



Stratification of portal vein-invaded hepatocellular carcinoma treated with transarterial chemoembolization monotherapy

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ABSTRACT

Purpose: The study aimed to establish a prognostic prediction model and an artificial neural network (ANN) model to determine who will benefit from transarterial chemoembolization (TACE) monotherapy for patients with hepatocellular carcinoma (HCC) invading portal vein.

Methods: Treatment-naïve patients with HCC and portal vein invasion who were treated with TACE monotherapy at hospital A as training cohort and hospital B as validation cohort were included. The primary endpoint was overall survival (OS). In training cohort, independent risk factors associated with OS were identified by univariate and multivariate analysis. The prognostic prediction (PP) and ANN models based on the independent risk factors were established to find out who will benefit most from TACE monotherapy. The type of portal vein tumor thrombosis was classified based on the Cheng's Classification. The accuracy of the models was validated in validation cohort.

Results: Totally, 242 patients (training cohort: n = 159; validation cohort: n = 83) were included. The median OS was 7.1 and 8.5 months in training and validation cohort, respectively. In training cohort, the PP model was established based on the following five independent risk factors: Cheng's Classification, Eastern Cooperative Oncology Group score, maximum tumor size, number of HCC nodules, and Child-Pugh stage. PP score of 17.5 was identified as cut-off point and patients were divided into two groups by PP score <17.5 and >17.5 in survival benefit and prognostication (8.8 vs. 5.5 months; P < 0.001). These five factors were included and ranked based on the importance associated with OS in the ANN model. Both of the two models received high accuracy after validation.

Conclusions: Portal vein invaded HCC patients with PP score <17.5 may benefit most from TACE monotherapy. For these patients, TACE monotherapy should be considered.

Introduction

Despite surveillance programs for hepatocellular carcinoma (HCC), more than half of the cases are diagnosed at an advanced stage, with vascular invasion or extrahepatic spread corresponding to Barcelona Clinic Liver Cancer (BCLC) stage C.^{1–4} The presence of portal vein tumor thrombosis (PVTT) is regarded as a hallmark of advanced HCC, with a high incidence of 39%–63%.^{5,6} The median survival of these patients is

2.7–4.0 months.^{7,8} According to the BCLC staging system, the recommended treatment for HCC patients with PVTT is systemic therapy including lenvatinib and sorafenib, which was shown to be effective and safe by the SHARP and Asia-Pacific sorafenib trials.^{9–11}

However, for the SHARP trial, a mixed group of patients with heterogeneous prognoses associated with the presence and degree of vascular invasion were included, and only 38.5% of the patients were confirmed by macroscopic vascular invasion.⁹ Subgroup analyses, which

