

# The Impact of Hypoxaemia on the Outcome in Liver Cirrhosis

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## ABSTRACT

**Background & Aims:** Prognostic factors for poor evolution are critical in the setting of limited access to liver transplantation for patients with cirrhosis. We aimed to investigate the impact of hypoxaemia on the outcome in cirrhosis and the evolution of arterial oxygen tension during long-term follow-up in these patients.

**Methods:** Consecutive cirrhotic patients were prospectively enrolled and followed-up in our tertiary referral center. Clinical features, biological tests, arterial blood gases, NT-proBNP levels, pulse oximetry measurements, 12-lead ECG, and transthoracic contrast echocardiography were documented on enrolment. The main outcomes were death and decompensation due to liver disease.

**Results:** 87 cirrhotic patients were included in the analysis and followed-up for a mean of 16 months. At enrolment, 27 (31%) patients were hypoxaemic, 19 had hepatopulmonary syndrome (HPS), but only 6 of those who were sampled at follow-up had persistent hypoxaemia. During the study period, 22 patients died of liver-related complications. Nine of them (41%) were hypoxaemic on enrolment but none had severe hypoxaemia. Hypoxaemia present at enrollment was not a risk factor for death ( $p=0.29$ ) or decompensation of liver disease ( $p=0.7$ ). A higher MELD score at baseline or increase during follow-up was a risk factor for death ( $p=0.02$ ) and correlated with the presence of hypoxaemia. Normalization of the arterial oxygen levels was accompanied by a significant decrease in NT-proBNP (83 pg/ml vs 0 pg/mL,  $p=0.023$ ).

**Conclusion:** Mild and moderate hypoxaemia was frequent in our patients but was not associated with adverse outcome in cirrhosis. Repeated arterial blood gas sampling is advisable, especially in patients diagnosed with hepatopulmonary syndrome.

**Key words:** cirrhosis – end-stage liver disease – hypoxaemia – hepatopulmonary syndrome – NT-proBNP – echocardiography – follow-up studies.

**Abbreviations:** AaO<sub>2</sub>: alveolar-arterial oxygen gradient; IPVDs: intrapulmonary vascular dilations; HBV: hepatitis B virus; HCV: hepatitis C virus; HPS: hepatopulmonary syndrome; MELD: model for end-stage liver disease; NT-proBNP: aminoterminal pro-brain natriuretic peptide; PaCO<sub>2</sub>: arterial carbon dioxide tension; PaO<sub>2</sub>: arterial oxygen tension.

## INTRODUCTION

Cirrhosis is the final stage of chronic liver diseases and is associated with high morbidity and mortality as well as significant healthcare costs [1]. Pulmonary function in cirrhosis may be severely altered due to complications such as the hepatopulmonary syndrome (HPS), portopulmonary hypertension or hepatic hydrothorax [2-4]. Furthermore, muscle wasting, the propensity

for bacterial infections and aspiration pneumonia as well as large-volume ascites negatively impact the mechanics of respiration in these vulnerable patients.

Pulmonary function and arterial oxygenation are not routinely investigated in cirrhotics and, thus, their influence on the outcome is incompletely characterized. Severe chronic hypoxemia in HPS is the only setting in which reliable follow-up data show an increased mortality [4, 5]. But while this has allowed regulatory bodies to grant exception points for prioritization of cirrhotic patients with HPS on the liver-transplant list, recent data questions the appropriateness of the current policy [6]. Thus, new prospective studies investigating the impact of pulmonary complications and hypoxaemia on the outcome of cirrhotic patients are required to improve prognosis and stratification of the patients for liver transplantation.

The main aim of this prospective study was to assess the influence of arterial oxygen levels on mortality and morbidity in the natural history of a cohort of cirrhotic patients. Our secondary aims were to analyze the variation of arterial blood gases one year after enrolment and its relationship with the evolution of Child-Pugh and MELD scores.

## PATIENTS AND METHODS

This study presents prospectively collected data from a cohort of patients with cirrhosis enrolled at our tertiary-referral center. Between November 2013 and April 2015 all patients referred to our unit with clinical, imaging, biochemical or histological evidence of cirrhosis were invited to participate in an observational long-term follow-up study regarding cardiovascular and pulmonary complications [7]. Two hundred and eleven cirrhotic patients were screened for inclusion during this period and the initial cohort excluded patients with documented lung disease or other conditions that could affect lung function or oxygenation such as severe anaemia or heart failure, as well as patients with known malignancy, active inflammatory disorders, uncontrolled arterial hypertension or diabetes.

