

Prevalence and prognostic impact of hepatopulmonary syndrome in patients with unresectable hepatocellular carcinoma undergoing transarterial chemoembolization: a prospective cohort study

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Abstract

Background: To determine the prevalence and prognostic impact of hepatopulmonary syndrome (HPS) in patients with unresectable hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE).

Methods: Fifty-four patients with unresectable HCC undergoing TACE between December 2014 and December 2015 were prospectively screened for HPS and were followed up for a maximum of 2 years or until the end of this prospective study.

Results: Nineteen of the 54 (35.2%) patients were considered to have HPS, including one (5.3%) with severe HPS, nine (47.4%) with moderate HPS, and nine (47.4%) with mild HPS. The median overall survival (OS) was 10.1 (95% confidence interval [CI], 3.9–16.3) months for patients with HPS and 15.1 (95% CI, 7.3–22.9) months for patients without HPS, which is not a significant difference ($P = 0.100$). The median progression-free survival was also not significantly different between patients with and without HPS (5.2 [95% CI, 0–12.8] vs. 8.4 [95% CI, 3.6–13.1] months; $P = 0.537$). In the multivariable Cox regression analyses, carbon monoxide diffusing capacity (hazard ratio [HR] = 1.033 [95% CI, 1.003–1.064]; $P = 0.028$) and Child-Pugh class (HR = 1.815 [95% CI, 1.011–3.260]; $P = 0.046$) were identified to be the independent prognostic factors of OS.

Conclusion: Mild or moderate HPS is common in patients with unresectable HCC undergoing TACE, but it does not seem to have a significant prognostic impact.

Keywords: Hepatocellular carcinoma; Hepatopulmonary syndrome; Chemoembolization; Therapeutic; Prognosis; Prevalence

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common malignancy and the fourth leading cause of cancer-related mortality worldwide.^[1,2] Approximately 80% to 85% of patients with HCC have unresectable disease at present and therefore, curative treatment options are available to only 15% to 20% of patients.^[3,4] Transarterial chemoembolization (TACE) is the most widely used palliative treatment option for unresectable HCC.^[5] TACE is effective in controlling disease progression as the blood supply for HCC preferentially originates from the hepatic artery.^[6,7] However, since HCC usually arises in the setting of chronic liver disease, it is therefore not uncommon for HCC patients to present with major complications of liver dysfunction and/or portal hypertension (eg, ascites, variceal bleeding, and hepatic

encephalopathy), which may negatively affect prognosis and treatment outcomes.^[7]

Hepatopulmonary syndrome (HPS) is a common pulmonary complication of liver disease and/or portal hypertension and is defined as an arterial oxygenation defect induced by intra-pulmonary vascular dilation (IPVD).^[8] HPS has been mostly reported in cirrhotic patients, with a prevalence of 12% to 32% in those evaluated for liver transplantation (LT) or transjugular intra-hepatic portosystemic shunt (TIPS) creation,^[8] and negatively affects the prognosis of patients with cirrhosis.^[9] HPS has also been reported in patients with unresectable HCC, but the prevalence and prognostic impact of HPS in this population remain unknown.^[10] Consequently, whether HPS screening and treatment are necessary for patients

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with unresectable HCC undergoing TACE is still unclear. The purpose of this study was to assess the prevalence and the prognostic impact of HPS in patients with unresectable HCC undergoing TACE.

Methods

Study design

This prospective cohort study was approved by the institutional review board of West China Hospital (Identifier, 2014–249), and written informed consent was obtained from all patients. All patients with unresectable HCC undergoing TACE at a single institution between December 2014 and December 2015 were eligible for inclusion in this study and were screened for HPS. The diagnosis of HCC was established by clinical, laboratory, imaging, and when necessary, histologic findings. The diagnosis of HPS in patients with HCC was established by a positive contrast-enhanced echocardiography (CEE) result (ie, the appearance of microbubbles in the left heart chambers within 3 to 6 heartbeats after their initial appearance in the right heart chambers) and an elevated alveolar-arterial oxygen gradient (AaO_2) (≥ 15 or ≥ 20 mmHg if age ≥ 65 years).^[8,11] CEE was performed using 10 mL agitated saline and transthoracic echocardiography in the parasternal four-chamber view as described previously.^[12,13] The appearance of any microbubble in the left heart chambers < 3 heartbeats after their initial appearance in the right heart chambers indicates the presence of an intra-cardiac shunt. Arterial blood gas sampling was performed while the patient was in an upright position and was breathing room air. The severity of HPS was categorized as very severe (partial arterial pressure of oxygen [PaO_2] < 50 mmHg), severe (PaO_2 50–59 mmHg), moderate (PaO_2 60–79 mmHg), or mild (PaO_2 ≥ 80 mmHg), as described previously.^[14,15] The exclusion criteria were age < 18 years, uncontrolled infection, other known malignancies, intracardiac shunts, heart failure, pulmonary hypertension, pregnancy, and previous TIPS creation.