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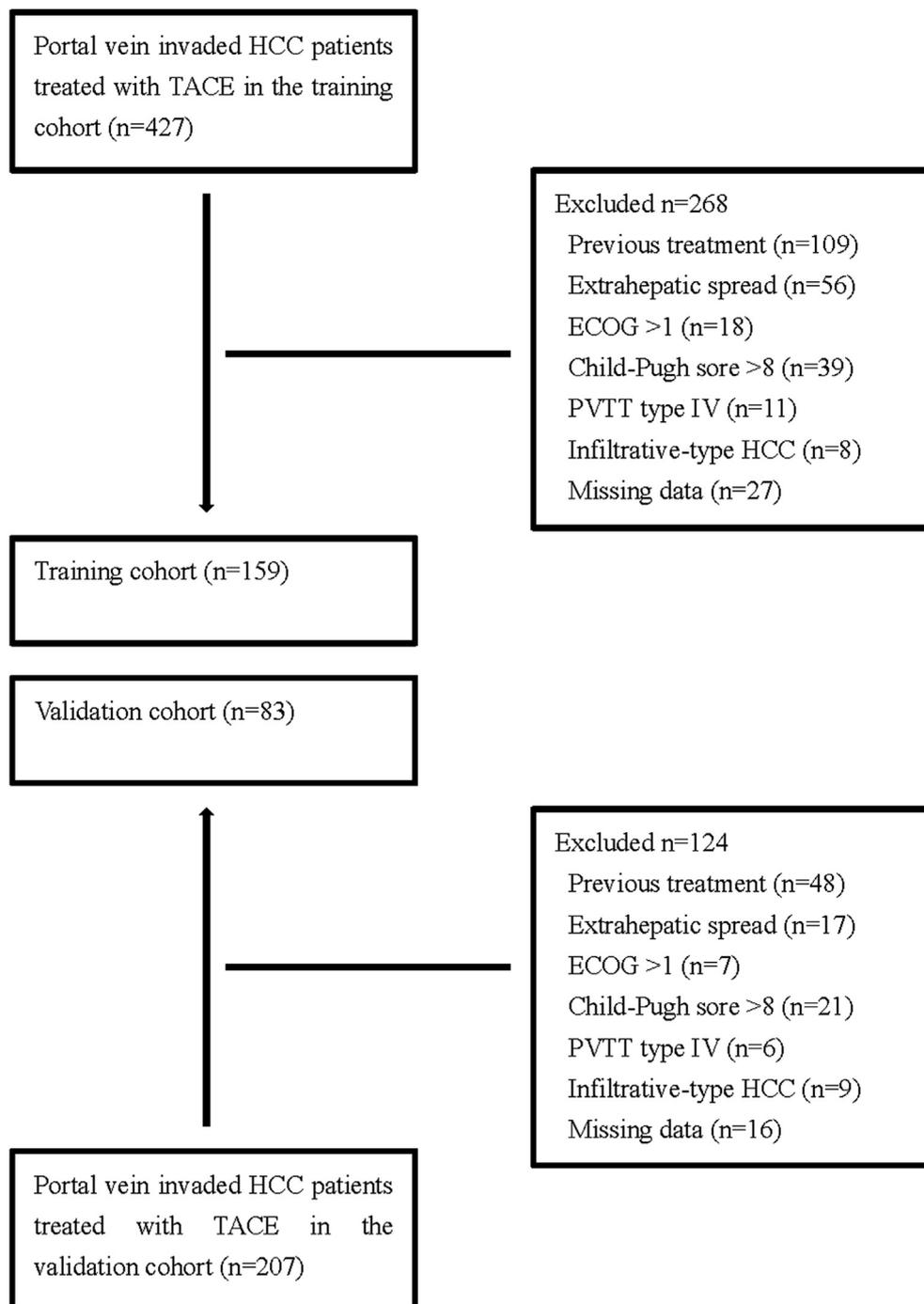


Fig. 1. Flow diagram of patient selection.

focused on HCC with PVTT, demonstrated that sorafenib monotherapy did not achieve satisfactory outcomes, with a median survival time of 5.6–8.1 months.^{12,13} Based on this, transarterial chemoembolization (TACE), which targets the primary tumor in the liver as well as tumor thrombosis, should be a reasonable and theoretically effective approach for HCC with PVTT. Previous studies have shown that TACE induces an objective tumor response in 36% to >50% of patients.^{14,15} In addition, the efficiency and safety of TACE for HCC patients with PVTT have been demonstrated by several studies.^{16–19} However, individual responses to TACE may be variable.²⁰ Therefore, a personalized prediction model, which could identify patients who would likely benefit from TACE monotherapy, is crucial for treatment decision-making.

The aim of this study was to explore which patients with HCC and

PVTT would benefit from TACE monotherapy by establishing a prognostic prediction model and to develop a computer technology assisted artificial neural network (ANN) model to select the appropriate candidates for TACE.

Methods

Study design

This retrospective study consisted of consecutive treatment-naïve HCC patients with PVTT who were treated with TACE monotherapy at two hospitals in China (training cohort: patients from hospital A (First Affiliated Hospital of Soochow University) between January 2008 and

May 2018; validation cohort: patients from hospital B (Lishui Central Hospital) between May 2012 and May 2018). The diagnosis of HCC was based on the criteria used by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases.^{2,3} The presence of PVTT was confirmed when a low-attenuation intraluminal mass invading the portal vein and/or filling defects in the portal vein were identified using three-phase dynamic computed tomography (CT), with a slice thickness ranging from 3 mm to 5 mm.²¹ The type of PVTT was classified based on Cheng's Classification, which may be the most suitable for Chinese HCC patients with PVTT who undergo TACE.^{22,23} The inclusion and exclusion criteria are presented in [Appendix E1](#). The TACE procedure and details are presented in [Appendix E2](#).

