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Cohort Study

Tumor multifocality and serum albumin levels can identify groups of patients with hepatocellular carcinoma and portal vein thrombosis having distinct survival outcomes

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ABSTRACT

Background: Macroscopic portal vein thrombosis (PVT) is a major poor prognosis factor in patients with hepatocellular carcinoma (HCC), but constitute a heterogeneous group.
Aims: To examine blood and tumor parameters of 1667 HCC patients who had PVT to identify factors that could differentiate different survival subsets.
Methods: a large HCC database was examined for presence of patients with PVT and analyzed retrospectively for PVT-associated factors and prognosis.
Results: A logistic regression model was calculated for presence of PVT. Highest odds ratios were found for tumor multifocality and serum albumin levels, as well as serum alpha-fetoprotein (AFP) and bilirubin levels. A Kaplan-Meier and Cox model on survival also showed the highest hazard ratios for tumor multifocality and serum albumin. A model was constructed on all 4 possible combinations of tumor focality and serum albumin in PVT patients. The longest survival group had <2 tumor nodules plus serum albumin >3.5 g/dL. Conversely, the shortest survival group had >2 tumor nodules plus serum albumin <3.5 g/dL. These 2 patient groups differed in maximum tumor diameter and levels of serum AFP, AST and bilirubin.
Conclusions: Combination low tumor focality and high serum albumin identifies prognostically better PVT patient subgroups that might benefit from aggressive therapies.

1. Introduction

Macroscopic portal vein thrombosis (PVT) is a characteristic feature of up to 40% of patients with hepatocellular carcinoma (HCC), involving invasion and eventual obstruction by HCC cells of the portal veins [1–3] and is considered to be one of the most important adverse prognostic factors for survival in HCC patients. Due to the high associated risks of HCC metastasis, recurrence and parenchymal liver damage, it is often an exclusion factor for liver transplant, large surgical resections and, for those patients with poor liver function, often for chemoembolization in HCC patients.

Several factors have been thought to be associated with PVT, including markers of inflammation, such as NLR, PLR, Glasgow index (CRP plus albumin) [4–6] and indices of tumor aggressiveness, such as large tumor size, tumor multifocality and elevated levels of the HCC tumor markers serum alpha-fetoprotein (AFP) [7,8] as well as serum levels of des-gamma-carboxy prothrombin [9,10]. The aims and objectives of this study were to attempt to identify clinical subgroups of HCC patients with PVT who might have better prognosis than others. In the current study, we used the results of a logistic regression model on PVT and the results of a Cox model on PVT patient survival, to identify 2 parameters, namely tumor multifocality and serum albumin levels, to build a model that could identify different PVT patient subsets that were associated with differing survival.

2. Methods

2.1. Patient data

A database was retrospectively analyzed of 1667 non-transplant HCC patients who had macroscopic PVT and who had both survival data and baseline tumor parameter data, including CT scan information on maximum tumor diameter (MTD), number of tumor nodules and

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Abbreviations

PVT	macroscopic Portal Vein Thrombosis
MTD	Maximum Tumor diameter
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
GGTP	Gamma Glutamyl Transpeptidase
HDL	High Density Lipoprotein Cholesterol
LDL	Low Density Lipoprotein Cholesterol
AFP	Alpha-fetoprotein
ALKP	Alkaline phosphatase
AST	aspartate aminotransaminase
ALT	alanine transaminase
WBC	White Blood Cell
KM	Kaplan-Meier
HR	hazard ratio

presence or absence of macroscopic portal vein thrombosis (PVT); serum alpha-fetoprotein (AFP) and C-reactive protein (CRP) levels; complete blood count with platelet levels and routine serum liver function tests. Diagnosis was made either via tumor biopsy or according to AASLD/EASL guidelines. They were compared to 4467 HCC patients without evidence of PVT.

Database management conformed to legislation on privacy and this study conforms to the ethical guidelines of the Declaration of Helsinki and approval for this retrospective study on de-identified HCC patients was obtained by the Institutional Ethics Committee. This work has been reported in line with the STROCSS criteria [35]. The clinicaltrials.gov registration number was: NCT0447772.

2.2. Statistical analysis

Patient characteristics were reported as Mean ± Standard Deviation (M±SD) or as Median for continuous variables, and as frequencies and percentages (%) for categorical variables.

