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Prevalence and clinical significance of clinically evident portal hypertension in patients with hepatocellular carcinoma undergoing transarterial chemoembolization

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Abstract

Background: Clinically evident portal hypertension (CEPH) was previously identified as a prognostic factor for patients with hepatocellular carcinoma (HCC). However, little is known about the prognostic influence of CEPH on the long-term outcome of patients with HCC undergoing transarterial chemoembolization (TACE), particularly in Western populations.

Objectives: This study investigated the prevalence and prognostic influence of CEPH in a Western population of patients with HCC undergoing TACE.

Methods: This retrospective study included 349 treatment-naïve patients that received initial TACE treatment at our tertiary care center between January 2010 and November 2020. CEPH was defined as a combination of ascites, esophageal/gastric varices, splenomegaly and a low platelet count. We assessed the influence of CEPH and its defining factors on median overall survival (OS) in HCC patients. We compared the effects of CEPH to those of well-known prognostic factors.

Results: Of the 349 patients included, 304 (87.1%) patients had liver cirrhosis. CEPH was present in 241 (69.1%) patients. The median OS times were 10.6 months for patients with CEPH and 17.1 months for patients without CEPH (log rank $p = 0.036$). Median OS without a present surrogate was 17.1 months, while patients with one respectively more than two present CEPH surrogates had a median OS of 10.8 and 9.4 months (log rank $p = 0.053$). In multivariate analysis, CEPH was no significant risk factor for OS ($p = 0.190$). Of the CEPH-defining factors, only ascites reached significance in a univariate analysis.

Conclusion: CEPH was present in more than two thirds of the patients with HCC undergoing TACE in our cohort of Western patients. Patients with CEPH had a

significantly impaired survival in univariate analysis. However, no significance was reached in multivariate analysis. Thus, when TACE treatment is deemed oncologically reasonable, patients should not be excluded from TACE treatment due to the presence of surrogates of portal hypertension alone.

KEYWORDS
cirrhosis, clinically evident portal hypertension, hepatocellular carcinoma, liver cirrhosis, long-term outcomes, portal hypertension, prognosis, survival, transarterial chemoembolisation

INTRODUCTION

Hepatocellular carcinoma (HCC) is among the most common cancer entities, and it ranks second among diseases responsible for cancer-related deaths.[1,2] The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines have recommended the Barcelona Clinic Liver Cancer (BCLC) classification system as framework for patient stratification, treatment allocation, and prognosis prediction.[3,4] According to the BCLC classification, transarterial chemoembolization (TACE) is the treatment of choice for patients with intermediate stage HCC.[5] However, in clinical settings, the intermediate stage includes a heterogeneous subgroup of patients with broad variations in tumor spread and remnant liver function.[6] Due to these remarkable differences, prognosis prediction remains challenging in this patient subgroup, and several proposed scoring systems have failed in external validation.[7–12] Thus, there is a strong need for novel predictive markers and improved scoring systems.

Over 80% of patients develop HCC as a consequence of liver cirrhosis.[3] Liver cirrhosis causes progressive changes in the splanchnic circulation, which lead to an increase in portal pressure.[13] Clinically relevant portal hypertension is defined as >10 mmHg increase in the hepatic vein pressure gradient (HVPG), and the current gold standard for its assessment is direct measurement, through a transjugular approach.[3,14] Clinically relevant portal hypertension increases the risk of hepatic decompensation, which impairs survival in patients with HCC.[14,15] However, due to its invasive character and high effort, HVPG measurement is not a standard tool in the initial diagnostic evaluation of patients with HCC. Consequently, several clinical parameters, like splenomegaly, a low platelet count, and the presence of esophageal/gastric varices and ascites, were suggested as surrogates for defining clinically evident portal hypertension (CEPH).[16–18]

CEPH plays an important role in HCC treatment stratification in the early BCLC stages, because it increases the risk of post-operative liver decompensation; thus, it is a contraindication for tumor resections.[3,19] However, its influence on survival outcome in these patients remains unclear.[15,20] The same is true for patients within more advanced stages, as literature is scarce and results on the long-term outcome differ.[16,18] Furthermore, no previous study has investigated the influence of the different CEPH surrogates on median overall survival (OS) after TACE.

Key summary

Current knowledge

- CEPH was previously identified as a prognostic factor for patients with hepatocellular carcinoma (HCC).
- However, little is known about the prognostic influence of CEPH on the long-term outcome of patients with HCC that undergo transarterial chemoembolization (TACE), particularly in Western populations.

What are the new findings?

- CEPH was present in more than two thirds of the patients with HCC that underwent TACE in our cohort of Western patients.
- Patients with CEPH had an significantly impaired survival in univariate analysis. However, no significance was reached in multivariate analysis and other factors seem to be more important for OS stratification.

Additionally, the influence of CEPH has only been evaluated in Asian patient cohorts; thus, its influence is unknown in a Western patient population.

This study aimed to determine the prevalence of clinical surrogates of portal hypertension in patients with HCC that had undergone TACE and the prognostic impact of these factors on the median OS in a Western patient population.

MATERIALS AND METHODS

The Ethics Committee of the Medical Association of Rhineland Palatinate, Mainz, Germany approved this study (permit number 2021-15984). The requirement for informed consent was waived, due to the retrospective nature of the study. Patient records and information were anonymized prior to analysis. This report followed the guidelines for Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD).[21]

Patients

Among all 714 patients with HCC that underwent TACE at our tertiary care center between January 2010 and November 2020, a total of 349 patients met the following inclusion criteria: (1) age above 18 years, (2) histologically or image-derived HCC diagnosis based on the EASL criteria,[3] (3) no treatment performed at a different (external) institution before or after TACE, (4) no treatment performed prior to TACE at our institution, (5) no liver transplantation or tumor resection during the follow-up period after TACE, (6) complete clinical, laboratory and imaging data. Following these criteria, 365 patients had to be excluded for the reasons depicted in Figure 1.