Outcome assessments

To evaluate the safety and tolerability of treatment, all patients received routine laboratory examinations before their first TACE treatment and every 4 weeks thereafter. Tumor response was assessed using contrast-enhanced CT (Somatom Sensation 64; Siemens Medical Solutions, Erlangen, Germany) or magnetic resonance imaging (MRI; Magnetom Trio; Siemens) before treatment and 4–6 weeks after each TACE treatment, along with chest CT and/or bone scanning if applicable, on the basis of the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.²⁴ Using the PACS system (NEUSOFTPACS/RIS, Shengyang Neusoft Co., Ltd, China), assessment of tumor response was performed on the target lesions ($n \leq 2$) by two radiologists (Lei Zhang and Bin-Yan Zhong) with more than five years of experience in diagnostic radiology. In cases of disagreement, a third radiologist (Cai-Fang Ni) made the final decision. Safety was assessed at each follow-up visit. Treatment-related adverse events were recorded according to the Common Terminology Criteria for Adverse Events v4.0.

The primary outcome measured was overall survival (OS). OS was defined as the amount of time from the initial HCC diagnosis to the date of death or the last follow-up (January 31, 2019). The second outcome studied was treatment safety.

Statistical analysis

Continuous variables were summarized as medians with 95% confidence intervals (CI) or as the mean with the standard deviation (SD). Categorical variables are expressed as frequencies and percentages. Baseline characteristics between the two centers were compared using χ^2 tests for categorical variables. Factors with a P-value ≤ 0.20 for the univariate analysis were entered as candidate variables into a Cox proportional hazards analysis to identify the independent risk factors associated with survival. A cut-off value of 0.20 was chosen to improve the accuracy of multivariate analysis by avoiding the exclusion of too many risk factors. Factors with a P-value ≤ 0.05 in the Cox proportional hazards model were considered independent prognostic factors associated with survival. The prognostic prediction model (PP) score was established based on identified independent prognostic factors. To facilitate the use of point numbers to calculate the PP score, the regression coefficients (B-values) of the Cox proportional hazards model were multiplied by 5 and rounded. After that, the concordance (c)-statistic, using the receiver operating characteristic (ROC) curve, was used to validate the accuracy of subgroup categorizations. Cut-off values were calculated on the basis of the ROC curves and used to classify the patients treated with TACE into two groups. The performance of the prediction model was validated externally using the concordance index. These statistical analyses were performed using SPSS 18.0 for Windows (IBM Corporation, Somers, NY, USA). The ANN was established using SPSS Clementine version 12.0 software for Windows (IBM Corp, USA).

Table 1
Patient characteristics in the training and validation cohort.

Characteristic	Overall (n = 242)	Training cohort (n = 159)	Validation cohort (n = 83)	P value ^a
Gender				0.982
Male	213 (88.0%)	140 (88.1%)	73 (88.0%)	
Female	29 (12.0%)	19 (11.9%)	10 (12.0%)	
Age (years)				0.210
≤ 55	75 (31.0%)	45 (28.3%)	30 (36.1%)	
> 55	167 (69.0%)	114 (71.7%)	53 (63.9%)	
ECOG				0.510
0	144 (59.5%)	97 (61.0%)	47 (56.6%)	
1	98 (40.5%)	62 (39.0%)	36 (43.4%)	
Hepatitis B (Yes)	173 (71.5%)	109 (68.6%)	64 (77.1%)	0.162
Child-Pugh stage				0.007
A	185 (76.4%)	130 (81.8%)	55 (66.3%)	
B7	57 (23.6%)	29 (18.2%)	28 (33.7%)	
Tumor size				0.006
≤ 5 cm	43 (17.8%)	21 (13.2%)	22 (26.5%)	
5–10 cm	106 (43.8%)	67 (42.1%)	39 (47.0%)	
> 10 cm	93 (38.4%)	71 (44.7%)	22 (26.5%)	
No. of nodules				< 0.001
1	125 (51.7%)	69 (43.4%)	56 (67.5%)	
> 1	117 (48.3%)	90 (56.6%)	27 (32.5%)	
Cheng's classification				0.967
Type I	99 (40.9%)	65 (40.9%)	34 (41.0%)	
Type II	78 (32.2%)	52 (32.7%)	26 (31.3%)	
Type III	65 (26.9%)	42 (26.4%)	23 (27.7%)	
AFP (ng/dl)				0.109
≤ 400	114 (47.1%)	69 (43.4%)	45 (54.2%)	
> 400	128 (52.9%)	90 (56.6%)	38 (45.8%)	
AST (U/L)				0.068
≤ 40	67 (27.7%)	38 (23.9%)	29 (34.9%)	
> 40	175 (72.3%)	121 (76.1%)	54 (65.1%)	
ALT (U/L)				0.099
≤ 40	131 (54.1%)	80 (50.3%)	51 (61.4%)	
> 40	111 (45.9%)	79 (49.7%)	32 (38.6%)	

