

Hepatopulmonary syndrome is associated with the presence of hepatocellular carcinoma in patients with decompensated cirrhosis

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Abstract

Background Hepatopulmonary syndrome (HPS) is a relatively common complication in patients with decompensated cirrhosis. Our aim was to evaluate the prevalence of HPS, its clinical impact, and the possible association between HPS and characteristics of patients with decompensated cirrhosis.

Methods Patients with stable decompensated cirrhosis admitted to our department and assessed for HPS were included. For each patient, several clinical, laboratory and echocardiographic parameters as well as renal function were recorded. The severity of liver disease was evaluated according to the Model for End-stage Liver Disease and Child-Pugh scores, and renal function was assessed using ⁵¹chromium complexed with ethylene diamine tetracetic acid. In addition, the short synacthen test was performed in each patient to evaluate the adrenal function.

Results Sixty-three patients were enrolled, 26 (41.3%) of whom diagnosed with HPS. In multivariate analysis, the presence of hepatocellular carcinoma [odds ratio (OR) 8.1, 95% confidence interval (CI) 5.3-27.9, P=0.045] and salivary cortisol at T60 (60 min after the intravenous injection of 250 µg corticotropin) (OR 0.88, 95%CI 0.71-0.98, P=0.045) were the factors independently associated with HPS. T60 salivary cortisol had relatively good discriminative ability for the presence of HPS (area under the curve=0.73). The presence of HPS was not associated with the outcome (P=0.22).

Conclusion In our cohort of patients with decompensated cirrhosis, the presence of hepatocellular carcinoma and T60 salivary cortisol were the only factors independently associated with HPS.

Keywords Cirrhosis, hepatopulmonary syndrome, hepatocellular carcinoma, salivary cortisol, adrenal dysfunction

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Introduction

Decompensated cirrhosis is considered a systematic disease affecting several extrahepatic organs. Portopulmonary hypertension and hepatopulmonary syndrome (HPS) are pulmonary complications that, not infrequently, manifest in cirrhotic patients. HPS consists of the presence of arterial deoxygenation with an increased alveolar-arterial gradient and signs of intrapulmonary vasodilatation that result in a right-to-left intrapulmonary shunt in patients with chronic liver disease [1]. The pathogenesis of HPS has not been clarified, but previous studies have found that nitric oxide (NO) might be the main cause leading to intrapulmonary shunt and ventilation-perfusion mismatch [2,3], while in other studies carbon monoxide and von Willebrand factor antigen have been identified as factors that contribute to the development of HPS [4,5].

HPS is a relatively common complication of decompensated cirrhosis. Its prevalence varies from 4-47% in cirrhotic patients among different studies, depending on the criteria used to set the diagnosis of HPS [6]. The most frequent clinical symptoms of HPS are progressive dyspnea and platypnea, but neither is specific for HPS [7]. Digital clubbing, with a positive predictive value of 75%, was the best clinical sign associated with the presence of HPS [8], while a correlation between the presence of spider angiomas and HPS was also demonstrated recently, suggesting that they could be used as skin markers of HPS [9].

Although the association between HPS and ascites, jaundice or the severity of liver disease (based on evaluation of Model for End-stage Liver Disease [MELD] and Child-Pugh scores) has not been confirmed in all studies [10,11], the presence of HPS has been correlated with specific echocardiographic parameters reflecting higher cardiac output, a manifestation of hyperdynamic circulation in portal hypertension [12-14]. In addition, previous studies have provided conflicting results regarding the association between HPS and mortality in cirrhotic patients, since some studies [11,15,16] have shown that, compared to those without HPS, patients with HPS had no significant difference in overall survival rates, while other studies (including a prospective multicenter study) suggested that the presence of HPS was associated with higher mortality among cirrhotic patients [17,18].

The aim of the present study was to investigate the prevalence of HPS and its clinical impact on the outcome (death or liver transplantation [LT]), as well as the possible association between HPS and clinical or laboratory characteristics of patients with decompensated cirrhosis.