TACE procedure

With the patient under local anesthesia, right femoral access was obtained, and angiography of the superior mesenteric and common hepatic arteries was performed using a 5-Fr Rösch hepatic catheter (Radiofocus; Terumo, Tokyo, Japan). A 3-Fr microcatheter (MicroFerret; Cook, Indiana, USA) was coaxially placed into the proper, lobar, segmental, or subsegmental hepatic artery, and 500 to 1000 mg 5-fluorouracil was infused through the microcatheter for 10 to 15 min. Subsequently, 20 to 40 mg doxorubicin mixed at a 1:1 ratio in an emulsion of iodized oil (Lipiodol; Guerbet, France) was infused, which was followed by embolization with gelatin sponge pledgets (Gelfoam; Upjohn, Missouri, USA) until stasis or near stasis of arterial flow was achieved. Hemostasis at the access site was achieved by manual compression.

Follow-up

Follow-up visits were scheduled every 4 to 12 weeks until death up to a maximum of 2 years or until the end of the

study (June 2017). Contrast-enhanced computed tomography or magnetic resonance imaging was performed at each follow-up visit to evaluate the tumor response (ie, the best overall response) by modified Response Evaluation Criteria in Solid Tumors Criteria.^[16] Progression-free survival (PFS) was defined as the interval from study entry to disease progression, death from any cause, or when the patient was lost to or refused follow-up, up to a maximum of 2 years or until the end of the study.^[17] Overall survival (OS) was defined as the interval from study entry to death from any cause or when the patient was lost to or refused follow-up, up to a maximum of 2 years or until the end of the study. Repeat TACE was performed every 4 to 8 weeks as needed if residual or new tumor tissue was detected at follow-up.

Statistical analysis

Continuous variables were compared using Student's *t*-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the chi-squared or Fisher's exact test. The time-to-event distributions were estimated using the Kaplan–Meier method and compared using the log-rank test. According to the results of univariate analyses and clinical relevance, variables were included in the multivariate Cox regression analyses to identify independent prognostic factors. All analyses were performed using SPSS software (version 19.0; SPSS, Chicago, IL, USA). A two-sided *P* value < 0.05 was considered statistically significant.

Results

Prevalence of HPS and clinical characteristics of the patients

A total of 60 patients with HCC undergoing TACE were eligible for inclusion in this study [Figure 1]. Six of these patients were excluded from the study due to previous TIPS creation ($n = 2$), discontinued treatment ($n = 1$), a poor echocardiographic window ($n = 1$), and intra-cardiac shunt ($n = 2$). The remaining 54 patients were included in the study and were screened for HPS. Among these patients, 31 (57.4%) had a positive CEE result. Of these patients, 19 (61.3%) had an elevated AaO_2 . These patients were considered to have HPS, including one (5.3%) with severe HPS, nine (47.4%) with moderate HPS, and nine (47.4%) with mild HPS. Therefore, the prevalence of HPS was 35.2% (19/54).

The demographics, etiology of liver disease, cirrhosis status, Child-Pugh class, performance status, tumor characteristics, and history of prior treatments were not significantly different between those with and without HPS (all $P > 0.050$) [Table 1]. The number of patients who complained of dyspnea was significantly higher in the group with HPS than in the group without HPS (8/19 *vs.* 4/35; $P = 0.016$). However, the number of patients who had cyanosis (3/19 *vs.* 2/35; $P = 0.332$) and digital clubbing (2/19 *vs.* 2/35; $P = 0.607$) was not significantly different between those with and without HPS. Significantly more patients with HPS had spider angioma than those without HPS (8/19 *vs.* 3/35; $P = 0.010$).