^a Chi-square test. ECOG = Eastern Cooperative Oncology Group. AFP = alpha-fetoprotein. AST = aspartate transaminase. ALT = alanine transaminase.

Ethical approval

The study was approved by the ethics committee of the two hospitals. All clinical practices and observations were conducted in accordance with the Declaration of Helsinki.

Patient consent

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

Declaration of interests

The authors declare that they have no conflicts of interests to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

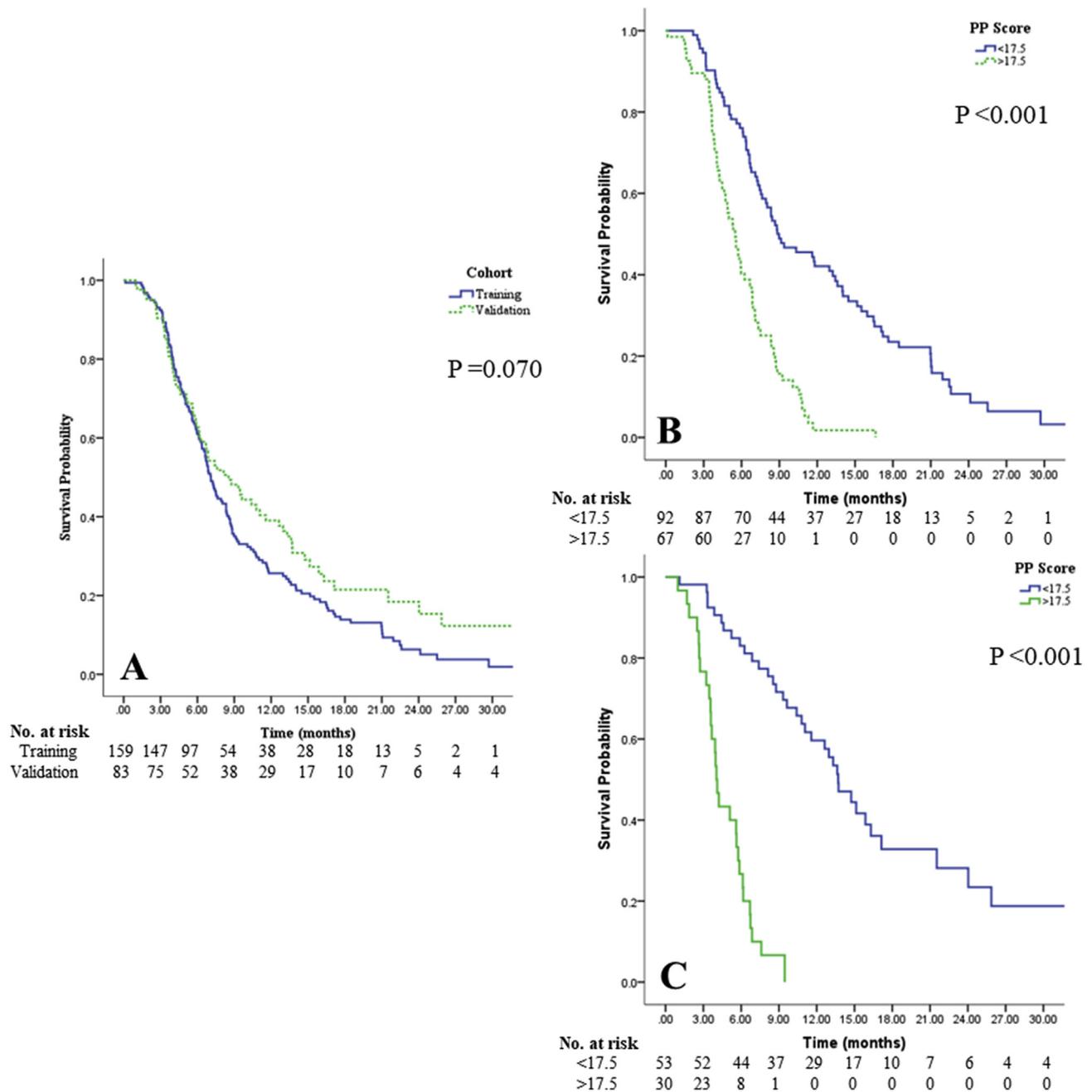


Fig. 2. Kaplan-Meier analyses of overall survival (OS). (A) Median OS was 7.1 and 8.5 months in the training and validation cohorts, respectively ($P = 0.070$). (B) Median OS was 8.8 and 5.5 months for patients with a PP score <17.5 and >17.5 in the training cohort, respectively ($P < 0.001$). (C) Median OS was 13.7 and 4.0 months for patients with a PP score <17.5 and >17.5 in the validation cohort, respectively ($P < 0.001$).

Results

Patient characteristics

A total of 242 patients (training cohort, hospital A: $n = 159$; validation cohort, hospital B: $n = 83$) were included in this study (Fig. 1). The only statistical differences in the baseline characteristics between the training and validation cohorts found were in the Child-Pugh (CP) stage, maximum tumor size, and number of nodules. The detailed demographic characteristics of the patients in both cohorts are shown in Table 1.

Efficiency and safety evaluation of the training cohort

The median OS was 7.1 (95% CI: 6.4–7.8) months and 8.5 (95% CI:

6.0–11.1) months in the training and validation cohort, respectively (Fig. 2A). No TACE-related deaths occurred in this study. Thirty-eight and 23 adverse events that were grade 2 or higher were observed in 35 patients (22.0%) in the training cohort and 22 patients (26.5%) in the validation cohort. The mean number of TACE procedures per patient were 2.2 (1.6) and 2.7 (1.0) in the training and validation cohort, respectively.

Independent prognostic factors, the prognostic prediction model, and the ANN model established in the training cohort

In the training cohort, the factors with a $P \leq 0.2$ after univariate analyses were Cheng’s classification, the Eastern Cooperative Oncology Group (ECOG) score, maximum tumor size (<5 cm, 5–10 cm, >10 cm),

Table 2
Univariate analysis of risk factors associated with OS in the training cohort.

Characteristic	HR	95%CI	P value ^a
Gender (male, female)	1.267	0.780–2.058	0.338
Age (year) (<55, >55)	0.761	0.547–1.059	0.270
HBV (no, yes)	1.202	0.862–1.676	0.278
Cirrhosis (no, yes)	0.882	0.635–1.226	0.456
ECOG (0, 1)	1.622	1.143–2.302	0.007
Child-Pugh stage (A, B7)	1.698	1.106–2.606	0.016
Tumor size (<5 cm, 5–10 cm, >10 cm)	1.240	0.976–1.574	0.078
No. of nodules (1, >1)	1.588	1.134–2.224	0.007
Bilobar disease (No, Yes)	1.093	0.928–1.288	0.288
Cheng's classification			
Type I	1		<0.001
Type II	1.980	1.325–2.958	0.001
Type III	2.975	1.930–4.587	<0.001
AFP (ng/dl) (<400, >400)	1.054	0.751–1.478	0.762
NLR (<5, >5)	1.048	0.706–1.556	0.816

^a Log Rank test was used. OS = overall survival. HR = hazard ratio. CI = confidence interval. HBV = hepatitis B virus. ECOG = Eastern Cooperative Oncology Group. AFP = alpha-fetoprotein. NLR = neutrophil-lymphocyte ratio.

Table 3
Multivariate Cox proportional hazards regression analysis of risk factors associated with OS in the training cohort.