Patients and methods

Consecutive adult patients with stable decompensated cirrhosis who were admitted to our department during the period from September 2010 to December 2014 and assessed for HPS were prospectively evaluated. Their outcome (survival, death or LT) was recorded after a follow up of at least 6 months (unless death or LT occurred earlier). HPS was defined by the presence of: 1) chronic liver disease; 2) an alveolar-arterial gradient greater than 15 mmHg (or >20 mmHg for patients >65 years old); and 3) documented intrapulmonary vascular dilatation in contrast-enhanced echocardiography [19]. The degree of HPS severity was classified as mild, moderate, severe or very severe when the patient's partial pressure of oxygen (PaO₂) while breathing ambient air was ≥80 mmHg, ≥60 to <80 mmHg, ≥50 to <60 mmHg or <50 mmHg, respectively [19].

In our study, decompensated cirrhosis was defined as a history of ascites, variceal bleeding or encephalopathy in patients with known cirrhosis. We included only patients with stable decompensated cirrhosis: i.e., those without any evidence of infection (e.g. spontaneous bacterial peritonitis) or any episode of active bleeding or encephalopathy, at baseline and during the last 1 month before admission.

For each patient included in this study, an arterial blood gas test was performed and alveolar-arterial oxygen gradient

was calculated. All patients underwent contrast-enhanced echocardiography, performed after the injection of 20 mL of agitated saline into the patient's right cubital vein. Microbubble opacification of the left atrium within the 4th and 8th cardiac cycle after right atrial opacification was considered to be indicative of intrapulmonary shunts. The appearance of microbubbles earlier than the 4th cardiac cycle in the left cardiac chambers was indicative of intracardiac shunt. Other echocardiographic variables were also evaluated, such as left and right ventricular dimensions, left and right atrial volumes, mitral and tricuspid inflow velocities at the tip of the valves leaflet (E- and A-waves, cm/sec), as well as left and right ventricular Tei index, which has been used to quantitatively assess myocardial performance [20].

The following demographic and clinical variables were prospectively recorded for each patient on admission: age, sex, cause of cirrhosis, previous complications of cirrhosis, and concomitant disease (e.g. diabetes mellitus, coronary artery disease). The diagnosis of hepatocellular carcinoma (HCC) was confirmed by recent imaging techniques according to the current guidelines, using a 4-phase multidetector computed tomography (CT) scan and/or dynamic contrast-enhanced magnetic resonance imaging (MRI) (hypervascular lesions in the arterial phase with washout in the portal venous or delayed phases) [21]. Laboratory blood tests included hematocrit, white blood count, platelet count, creatinine, urea, sodium, potassium, calcium, phosphate, magnesium, protein, albumin, bilirubin and clotting profile [prothrombin time, international normalized ratio (INR), activated partial thromboplastin time]. The severity of the liver disease was evaluated by the Child-Pugh and MELD scores. These scores were calculated as published and were evaluated on admission [22,23].

The short synacthen test was performed on each patient as previously described [24] as part of the pre-LT evaluation performed in our center. Shortly after proper preparation, at 08:00 am (time T₀), a blood draw was performed for measurement of basal total serum cortisol levels and simultaneously a specific cotton was given (Plain Salivette; Sarstedt, Newton, North Carolina, USA) in order to calculate the basic (T₀) salivary cortisol values (Roche Diagnostics Ltd, Rotkreuz, Switzerland). Subsequently, 250 µg corticotropin (Synacthen, Novartis Pharma, Basel, Switzerland) was given as an intravenous bolus, and a second blood sample and salivary collection were performed, following the same procedure as at baseline, for measurement of serum total cortisol levels and salivary cortisol at 09:00 am (T₆₀). Salivary cortisol is considered to be a more accurate index of relative adrenal dysfunction in patients with decompensated cirrhosis, since low levels of serum albumin are commonly found in patients with chronic liver failure [24].