Normal distributions of quantitative variables were tested using the Kolmogorov-Smirnov test.

For testing the associations between groups, the Chi-square test or Fisher's exact test for categorical variables was used when necessary. When the variables were not normally distributed, the Wilcoxon rank sum (Mann-Whitney) test for continuous variables was used.

The medians of single parameters examined were used to evaluate the differences between Portal Vein Thrombosis (PVT (−/+)) and between the combination of Multifocality (n ≤ 2/n > 2) and Albumin (≥3.5/<3.5 g/L).

A logistic regression model was used to evaluate the associations of PVT on the single variables examined, with 95% Confidence Interval (95% CI).

For studying the time between entry to a study and a subsequent event, the non-parametric Kaplan–Meier method was used to explore survival probability, and the log-rank test was applied to evaluate the equality of survival among categories.

As the Cox model is a statistical technique for exploring the relationship between the survival of a patient and singular or several explanatory variables, it also allows us to estimate the hazard risk (HR) of survival for an individual, given their prognostic variables (measured as continuous or categorical), and was therefore used.

The Cox proportional hazard model was fitted to the data, and the proportional hazard assumption was evaluated by means of Schoenfeld residuals (SRT).

All models for fitting were evaluated by means of Akaike Information Criteria (AIC) and Bayesian information criterion (BIC). Risk estimators was expressed as Hazard Ratios (HR) and 95% Confidence Interval (95% CI). In the models, multicollinearity was evaluated through the variance inflation factor (VIF), using the score of 2 as cut-off for exclusion.

When testing the null hypothesis of no association, the probability level of error at two tails, was 0.05.

All the statistical computations were made using STATA, StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

3. Results

3.1. Clinical, tumor and laboratory features of PVT patients

We dichotomized patients according to presence (n = 1667) or absence (n = 4467) of PVT (Table 1). Patients with PVT compared to non-PVT comprised significantly more males (81.9% with PVT vs. 76.3% without PVT) and were slightly younger. PVT patients compared to non-PVT patients had significantly larger maximum tumor diameters (MTD) of 6 cm vs. 3 cm, significantly lower serum levels of albumin and Hb and significantly higher levels of serum AFP (181 vs. 11 IU/mL), GGTP, ALKP, AST and total bilirubin. Interestingly, only 57.7% of PVT patients had elevated AFP levels and conversely, 43.3% of PVT patients did not have elevated AFP. The inflammation markers CRP and ESR also did not differ significantly between the 2 groups.

A logistic regression model was calculated on single variables in the PVT patients (Table 2). The highest odds ratios (OR) were found for tumor multifocality (>2 tumor nodules), OR = 7 and serum albumin (<3.5 g/dL), OR = 2.28. All other parameters had OR less than 2, excepting serum AFP levels (>100 IU/mL), OR = 4.65 and total serum

Table 1
Comparison of clinical and lab parameters in HCC patients without PVT (−) or with PVT (+).

Parameters[a]	PVT (−) (n = 4467)	PVT (+) (n = 1667)	P[b]
Gender, Males (%)	76.38	81.92	<0.001 [c]
Age (yr)	68	66	<0.0001
Cirrhosis (%)	87.40	89.94	0.01 [c]
MTD (cm)	3	6	<0.0001
# Tumor Nodules (>2) (%)	7.23	35.30	<0.001 [c]
Albumin (g/dl)	3.6	3.2	<0.0001
CRP (mg/L)	10	10	0.09
ESR (mm/hr)	26	30.5	0.08
GGTP (IU/L)	180	254	<0.0001
HDL (mg/dL)	41	35	<0.0001
LDL (mg/dL)	82	94.8	<0.0001
Total Cholesterol (mg/dL)	146	145	0.65
AFP (IU/mL)	11	181.2	<0.0001
AFP≥100 (IU/mL) (%)	22.76	57.77	<0.001[c]
ALKP (IU/L)	220	268.4	<0.0001
AST (IU/L)	60	80	<0.0001
Total Bilirubin (mg/dl)	1	1.4	<0.0001
Hemoglobin (g/dL)	12.9	12.3	<0.0001
WBC (10^3/μL)	4.91	5	0.01
Platelets (10^9/μL)	117	136	<0.0001

Abbreviations: PVT, macroscopic Portal Vein Thrombosis; MTD, Maximum Tumor diameter; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; GGTP, Gamma Glutamyl Transpeptidase; HDL, High Density Lipoprotein Cholesterol; LDL, Low Density Lipoprotein Cholesterol; AFP, Alpha-fetoprotein; ALKP, Alkaline phosphatase; AST, aspartate aminotransaminase; ALT, Alanine transaminase; WBC, White Blood Cell.