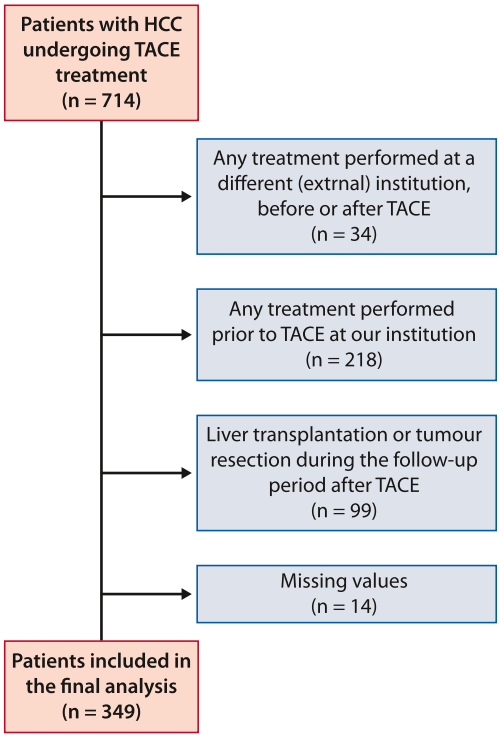

FIGURE 1 Flowchart of the patient inclusion/exclusion process. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization

Diagnosis, treatment, and follow-up

As previously reported, HCC was diagnosed based on histological or image-derived EASL criteria.[3,22] For treatment planning, all patients underwent contrast-enhanced CT or MRI. Prior to each treatment cycle, indications for TACE were discussed in an interdisciplinary tumor board, which included hepatologists/oncologists, diagnostic and interventional radiologists, visceral surgeons, pathologists, and radiation therapists. TACE was performed in a standardized manner, as previously described.[23,24] Follow-up consisted of cross-sectional imaging, a clinical examination, and blood sampling. Follow-ups were performed every six or 12 weeks, depending on the presence of viable tumor tissue.[22] Radiologic response was assessed according to the mRECIST criteria.[3,25] The primary endpoint was the median OS, defined as the duration between the initial TACE session and death or last follow-up. Progression free survival (PFS) was defined as time of progression or last-follow up staging.

Data acquisition

The dataset was acquired from the clinical registry unit.[22] This dedicated, prospectively populated database contained data on all patients with primary liver cancer. Additional imaging and laboratory data were acquired from the radiology information system, the picture archiving and communication system and the laboratory database. The final dataset included all available data on demographics, clinical assessments of the underlying liver disease and tumor, imaging, factors related to the TACE treatment, and laboratory parameters measured prior to the initial TACE treatment.[22]

Assessment and definition of CEPH

CEPH was defined when was one of the following surrugates was present: (a) presence of ascites, (b) presence of esophageal/gastric varices, or (c) splenomegaly (>120 mm spleen diameter in the axial plane) and a low platelet count (<100,000/mm^3).[18] CT image analyses were performed by one resident and one board-certified radiologists with three and 10 syears of experience in liver imaging, respectively. Esophageal/gastric varices were evaluated, based on either the last endoscopy report (when less than six month prior to TACE) or the CT images used for TACE procedure planning. Platelet counts were acquired from laboratory data.

Statistical analysis

We performed statistical analyses and graphics in RStudio (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, http://www.rstudio.com, last accessed on the 30 06 2021) using R 4.0.3 (A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, http://www.R-project.org; last accessed on the 30 06 2021). Binary and categorial baseline parameters were reported as absolute numbers and percentages, and continuous data are reported as the median and range. Subgroups were compared with the Chi-Square test and Mann-Whitney *U*-test. Survival analyses were performed with the packages "survminer" and "survival" (https://cran.r-project.org/package=survminer, https://CRAN.R-project.org/package=survival, last accessed on the 30 06 2021). To determine the effect of risk stratification, we built univariate and multivariate Cox proportional hazards regression models and assessed hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). *p*-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics and CEPH prevalence

Among all 349 patients included in the final analysis, 304 (87.1%) patients had liver cirrhosis. Table 1 presents the etiologies of liver disease as well as all additional baseline characteristics.

Distribution of CEPH-defining factors

Among the 304 (87.1%) patients with liver cirrhosis, CEPH was observed in 70 (54.7%), 131 (89.7%), and 27 (90.0%) patients with Child-Pugh stages A, B, and C, respectively. In addition, 13 (28.9%) patients without proven liver cirrhosis showed signs of CEPH. Figure 2 displays the distributions of CEPH-defining factors among these patients.

Influence of CEPH on the radiological response after TACE

Radiologic response based on the mRECIST criteria was evaluated for 320 patients with available follow-up imaging.[3,25] No significant differences were observed between patients with CEPH and those without ($p = 0.450$, Table 2).

Influence of CEPH and its defining factors on survival after TACE

Among all patients with signs of CEPH, the median OS was 10.6 months. Patients without CEPH had a median OS of 17.1 months after the initial TACE (log rank $p = 0.036$; Figure 3a). When stratifying patients according to the number of present surrogates as suggest by Choi et al.,[18] median OS for patients without a surrogate was 17.1 months, while patients with one present surrogate had a survival of 10.8 months and patients with two or more surrogates present had a median OS of 9.4 months ($p = 0.053$; Figure 3b).

