confirmed with hypodensity of an intraluminal mass expanding the portal vein or filling defects in the main portal vein or portal vein branches or both. The type of PVTT was classified by the Liver Cancer Study Group of Japan (LCSGJ) as follows: (1) VP1 was segmental portal vein invasion, (2) VP2 was invasion of right anterior or posterior portal vein, (3) VP3 was right or left portal vein invasion, and (4) VP4 was tumour thrombus in the main trunk and/or contralateral portal vein branch to the primarily involved lobe [27].

The patients were enrolled based on the criteria as follows: (1) patients were older than 18 years, (2) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, (3) had portal vein tumour thrombus on three-phase dynamic CT images within 1 week before treatment, (4) had no previous administration of HCC-related treatment, such as resection, locoregional therapy, or chemotherapy, (5) had a Child–Pugh class A to B7, and had (6) adequate haematological, clotting, and renal function.

The patients were excluded from the enrolment if they met the following criteria: (1) comorbidity with other primary malignancies, (2) contraindications to sorafenib or cTACE treatment, (3) previous HCC-related treatment, including resection, ablation, TACE, or radiotherapy, (4) the absence of baseline imaging and clinical data, (5) evidence of bleeding diathesis or coagulopathy, or (6) discontinuation of sorafenib administration of more than 1 month.

TACE Procedure

Briefly, TACE was performed with a 2.7 F microcatheter (Progret; Terumo; Tokyo; Japan) as super-selectively as possible through the segmental or subsegmental feeding arteries, depending on the tumour distribution and hepatic functional reserve. Chemoembolization was performed based on the practice of each centre with intra-arterial doxocubicin (10–50 mg) and oxaliplatin (100–200 mg) mixed with lipiodol (2–20 ml, lipiodol ultra-fluid, 480 mg I/mL; Guerbet, France) followed by injection of gelatin sponge (Aili Kang Pharmaceutical Technology Co. Ltd., Hangzhou, China), until arterial flow was substantially reduced, as observed via fluoroscopy. The injection volume of the emulsion was determined based on the tumour volume. TACE cycles were repeated on an "on demand" basis in the setting of detecting residual or new tumour on follow-up imaging. A ECOG performance status of 0 or 1 was required from the patients before undergoing additional TACE treatment. If patients were not candidates for further TACE, they received best supportive care. All TACE procedures were performed by 6 interventional radiologists with more than 8 years of experience.

Sorafenib Administration

Sorafenib (Bayer Healthcare, Leverkusen, Germany) was administered orally to patients within 7 days after every TACE session. To preserve liver function, sorafenib administration was stopped before the day of each TACE session. In principle, the dose of sorafenib was 400 mg twice daily (800 mg/day). Nevertheless, treatment interruptions and dose reductions (400 mg once-daily, 400 mg alternated days) were permitted for drug-related adverse events (AEs). If any grade 3 or grade 4 adverse events continued after dose reductions, the administration of sorafenib was interrupted until the adverse effects were alleviated or disappeared. The patients were excluded if they did not adhere to the regimen.

Assessments

The primary outcome measurement of the study was OS. OS was defined as the time from the initial TACE procedure until death or last follow-up (September 30th, 2019). The secondary outcome measurement was progression-free survival (PFS). PFS was defined as the time from the date of TACE until the time of radiological progression, which was evaluated by modified Response Evaluation Criteria in Solid Tumour (mRECIST). Radiological progression was assessed by 2 independent radiologists who were blinded to the clinical information. All imaging was read by both with reconciliation mechanism for cases of disagreement. In patients who did not die or progress, the censoring date was defined as the last radiological assessment date. For subgroup analyses, the outcomes of patients with different PVTT types (Vp1-3 vs. Vp4, Vp1-2 vs. Vp3) were compared.

The albumin-bilirubin (ALBI) grade was calculated pretreatment by the formula: linear predictor = $(\log_{10}$ bilirubin $\times$ 0.66) + (albumin $\times$ −0.085), where albumin is in g/L and bilirubin in μmol/L. The cut-off points included xb $\leq$ −2.60 (ALBI grade 1), more than −2.60 to $\leq$ −1.39 (ALBI grade 2), and xb more than −1.39 (ALBI grade 3) [28]. Continuous variables were transformed into categorical variables based on recognized cut-off values. All patients received routine laboratory examination before the initial TACE treatment and every 4 weeks afterwards. Side effects of sorafenib and TACE were reported using Common Terminology Criteria of AEs (CTCAE) version 5.0.