Variables	HR	95% CI	B-values	PP score	P value ^a
Cheng's classification					
Type I	1		0	0	
Type II	1.788	1.191–2.684	0.581	3	0.005
Type III	2.681	1.732–4.150	0.986	5	<0.001
ECOG	1.857	1.288–2.676	0.619		0.001
0				0	
1				3	
Maximum tumor size	1.461	1.135–1.882	0.379		0.003
<5 cm				2	
5–10 cm				4	
>10 cm				6	
No. of nodules	1.766	1.232–2.532	0.569		0.002
1				3	
>1				6	
Child-Pugh stage	1.830	1.184–2.827	0.604		0.006
A				3	
B7				6	

^a Cox Regression analysis was used. OS = overall survival. HR = hazard ratio. CI = confidence interval. B-values were regression coefficients. ECOG = Eastern Cooperative Oncology Group.

number of HCC nodules (1 or > 1 lesion), and CP stage (Table 2). We then put these five factors into a Cox proportional hazards analysis, which showed that these five variables were independent prognostic factors associated with survival (Table 3). The median OS was 10.7 (95% CI: 7.3–14.2), 6.7 (95% CI: 5.7–7.7), and 4.7 (95% CI: 3.6–5.9) months ($P < 0.001$) for patients with PVTT type I, II, and III, respectively. For patients with ECOG scores of 0 and 1, the median OS was 7.9 (95% CI: 6.2–9.7) and 6.7 (95% CI: 6.0–7.4) months ($P = 0.001$), respectively. The median OS was 8.8 (95% CI: 7.9–9.8), 7.1 (95% CI: 5.9–8.3), and 6.8 (95% CI: 5.5–8.1) months ($P = 0.004$) for patients with a maximum tumor size of <5 cm, 5–10 cm, and >10 cm, respectively. The median OS was 8.4 (95% CI: 6.3–10.5) and 6.2 (95% CI: 5.1–7.3) months ($P = 0.006$) for patients with 1 and more than 1 HCC nodule, respectively. Similarly, the median OS was 7.5 (95% CI: 6.3–8.7) and 6.1 (95% CI: 5.2–7.0) months ($P = 0.016$) for patients with CP stage A and B7, respectively.

The patients' PP scores were calculated based on the regression coefficients (B-values) of the Cox proportional hazards model (Table 3). The cut-off value used to identify two subgroups with distinct prognoses was 17.5. Patients with a PP score <17.5 points ($n = 92$) had a median OS of 8.8 (95% CI: 5.8–11.8) months. In contrast, patients with a PP score >17.5 points ($n = 67$) had a median OS of 5.5 (95% CI: 4.5–6.5) months ($P < 0.001$) (Fig. 2B).

The ANN model was built based on the independent risk factors identified by the univariate and multivariate analyses (Fig. 3). Through the ANN model, all variables were ranked based on their importance and association with OS (Fig. 3).

Validation of the PP score and ANN model in the validation cohort

In the validation cohort, 53 and 30 patients had PP scores <17.5 and >17.5, respectively. The median OS was 13.7 (95% CI: 11.5–15.9) and 4.0 (95% CI: 3.6–4.4) months ($P < 0.001$) for patients with a PP score <17.5 and >17.5, respectively (Fig. 2C). The area under the ROC curve values for the PP score in the validation cohort was 0.827 (95% CI: 0.720–0.933), and for the ANN model it was 0.806 (95% CI: 0.711–0.909) when validated in the validation cohort.

Discussion

Based on a dual center cohort comprising 242 HCC with PVTT who were treated with TACE monotherapy, we established a prognostic model (PP score) as well as an ANN model. Patients with PP scores <17.5 were found to most likely benefit from TACE monotherapy. Therefore, for these patients, TACE should be recommended as a potential approach. It remains unclear if TACE can be safely and effectively performed on portal vein-invaded HCC patients due to the different types of PVTT.^{16,17} The progressively broadening use of TACE beyond the recommended eligibility criteria has further widened the heterogeneity in treatment-induced survival benefit, making patient selection and prognostication difficult for clinicians.²⁵ Therefore, an accurate prognostic model is necessary to appropriately stratify and select patients preoperatively who will benefit from TACE.