Finally, the assessment of renal function was based on the calculation of the estimated glomerular filtration rate (eGFR), according to the Modification of Diet in Renal Disease (MDRD) [25], and the chronic kidney disease-epidemiology creatinine-based equations [26]. In addition, the "true" GFR assessed with ⁵¹Chromium complexed with ethylene diamine tetracetic acid (⁵¹Cr-EDTA) by sampling blood, after intravenous injection of tracer, at 2, 4 and 6 h, was measured

in all our patients. “True” GFR was calculated using the slope-intercept technique, correcting for body surface area, and the fast exponential curve recommended by the British Nuclear Medicine Society guidelines [27].

Statistical analysis

Statistical analysis was performed using the SPSS version 20.0 statistical package for Windows (version 22.0 IBM Corp: Armonk, NY, USA). Quantitative variables which were normally distributed were expressed as mean values \pm one standard deviation and those non-normally distributed were expressed as median values (range). Comparisons of parameters between patients with and without HPS were performed using Student’s *t* or Mann-Whitney *U* tests, as appropriate, for continuous variables and chi-square test for categorical variables. Multivariate analysis by stepwise logistic regression was performed, including all variables with $P < 0.05$ in univariate analysis, in order to identify those factors that were independently associated with HPS. The discriminative ability of the independent variables to predict the presence of HPS was evaluated by using the area under a receiver operating characteristic curve (AUC). At the best cutoff point (at which the sum of sensitivity plus specificity is maximal), sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated. The patients’ survival was calculated using Kaplan-Meier analysis and compared with the log-rank sum test. A P -value ≤ 0.05 was considered statistically significant.

Results

Sixty three patients were admitted to our department and evaluated for the presence of HPS during the study period. The median age of our cohort was 56 (range: 24-75) years and 47 (74.6%) were male. The most common cause of liver disease was viral hepatitis (54%), followed by alcoholic liver disease (19%). Ten (15.8%) of the 63 patients had HCC [8 (80%) of them had increased α -fetoprotein, the other 2 had typical HCC based on both CT and MRI]. Only 7 (11%) of the included patients had refractory ascites and/or hepatorenal syndrome at the time of evaluation. The mean MELD and Child-Pugh scores in our cohort were 15 ± 7 and 8 ± 3 , respectively. Demographic and clinical data are summarized in Table 1.

Characteristics of patients with or without HPS (Table 2)

Twenty six (41.3%, group A) of the patients were diagnosed with HPS and 37 (58.7%, group B) did not fulfill the criteria for the diagnosis of HPS. Regarding the severity of HPS, 36 (57.2%) had mild, 24 (38%) had moderate and 3 (4.8%) had severe HPS. Several clinical, laboratory and echocardiographic parameters were evaluated in association with the presence of HPS. Group A vs. group B patients had similar mean

Table 1 Baseline clinical and laboratory characteristics of patients with decompensated cirrhosis in our cohort

Variable	Patients, n=63
Age, years, median (range)	56 (24-75)
Male sex, n (%)	47 (74.6)
Cause of cirrhosis, n (%)	
Viral hepatitis	34 (54)
Alcohol	12 (19)
NASH/cryptogenic	7 (11)
Other	10 (16)
Refractory ascites and/or HRS type II, n (%)	7 (11)
Hepatocellular carcinoma, n (%)	10 (15.8)
CKD-EPI-estimated GFR (mL/min), median (range)	79 (32-141)
MDRD-estimated GFR (mL/min), median (range)	81 (35-152)
“True” GFR by $^{51}\text{Chromium-EDTA}$ (mL/min), median (range)	76 (26-117)
Child-Pugh score, mean \pm SD	8 ± 3
MELD score, mean \pm SD	15 ± 7