At enrolment, a thorough history was taken and physical examination, abdominal ultrasonography and routine blood work were performed. Severity of cirrhosis was assessed accordingly to Child-Pugh classification and Model for End-stage Liver Disease (MELD) score. Lung function investigation and chest X-rays were used to identify and exclude patients with significant obstructive or restrictive lung disease. None of the patients had significant pleural effusions at enrolment and only two had developed large-volume hepatic hydrothorax that was resolved during the follow-up period. Echocardiography, NT-proBNP levels and standard 12-lead electrocardiography were recorded in order to detect a possible cardiac component of oxygenation abnormalities.

Pulse oximetry measurements were carried out after at least 10 minutes of bed-rest, in both supine and sitting positions. The difference between supine and orthostatic oxygen saturation was calculated in each case. Immediately after pulse oximetry, arterial blood from the radial artery was sampled in the supine position. Hypoxaemia was diagnosed when oxygen levels ( $\text{PaO}_2$ ) were below 80 mmHg, while hypercapnia was defined as partial carbon dioxide ( $\text{PaCO}_2$ ) levels above 45 mmHg. The alveolar-arterial oxygen gradient ( $\text{AaO}_2$ ) was calculated according to the formula:  $\text{AaO}_2 = [(\text{FiO}_2) \times (\text{Patm} - \text{PH}_2\text{O}) - (\text{PaCO}_2/0.8)] - \text{PaO}_2$  [8] where  $\text{FiO}_2$  is an inspiratory oxygen fraction,  $\text{Patm}$  is atmospheric pressure (760 mmHg at sea level) and  $\text{PH}_2\text{O}$  is water vapour partial pressure. An oxygen gradient over 15 mmHg in patients aged under 65 was considered increased while a cut-off of 20 mmHg was used for patients  $\geq 65$  years, according to current recommendations for the diagnosis of HPS [9].

Echocardiographies were performed by an experienced cardiologist (I.D.) on an iE33 ultrasonographer (Philips Medical Systems, Best, the Netherlands). Severe valvulopathies, intracardiac shunts, dyskinesia or akinesia suggesting infarction were considered exclusion criteria. In order to detect intrapulmonary vascular dilations (IPVDs) an injection of a

10 mL aliquot of agitated saline in the antecubital vein was performed while in the 4-chamber apical window. Appearance of bubbles in the left heart chambers after 3-6 cycles was considered a positive test and signified the existence of extracardiac intrapulmonary shunting. A diagnosis of HPS was made when  $\text{AaO}_2$  was increased in patients diagnosed with IPVDs.

Patients were followed-up by regular 3-month interval telephonic interviews. Patients were recalled for a study visit at one year after enrolment in addition to the scheduled consultations according to the international surveillance guidelines. The same blood work, ultrasonography and arterial blood gas analysis were performed at this control visit. Decompensation of liver disease (acute renal failure, new-onset or worsening of ascites, hemorrhage, encephalopathy, bacterial infections, hepatocarcinoma) and death were the main adverse events recorded. Data was censored at the last recorded contact in case of patients lost to follow-up or recipients of liver transplant.

### Statistical analysis

SPSS 16 (Chicago, Illinois) was used for data recording and analysis. Results are reported as means and standard deviations for variables with a normal distribution and median, minimum and maximum respectively for variables with a non normal distribution. We conducted univariable analysis using parametric (Student *t*-test) and nonparametric tests (Mann Whitney U, Wilcoxon) to check for differences in biologic parameters (i.e. albumin and bilirubin levels, the MELD score, NT proBNP levels) between patients with hypoxaemia at baseline and those without. We also conducted Kaplan Meier survival analysis using the log-rank test to compare the time to first event and overall survival for patients according to their oxygenation status. Multivariate regression analysis using a forward conditional stepwise method was performed in order to control other factors affecting survival (age, gender, etiology of liver disease, MELD score). In order to describe the progression of biological status we compared each parameter recorded at the two separate time points (enrolment and one-year visit) using the paired samples *t* test. Results were considered statistically significant at a *p* value  $< 0.05$ .