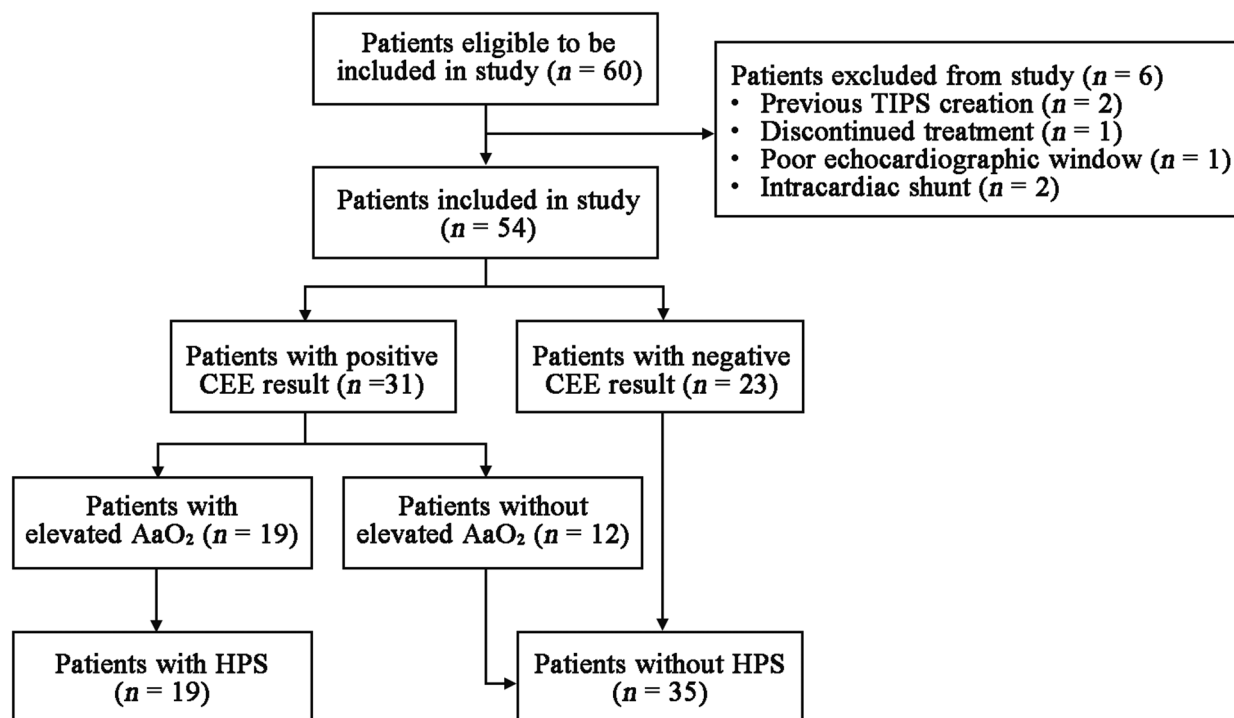


Figure 1: Flow chart of the patient selection and HPS screening processes. AaO₂: Alveolar-arterial oxygen gradient; CEE: Contrast-enhanced echocardiography; HPS: Hepatopulmonary syndrome; TIPS: Transjugular intra-hepatic portosystemic shunt.

Patients with HPS had significantly higher AaO₂ values (26.1 ± 9.3 vs. 15.5 ± 11.6 mmHg; $P = 0.001$), significantly lower arterial oxygen saturation (95.4 ± 2.5 vs. 96.8 ± 1.7 ; $P = 0.019$), and PaO₂ values (76.8 ± 10.0 vs. 85.0 ± 12.0 mmHg; $P = 0.015$) than those without HPS. However, the partial arterial pressure of carbon dioxide was not significantly different between patients with and without HPS (37.4 ± 4.1 vs. 39.4 ± 4.2 mmHg; $P = 0.104$). In addition, the carbon monoxide diffusing capacity (DLCO) was the only pulmonary function test result that was significantly different between patients with and without HPS ($83.3 \pm 14.2\%$ predicted vs. $93.1 \pm 15.2\%$ predicted; $P = 0.032$).

Clinical outcome of TACE for HCC according to HPS status

The median interval from HCC diagnosis to study entry was not significantly different between patients with and without HPS (8.5 [95% CI, 3.2–13.8] vs. 3.9 [95% CI, 0–9.9] months; $P = 0.613$). A total of 172 TACE sessions were performed for the patients during the study, with no significant difference between those with and without HPS (3.1 ± 1.5 sessions per patient vs. 3.3 ± 1.6 sessions per patient; $P = 0.549$). No major complications, defined according to the Society of Interventional Radiology clinical practice guidelines, were observed in any patients.^[18] Five (9.3%) patients, including one with HPS and four without HPS, were lost to or refused the follow-up after 3.3, 2.5, 3.8, 5.2, and 5.3 months. The median overall survival (OS) was not significantly different between patients with and without HPS (12.0 [95% CI, 8.2–15.7] vs. 14.9 [95% CI, 11.9–17.9] months; $P = 0.223$).