Median Progression free survival (PFS) for patients with CEPH was 6.7 months, while patients without CEPH had a median PFS of 7.3 months ($p = 0.280$) (Figure S1A). Median PFS for patients without a surrogate was 7.3 months, while patients presenting with one surrogate for CEPH had median PFS of 7.5 months and patients with two or more surrogates had a median PFS of 6.5 months ($p = 0.550$) (Figure S1B)

A subgroup analysis of patients on the role of CEPH in the different Child-Pugh stages also showed no significant difference in the median OS (Figure 4). Regarding the PFS, only in the subgroup of patients with Child-Pugh stage A CEPH was a significant prognostic factor ($p = 0.022$) (Figure S2). In an additional subgroup analysis of patients within the intermediate stage (BCLC B) for whom TACE is the recommended standard treatment, patients with the presence of CEPH had also a significantly impaired survival (12.3 vs. 20.8 months, $p = 0.040$) (Figure S3A). However, no difference was observed regarding the influence of CEPH on the PFS (7.3 vs. 6.9 months, $p = 0.640$) (Figure S3B).

Among the CEPH-defining factors, that only ascites was associated with a significant difference in the median OS (Figure 5). Subsequently, an additional analysis has been performed regarding the modalities where varices have been identified. A total of 167/349 (47.9%) patients had varices in CT. Among the 299 patients with available endoscopy reports, 187 (62.5%) had varices. Neither the presence of varices in CT nor the presence of varices in endoscopy was a significant prognostic factor for median OS (10.8 vs. 14.2 months, $p = 0.59$, HR = 1.07 (95% CI 0.84–1.36) and 10.6 versus 16.1 months, $p = 0.45$, HR = 1.11 (95% CI 0.85–1.45), respectively) (Figure S4). Presence of ascites was the only of the CEPH-defining factors associated with an impaired median PFS (4.8 vs. 8.0 months, $p = 0.015$) (Figure S5).

We also analyzed 15 known risk factors of survival in patients with HCC that underwent TACE. Among these risk factors, we found that low albumin, elevated bilirubin, elevated aspartate aminotransferase, a large tumor size, and the presence of ascites were independent prognostic factors (Table 3).

External validation of the prognostic role of CEPH

An external validation was performed on a dataset of patients with HCC that underwent TACE at a second tertiary care center (Charité, Berlin, Germany) during the same period. A total of 60 patients met the inclusion and exclusion criteria. The baseline characteristics of this cohort can be found in the Table S1. In univariate analysis the median OS of patients with CEPH was 34.3 months, while patients without CEPH had a median OS of 9.7 months ($p = 0.029$) (Figure S6). Other significant risk factors for the OS in univariate analysis were a low albumin level, an elevated INR, reduced thrombocytes, the presence of ascites and the presence of varices (Table S2). In multivariate Cox regression analysis, only the presence of ascites remained an independent prognostic factor, while CEPH reached no significance ($p = 0.552$) (Table S2).

DISCUSSION

To the best of our knowledge, this study is the first to evaluate the role of surrogates for CEPH in Western patients with HCC that underwent TACE. We found that CEPH was present in more than two thirds of the patients. Patients with CEPH had an significantly impaired survival in univariate analysis. However, the influence of CEPH on the median OS reached no significance in multivariate analysis yielded and other factors seem to be more important for OS stratification. Additionally, of the individual surrogate parameters for CEPH that we examined only the presence of ascites had an influence

TABLE 1 Baseline characteristics of patients with HCC prior to TACE treatment

Variable	All patients (n = 349)	Patients with CEPH (n = 241)	Patients without CEPH (n = 108)	p value
Median age, years (IQR)	68.8 (62.0–75.2)	67.2 (61.6–73.2)	71.6 (65.0–77.0)	<0.01
Sex, n (%)				
Female	57 (16.3)	40 (16.6)	17 (15.7)	0.96
Male	292 (83.7)	201 (83.4)	91 (84.3)	
Etiology[a], n				<0.01
Alcohol	168	124	44	
Hepatitis C	57	45	12	
Hepatitis B	31	22	9	
NAFLD	29	18	11	
Hemochromatosis	9	6	3	
AIH/PBC/PSC	6	5	0	
Unknown/Other	39	18	17	
Child-pugh stage, n (%)				<0.01
A	128 (36.7)	70 (29.0)	58 (53.7)	
B	146 (41.8)	131 (54.4)	15 (13.9)	
C	30 (8.6)	27 (11.2)	3 (2.8)	
No cirrhosis	45 (12.9)	13 (5.4)	32 (29.6)	
ALBI grade, n (%)				<0.01
1	20 (5.7)	8 (3.3)	12 (11.1)	
2	220 (63.1)	134 (55.6)	86 (79.6)	
3	109 (31.2)	99 (41.1)	10 (9.3)	
BCLC stage, n (%)				0.02
0	0	0	0	
A	63 (18.1)	49 (20.3)	14 (12.9)	
B	179 (51.3)	115 (47.7)	64 (59.3)	
C	77 (22.1)	51 (21.2)	26 (24.1)	
D	30 (8.6)	26 (10.8)	4 (3.7)	
Median tumor size, mm (IQR)	42 (29–64)	39 (27–57)	50 (37–88)	<0.01
Tumor number, n (%)				0.86
Unifocal	76 (21.8)	53 (22.0)	23 (21.3)	
Multifocal	237 (67.9)	162 (67.2)	75 (69.4)	
Diffuse growth pattern	36 (10.3)	26 (10.8)	10 (9.3)	
Median albumin level, (IQR)	31(27–35)	30(26–34)	35(31–37)	<0.01
Median bilirubin level, (IQR)	1.4 (0.8–2.2)	1.7 (1.1–2.5)	0.8 (0.6–1.2)	<0.01
Median AST level, (IQR)	65 (47–100)	69 (51–106)	59 (42–81)	<0.01
Median ALT level, (IQR)	42 (28–62)	42 (28–62)	42 (29–61)	0.72
Median INR, (IQR)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.1 (1.0–1.2)	<0.01
Median AFP level, (IQR)	39 (8–869)	41 (8–1158)	30 (8–703)	0.58
Median platelet count, (IQR)	127 (86–191)	100 (73–152)	188 (145–232)	<0.01

(Continues)

TABLE 1 (Continued)