All patients were included after signing an informed consent form. The study design complied with the updated provisions of the Declaration of Helsinki and was approved by the Colentina Hospital Ethics Committee for Clinical Research.

## RESULTS

### Study population

Of the initial cohort of 90 cirrhotic patients, 87 (36 female and 51 male) were included in the final analysis as 3 fulfilled exclusion criteria during workup (Fig.1). The mean age at enrolment was  $59 \pm 10$  years. Thirty-three (38%) patients had alcoholic cirrhosis while 54 (62%) had non-alcoholic etiology (32 had HCV, 12 had HBV, and 7 had mixed viral infection, while 3 patients had other causes). The median MELD score for the cohort was 11 (range 6-27); 48 (55%) had compensated (Child A) and 39 (45%) had decompensated cirrhosis according to the Child-Pugh classification.

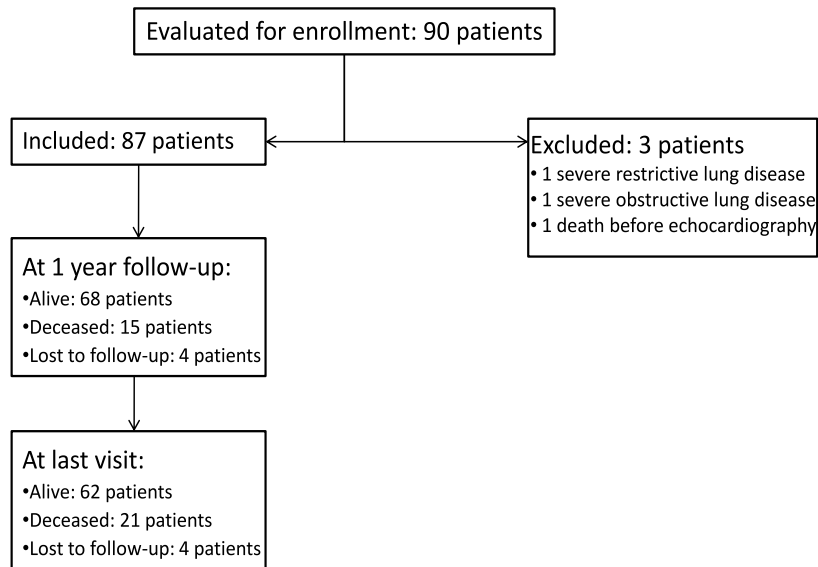


Fig. 1. Study flow-chart

Thirty-one (36%) patients had ascites at enrolment with 6 of them suffering from large volume ascites that was drained at least 48 hours before further study-related measurements. Twenty-nine (33%) of the patients were smokers, but all had normal lung function values on spirometry and unremarkable chest radiographies. Four patients had a body-mass index below 20 kg/m<sup>2</sup>.

#### Evaluation of hypoxaemia

Twenty seven (31%) patients of the 87 enrolled were hypoxaemic at the initial visit and 9 of these patients (33%) died during follow-up (5 of them before 12 months). The mean PaO<sub>2</sub> for the cohort was 86±13 mmHg, the mean PaCO<sub>2</sub> was 34.4±5 mmHg and the mean AaO<sub>2</sub> was 21 ± 13 mmHg. Of the 27 patients, only one had severe hypoxaemia, while the rest had PaO<sub>2</sub> values above 60 mmHg. Patients with hypoxaemia on arterial blood gas analysis had significantly lower median oxygen saturations on pulse oximetry in both the supine (96% in hypoxaemic patients vs 97% in nonhypoxaemic patients,  $p=0.032$ ) and standing positions (97% in hypoxaemic patients vs 98% in nonhypoxaemic patients,  $p=0.046$ ). A higher MELD score indicative of more severe cirrhosis was correlated with the presence of hypoxaemia (median MELD=13 in hypoxaemic vs 11 in non-hypoxaemic patients,  $p=0.035$ ). Age, albumin, creatinine, bilirubin, prothrombin time, PaCO<sub>2</sub>, NT-proBNP, smoking status, degree of ascites or Child class were not correlated with hypoxaemia. BMI was higher in patients with hypoxaemia (28±4.7 vs 26±4.4 kg/m<sup>2</sup>) and this may be explained by the influence of ascites or adipose tissue on the mechanics of respiration. This data is presented in Table I.