In this study, Cheng's classification was an independent risk factor correlated with OS for portal vein-invaded HCC patients receiving TACE monotherapy. Using the PP score, patients with invasion in the main portal vein had the highest potential benefit from receiving TACE monotherapy only if they had preserved hepatic function and performance status. Considering the risk of deteriorating hepatic function from TACE-associated ischemic liver damage, patients with PVTT must be screened pre-TACE to determine whether they would benefit from the procedure.¹⁸ In addition, the super-selective catheterization of tumor-feeding arteries using a microcatheter is strongly recommended to minimize the normal parenchymal damage caused by chemoembolization.¹⁶

This study showed that tumor burden (number of tumors and maximum tumor size) was an independent risk factor associated with OS. Multifocal nodules and a larger maximum tumor size could increase the tumor burden as well as worsen hepatic function, and previous studies have demonstrated that tumor burden is a predictive risk factor for hepatic decompensation after TACE and is associated with prognosis.¹⁹ According to the BCLC staging system, the number of tumor nodules and tumor size are not referenced characteristics when classifying patients into stage C. Thus, this study may encourage the stratification of BCLC stage C.

The CP stage was identified as an independent risk factor associated with OS, as it is directly related to patients' hepatic function. Patients with a poorer CP stage have a higher risk of hepatic decompensation after TACE, since embolization of the hepatic arteries can aggravate ischemic liver damage in patients with portal vein invasion.²⁶ Similar to some previous studies, this study showed that the benefits of TACE were significantly higher in CP stage A portal vein-invaded patients.^{27,28} Chan et al. in their study, concluded that liver function remains a very important criterion for selecting which patients with portal vein invasion should receive TACE treatments.²⁹

An important strength of this study is that we established a prognostic prediction model to help select the patients with HCC and portal vein invasion who would benefit from TACE monotherapy. This guidance will be useful in reducing potential drug toxicities and spending on sorafenib or lenvatinib, which are highly expensive therapies.³⁰