HRS, hepatorenal syndrome; NASH, non-alcoholic fatty liver disease; GFR, glomerular filtration rate; CKD-EPI, chronic kidney disease-epidemiology; MDRD, modification of the diet in renal disease

arterial blood pressure (114 ± 13 vs. 110 ± 23 mmHg, $P=0.43$), total bilirubin (median: 3.3 vs. 5.2 mg/dL, $P=0.27$), INR (1.4 ± 0.2 vs. 1.4 ± 0.2 , $P=0.99$) and renal function (“true” GFR: 73 ± 24 vs. 77 ± 26 mL/min, $P=0.21$). In addition, no difference was observed regarding the severity of liver disease based on MELD (14 ± 4 vs. 16 ± 6 , $P=0.24$) and Child-Pugh scores (9 ± 2 vs. 7 ± 4 , $P=0.11$). However, compared to group B patients, those in group A had HCC more frequently (27% vs. 8%, $P=0.044$). In addition, patients with HPS had lower levels of triglycerides compared to those without (81 ± 31 vs. 110 ± 56 mg/dL, $P=0.016$), as well as lower mean salivary total cortisol at baseline (T0) (4.1 ± 2 vs. 8.8 ± 9 ng/mL, $P=0.044$) and at time 60 min (T60) (12 ± 5 vs. 21 ± 11 ng/mL, $P=0.011$) after the intravenous injection of 250 μg of corticotropin (Table 2). Concerning the echocardiographic parameters that were evaluated, it was observed that patients with HPS had significantly greater mitral valve E-wave peak velocity (0.86 ± 0.29 vs. 0.73 ± 0.16 m/s, $P=0.034$) and mean right ventricular Tei index (0.39 ± 0.2 vs. 0.27 ± 0.14 , $P=0.04$) compared to patients without HPS.

In the multivariate analysis, we included only the variables significantly associated with HPS in univariate analysis. The only factors independently associated with HPS were the presence of HCC [odds ratio (OR) 8.1, 95% confidence interval (CI) 5.3-27.9, $P=0.045$] and T60 salivary cortisol (OR 0.88, 95%CI 0.71-0.98, $P=0.045$) (Table 3). In ROC curve analysis, T60 salivary cortisol had relatively good discriminative ability for the presence of HPS (AUC=0.73, 95%CI 0.69-0.77). The best cutoff point for salivary cortisol at T60 was < 2.8 ng/mL, giving a sensitivity of 70%, specificity 65%, PPV 49% and NPV 82%. Interestingly, for T60 salivary cortisol < 3.5 ng/mL, sensitivity, specificity, PPV and NPV were 92%, 23%, 36%, and

Table 2 Univariate analysis to evaluate the factors associated with the presence of hepatopulmonary syndrome (HPS) in 63 patients with decompensated cirrhosis

Variables	Patients with HPS (n=26, 41.3%)	Patients without HPS (n=37, 58.7%)	P value
History of complications, n (%)			
Encephalopathy	10 (38)	7 (19)	0.08
GI bleeding	8 (31)	6 (16)	0.21
SBP	2 (7.7)	6 (16)	0.29
Hepatocellular carcinoma, n (%)	7 (27)	3 (8)	0.044
Systolic arterial blood pressure (mmHg), mean±SD	114±13	110±23	0.43
Hematocrit, %	32±6	33±6	0.42
Albumin, (g/dL), mean±SD	2.8±0.5	3.1±0.5	0.14
Bilirubin (mg/dL), median (range)	3.3 (0.4-33)	5.2 (0.31-52)	0.27
PT (sec), mean±SD	15.6±2.9	15±4.2	0.68
aPTT (sec), mean±SD	43±7	41±8	0.35
INR, mean±SD	1.4±0.2	1.4±0.2	0.99
Creatinine (mg/dL), mean±SD	1.05±0.3	1.04±0.4	0.23
“True” GFR by ⁵¹ Chromium-EDTA (mL/min), median (range)	74 (26-110)	77 (30-117)	0.31
CKD-EPI-estimated GFR (mL/min), median (range)	77 (32-130)	80 (38-141)	0.48
MDRD-estimated GFR (mL/min), median (range)	78 (35-128)	82 (43-152)	0.39
Sodium (mmol/L), mean±SD	135±5	135±5	0.98
Salivary cortisol at T0 min (ng/mL), mean±SD	4.1±2	8.8±9	0.044
Salivary cortisol at T60 min (ng/mL), mean±SD	12±5	21±11	0.011
Total serum cortisol at T0 min (µg/dL), mean±SD	11±5	12±5	0.44
Total serum cortisol at T60 min (µg/dL), mean±SD	21±6	22±6	0.82
Ferritin (µg/dL), mean±SD	197±25	444±67	0.21
Cholesterol (µg/dL), mean±SD	138±53	148±56	0.51
Triglycerides (µg/dL), mean±SD	81±31	110±56	0.016
High density lipoprotein (µg/dL), mean±SD	35±17	34±15	0.80
CPK (IU/L), mean±SD	60±28	87±41	0.39
Child-Pugh score, mean±SD	9±2	7±4	0.11
MELD score, mean±SD	14±4	16±6	0.24