Contrast echocardiography was adequately performed in all but one of the patients, and it identified intrapulmonary vascular dilations in 38/86 (44%) cases. Only 19 (22%) associated an increased alveolar-arterial gradient and were thus diagnosed with HPS. None of the patients had dyskinesia or akinesia on examination. One patient had both HPS and severe portopulmonary hypertension with an estimated systolic pulmonary artery pressure of 115 mmHg.

#### Follow-up

The patients were followed-up for a mean of 16±6 months and a total of 194 patient-years. Four patients were lost to follow-up while one patient received a liver transplant before 12 months and their data was censored at the last recorded visit. Of the initial cohort only 68 (77%) were alive at one year and 6 further patients died in the second year of follow-up. During the study period, 22 (25%) patients died of liver-related complications. Ten patients died due to severe hemorrhage, 4 of renal failure, 3 of encephalopathic coma, 3 due to sepsis, 2 of unknown causes. Nine of them (41%) were hypoxaemic on enrolment but none had severe hypoxaemia. Body mass index, mean arterial pressure, bilirubin, creatinine, MELD score, PaO<sub>2</sub>, AaO<sub>2</sub>, NT-proBNP levels were similar between enrolment and the one-year visit. Albumin and PaCO<sub>2</sub> were significantly different in a per-patient analysis at follow-up compared to baseline. The comparison between the main parameters at baseline and one-year is presented in Table II.

Hypoxaemia at enrolment was not associated with death during the follow-up period ( $p=0.29$ , HR= 1.8 95% CI 0.57-5.5, Fig.2), nor with decompensation of liver disease ( $p=0.7$ , HR= 0.84 0.3-2.4, Fig.3). On Kaplan-Meier survival analysis HPS showed a trend towards decreased survival but was not a statistically significant prognostic factor ( $p=0.1$ ). Severity of cirrhosis as assessed by MELD score was associated with death during the study period (median 13 vs 11,  $p=0.026$ ). Considering the 62 patients with biological data available at the second visit, an increase in MELD score represented a risk factor for death (increase by a median of 4 points versus decrease by 1 point,  $p=0.02$ ). On multivariate analysis including age, gender, etiology, severity of liver disease and PaO<sub>2</sub>, only MELD score predicted death (HR=1.11, 95% CI 1.03-1.20) or decompensation of liver disease (HR=1.11, 95% CI 1.06-1.18).

Laboratory data was available for 62 of the 68 patients at the one-year visit but only 55 had arterial blood gas sampling at this point. Fourteen of the patients with hypoxaemia at

**Table I.** Study group data at enrolment

Patient characteristic (n=87)	No hypoxaemia (n=60)	Hypoxaemia (n=27)	p
Age (years)	59±10	59±10	0.71
Gender (female/male)	25 (42%) / 35 (58%)	11 (41%) / 16 (59%)	1
Etiology (alcoholic/ nonalcoholic)	21 (35%) / 39 (65%)	12 (44%) / 15 (56%)	0.48
Smoking (yes/no)	23 (38%) / 37 (62%)	6 (22%) / 21 (78%)	0.22
MELD score	11 (6-27)	13 (6-26)	0.03
Child class (A/B/C)	36 (60%) / 12 (20%) / 12 (20%)	12 (44%) / 5(19%) / 10 (37%)	0.22
Ascites (yes/no)	17 (28%) / 43 (72%)	14 (52%) / 13 (48%)	0.052
MAP (mmHg)	89±12	90±12	0.68
Albumin (g/dL)	3.4±0.7	3.2±0.8	0.29
Bilirubin (mg/dL)	2±2.2	2.7±2.3	0.07
Creatinine (mg/dL)	0.76±0.2	0.73±0.2	0.34
PT (seconds)	17.1±3.8	18±4.3	0.26
NT-proBNP (pg/mL)	147 (17-1152)	231 (12-562)	0.64
PaO <sub>2</sub> (mmHg)	92±9.3	71±5.5	<0.001
PaCO <sub>2</sub> (mmHg)	34±4.6	35±5.8	0.56
AaO <sub>2</sub> (mmHg)	14.8±10.1	34±9.1	<0.001
SpO <sub>2</sub> orthostatism (%)	98 (93-100)	97 (83-100)	0.04
SpO <sub>2</sub> clinostatism (%)	97 (93-100)	96 (89-100)	0.03
IPVDs (present/absent)	26 (43%) / 34 (57%)	12 (44%) / 14 (56%)	0.82
HPS (yes/no)	7 (12%) / 53 (88%)	12 (44%) / 14 (56%)	0.01