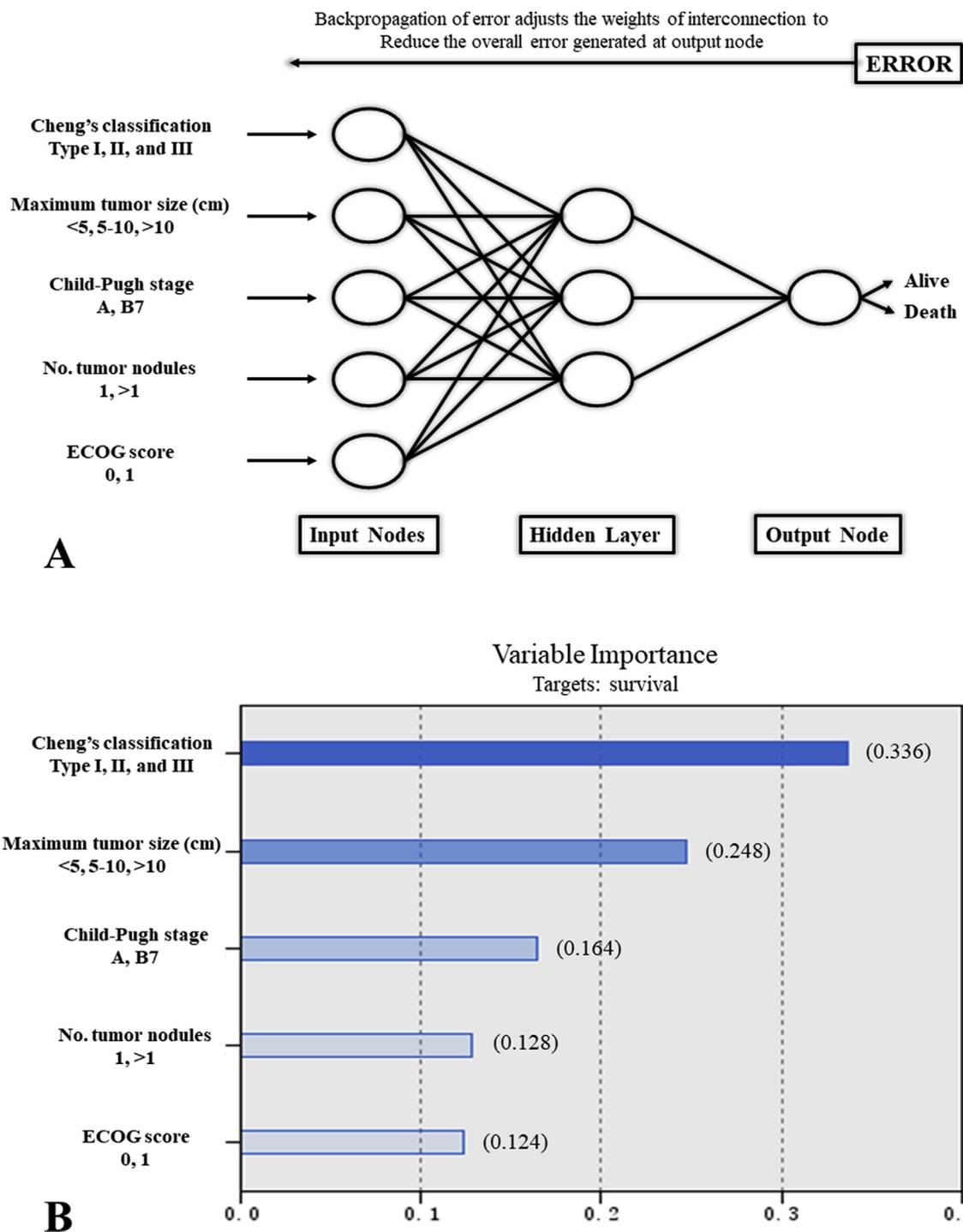


Fig. 3. (A) Schematic representation of the artificial neural network (ANN) developed to predict the survival of patients with hepatocellular carcinoma and portal vein tumor thrombosis after transarterial chemoembolization monotherapy. (B) Importance of each variable in the ANN model.

Accurate prognostic predictions are of paramount importance in oncology, especially for palliative treatments, to predict treatment-related survival benefits. In addition to a prognostic model, this study also established an ANN model to assess the importance of every independent risk factor for the prediction of prognosis. The ANN model is likely more accurate than conventional models since it can assign outputs (diagnoses) to new input data that were not used during the learning process based on knowledge learned during training.³¹ According to the ANN model, Cheng's classification is the most important factor associated with OS, as expected from clinical practice.

This study has several limitations. First, the retrospective nature of

the study limits its preciseness. A prospective cohort study is needed to validate the accuracy of both the prognostic prediction model and ANN model. However, we did validate both the models in an external independent validation cohort and found high accuracy. Second, we did not compare TACE monotherapy with sorafenib monotherapy, which is the standard therapy for advanced stage HCC. With this limitation, we were unable to determine whether the patients selected according to the PP score would have had a comparable OS to sorafenib monotherapy. Third, many patients with portal vein-invaded HCC have infiltrative disease, for which the tumor size cannot be measured. Since infiltrative HCCs were excluded from this study, the broad application of the PP score in real

practice may be limited.

In conclusion, this study verified that for patients with HCC and portal vein invasion who receive TACE monotherapy, Cheng's Classification, the ECOG score, maximum tumor size, number of HCC nodules, and CP stage are independent risk factors associated with OS. From this, the PP score was developed, which showed that patients with PP scores <17.5 were most likely to benefit from TACE monotherapy. Therefore, for these patients, TACE monotherapy should be considered. Further prospective studies are warranted to validate the prognostic prediction of the models.

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Author contributions

All authors contributed to review and critical revision of the manuscript and approved the final version of the manuscript. Cai-Fang Ni, Jian-Song Ji, Lei Zhang, Bin-Yan Zhong contributed to the study concept and design, Lei Zhang, Bin-Yan Zhong, Bo Hu, Wei Li, Zhong-Heng Hou, Peng Huang, Shen Zhang, and Jin-Jin Song contributed to acquisition of data, Lei Zhang, Bin-Yan Zhong contributed to analysis and interpretation of data, Lei Zhang contributed to statistical analysis, Lei Zhang and Bin-Yan Zhong contributed to drafting of the manuscript. The corresponding author had full access to all of the data and took full responsibility for the veracity of the data and the statistical analyses.

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.

Consent to participate

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

Declaration of competing interest

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

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jimed.2020.08.001>.

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