GI, gastrointestinal; SBP, spontaneous bacterial peritonitis; PT, prothrombin time; aPTT, activated partial thromboplastin time; GFR, glomerular filtration rate; T0 and T60, baseline and 60 min after intravenous injection of 250 µg corticotropin; CPK, creatine phosphokinase

Table 3 Multivariate analysis to identify the independent factors associated with the presence of hepatopulmonary syndrome in 63 patients with decompensated cirrhosis

Variable	Odds ratio	Value	95% confidence interval	
			Lower	Upper
Hepatocellular carcinoma	8.1	0.045	5.3	27.9
Salivary cortisol at T0	0.9	0.72	0.67	1.31
Salivary cortisol at T60	0.88	0.045	0.71	0.98
Triglycerides	0.9	0.52	0.96	1.018

T0 and T60: baseline and 60 min after intravenous injection of 250 µg corticotropin

85%, respectively, while for T60 salivary cortisol <2.1 ng/mL, sensitivity, specificity, PPV and NPV were 12%, 98%, 80%, and 70%, respectively (Table 4).

The patients with mild HPS (n=36) had similar characteristics compared to those with moderate (n=24) HPS (the patients with severe HPS were not analyzed because of the very small number of patients).

HPS and outcome

During the follow-up period [median: 12 (1-48) months], 43 patients died or underwent LT and 20 remained alive. All patients who died had liver-related deaths. The presence of

HPS was not associated with the outcome (log-rank, $P=0.22$) (Fig. 1). Finally, the outcome was similar between patients with mild HPS ($n=36$) and those ($n=24$) with moderate/severe HPS (although only 3 patients had severe HPS).

Discussion

HPS is a relatively frequent complication of cirrhosis. In our cohort of patients with decompensated cirrhosis the prevalence of HPS was 41% (26/63), based on the current diagnostic criteria [19]. Among different studies the prevalence of HPS varies from 4-47% [10,28,29]. The observed fluctuation in HPS prevalence reflects the different populations included in each study, as well as the different criteria used to establish the diagnosis of the syndrome, especially before 2004 when alveolar-arterial oxygen gradient was formally defined. Similar to previous studies [10,30,31], we showed that there was no correlation between the severity of liver disease and the presence of HPS, since MELD and Child-Pugh scores were not significantly associated with HPS in our cohort. Thus, HPS was not associated with worse outcomes in our cohort, but it should be mentioned that none of our patients had very severe

HPS (i.e., $\text{PaO}_2 < 50$ mmHg) and only 3 patients had severe HPS (i.e., $\text{PaO}_2 \geq 50$ to < 60 mmHg).

In our study, we found for the first time that HPS was independently associated with the presence of HCC (OR 8.1, 95%CI 5.3-27.9, $P=0.045$). Although there is no clear explanation for this finding, it could be postulated that vascular endothelial growth factor (VEGF), a regulator of angiogenesis, may be implicated in this association. More specifically, it is known that intrapulmonary capillary vasodilatation, arteriovenous shunts and angiogenesis seem to be the main mechanisms explaining the pathophysiology of HPS [32]. Studies on animal experimental models have shown that excess production of pulmonary vasodilators, such as NO, is responsible for vascular dilatation and the development of HPS [33,34]. In addition, angiogenesis engendered by VEGF has also been proposed as a contributing mechanism for HPS development, since NO inhibitors failed to improve oxygenation when used as a treatment for HPS [35]. Angiogenesis is also crucial for the development, invasion and extension of HCC [36]. Interestingly, a study in experimental animal models showed that sorafenib improves HPS through inhibition of the VEGF pathway, leading to a reduction of pulmonary angiogenesis and intra-pulmonary shunting [37]. Nevertheless, further larger studies with measurements of VEGF are needed to confirm this hypothesis.

