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ORIGINAL ARTICLE

Outcomes of liver transplantation for hepatopulmonary syndrome in patients with concomitant respiratory disease

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Abstract

Background & aims: Concomitant respiratory disease is a common finding in patients with hepatopulmonary syndrome (HPS). Among patients who underwent liver transplantation (LT) for HPS, we compared characteristics and outcome of patients with versus without concomitant respiratory disease.

Methods: This single center retrospective observational study included patients with HPS who underwent LT between 1999 and 2020.

Results: During the study period, 32 patients with HPS received a LT; nine (28%) with concomitant respiratory disease of whom one required a combined lung-liver transplantation. Patients with concomitant respiratory disease had higher PaCO2 (38 vs. 33 mm Hg, $p = .031$). The 30-day postoperative mortality was comparable, but the estimated cumulative probability of resolution of oxygen therapy after LT in HPS patients with versus those without concomitant respiratory disease was lower: 63% versus 91% at 12 months and 63% versus 100% at 18 months (HR 95% CI .140–.995, $p = .040$). In addition to the presence of concomitant respiratory disease ($p = .040$), history of smoking ($p = .012$), and high baseline 99mTcMAA shunt fraction (≥20%) ($p = .050$) were significantly associated with persistent need of oxygen therapy. The 5-year estimated cumulative probability of mortality in patients with concomitant respiratory disease was worse: 50% versus 23% (HR 95% CI .416–6.867, $p = .463$).

Conclusions: The presence of a concomitant respiratory disease did not increase the short-term postoperative mortality after LT in patients with HPS. However, it resulted in a longer need for oxygen therapy.

KEYWORDS
hepatopulmonary syndrome, liver transplantation, oxygen therapy, respiratory disease

1 | INTRODUCTION

Hepatopulmonary syndrome (HPS) has been reported in 5%–32% of patients with cirrhosis being evaluated for liver transplantation (LT). HPS is defined by a triad of (i) impaired arterial oxygenation caused by (ii) intrapulmonary vascular dilatations (IPVDs) in the setting of (iii) liver disease, portal hypertension, or portosystemic shunts.[1,2] The presence of HPS worsens the prognosis of patients with cirrhosis.[2,3] The only definitive treatment for HPS is LT which frequently results in complete resolution of HPS within 6–18 months.[2,4] The 5-year

survival is 76% with LT versus 23% in those who do not under transplantation.[3]

Little is known about prognostic factors in patients with HPS who undergo LT. Studies suggest that severe hypoxemia ($PaO_2 \leq 50$ mm Hg) or a higher baseline shunt fraction (≥20%) on Technetium-99m-labeled macro-aggregated albumin lung perfusion scan (99mTcMAA) may be associated with a lower rate of improvement in oxygenation after LT and greater need for postoperative long-term supplemental oxygen therapy.[3–8] However, this finding has not been replicated in all observational studies.[9,10]

Until now, less attention has been given to the presence of chronic intrinsic respiratory conditions which may coexist with HPS and may affect both preoperative and postoperative hypoxemia and outcome.[2,11,12] This study aimed to determine the outcome after LT in a cohort of patients with HPS with versus without concomitant respiratory disease.

2 | METHODS

2.1 | Study design and participants

This retrospective observational cohort study was carried out at the University Hospitals Leuven, which performs about 70–80 liver transplantations and 60–70 lung transplantations per year. All patients aged 18 years or older with a diagnosis of HPS between December 1, 1999 and July 17, 2020 were eligible for inclusion. HPS was diagnosed using the following criteria: (1) presence of liver disease and portal hypertension; (2) hypoxia with a partial pressure of oxygen (PaO_2) < 80 mm Hg or an alveolar-arterial oxygen (A-a O_2) gradient ≥ 15 mm Hg in ambient air (≥20 mm Hg in patients older than 65 years); and (3) IPVDs with positive findings on contrast echocardiography or abnormal uptake over the brain with 99mTcMAA.[2]

2.1.1 | Baseline data

The data reported were those determined at the time of transplant. Age, gender, smoking, body mass index (BMI), and the primary etiology of underlying liver disease were collected. Child–Pugh score and MELD score were determined to characterize the severity of liver disease and complications of portal hypertension were reported.[13] We included information on history of cyanosis (peripheral or central),[14] clubbing, pulmonary function testing, arterial blood gas, and need for supplemental oxygen therapy prior to LT. Special attention was given to the presence of concomitant respiratory disease and whether there was a need for combined lung transplantation. Concomitant respiratory disease was defined as a chronic illness of the respiratory system. Indications for continuous supplemental long-term oxygen therapy were: (1) $PaO_2 \leq 55$ mm Hg or $SaO_2 \leq 88\%$, or, (2) $PaO_2 \leq 59$ mm Hg or $SaO_2 \leq 89\%$ in the presence of cor pulmonale, right heart failure, or erythrocytosis (hematocrit > 55%).[15,16]

2.2 | Procedures

Transthoracic contrast echocardiography was used to diagnose IPVD based on the appearance of microbubbles in the left heart three to eight heart beats after its appearance in the right atrium.[17] 99mTCMAA lung and perfusion scan was performed to quantify the degree of IPVDS. A brain uptake >6% was considered positive. Pulmonary function studies followed the European Respiratory Society recommendations.[18–20]

2.3 | Post-LT management protocol

All patients followed a standardized post-LT management protocol for intensive care unit (ICU), transplant ward and specialist consultation.