Variable	All patients (n = 349)	Patients with CEPH (n = 241)	Patients without CEPH (n = 108)	p value
Platelet count <100.000/μL, n (%)				<0.01
Yes	123 (35.2)	119 (49.4)	4 (3.7)	
No	226 (64.8)	122 (50.6)	104 (96.3)	
Median spleen size, mm	130 (113–148)	139 (124–158)	112 (101–125)	<0.01
Spleen size >120 mm, n (%)				<0.01
Yes	231 (66.2)	195 (80.9)	36 (33.3)	
No	118 (33.8)	46 (19.1)	72 (66.7)	
Esophageal/gastric varices, n (%)				<0.01
Yes	214 (61.3)	214 (88.8)	0	
No	135 (38.7)	27 (11.2)	108 (100.0)	
Ascites, n (%)				
Yes	119 (34.1)	119 (49.4)	0	<0.01
No	230 (65.9)	122 (50.6)	108 (100.0)	
Type of TACE				0.29
cTACE	139 (39.8)	101 (41.9)	38 (35.2)	
DEB-TACE	210 (60.2)	140 (58.1)	70 (64.8)	

Abbreviations: AFP: alpha-fetoprotein; AIH: autoimmune hepatitis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BCLC: Barcelona clinic liver cancer classification system; CEPH: clinically evident portal hypertension; cTACE: conventional TACE; DEB-TACE: drug-eluting beads TACE; INR: international normalized ratio; IQR: interquartile range; HCC: hepatocellular carcinoma; NAFLD: non-alcoholic fatty liver disease; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; TACE: transarterial chemoembolization.

[a]more than one possible and also patients without a pre-existing liver disease; thus, no percentages were calculated.

on the median OS. Our results were confirmed in an additional Western patient cohort, which we used for an additional external and independent validation.

The proportion of patients with CEPH in our study was similiar to the incidences previously reported in patients with HCC that underwent TACE.[16,18] However, those studies found that viral infections comprised the most common cause of the underlying liver disease; in contrast, in our study, alcohol was the most common etiology. To represent a more real-world situation, we included all patients, regardless of the Child-Pugh or BCLC stage. Therefore, a priori, we expected a relatively high prevalence of CEPH in our cohort, compared to previous studies.[16,18] Kim et al. included only patients in Child-Pugh stage A, and Choi et al. included patients in stages A and B.[16,18]

We found that the median albumin level, which served as an indicator of liver function, was significantly lower in patients with CEPH than in those without CEPH. This finding was consistent with previous findings by Kim et al.[16] In contrast to their results, we found a considerably larger tumor size in patients without CEPH than in those with CEPH. Unfortunately, Choi et al. did not provide any comparison of baseline characteristics between patients with and without CEPH.[18]

In our study, CEPH had no siginificant influence on the median OS in multivariate analysis. Therefore, we could not confirm the previously reported strong prognostic role of CEPH on survival outcome after TACE.[16,18] However, this discrepancy might be due to the different definitions of CEPH among these studies. Kim et al. defined CEPH as splenomegaly, in combination with either a low platelet count or esophageal/gastric varices. In contrast, Choi et al. defined CEPH as the presence of ascites, esophageal/gastric varices, or splenomegaly/low platelet count. Additionally, Choi et al. stratified patients according to the number of CEPH surrogates (one vs. two vs. ≥2). Interestingly, only the presence of two or more CEPH surrogates was identified as an independent prognostic factor in their multivariate Cox regression analysis. Moreover, their Kaplan Meier curves showed a remarkable overlap between groups. However, their cohort was limited by the absence of patients with multifocal HCC. Thus, that cohort was quite different from our study cohort, where more than half the patients had multifocal disease. According to current guidelines, particularly for patients with a multifocal tumor burden, TACE is a favorable treatment option.[3] Both previous studies had earlier inclusion periods (Kim et al.: 2000–2014, Choi et al.: 2005–2007), compared to our inclusion period (2010–2020). Thus, subsequent improvements in therapies and complication management might have been underrepresented in those studies.

Recently, Scheiner et al. investigated the role of invasive HVPG measurements for predicting OS before and during TACE treatment. They analyzed 28 patients with early or intermediate stage HCC that had been included in the AVATACE trial.[26,27] Consistent with our findings, patients with CEPH had an impaired median OS. Hwoever,