Statistical Analysis

Categorical variables were summarized as frequencies or counts with percentages, whereas continuous variables were presented as medians with 95% confidence intervals (CIs). Chi-square tests and Mann–Whitney *U* tests were used to compare differences among three institutions in baseline characteristics. As generated by the Kaplan–Meier method, survival curves were compared with two-sided log-rank tests. Univariate analysis was employed to assess the statistical significance of clinical features, and variables with statistical significance were included in the multivariate analysis using a Cox regression model to identify the predictors associated with OS. The features with *P* value less than 0.05 were considered to be significant factors in both the univariate and multivariate analysis. Statistical analyses to identify prognostic factors were performed using SPSS 13.0 for Windows (SPSS, Chicago, IL). The prognostic nomogram was established based on the predictors and performed with interval validation. For internal validation, the performance of nomograms was assessed by calculating the concordance index (C-index) with 1000 bootstrap resamples. The value of the C-index ranges from 0.5 to 1, and a higher C-index means greater predictive performance. A C-index of 0.5 indicates a random chance, and 1 indicates perfect prediction. The larger the C-index is, the more accurate the prognostic prediction is. All statistical tests were two sided, and a *P* value < 0.05 was used as the criterion to indicate statistical significance. The nomogram was programmed through the regression model strategies package in R.

Results

Baseline Characteristics

An amount of 185 treatment-naïve HCC patients with PVTT who underwent TACE plus sorafenib treatment during January 1st, 2012 and December 31st, 2017 were enrolled in this multicentre study. The workflow of this study is shown in Fig. 1. Conventional TACE (cTACE) was performed in all patients. The baseline characteristics of the enrolled patients are shown in Table 1. The median age of the entire cohort was 53 (range, 26–81) years. Hepatitis B virus (HBV) was the main aetiology of HCC (84.3%). There was no significant difference in the clinical characteristics in the three hospitals (Supplemental Table 1). In the subgroups of patients with different PVTT types, the baseline characteristics were not significantly different (Table 1). The median duration of sorafenib administration was 6.1 (range, 0.2–40) months. The median daily dose of sorafenib was 505 mg. Dose reduction or interruption was required in 82 (44.3%) patients, mainly due to drug-related adverse events or disease progression.

Outcomes and Subgroup Analyses

The median follow-up for the entire cohort was 12.8 (95% CI, 8.2–19.1) months. A total of 23 patients were lost to follow-up. The median OS and PFS of the entire cohort were 11.2 months (95% CI, 9.6–12.8) and 6.0 months (95% CI, 5.0–7.0), respectively. For the subgroup analyses, the median OS and PFS of the Vp1-3 and Vp4 groups were 12.4 months (95% CI, 11.7–18.9) vs. 8.5 months (95% CI, 7.6–11.2) ($P = 0.00098$), 6.2 months (95% CI, 5.4–9.7) vs. 4.2 months (95% CI, 3.8–5.6) ($P = 0.0007$), respectively, and for the Vp1-3 subgroup analyses, there were significant differences in the median OS and PFS between the Vp1-2 and Vp3 subgroups (16.4 months (95% CI, 12.2–27.9) vs. 10.9 months (95% CI, 8.4–18.1), $P = 0.041$, and 9.2 months (95% CI, 6.1–14.22) vs. 5.4 months (95% CI, 3.9–9.0), $P = 0.045$, respectively) (Fig. 2).

Factors Associated with Overall Survival (OS) and Nomogram Development

The multivariate Cox regression analysis suggested that larger tumour size, higher ALBI grade, and more advanced PVTT type were independent prognostic factors to be considered for model development (Table 2).

A nomogram was established based on the significant risk factors identified by the univariable and multivariable analyses (Fig. 3A). Each patient was assigned one individualized grade, which was the total of points from the three prognostic factors, to accurately predict the outcome. The C-index value of the nomogram in the entire cohort was 0.731 (95% CI, 0.628–0.833). The median value of the scores predicted by the nomogram was determined as the cut-off for stratifying the patients in the entire cohort into