The tumor response was not significantly different between patients with and without HPS ($P = 0.748$). For patients with HPS, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were observed in 2 (10.5%), 8 (42.1%), 1 (5.3%), and 8 (42.1%) patients, respectively. For patients without HPS, CR, PR, SD, and PD were observed in 7 (20.0%), 15 (42.9%), 1 (2.9%), and 12 (17.1%) patients, respectively. Of the patients with PD, 18 (90%, 18/20) died before the 6-month evaluation, including 6 of the 19 (31.6%) patients with HPS and 12 of the 35 (34.3%) patients without HPS. The 6-month overall response rates (ie, the percentage of patients in whom CR or PR was observed) for patients with and without HPS were 53.8% (7/13) and 78.3% (18/23), respectively, and the difference was not significantly different ($P = 0.153$).

A total of 32 (59.3%) patients died at the end of the study, mainly due to disease progression (87.5% [28/32]), with no significant difference of mortality between patients with and without HPS (73.7% [14/19] vs. 51.4% [18/35]; $P = 0.112$). The median OS was 10.1 (95% CI, 3.9–16.3) months for patients with HPS and 15.1 (95% CI, 7.3–22.9) months for patients without HPS, which was not a significant difference ($P = 0.100$) [Figure 2]. The median PFS was also not significantly different between patients with and without HPS (5.2 [95% CI, 0–12.8] vs. 8.4 [95% CI, 3.6–13.1] months; $P = 0.537$) [Figure 3]. In the multivariate Cox regression analyses, DLCO (hazard ratio [HR] = 1.033 [95% CI, 1.003–1.064]; $P = 0.028$) and Child-Pugh class (HR = 1.815 [95% CI, 1.011–3.260]; $P = 0.046$) were identified to be the independent prognostic factors of OS [Table 2].

Table 1: Clinical characteristics of patients with and without HPS.

Characteristics	HPS (n = 19)	Non-HPS (n = 35)	Statistics	P value
Age (years)	59.6 ± 12.1	55.8 ± 8.6	1.355*	0.181
Male	16 (84.2)	32 (91.4)	NA†	0.653
Etiology of liver disease			3.451†	0.390
HBV	18 (94.7)	31 (88.6)		
HCV	0 (0)	1 (2.9)		
HCV and alcohol	1 (5.3)	0 (0)		
Unknown	0 (0)	3 (8.6)		
Cirrhosis	9 (47.4)	10 (28.6)	1.908‡	0.167
Child-Pugh class			3.226†	0.232
A	12 (63.2)	28 (80.0)		
B	4 (21.1)	6 (17.1)		
C	3 (15.8)	1 (2.9)		
ECOG performance status			NA†	0.687
0	16 (84.2)	31 (88.6)		
1	3 (15.8)	4 (11.4)		
Ascites	5 (26.3)	4 (11.4)	NA†	0.251
Pleural effusion	4 (21.1)	1 (2.9)	NA†	0.050
History of variceal bleeding	2 (10.5)	8 (22.9)	NA†	0.465
History of overt HE	1 (5.3)	2 (5.7)	NA†	0.607
Prior curative treatment			0.603†	>0.999
Liver transplantation	0 (0)	0 (0)		
Surgical resection	3 (15.8)	6 (17.1)		
Percutaneous ablation	0 (0)	1 (2.9)		
Prior TACE sessions			5.339†	0.151
1	5 (26.3)	6 (17.1)		
2	5 (26.3)	4 (11.4)		
≥3	5 (26.3)	7 (20.0)		
Maximum tumor diameter (cm)	7.0 ± 4.5	5.3 ± 3.7	-1.231*	0.227
Multicentric tumors	8 (42.1)	15 (42.9)	0.003‡	0.957
Bilobar involvement	5 (25.7)	9 (26.3)	NA†	>0.999
Macrovascular invasion	7 (36.8)	7 (20.0)	NA†	0.206
Extrahepatic spread	0	0		
AFP >400 ng/mL	6 (31.6)	10 (28.6)	0.053‡	0.817
Active tobacco smokers	4 (21.1)	9 (25.7)	NA†	>0.999
Dyspnea	8 (42.1)	4 (11.4)	NA†	0.016
Cyanosis	3 (15.8)	2 (5.7)	NA†	0.332
Digital clubbing	2 (10.5)	2 (5.7)	NA†	0.607
Spider angioma	8 (42.1)	3 (8.6)	NA†	0.010
SaO ₂ (%)	95.4 ± 2.5	96.8 ± 1.7	-2.425*	0.019
ABG analysis				
AaO ₂ (mmHg)	26.1 ± 9.3	15.5 ± 11.6	3.410*	0.001
PaO ₂ (mmHg)	76.8 ± 10.0	85.0 ± 12.0	-2.513*	0.015
PaCO ₂ (mmHg)	37.4 ± 4.1	39.4 ± 4.2	-1.653*	0.104
Pulmonary function tests				
TLC (% predicted)	96.4 ± 12.8	94.4 ± 12.1	0.529*	0.600
FEV ₁ (% predicted)	89.0 ± 17.6	76.5 ± 37.8	1.654*	0.104
FVC (% predicted)	90.3 ± 15.6	93.7 ± 14.2	-0.766*	0.447
FEV ₁ /FVC (% predicted)	79.8 ± 12.0	79.2 ± 7.8	0.223*	0.825
DLCO (% predicted)	83.3 ± 14.2	93.1 ± 15.2	-2.216	0.032