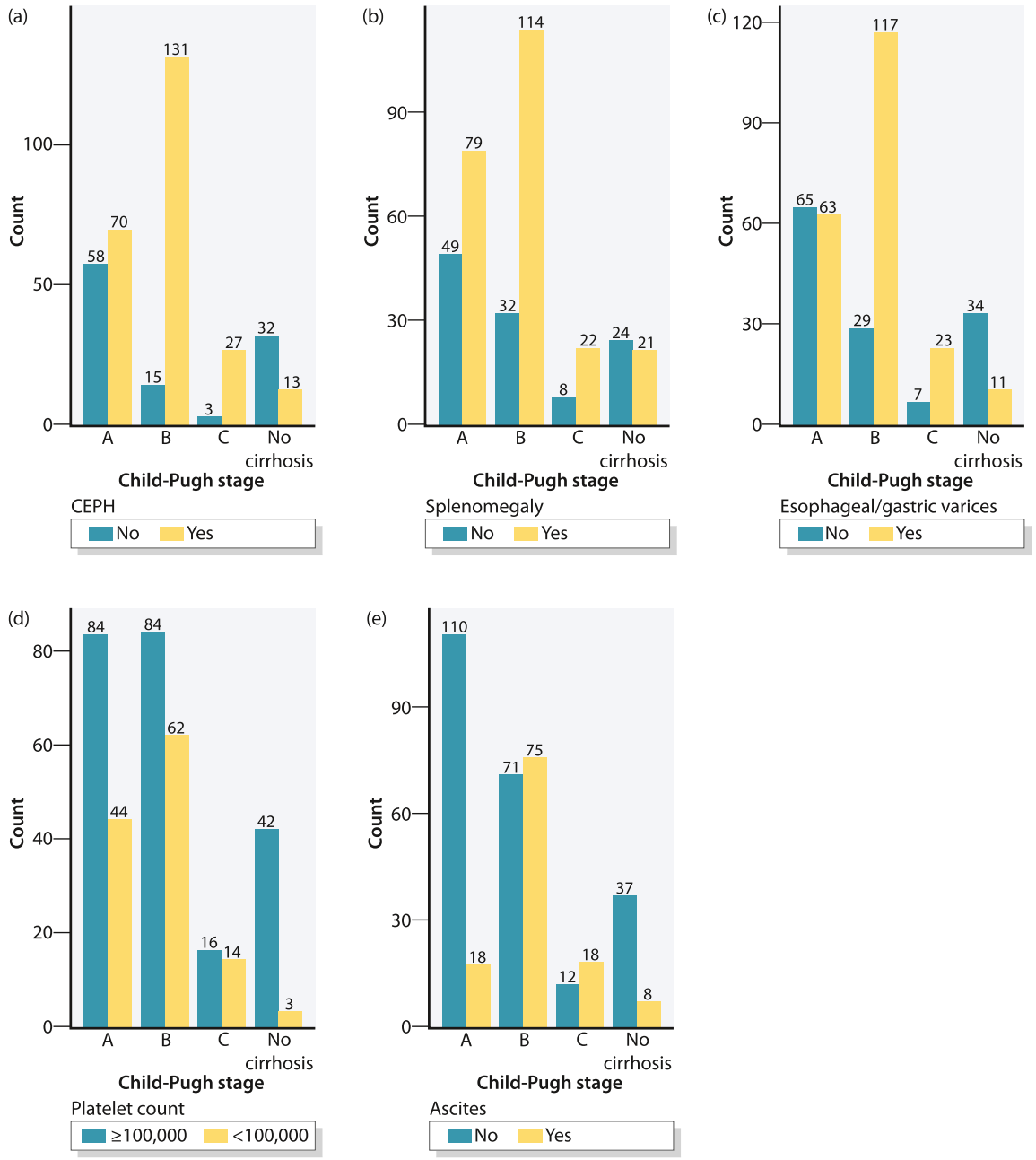

FIGURE 2 Distribution of clinically evident portal hypertension (CEPH) and CEPH-defining factors in patients with hepatocellular carcinoma. (a) Distribution of CEPH among the various child pugh stages; (b–d) distribution of the three CEPH-defining factors: (b) splenomegaly, (c) esophageal/gastric varices, (d) low platelet counts and (e) ascites among the various child pugh stages

TABLE 2 Radiologic response according to the mRECIST criteria for patients with and without CEPH (follow-up imaging available for 320 patients)

Radiologic response	Patients with CEPH (n = 218), n (%)	Patients without CEPH (n = 102), n (%)	p value
CR/PR	104 (47.7)	41 (40.2)	0.450
SD	61 (28.0)	33 (32.4)	
PD	53 (24.3)	28 (27.4)	

Abbreviation: CEPH: clinical evident portal hypertension.

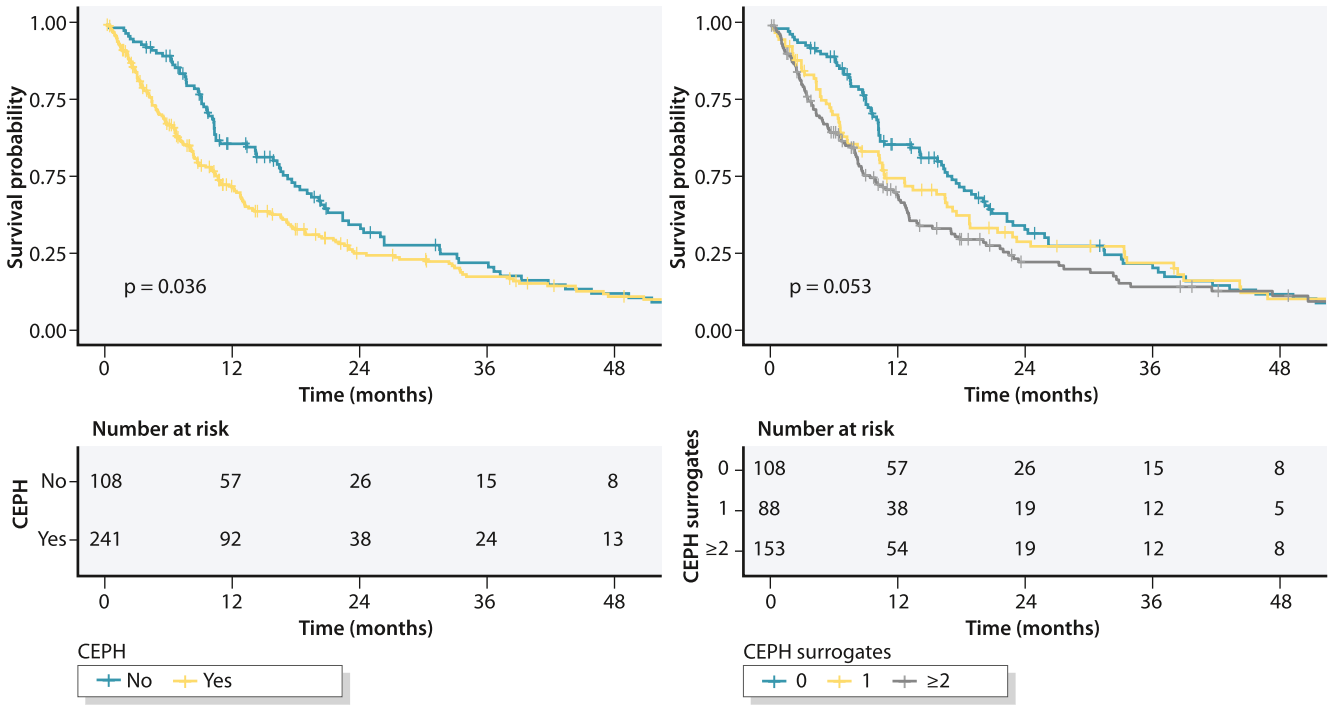

FIGURE 3 Kaplan Meier curves show overall survival of patients with hepatocellular carcinoma, stratified by the presence/absence of clinically evident portal hypertension (CEPH) (a) and in dependence of the present number of CEPH surrogates (b)

they found no significant difference in the median OS. Thus, other factors related to remnant liver function or tumor burden seem to have a more important influence on median OS.