2.4 | Statistical analysis

Data were recorded and analyzed using SPSS software version 27 (IBM Corp©, Armonk, NY). Categorical data were reported as frequencies (%) and continuous variables as median ± interquartile range (IQR). Univariate analysis was conducting using a Chi-square test or Fisher's exact test for categorical variables and nonparametric Mann–Whitney *U* test for continuous endpoints.

Within the group of patients with HPS and concomitant respiratory disease, the primary aim was to describe characteristics associated with the need of supplemental oxygen therapy post-LT and to describe factors that may call for combined lung transplantation.

For secondary analyses, patients were stratified into two groups according to the presence or absence of concomitant respiratory disease. Estimates on the rate of resolution of oxygen therapy and mortality were analyzed with the use of the Kaplan-Meier method, and the difference was determined using the log-rank test. Univariate analyses (log-rank tests) to identify variables associated with resolution of oxygen therapy included concomitant respiratory disease (yes vs. no), age (continuous variable), male sex (yes vs. no), history of smoking (yes vs. no), obesity (yes vs. no), Child–Pugh Score (continuous variable), MELD score (continuous variable), ascites (yes vs. no), pleural effusion (yes vs. no), cyanosis (yes vs. no), clubbing (yes vs. no), MAA shunt fraction ≥ 20% (yes vs. no), Forced Expiratory Volume in 1 second (FEV_1) % predicted (continuous variable), Forced Vital Capacity (FVC) % predicted (continuous variable), FEV_1/FVC (continuous variable), total lung capacity (TLC) % predicted (continuous variable), Diffusing capacity for carbon monoxide (DL_{CO}) % predicted (continuous variable), $PaO_2 \leq 60$ mm Hg (yes vs. no), $PaCO_2$ mm Hg (continuous variable), baseline supplemental oxygen therapy (yes vs. no). Multivariate analyses were not performed due to expected data sparseness. The level of statistical significance was set at $p < .050$ in two-tailed tests.