Data are presented as mean ± standard deviation or n(%). * Student's t test. † Fisher's exact test. ‡ Pearson chi-square. AaO₂: Alveolar-arterial oxygen gradient; ABG: Arterial blood gas; AFP: Alpha-fetoprotein; DLCO: Carbon monoxide diffusing capacity; ECOG: European Cooperative Oncology Group; FEV₁: Forced expiratory volume in 1 s; FVC: Forced vital capacity; HBV: Hepatitis V virus; HCV: Hepatitis C virus; HE: Hepatic encephalopathy; HPS: Hepatopulmonary syndrome; PaCO₂: Partial arterial pressure of carbon dioxide; PaO₂: Partial arterial pressure of oxygen; SaO₂: Arterial oxygen saturation; TACE: Transcatheter arterial chemoembolization; TLC: Total lung capacity.

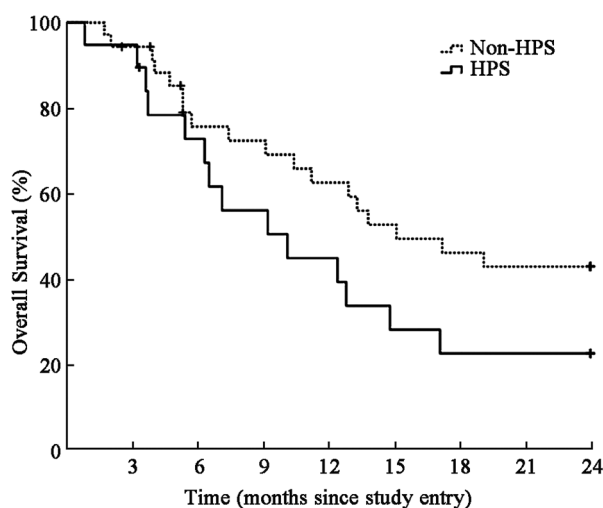


Figure 2: Kaplan-Meier curve of OS according to HPS status. HPS: Hepatopulmonary syndrome; OS: Overall survival.

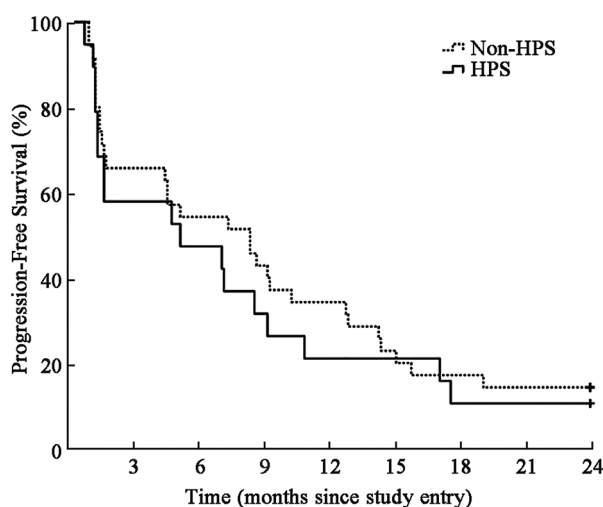


Figure 3: Kaplan-Meier curve of PFS according to HPS status. HPS: Hepatopulmonary syndrome; PFS: Progression-free survival.