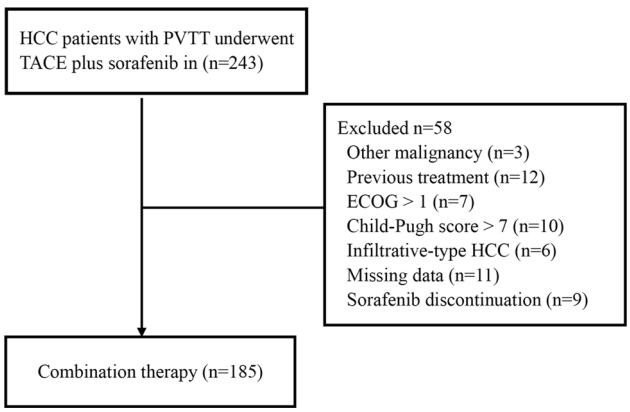

Fig. 1 Workflow of this study

Table 1 Baseline characteristics

Characteristic	Overall (n = 85)	Vp1-2 (n = 42)	Vp3 (n = 43)	P value	Overall (n = 185)	Vp1-3 (n = 85)	Vp4 (n = 100)	P value
Gender				0.738				0.512
Male	76	37	39		162	76	86	
Female	9	5	4		23	9	14	
Age (years)				0.330				0.515
≤ 55	63	29	34		132	63	69	
> 55	22	13	9		53	22	31	
ECOG				0.782				0.214
0	70	34	36		144	70	74	
1	15	8	7		41	15	26	
Pathogeny				0.771				0.841
Hepatitis B	71	36	35		156	71	85	
Hepatitis C	0	0	0		0	0	0	
Other	14	6	8		29	14	15	
Tumour size (cm)				0.801				0.094
≤ 5	13	6	7		35	13	22	
5–10	39	21	18		83	39	44	
> 10	33	15	18		67	33	34	
No. of nodules				0.128				0.460
1	48	20	28		98	48	50	
> 1	37	22	15		87	37	50	
Tumour distribution				0.091				0.209
Unilobar	62	27	35		126	62	64	
Bilobar	23	15	8		59	23	36	
Extrahepatic spread				0.382				0.179
(PVTT excluded)	14	5	9		23	14	9	
AFP (ng/dl)				1.000				0.097
≤ 200	27	13	14		71	27	44	
> 200	58	29	29		114	58	56	
AST (U/L)				0.649				0.144
≤ 40	29	13	16		53	29	24	
> 40	56	29	27		132	56	76	
ALT (U/L)				0.827				0.140
≤ 40	50	24	26		97	50	47	
> 40	35	18	17		88	35	53	
ALBI grade				1.000				0.003
1	41	21	20		65	41	24	
2	42	20	22		108	42	66	
3	2	1	1		12	2	10	
CTP grade				0.52				1.000
A	75	36	39		163	75	88	
B	10	6	4		22	10	12	

AFP alpha-fetoprotein, *ALBI* albumin-bilirubin, *ALT* alanine transaminase, *AST* aspartate transaminase *CTP* Child-Turcotte-Pugh, *ECOG* Eastern Cooperative Oncology Group, *PVTT* portal vein tumour thrombus