For patients undergoing HCC resections, portal hypertension is highly predictive of the risk of postoperative liver decompensation.[15] Thus, current EASL guidelines recommend taking portal hypertension into account in making treatment decisions for early-stage HCC.[3] However, results have varied on the influence of portal hypertension on the long-term outcome of these patients.[15,20] For patients undergoing TACE, CEPH has not been considered in the guidelines. Our results have suggested that TACE should not be refused, due to the presence of surrogate markers of portal hypertension alone.

Of the CEPH-defining factors (ascites, splenomegaly, esophageal/gastric varices, and low platelet count) only ascites was a potential risk factors for OS after TACE. However, the definition and measurement of splenomegaly remain controversial. In this study, we measured the largest diameter in the axial plane, consistent with previous studies.[16,18] Nevertheless, it remains unclear whether the largest diameter in the axial plane is the ideal surrogate for the splenic volume.[28,29] Additionally, various cut-off values have been proposed, and evidence for an ideal cut-off value in patients with HCC is lacking. Several studies have shown that spleen volume was the best surrogate for survival outcome.[30,31] However, manual volumetry of the spleen is a time-consuming process. In comparison, measuring the axial plane diameter is easy to implement in clinical routines. Nevertheless, the first results from a fully automated spleen segmentation with the use of artificial intelligence methods have shown promising results and it is likely that those tools will become increasingly available in the daily clinical routine.[32,33] These novel methods offer an automated report of the splenic volume, ad hoc after imaging, which will tremendously reduce the time investment. Thus, large studies on this topic will become feasible in the near future, and new insights will be gained into the prognostic role of spleen volume for patients with HCC undergoing TACE.

In addition to a large tumor size, we found that signs of a decompensated liver cirrhosis (i.e., elevated AST, elevated bilirubin, the presence of ascites, and low albumin) remained independent prognostic factors in our multivariate analysis. These results suggested that close monitoring of liver synthesis parameters remains highly important. Interestingly, we found that, in patients with CEPH, albumin was significantly lower and ascites was observed more frequently than in patients without CEPH. Hypothetically, patients with CEPH might be at a higher risk of developing hepatic decompensation during the treatment. Thus, one future avenue of research could be to evaluate CEPH and liver function decompensation during the course of repeated TACE treatments. As mentioned above, the average albumin level was lower and the bilirubin level higher in patients with CEPH. However, the prognostic influence of these factors might be partly equalized by the higher tumor burden in the group of patients without CEPH.

The present study had several limitations. First, the study was retrospective in design, and the existing dataset comprised a moderate sample size ($n = 349$). However, this dataset was well investigated, and we only included patients with complete clinical, laboratory, and imaging data. Missing values were not imputed. To control for a time bias, we actively decided to include only patients from 2010 and later, which further reduced the final sample size. However, these criteria minimized differences in the diagnosis and treatment decisions, which