[a] All values: Median as continuous; Frequencies and Percentage (%) as categorical.

[b] Wilcoxon rank-sum (Mann-Whitney) test.

[c] Chi-square test.

Table 2
Logistic regression model of PVT (−/+) on single variables in HCC patients.

	OR	se (OR)	p	95% C.I.
# of Tumor Nodules				
≤2 *Reference*	1			
>2	7.002	0.58	<0.001	(5.95–8.24)
Albumin (g/dL)				
≥3.5 *Reference*	1			
<3.5	2.28	0.15	<0.001	(2.01–2.60)
CRP (mg/L)				
≤10 *Reference*	1			
>10	1.88	0.27	<0.001	(1.42–2.48)
ESR				
≤15 *Reference*	1			
>15	1.83	0.43	0.01	(1.15–2.91)
GGTP (IU/L)				
<100 *Reference*	1			
≥100	1.52	0.16	<0.001	(1.24–1.86)
AFP (IU/mL)				
<100 *Reference*	1			
≥100	4.65	0.34	<0.001	(4.03–5.38)
ALKP (IU/L)				
<100 *Reference*	1			
≥100	1.30	0.20	0.09	(0.96–1.76)
AST (IU/L)				
≤40 *Reference*	1			
>40	1.38	0.09	<0.001	(1.20–1.57)
Bilirubin (mg/dL)				
<1.2 *Reference*	1			
≥1.2	2.05	0.14	<0.001	(1.80–2.34)
Hemoglobin (g/dL)				
≥13 *Reference*	1			
<13	1.55	0.10	<0.001	(1.35–1.77)
Platelets (10^9/μL)				
<100 *Reference*	1			
≥100	1.46	0.10	<0.001	(1.27–1.68)
MTD (cm)	1.21	0.01	<0.001	(1.19–1.23)

Abbreviations: OR, Odds-Ratio; se(OR), standard error of OR; PVT, Portal Vein Thrombosis; AFP, Alpha-fetoprotein; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; GGTP, gamma glutamyl transpeptidase; ALKP, Alkaline phosphatase; ALT, Alanine transaminase.

bilirubin (>1.2 mg/dL), OR = 2.05.

3.2. Parameters relating to survival in PVT patients

A Kaplan-Meier (KM) and Cox model analysis were then calculated (Table 3). The 2 parameters with highest HRs, were tumor multifocality and low serum albumin levels. Tumor multifocality had a hazard ratio (HR) of 1.56, $p < 0.001$ by univariate Cox regression. The median survival time by KM was 11 months for patients with <2 tumor nodules versus 6 months for patients with >2 tumor nodules, $p < 0.0001$. Patients with serum albumin <3.5 g/dL compared to normal levels of >3.5 g/dL had an HR by Cox of 1.54, $p < 0.001$. The median survival time by KM was 13 months for patients with normal serum albumin levels >3.5 g/dL versus 7 months for low serum albumin levels of <3.5 g/dL, $p < 0.0001$. Patients with elevated serum total bilirubin or AFP levels had HRs of 1.49 and 1.41 respectively, significantly higher than their reference values. Several other parameters also had significantly higher HRs than their reference values, but all with HRs <1.4.

We then constructed a 2 parameter model on survival, using the combination of tumor multifocality and serum albumin levels (Table 4), as they had both the highest ORs, as well as the largest spread between long and short survival as single parameters, as shown in Table 3. All 4 possible combinations of these 2 parameters are shown in Table 4a. The significantly longest median survival of 17 months was found for patients who had <2 tumor nodules plus serum albumin levels >3.5 g/dL. The shortest median survival of 5 months was found for patients who had >2 tumor nodules plus serum albumin levels <3.5 g/dL. The other 2 combinations had intermediate survival values.