*Fisher's exact test was used

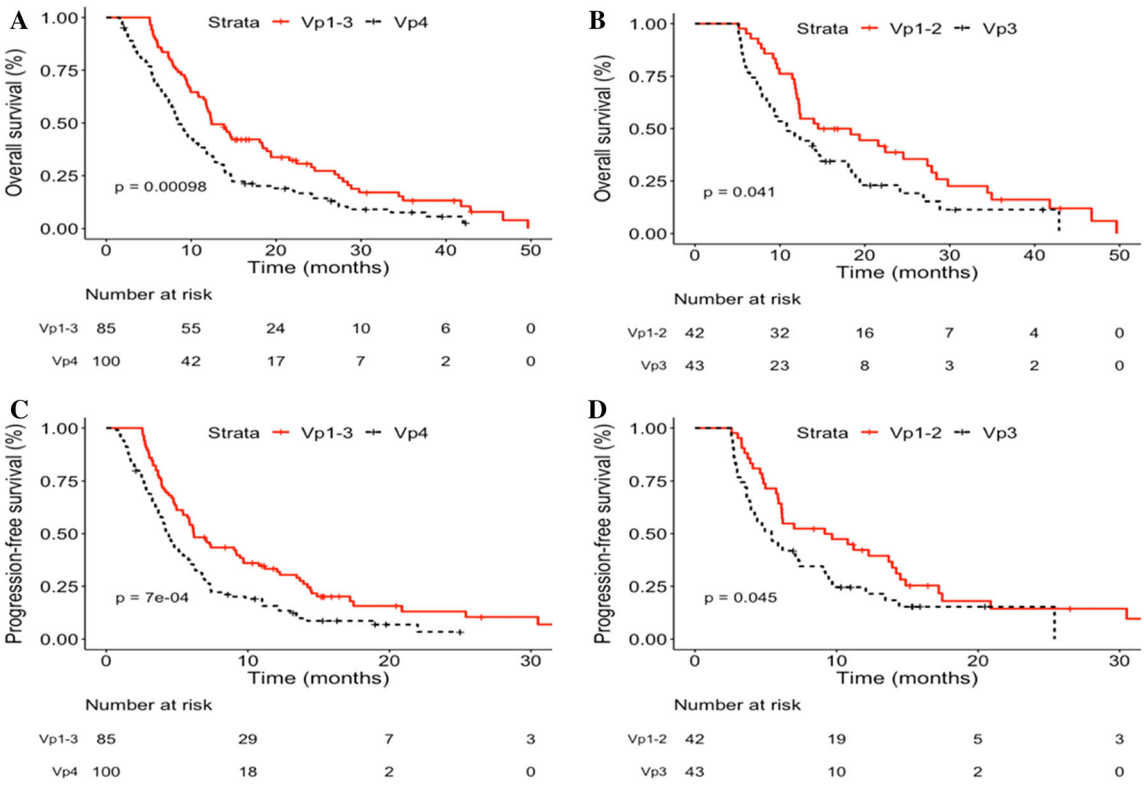

Fig. 2 Kaplan–Meier curves of subgroup analyses of overall survival (OS) **A** and **B** and progression-free survival (PFS) **C** and **D** for the entire cohort

two subgroups. The subgroup with scores higher than the median score was considered the high-risk group, and the other subgroup was considered the low-risk group. The patients in the low-risk group had better OS than the high-risk group ($P < 0.001$, Fig. 3B).

Adverse Events

Adverse events related to TACE or sorafenib after treatment are listed in Table 3. AEs occurred in > 10.3% of the enrolled patients. The most common grade3/4 AEs included increased aspartate aminotransferase (AST) (11.3%), increased alanine aminotransferase (ALT) (8.6%), abdominal pain (8.1%), hand-foot skin reaction (11.9%), and fatigue (4.9%). Severe AEs included gastrointestinal haemorrhage, which occurred in two men (70 and 66 years old) with portal hypertension and the patients were discharged from the hospital after abrosia, somatostatin and antibiotic treatment 1 week after TACE. There were no treatment-related deaths within 4 weeks of the combination therapy without clear evidence of a cause, such as disease progression.

Table 2 Multivariate cox proportional hazards regression analysis of risk factors associated with overall survival

Variables	HR	95% CI	*B*-value	*P* value *
PVTT type				
Vp1-2	1			
Vp3	1.375	(0.825–2.291)	0.318	0.222
Vp4	2.27	(1.455–3.500)	0.814	< 0.001
Tumour size (cm)				
< 5	1			
5–10	1.599	(1.019–2.508)	0.469	0.041
> 10	2.100	(1.279–3.449)	0.742	0.003
ALBI				
1	1			
2	1.697	(1.173–2.454)	0.529	0.005
3	4.234	(2.007–8.931)	1.443	< 0.001