MELD: model for end-stage liver disease, MAP: mean arterial pressure, PT: prothrombin time, NT-proBNP: aminoterminal brain natriuretic peptide, PaO<sub>2</sub>: arterial blood oxygen tension, PaCO<sub>2</sub>: arterial blood carbon dioxide tension, AaO<sub>2</sub>: alveolar-arterial gradient of oxygen, SpO<sub>2</sub>: oxygen saturation, IPVDs: intrapulmonary vascular dilatations, HPS: hepatopulmonary syndrome

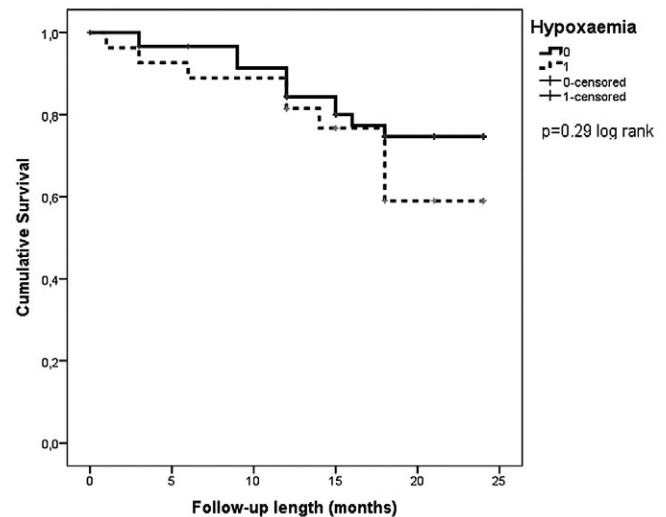
**Table II.** Comparison between patient data available at the initial and follow-up visits

Patient characteristic	Enrolment (n=87)	One-year (n=62)	P
BMI (kg/m <sup>2</sup> )	27.3±4.9	27.8±5.4	0.09
MAP (mmHg)	91±12	91±13	0.98
Albumin (g/dL)	3.3±0.7	3.5±0.7	0.006*
Bilirubin (mg/dL)	2±1.4	2.1±1.8	0.86
Creatinine (mg/dL)	0.7±0.2	0.8±0.5	0.42
PT (seconds)	17.2±3.5	17.2±3.8	0.95
NT-proBNP (pg/mL)	149 (1139.5)	132 (2368.6)	0.68#
MELD score	11 (21)	11 (24)	0.69#
PaO <sub>2</sub> (mmHg)	86.7±12.4	88.3±10.7	0.4
PaCO <sub>2</sub> (mmHg)	34.3±5.1	35.8±4.8	0.04*
AaO <sub>2</sub> (mmHg)	19.9±13.8	16.5±10.6	0.09

\*- paired samples t test was used to compare the parameters of patients sampled at both visits, while mean and standard deviations were derived from the entire study population sampled at the respective visit.

#- Wilcoxon test was used and median (range) are presented for the variables at both study visits (BMI: body mass index, PT: prothrombin time, NT-proBNP: aminoterminal pro-brain natriuretic peptide, MELD: model for end-stage liver disease, PaO<sub>2</sub>: arterial oxygen tension, PaCO<sub>2</sub>: arterial carbon dioxide tension, AaO<sub>2</sub>: alveolar-arterial oxygen gradient)