Since we had found (Table 1) that 43.3% of PVT patients did not have elevated AFP levels, we further examined our 2-parameter model for PVT patients who did not have elevated serum AFP levels (Table 4b). The model also worked in these patients. The main additional finding was that median survival was 21 months in the best survival group of

Table 3
Kaplan-Meier and Cox model analysis for PVT (+) HCC patient survival according to single parameters.

		Kaplan-Meier Analysis		Univariate Cox regression	
		Median Survival time (months) (95% C.I.)	Log-Rank p-value	HR[a] (95% CI)	HR p-value
# Tumor Nodules					
	≤2	11 [9–13]	<0.0001	Reference	
	>2	6 [5–7]		1.56 (1.38–1.77)	<0.001
Albumin (g/dL)					
	≥3.5	13 [11–16]	<0.0001	Reference	
	<3.5	7 [6,7]		1.54 (1.35–1.75)	<0.001
CRP (mg/L)					
	≤10	6 [4–8]	0.46	Reference	
	>10	7 [4–11]		0.91 (0.69–1.19)	0.48
ESR (mm/hr)					
	≤15	5 [3–8]	0.65	Reference	
	>15	6 [4–7]		0.91 (0.60–1.39)	0.67
GGTP (IU/L)					
	<100	10 [7–13]	0.40	Reference	
	≥100	8 [7–9]		1.08 (0.89–1.32)	0.41
AFP (IU/mL)					
	<100	12 [9–14]	<0.0001	Reference	
	≥100	7 [6,7]		1.41 (1.24–1.62)	<0.001
ALKP (IU/L)					
	<100	14 [8–24]	0.06	Reference	
	≥100	8 [7–9]		1.30 (0.97–1.74)	0.07
AST (IU/L)					
	≤40	11 [8–14]	0.002	Reference	
	>40	8 [7,8]		1.27 (1.09–1.48)	0.003
Bilirubin (mg/dL)					
	<1.2	14 [11–15]	<0.0001	Reference	
	≥1.2	7 [6,7]		1.49 (1.31–1.70)	<0.001
Hemoglobin (g/dL)					
	≥13	9 [8–12]	<0.0001	Reference	
	<13	7 [7,8]		1.36 (1.19–1.56)	<0.001
Platelets (10^9/μL)					
	<100	9 [8–11]	0.18	Reference	
	≥100	7 [7,8]		1.09 (0.95–1.25)	0.20
MTD (cm)					
	≤5	12 [11–14]	<0.0001	Reference	
	>5	7 [6–8]		1.30 (1.14–1.48)	<0.001

Abbreviations: PVT, macroscopic Portal Vein Thrombosis; AFP, Alpha-fetoprotein; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; GGTP, gamma glutamyl transpeptidase; ALKP, Alkaline phosphatase; AST, aspartate aminotransaminase; ALT, Alanine transaminase; WBC, White Blood Cell; MTD, Maximum Tumor Diameter.
[a] HR, Hazard Ratio.

Table 4a
Kaplan-Meier and Cox model analysis for survival in PVT (+) HCC patients according to combination of # of tumor nodules and serum albumin (g/dL).

		Kaplan-Meier Analysis		Univariate Cox regression	
	N	Median Survival time (months) (95% C.I.)	Log-Rank p-value	HR* (95% CI)	HR p-value
Combination Nodule # & serum Albumin (g/dL)					
# Nodules (≤2) & Albumin (≥3.5)[a]	312	17 mo [14–22].	<0.0001	Reference	
# Nodules (≤2) & Albumin (<3.5)[b]	477	8 mo [7–9].		1.58 (1.33–1.86)	<0.001
# Nodules (>2) & Albumin (≥3.5)[b]	152	8 mo [6–12].		1.65 (1.32–2.06)	<0.001
# Nodules (>2) & Albumin (<3.5)[c]	278	5 mo [4–6].		2.44 (2.03–2.94)	<0.001

Abbreviations: PVT, macroscopic Portal Vein Thrombosis; mo, months.
* HR, Hazard Ratio. Categories with different superscripts a, b, c are significantly different from each other.

Table 4b
Kaplan-Meier and Cox model analysis for survival in PVT (+) HCC patients according to combination of # of tumor nodules and serum albumin (g/dL) and having serum levels of AFP<100 (IU/mL).