B-values were regression coefficients

ALBI albumin-bilirubin, *PVTT* portal vein tumour thrombus

*Cox Regression analysis was used

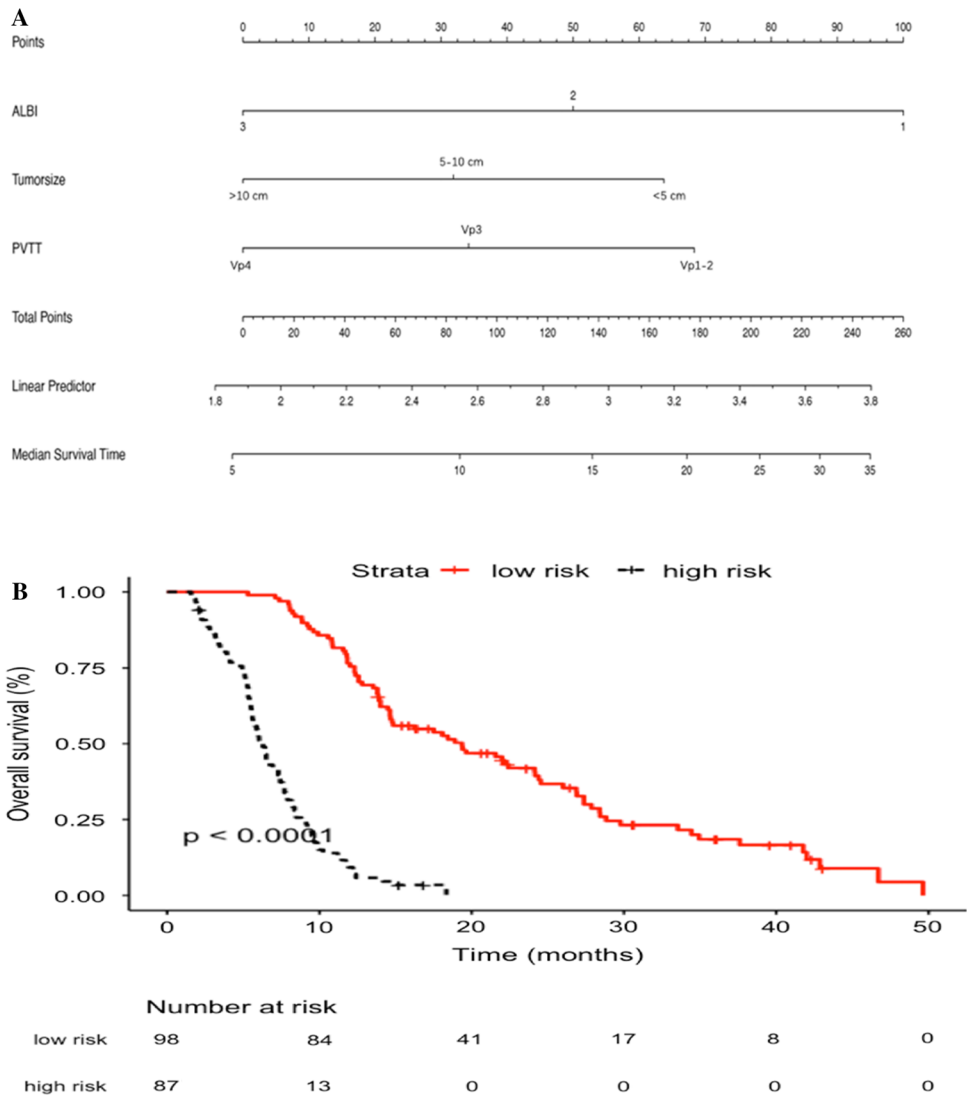

Fig. 3 **A** Prognosis nomogram for HCC patients with PVTT who underwent TACE plus sorafenib. To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis, and a line is drawn downward to the survival axis to determine the likely median survival time. **B** OS of low-risk and high-risk group in the entire cohort

Discussion

This multicentre retrospective study determined that advanced HCC patients with segmental or subsegmental PVTT showed better survival than those with main PVTT after the combined therapy of TACE and sorafenib. In addition, based on evaluating various survival risk factors for OS, a nomogram was established with a C-index of 0.731 to accurately predict the individual outcomes of patients with HCC and PVTT undergoing TACE plus sorafenib treatment.

Although sorafenib is the standard of care for advanced HCC patients according to the ASSLD and EASL, sorafenib monotherapy improved survival by approximately 3 months in both Western and Eastern populations [7, 8, 25, 26]. Historically, in terms of a potential risk of hepatic infarction or deterioration of liver function, the presence of PVTT was regarded as a relative contraindication for TACE [29]. Nevertheless, as was shown in the BRIDGE study, TACE was the most common therapeutic regimen in patients with advanced HCC [30]. Furthermore, previous studies indicated that TACE was a safe and efficacious treatment for patients with different locations of PVTT, even the main portal vein [11, 12]. Previous studies showed that the upregulation of angiogenic factors induced by ischaemic liver injury may limit the efficacy of TACE [15].

The combination of TACE plus an anti-angiogenic agent (sorafenib) may inhibit angiogenic factors and tumour growth [19, 31, 32]. Nonetheless, the phase 3 STAH trial showed the co-administration of conventional TACE and sorafenib did not improve OS compared with sorafenib alone for patients with advanced HCC [24]. The reason for this lack of improvement may be mainly due to the heterogeneity of the advanced HCC group, resulting in variable individual responses apart from the trial design