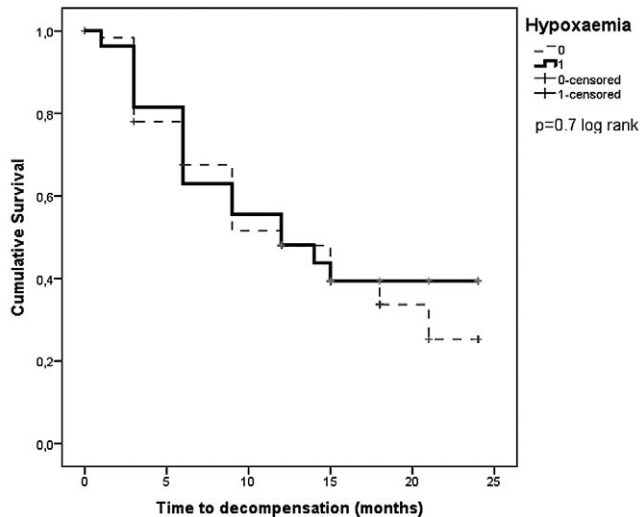
enrolment were also sampled at the one-year visit and only 6 (43%) still had values of PaO<sub>2</sub> below 80 mmHg, while the rest had normal values of arterial oxygen tension. The 8 patients who were hypoxaemic initially, but had normal oxygen levels



**Fig. 2.** Comparison of survival in patients with and without hypoxaemia at enrolment This Kaplan Meier survival analysis shows that up to 24 months of follow-up, the survival rates were not statistically different between cirrhotic patients with hypoxaemia compared to those without hypoxaemia (p=0.29).

at one-year, had a significant decrease in NT-proBNP levels (median proBNP decrease of 83 pg/ml vs 0 pg/mL, p=0.023). In these patients MELD score, Child class, presence or severity of ascites were not statistically significantly different between visits. However, NT-proBNP levels were significantly higher in patients who died during follow-up (median 264.65 vs 140 pg/mL, p=0.023).

The arterial blood gas analysis at the one year visit resulted in reclassification of 7 patients regarding HPS: 2 became hypoxaemic and thus progressed to HPS, while 5 had normal arterial oxygen tension at the second visit and thus could be reclassified as non-HPS.



**Fig. 3.** Comparison of decompensation of liver disease in patients with and without hypoxaemia at enrolment. No difference between patients with hypoxaemia and those without hypoxaemia on enrolment was identified on the analysis of liver-related adverse events during the study period ( $p=0.7$ ).

## DISCUSSION

In this prospective observational study of a cohort of cirrhotic patients we found that mild and moderate hypoxaemia correlated with the severity of cirrhosis but was not itself associated with death or decompensation during the study period. Reevaluation of blood gases at the follow-up visits allowed reclassification of almost half of the initially hypoxaemic patients and this improvement correlated with a significant decrease in NT-proBNP levels.

Models such as the Child-Pugh and the MELD scores which predict transplant-free survival are based on clinical and biochemical parameters of liver and renal but not on pulmonary function [10-12]. Pulse oximetry is generally employed as a screening tool to detect cirrhotic patients at risk for significant HPS and we found that oxygen saturation in both supine and orthostatic positions correlated with oxygen tension as determined by the arterial blood gas analysis.

Hypoxaemia is a recognized negative prognostic factor in many diseases and has been shown to significantly increase mortality in the setting of chronic obstructive pulmonary disease [13, 14]. Cirrhotic patients are a vulnerable group, at increased risk of developing alterations in respiratory function through several mechanisms including hypoperfusion and ventilation-perfusion mismatch. While some complications such as portopulmonary hypertension and severe HPS are known to be detrimental to prognosis, there is a lack of prospective, long-term follow-up studies concerning the impact of hypoxaemia on outcome in this population. The

majority of investigations in this field are retrospective and concerned with the peri-transplantation period. We decided to prospectively evaluate the frequency, severity, progression and impact on the survival of hypoxaemia in a prospective cohort of consecutive cirrhotic patients with no prior lung or heart disease.

Nearly one in three cirrhotics in our group were hypoxaemic at enrolment, but more than half of them showed normalization of arterial oxygen tension at one year. Furthermore, considering the variation in blood gas levels between visits, several patients with echocardiographically proven intrapulmonary vascular dilatations suffered a change in the diagnosis of HPS. Blood gas analysis with evidence of hypoxaemia and increased alveolar-arterial gradient is a requirement for the diagnosis of HPS [10] and this fluctuation in values between visits represents an interesting insight into the disease progression and raises questions regarding reliability of measurements. Since HPS has been awarded exception points for prioritization on liver transplant lists, this finding could impact future policy reevaluations. A recent retrospective study evaluating the consistency of arterial blood gas parameters in cirrhotic patients concluded that up to 15% of measurements were discrepant in a per-patient analysis [15]. This is in accordance with our results and poses a particular challenge as it entails repeated sampling in order to avoid misclassification of patients with asymptomatic IPVDs and overdiagnosis of HPS.