		Kaplan-Meier Analysis		Univariate Cox regression	
	N	Median Survival time (mo.) (95% C.I.)	Log-Rank p-value	HR* (95% CI)	HR p-value
Combination Nodule # & serum Albumin (g/dL)					
Nodule # (≤2) & Albumin (≥3.5)[a]	139	21 mo [15–27].	<0.0001	Reference	
Nodule # (≤2) & Albumin (<3.5)[b]	186	9 mo [8–13].		1.56 (1.20–2.02)	0.001
Nodule # (>2) & Albumin (≥3.5)[b]	50	12 mo [8–21].		1.48 (1.02–2.15)	0.04
Nodule # (>2) & Albumin (<3.5)[c]	73	5 mo [4–7].		2.80 (2.03–3.87)	<0.001

Abbreviations: PVT, macroscopic Portal Vein Thrombosis; AFP, Alpha-fetoprotein; mo, months.
* HR, Hazard Ratio. Categories with different superscripts a, b, c are significantly different from each other.

patients who had <2 tumor nodules plus serum albumin levels >3.5 g/dL in the low AFP subcohort of Table 4b. The worst survival group had a median survival of 5 months, for patients with patients who had >2 tumor nodules plus serum albumin levels <3.5 g/dL.

3.3. Clinical differences between patients with PVT having long or short survival

In order to evaluate the clinical differences between the PVT patients with longest and shortest survival in Table 4a, we compared the demographics, laboratory values and tumor characteristics of PVT patients according to the combination of low tumor nodules and high serum albumin with the converse (Table 5). The main significant characteristics of the PVT patients with the longest median survival (<2 tumor nodules plus serum albumin >3.5 g/dL) compared to the shortest PVT survival group were older age, smaller MTD (5 cm vs. 8.25 cm), lower serum AFP levels (although 49.45% of these patients had elevated AFP levels versus 69.2% of short survival patients), significantly lower serum ALKP, AST and total bilirubin levels and significantly higher hemoglobin values.

4. Discussion

The analysis presented here shows that at least 2 groups of patients with macroscopic PVT can be identified, using common clinical parameters, that have significantly different survival. The 2 parameters were identified by KM and Cox regression analysis of clinical parameters

Table 5
Comparison of clinical and laboratory parameters in PVT (+) HCC patients, dichotomized by the combination of tumor nodules and serum albumin.

Parameters[a]	Nodule[d] (≤2) & serum Albumin (≥3.5 g/L)	Nodule[d] (>2) & serum Albumin (<3.5 g/L)	p [b]
Gender, Males (%)	82.37	82.73	0.91 [c]
Age (yr)	67	64	0.002
Cirrhosis (%)	88.04	92.2	0.10 [c]
MTD (cm)	5	8.25	<0.0001
CRP (mg/L)	10	10	0.57
ESR (mm/hr)	29.5	30	0.94
GGTP (IU/L)	230	270	0.32
HDL (mg/dL)	43.5	28	<0.0001
LDL (mg/dL)	94.9	105	0.23
Total Cholesterol (mg/dL)	155.5	147	0.04
AFP (IU/mL)	91	825	<0.0001
AFP % (≥100 IU/mL)	49.45	69.20	<0.001 [c]
ALKP (IU/L)	228.8	286	0.05
AST (IU/L)	76	94.8	<0.0001
Total Bilirubin (mg/dL)	1	1.7	<0.0001
Hemoglobin (g/dL)	13	11.75	<0.0001
WBC (10^3/μL)	5.1	5.23	0.29
Platelets (10^9/μL)	127	143	0.01

Abbreviations: PVT, macroscopic Portal Vein Thrombosis; NLR, Neutrophils to Lymphocyte Ratio; PLR, Platelet count to Lymphocyte Ratio; MTD, Maximum Tumor diameter; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; GGTP, Gamma Glutamyl Transpeptidase; HDL, High Density Lipoprotein Cholesterol; LDL, Low Density Lipoprotein Cholesterol; AFP, Alpha-fetoprotein; ALKP, Alkaline phosphatase; AST, aspartate aminotransaminase; ALT, Alanine transaminase; WBC, White Blood Cell.
[a] All values: Median as continuous; Frequencies and Percentage (%) as categorical.
[b] Wilcoxon rank-sum (Mann-Whitney) test.
[c] Chi-square test.
[d] Fisher's exact test.