Table 3 Adverse events

Adverse events	All grades	Grade ≥ 3
Sorafenib related		
Hand foot skin reaction	101 (54.6%)	22 (11.9%)
Hypertension	44 (23.8%)	3 (1.6%)
Diarrhea	55 (29.7%)	8 (4.3%)
Rash	30 (16.2%)	6 (3.2%)
TACE related		
AST elevation	45 (24.3%)	21 (11.3%)
ALT elevation	39 (21.1%)	16 (8.6%)
Abdominal pain	67 (36.2%)	15 (8.1%)
Fatigue	51 (27.6%)	9 (4.9%)
Nausea	38 (20.5%)	1 (0.5%)
Vomiting	21 (11.4%)	2 (1.1%)
Fever	33 (17.8%)	6 (3.0%)
Infection	19 (10.3%)	4 (2.2%)

Adverse events were graded using CTCAE version 5.0

ALT Alanine aminotransferase, *AST* Aspartate aminotransferase, *CTCAE* Common Terminology Criteria for Adverse Events

[15, 33]. What was encouraging was that the combination therapy significantly prolonged time to progression (TTP), PFS and tumour response rate (TTR). Surprisingly, patients with severe vascular invasion, such as Vp3-4, seemed to have a trend towards survival gain, although this did not reach statistical significance.[24].

As a sophisticated anatomical and clinical condition, the prognosis of patients with PVTT may range from 5 months to 5 years, leading to considerable variability [34]. Hence, it is crucial to focus on the most appropriate strategy to be applied to each HCC patient with PVTT. The current study indicated that treatment of TACE plus sorafenib may improve survival in patients with less advanced PVTT compared to those with more advanced PVTT. It was postulated that the decreased flow of hepatic arteries induced by TACE may compromise liver function in patients with main PVTT [23], sorafenib could inhibit upregulation of VEGF, which mediates collateral growth in ischaemic disease, and therefore reduced liver regeneration [35, 36]. Given these factors, this study suggested that the combination treatment could be regarded as an alternative approach in patients with HCC and segmental and subsegmental PVTT. The median OS of our study was 11.2 months, which was shorter than the STAH trial, possibly because of the different target population [24]. It was longer than the study developed by Choi, the reason may be the higher proportion (87.8%) of extrahepatic metastasis in the patients [21]. However, Zhu and Zhao found a median survival of 11.0 and 12.0 months, which was similar to the current study [20, 23]. The median PFS in this study was 6.0 months, and it is consistent with the STAH trial (5.2 months) [24].

As presented in this study, a nomogram including ALBI score, PVTT type and tumour size were built to individually predict the prognosis of HCC patients with PVTT treated by TACE plus sorafenib. It is well known that tumour burden and liver function are associated with the prognosis in HCC patients [28]. Previous predictive models showed that larger tumour size is a predictor of poor prognosis in HCC [10, 37]. As mentioned above, PVTT type was also relevant to HCC patient outcomes. After the multivariable analyses, it was shown that the ALBI grade and not the Child-Turcotte-Pugh (CTP) grade was a significant risk factor for OS. As a conventional model to quantify liver functional status, the CTP grade includes highly subjective variables, such as the grading of ascites and encephalopathy [38]. It was suggested that there was a 10-month gap between ALBI grade 1 and 2 groups after reclassifying CTP grade A patients [39]. Similarly, it was shown that there was a significant difference in OS between the three ALBI groups in the present study. Such heterogeneity was also observed in many clinical trials for sorafenib and may have impacted patient survival [38]. By avoiding interobserver variation and reducing heterogeneity, many prognosis models based on the ALBI grade can be applied to select patients who benefit most from different therapies [28, 38]. Thus, we concluded that ALBI grade may be an independent predictor of OS in HCC patients with PVTT who underwent TACE plus sorafenib treatment.

Some limitations in this study should be noted. First, there may have been selection bias in the study because of its retrospective nature. The number of patients was small, which may make it difficult to form definitive conclusions. Second, previous evidence suggested that concurrent rather than sequential administration of sorafenib may be the most effective approach because the growth factors are secreted hours after TACE [14]. However, to reduce the potential for AEs, physicians may prefer sequential administration in routine practice. Thirdly, chemoembolization was performed by using conventional approaches only, whereas the drug-eluting TACE (DEB-TACE) were often used in many other institutions. Finally, the study did not compare the efficacy and safety of combined treatment with sorafenib monotherapy.

In conclusion, in advanced HCC patients with segmental or subsegmental PVTT, the combination of TACE and sorafenib is effective and safe. Furthermore, a nomogram based on a novel predictor (ALBI) was developed to identify advanced HCC patients with PVTT who may benefit most from the combination treatment and may be helpful for making decision in clinical practice. Future

prospective studies with external validations are needed to validate the findings.

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Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent The requirement to obtain informed consent was waived due to the retrospective nature of this study.

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