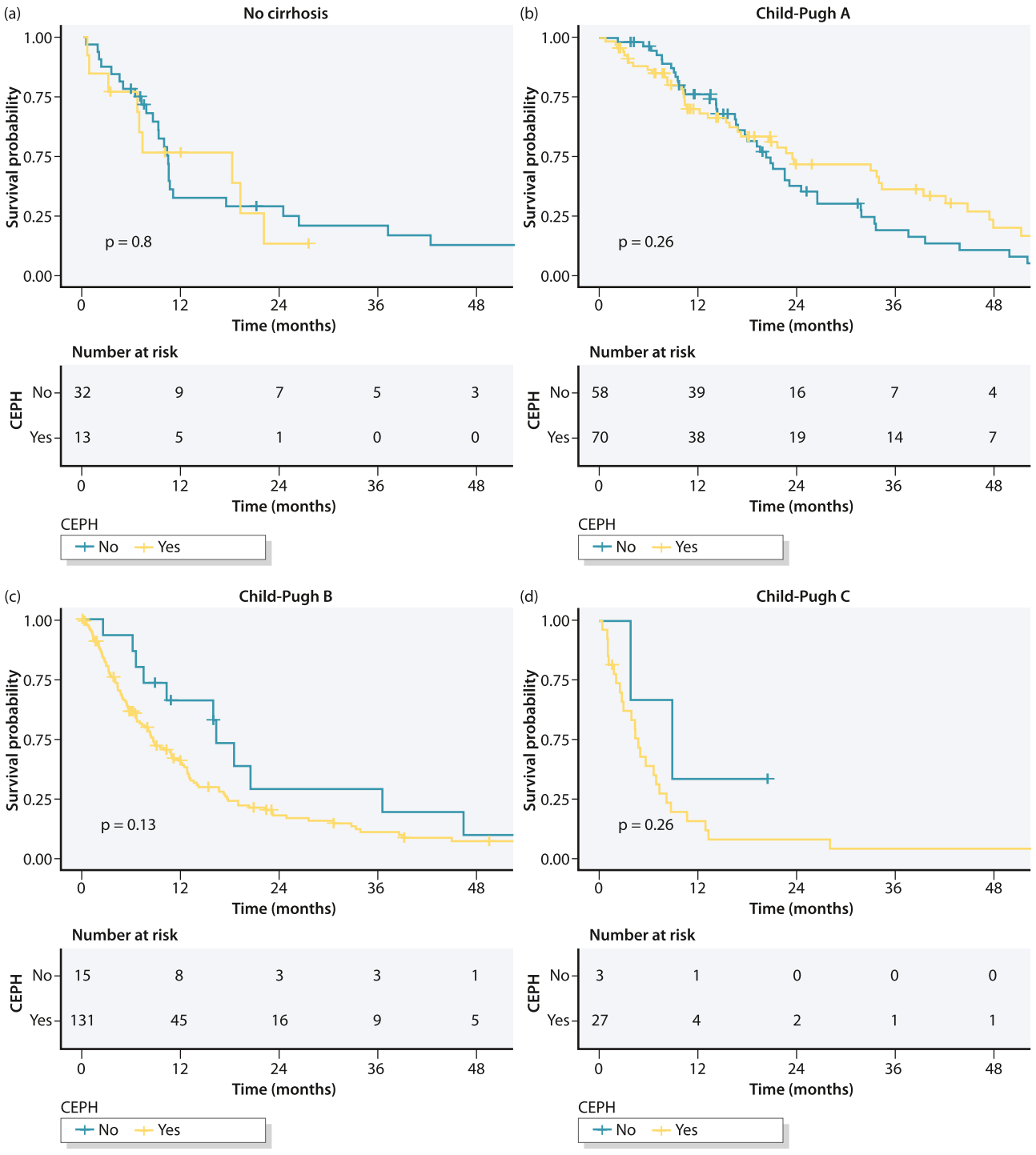

FIGURE 4 Kaplan Meier curves show overall survival of patients with hepatocellular carcinoma, stratified by the presence/absence of clinically evident portal hypertension in a subgroup analysis of (a) patients without liver cirrhosis and (b–d) patients with Child-Pugh stages A, B, and C

provided a more homogeneous study cohort. To avoid further bias, we excluded patients that underwent previous treatments. However, despite these strict inclusion criteria, our final sample size was comparable to those included in previous studies on this topic.[16,18] An additional limitation was that we did not separate patients that underwent cTACE and DEB-TACE, which are variations of the TACE procedure. However, several previous studies have shown that the TACE technique did not influence the OS.[34–36] Second, endoscopy reports were only available for 299 (85.7%) patients. The presence of esophageal/gastric varices should be considered as more important for the risk of gastrointestinal bleeding. However, in the subgroup analysis of patients with varices in endoscopy, we did not observe a significant difference regarding the long-term prognosis after TACE. These results are in-line with those observed for the presence of varices in CT.

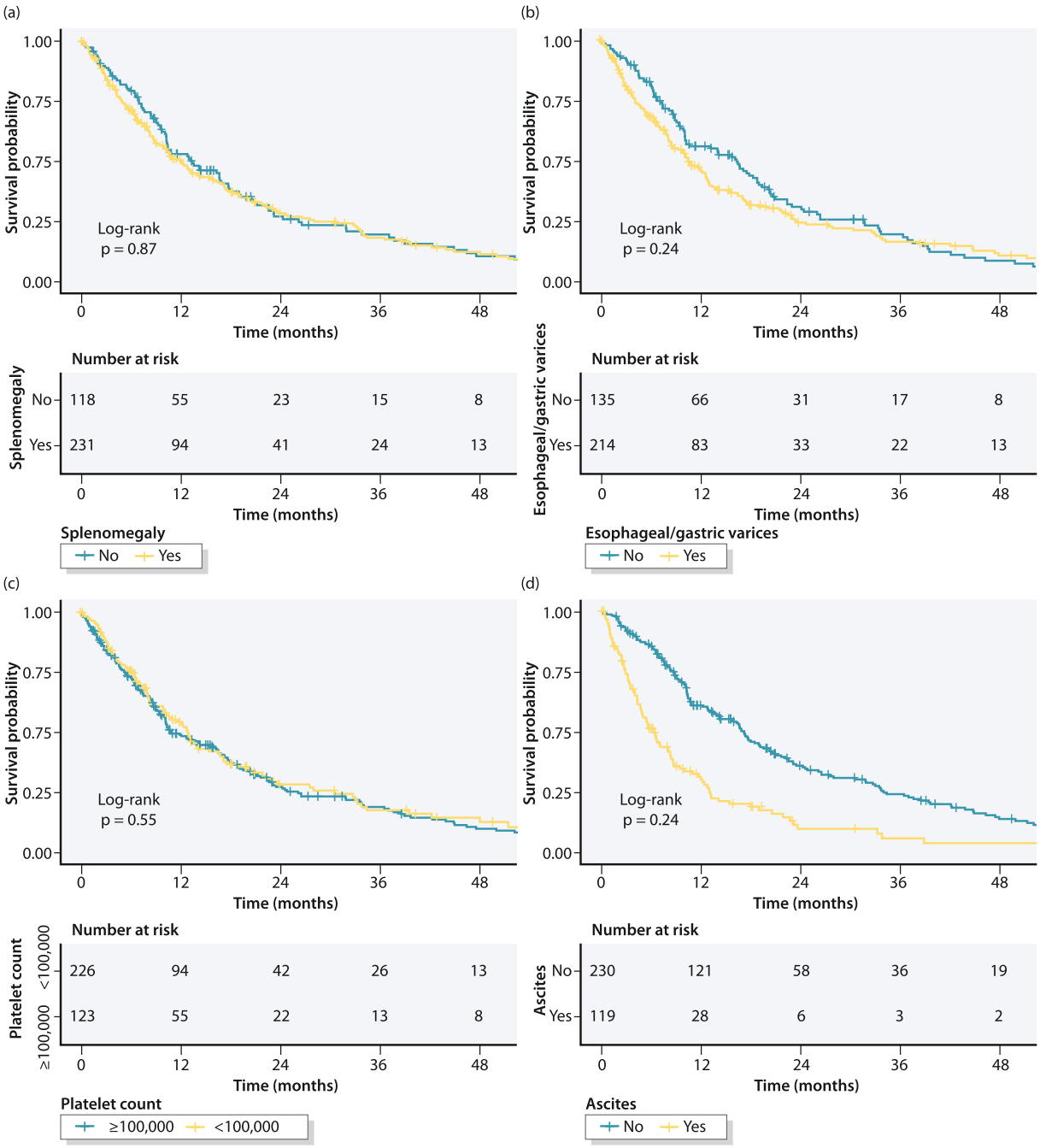

FIGURE 5 Kaplan Meier curves show overall survival of patients with or without the defining factors of clinically evident portal hypertension. Curves compare patients with and without (a) splenomegaly, (b) varices, (c) low platelet counts and (d) ascites