Discussion

The prevalence of HPS in cirrhotic patients evaluated for LT or TIPS creation ranges from 12% to 32%, and those with HPS have double the risk of death compared to those without HPS.^[9] Therefore, patients with HPS are eligible to receive higher priority on the transplant waitlist than patients without HPS.^[19] In patients with unresectable HCC, however, the prevalence and prognostic impact of HPS remain unknown. In this study, we found that: (1) the prevalence of HPS in patients with HCC undergoing TACE was very common, (2) HPS was mostly mild or moderate in patients with HCC; and (3) the median OS and PFS were not significantly different between patients with and without HPS.

Approximately 50% to 60% of cirrhotic patients evaluated for LT or TIPS creation have IPVD, as demonstrated by a positive CEE result; depending on

Table 2: Multivariate cox regression analyses to identify the prognostic factors of OS.

Items	P value	HR	95% CI
HPS	0.659	0.821	0.342–1.970
DLCO	0.028	1.033	1.003–1.064
AaO ₂	0.466	0.984	0.943–1.027
Maximum tumor diameter	0.148	1.071	0.976–1.176
Child–Pugh class	0.046	1.815	1.011–3.260

AaO₂: Alveolar-arterial oxygen gradient; DLCO: Carbon monoxide diffusing capacity; HR: Hazard ratio; HPS: Hepatopulmonary syndrome; OS: Overall survival.

the cut-off value of AaO₂ or PaO₂ used to define arterial oxygenation defects, 27% to 94% of these patients could meet the diagnostic criteria for HPS, resulting in a prevalence of 12% to 32% for HPS in this population.^[8,15] In this study, 35.2% (19/54) of patients met the diagnostic criteria provided by the clinical practice guidelines for HPS.^[8,11] These results suggest that the prevalence of HPS is comparable between cirrhotic patients evaluated for LT or TIPS creation and HCC patients undergoing TACE. Notably, however, the majority of the patients in this study had only mild to moderate HPS, which also explains why many patients had no apparent symptoms. Similarly, in two recent prospective studies including cirrhotic and Budd-Chiari syndrome patients undergoing TIPS creation or balloon angioplasty, where severe to very severe HPS was observed in only 0% to 8% of the study population.^[13,15] This indicates that while HPS is common, the majority of cases is mild to moderate in severity with no apparent symptom.

HPS substantially worsens the prognosis of cirrhosis.^[9] Swanson *et al*^[20] showed a median survival of approximately 25 months and a 5-year survival rate of 23% in cirrhotic patients with HPS, compared to a median survival of 87 months and a 5-year survival rate of 63% in cirrhotic patients without HPS matched for etiology and severity of the liver disease. In addition, mortality was mainly related to the major complications of liver dysfunction and/or portal hypertension, as opposed to those of a primary respiratory event. However, these findings are unlikely to be generalizable to patients with unresectable HCC since they have a much shorter survival and higher risk of death by disease progression.^[21] In this study, the median OS and PFS were not significantly different between patients with and without HPS. In addition, disease progression, rather than major complications of liver dysfunction and/or portal hypertension, was the cause of discontinuation in 87.5% (28/32) of the patients. These findings suggest that mild or moderate HPS may not have a prognostic impact in patients with unresectable HCC undergoing TACE, and therefore, HPS screening and treatment may be unwarranted in this population. However, for severe and very severe HPS in patients with unresectable HCC, screening (with pulse oximetry) and treatment (with oxygenation therapy and garlic) may be advisable,^[9,22] because mortality in HPS is associated with the severity of

hypoxemia,^[21,23] and HPS could worsen patient functional status and quality of life.^[9]

This study has several limitations. First, although this is the largest clinical cohort for patients with HCC and HPS to our knowledge, the sample size of the current study is still relatively small.^[11,24] Second, the HPS status was not reevaluated during the study to confirm that no changes had occurred since study entry, although HPS seldom resolves spontaneously and most patients with subclinical HPS seem to have stable arterial oxygenation over time.^[23,25] Third, the majority of the patients had only mild to moderate HPS, and the results may not be applicable for patients with severe and very severe HPS.

In conclusion, mild or moderate HPS is common in patients with unresectable HCC undergoing TACE but it does not seem to have a prognostic impact in patients with unresectable HCC. Therefore, HPS screening and treatment seem to be unwarranted in patients with HCC undergoing TACE and should, perhaps, be considered for those with only severe or very severe HPS.

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Conflicts of interest

None.

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