Previous large studies on the impact of HPS on outcome in cirrhosis have failed to show a direct correlation between hypoxaemia and negative outcome with the exception of severe pre-transplantation hypoxaemia [16]. It seems that the syndrome itself and not the absolute values of oxygen levels determine the outcome in this population [17]. While natural progression to more severe forms of HPS is possible, so far this has not been investigated in adequately powered studies [18]. The largest retrospective analysis to date, performed on the UNOS database, has failed to show any association between oxygenation and pre-transplantation waitlist survival [7]. However, the median transplant waiting time in that population was 55 days (compared to a median of 450 days in our study), thus precluding an analysis of the long-term effects of hypoxaemia on morbidity and mortality. Comparatively, the difficult access to liver transplant in our country allows the collection of extended follow-up information during the natural evolution of the disease and its complications.

In our cohort, the low arterial oxygen tension was not correlated with either death or decompensation of cirrhosis. These results confirm previous findings and suggest that mild and moderate hypoxaemia is not an independent predictor of negative outcome in cirrhotics. Morbidity and mortality are probably increased only in the setting of severely reduced oxygen tension or advanced (Child class C) cirrhosis [17]. Indeed, we also found that patients with higher MELD scores and thus, more severe liver dysfunction, were more likely to suffer from hypoxaemia. Thus, it is likely that low  $\text{PaO}_2$ , while indicative of an oxygenation abnormality, is only an epiphenomenon and that prognosis is dictated by progression towards end-stage liver disease. In HPS the well-documented imbalance in vasoactive and inflammatory mediators that generates the right-to-left shunting characteristic of the

syndrome also affects other systems, especially the already fragile cardiovascular milieu [3, 19, 20]. It could be that this cardiac dysfunction and not hypoxaemia represents the initial insult leading to decompensation and death in a sizable proportion of these cases [21]. If HPS is only a byproduct of the alteration in homeostasis due to aberrant vasoactive and angiogenetic activity inherent to advanced stages of liver disease this could explain its weak correlation to outcome. This hypothesis could be supported by our finding that in all patients with HPS and thus with hypoxaemia at baseline, normalization of arterial oxygen levels was accompanied by a significant decrease in NT-proBNP.

As in all prospective follow-up studies, the main limitation is due to the dropout rate that reduced biological sampling at the one-year visit. We found that repeating blood gas analysis may modify an initial HPS diagnosis but our design did not include reevaluation of IPVD status by echocardiography at follow-up visits so we cannot speculate on the true prevalence of HPS at that time point. Serial echocardiography in a prospectively enrolled cohort of cirrhotic patients represents an important issue that should be addressed in future studies. Our patients mainly had mild or moderate hypoxaemia and thus we cannot draw valid conclusions regarding severe hypoxaemia and its impact on the natural history of cirrhosis. It is possible that a survival effect was not noted due to the limited duration of the follow-up, but the generally rapid evolution of cirrhosis that generated a significant number of events during our study makes such a hypothesis less likely. Also, while statistically significant and thought-provoking, the relationship between the decrease in NT-proBNP and normalization of PaO<sub>2</sub> is based on a limited sample of cases and warrants further investigation.

## CONCLUSION

In our prospective study of a cohort of cirrhotic patients without concomitant lung or heart disease, mild and moderate hypoxaemia was not associated with a negative outcome during follow-up. Low arterial oxygen tension was frequent in our population but severe hypoxaemia was rare. Repeating arterial blood gas analysis is recommended, especially in patients diagnosed with HPS, as values may vary considerably and influence further treatment decisions and costs.

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**Authors' contributions:** A.V. and T.V. designed the study, collected the data and wrote the first draft. A.R. and B.S. collected the data and created the database. A.V., T.V. and C.B. performed the statistical analysis. M.D., B.M. and R.V. provided guidance in the design, collection of data and critical revision. All authors approved the final draft of the manuscript.

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