In our study, we also found for the first time that HPS was independently associated with adrenal function, since in multivariate analysis, HPS was associated with lower T60 salivary cortisol (OR 0.88, 95%CI 0.71-0.98, $P=0.045$). This finding could be explained by the fact that NO, considered to play a key role in HPS pathogenesis, has been shown to affect steroid production in animal experimental models via inhibition of corticosterone biosynthesis and reduction in adrenocorticotropic hormone-induced cortisol synthesis [38,39].

Previous studies have also evaluated the possible association between HPS and echocardiographic parameters reflecting higher cardiac output [12]. A more recent study by Pouriki *et al* confirmed these findings, and the authors suggested left ventricle enlargement and higher systolic velocity in the mitral valve as clinically useful echocardiographic indirect markers of HPS [13]. In contrast, Voiosu *et al* found no association between any echocardiographic marker and the presence of HPS [14]. In our study, we found in univariate analysis that mitral valve E-wave peak velocity (which increases in hyperdynamic circulation) and mean right ventricular Tei index were significantly greater in patients with HPS compared to those without HPS. However, neither of these parameters was independently associated with HPS in multivariate analysis. These conflicting results may underline the need for using modern, more accurate echocardiographic techniques, such as strain and tissue Doppler imaging, in order to improve our understanding of cardiac structure and function in HPS.

Our study had some limitations, including the fact that it was a single-center study with a relatively small cohort. Moreover, the lack of full comprehension of the pathogenic pathways prevents us from interpreting some of our results. Despite these limitations, it is, to our knowledge, the first study to suggest an

Table 4 Prediction of hepatopulmonary syndrome using salivary cortisol at 60 min in 63 consecutive patients with decompensated cirrhosis

Salivary cortisol T60 Cutoff point (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
2.8 (best cutoff point)	70	65	49	82
3.5	92	23	36	85
2.1	12	98	80	70

T60, 60 min after intravenous injection of 250 μg corticotropin; PPV, positive predictive value, NPV, negative predictive value

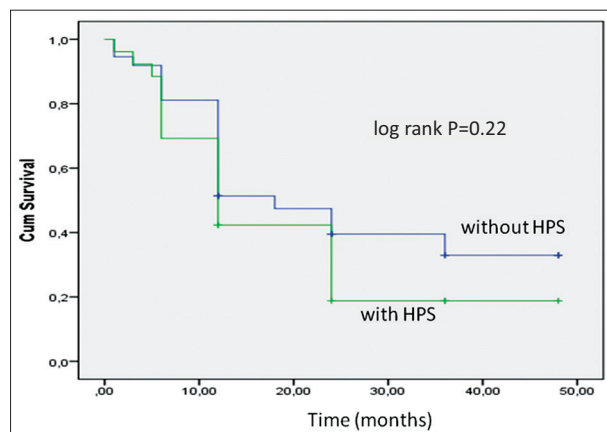


Figure 1 Survival of patients with decompensated cirrhosis in relation to the presence of hepatopulmonary syndrome (HPS) (log rank, $P=0.22$)

Summary Box

What is already known:

- Hepatopulmonary syndrome (HPS) is a relatively frequent complication of decompensated cirrhosis
- Nitric oxide is considered to play a significant role in the pathogenesis of HPS

What the new findings are:

- The presence of hepatocellular carcinoma is independently associated with HPS
- T60 salivary cortisol, based on the synacthen test, may be useful as an indirect marker of the presence of HPS

association between HPS and HCC and we believe that it can bring a new perspective to the existing literature.

In conclusion, in our study we found for the first time that HPS seems to be associated with the presence of HCC and adrenal dysfunction in patients with decompensated cirrhosis. However, further studies are needed in order to elucidate these findings further.

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