Third, in this study we follow the previously suggested definitions for CEPH in patients with HCC undergoing TACE.[16,18] Based on non-invasive laboratory and image-derived parameters, they differ considerably from the AASLD definition of "clinically significant portal hypertension".[37] The AASLD definition is mainly based on invasive HVPG measurement, which is no standard part of the diagnostic workflow for patients with HCC undergoing TACE. Our results indicate that especially spleen size and thrombocyte count are of limited prognostic relevance in patients with HCC undergoing TACE and that other definitions should be considered. Prospective future studies should therefore evaluate the correlation of non-invasive parameters with HVPG measurements in patients with HCC undergoing TACE in order to further investigate the thresholds of portal hypertension.

CONCLUSION

CEPH was present in more than two thirds of the patients with HCC that underwent TACE in our cohort of Western patients. In our study, patients with CEPH had a significantly impaired survival in

TABLE 3 Uni- and multivariate Cox proportional hazards regression model for evaluating the influence of CEPH - defining factors and other risk factors on overall survival in patients with hepatocellular carcinoma that underwent transarterial chemoembolization

Analysis		Univariate			Multivariate		
Covariate		**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age	≥70 years	1.0	0.8–1.3	0.960			
AFP	>200 ng/ml	1.3	1.0–1.6	0.056			
Albumin level	≥35 g/L	2.2	1.7–2.9	**<0.001**	1.7	1.1–2.3	**0.003**
Bilirubin level	≥1.2 mg/dl	2.1	1.6–2.7	**<0.001**	1.6	1.1–2.1	**0.002**
AST level	>31 U/l	1.9	1.1–3.2	**0.023**	1.9	1.1–3.3	**0.035**
ALT level	≥35 U/l	1.2	0.9–1.5	0.160			
INR level	>1.2	1.1	0.8–1.4	0.540			
CRP level	≥5 mg/dl	2.5	1.9–3.3	**<0.001**	2.1	1.5–2.8	**<0.001**
Tumor number	≥2	1.3	0.9–1.7	0.130			
Max. lesion size	>5.0 cm	1.4	1.1–1.8	**0.009**	1.2	0.9–1.6	**0.187**
Splenomegaly	Present	1.0	0.8–1.3	0.870			
Esophageal/gastric varices	Present	1.2	0.9–1.5	0.240			
Platelet count	<100.000/μL	0.9	0.7–1.2	0.550			
Ascites	Present	2.3	1.8–3.0	**<0.001**	2.0	1.4–2.7	**<0.001**
CEPH	Yes	1.3	1.0–1.7	**0.037**	0.8	0.6–1.1	**0.190**

Note: p-values <0.05 are depicted in bold.

Abbreviations: AFP: alpha fetoprotein; ALT: alanine aminotransferase, AST: aspartate aminotransferase, CEPH: clinical evident portal hypertension; CRP: C-reactive protein.

univariate analysis. However, no significance was reached in multivariate analysis and other risk factors seem to be more important for OS stratification. Thus, patients that are eligible for TACE treatment based on oncological evidence should not be excluded from TACE treatment solely due to the presence of surrogates for portal hypertension. Interdisciplinary decision-making whether to initiate a TACE treatment should be based on more prognosis-relevant factors, especially remnant liver function.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Lukas Müller, Felix Hahn, Aline Mähringer-Kunz, Fabian Stoehr, Simon Johannes Gairing, Friedrich Foerster, Arndt Weinmann, Peter Robert Galle, Jens Mittler, Daniel Pinto dos Santos, Michael Bernhard Pitton, Christoph Düber, Uli Fehrenbach, Timo Alexander Auer, Bernhard Gebauer and Roman Kloeckner devised the study, assisted in data collection, participated in the interpretation of the data and helped draft the manuscript. Lukas Müller, Felix Hahn, Fabian Stoehr, Aline Mähringer-Kunz, Uli Fehrenbach, Timo Alexander Auer, Bernhard Gebauer and Roman Kloeckner carried out the data collection. Simon Johannes Gairing, Friedrich Foerster, Arndt Weinmann, Peter Robert Galle, Jens Mittler, Michael Bernhard Pitton and Christoph Düber supported the data collection efforts. Lukas Müller, Felix Hahn, Daniel Pinto dos Santos and Roman Kloeckner created all of the figures and participated in the interpretation of data. Lukas Müller, Felix Hahn, Daniel Pinto dos Santos and Roman Kloeckner performed the statistical analysis. All authors read and approved the final manuscript.

ETHICS APPROVAL

The Ethics Committee of the Medical Association of Rhineland Palatinate, Mainz, Germany approved this study (permit number

2021-15984). The requirement for informed consent was waived, due to the retrospective nature of the study. Patient records and information were anonymized prior to analysis.

DATA AVAILABILITY STATEMENT

Data cannot be shared publicly because of institutional and national data policy restrictions im-posed by the Ethics committee of the Medical Association of Rhineland Palatinate, Mainz, Ger-many since the data contain potentially identifying patient information. Data are available upon request for researchers who meet the criteria for access to confidential data.

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