that significantly related to survival in PVT patients. We had supposed from earlier literature that serum AFP levels would be important [11]. However, only 57.7% of the PVT cohort had elevated AFP levels. Furthermore, in the logistic regression model on PVT shown in Table 2, tumor multifocality had a much higher odds ratio than AFP. Also, in the Cox model on survival in PVT patients shown in Table 3, tumor nodularity serum albumin and total bilirubin levels all had higher hazard ratios for survival than did AFP. Our 2-parameter model was thus neutral with respect to AFP, but was prognostically useful in PVT patients with either high or low serum AFP levels (Table 4). Also, when the clinical characteristics of the longest and shortest survival 2-parameter model groups were examined (Table 5), fully 49.4% of the longer survival group still had elevated serum AFP levels. Interestingly, the 2 inflammation markers ESR and CRP did not appear to be significant when either non-PVT patients were compared to PVT patients (Table 1), nor when longer versus shorter survival PVT patients were compared (Table 5), although AST and hemoglobin levels were significantly different in both tables. Thus, it is not clear from this analysis, how important inflammation is for survival prediction in PVT patients, although inflammation markers ESR, CRP, AST and GGTP were significant for occurrence of PVT in the regression analysis of Table 2, as found elsewhere [12,13]. We examined various subsets of the longer survival group of PVT patients (<2 tumor nodules plus albumin >3.5 g/dL) from Table 4b (low AFP patients), using dichotomized pairs of significant parameters from Tables 1 and 3, namely bilirubin, AST, HDL, MTD and GGTP, but we could not find any subcohort (analysis not shown) with significantly longer median survival than the 21 months shown in Table 4b.

The radiological characteristics of PVT in HCC patients have been well described and include expansion and vascularization of the portal vein [14]. Furthermore, non-operative diagnosis can also be definitively established through percutaneous biopsy [15]. Although des-gamma-carboxy-prothrombin (DCP) has been shown to be strongly associated with PVT [9,10], it was not available to us in our practice, nor are we aware of reports of its prognostic value for these patients. However, multiple reports suggest that resection for HCC patients with PVT has a survival advantage [16,17], although it is not clear that liver transplantation does, except a very recent report concerning treatment of PVT patients with neo-adjuvant stereotactic body radiotherapy (SBRT) prior to liver transplant, which seems to confer a survival benefit [18]. In this context, other reports have begun to show responses of the PVT to various forms of radiation and possibly also with associated survival benefits [19–21]. Additionally, chemoembolization of HCC patients with PVT who have a tumor response has also been reported to be associated with a survival advantage [22].

Albumin has been shown to be associated with prognosis in GI cancers including HCC and has been incorporated into the Glasgow prognostic score for this purpose [8,23–26] as well as in the prognostic ALBI score for HCC [27]. Serum albumin levels therefore provide an index of both hepatic reserve and systemic inflammation in HCC and albumin has also been shown to directly inhibit the growth of HCC cells [28]. If this were also an important mechanism of HCC growth control in vivo, then albumin infusions could be a possible HCC therapy, and have been used elsewhere in hepatology practice [29,30], while low serum albumin levels have also been shown to be related to PVT [8,31,32]. Perhaps albumin levels simply serve as a surrogate for good liver functional reserve and absence of inflammation, which might help to explain the good prognostic value here, in HCC and in gastrointestinal tumors in general [8,23–28,33]. However, it is also becoming clear that PVT is a dynamic process, with non-linear percent patient increases as MTD increases [34] and there is likely a 2-way interaction between PVT, MTD and liver function. Some weaknesses of this report include its retrospective nature and the use of so many different treatment modalities, including several in sequence, so that there were not enough patients in each therapy subgroup for useful analysis of survival by therapy.

Conclusions: the results presented here point to the possibilities that there are PVT subgroups that survive longer than others and that might benefit from aggressive HCC therapies. In this regard, the actions of the new checkpoint inhibitors that cause high and prolonged tumor responses in HCC patients are not yet explored for their therapeutic potential for PVT patients.

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Declaration of competing interest

The authors declare no conflict of interest.
All authors have read and agree with the contents of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102458.

Statement of ethics

This work complies with the guidelines of the World Medical Association, Declaration of Helsinki. This work was approved by each institution's IRB as documented in the methods section.

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