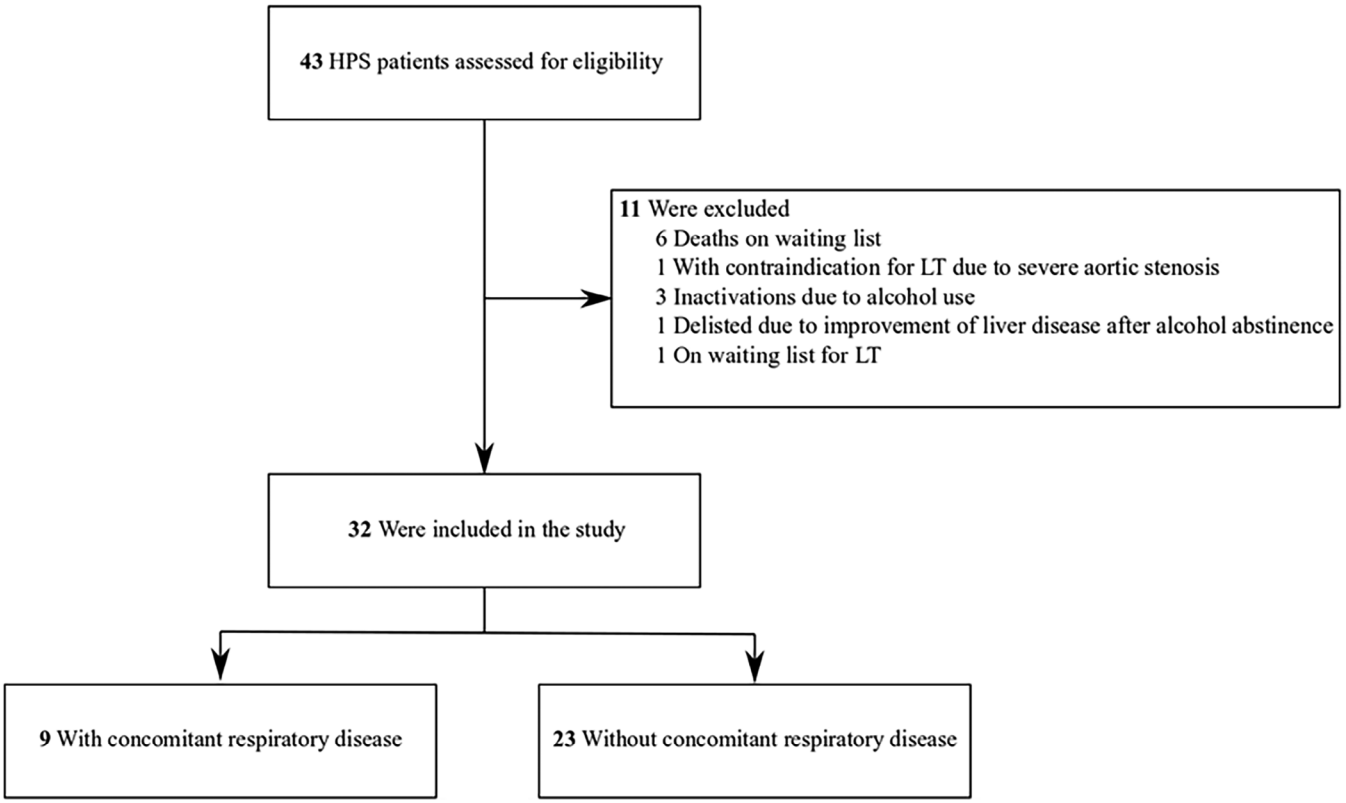

FIGURE 1 Flowchart of the study.

3 | RESULTS

Out of 43 patients with HPS, 32 were included according to in- and exclusion criteria (Figure 1). A total of 11 patients were excluded: six died on the waiting list, in three patients there was a relapse of alcohol abuse and they were withdrawn from the waiting list, in one patient the liver-related complications disappeared after alcohol abstinence, in one patient LT was contraindicated due to severe aortic stenosis and one patient was still on the waiting list at the time of analysis. In the excluded patient group, concomitant respiratory disease was present in three out of 11 (27.3%) patients: two with chronic obstructive pulmonary disease (COPD) and one with obstructive sleep apnea syndrome (OSAS).

Among the study population group, nine out of 32 (28.1%) patients had a concomitant respiratory disease: three with COPD of which one also suffered from anthracosilicosis, two with OSAS, two with idiopathic interstitial lung disease, one with asthma, and one with sarcoidosis.

Table 1 illustrates the baseline characteristics of the total study group, the HPS patients with concomitant respiratory disease and those without. Out of seven patients with cyanosis, six had central cyanosis. Patients with concomitant respiratory disease were comparable regarding PaO2 but had a higher $PaCO_2$ (38 vs. 33 mm Hg, $p = .031$). The difference in $PaCO_2$ was even more evident when exploring those with concomitant COPD or idiopathic interstitial disease ($n = 5$, $PaCO_2$ of 42 mm Hg), those with other concomitant respiratory disease ($n = 4$, $PaCO_2$ of 34 mm Hg) versus those without concomitant respiratory disease ($n = 23$, $PaCO_2$ of 33 mm Hg), $p = .011$.

3.1 | Hepatopulmonary syndrome outcomes in patients with concomitant respiratory disease

Out of nine HPS patients with concomitant respiratory disease, one received a combined lung-liver transplantation and one needed subsequent lung transplantation (1 year between liver and lung transplantation), both due to hypoxemic respiratory failure. The diagnosis among the two patients was idiopathic interstitial lung disease (in both cases related to underlying telomeropathy). Both patients with a need for lung-liver transplantation had $DL_{CO} < 45\%$ predicted and required supplemental oxygen therapy before transplantation.

The one patient with combined lung-liver transplantation at baseline was excluded from further descriptive analysis of patients with concomitant respiratory disease. Patients who received oxygen therapy more than 3 months after transplantation had the following characteristics: MAA shunt fraction ≥ 20%, $FEV_1 < 80\%$ predicted, $DL_{CO} < 45\%$ predicted, $PaO_2 < 60$ mm Hg, and need of supplemental oxygen therapy before transplantation.

TABLE 1 Baseline characteristics of patients with HPS and concomitant respiratory disease versus those without ($n = 32$).

Characteristic	Total study population ($n = 32$)	HPS with concomitant respiratory disease ($n = 9$)	HPS without concomitant respiratory disease ($n = 23$)	p-value
Age, years	57 ± 11.0	56 ± 15.0	60 ± 11.0	.528
Male sex, (%)	20 (62.5%)	6 (66.7%)	14 (60.9%)	1.000
History of smoking, (%)	8 (25.0%)	3 (33.3%)	5 (21.7%)	.654
BMI ≥ 30 kg/m^2, (%)	9 (28.1%)	3 (33.3%)	6 (26.1%)	1.000
Etiology of underlying liver disease, (%)				.383
Alcohol	17 (53.1%)	3 (33.3%)	14 (60.9%)	
NASH	6 (18.8%)	2 (22.2%)	4 (17.4%)	
HCV	1 (3.1%)	0 (.0%)	1 (4.3%)	
Others	8 (25.0%)	4 (44.4%)	4 (17.4%)	
Child–Pugh classification, (%)				.019
A	9 (28.1%)	5 (55.6%)	4 (17.4%)	
B	12 (37.5%)	4 (44.4%)	8 (34.8%)	
C	11 (34.4%)	0 (.0%)	11 (47.8%)	
Child–Pugh score	9 ± 5.0	5 ± 4.0	9 ± 4.0	.008
MELD score	14 ± 7.0	14 ± 8.0	13 ± 9.0	.672
Ascites, (%)	15 (46.9%)	2 (22.2%)	13 (56.5%)	.122
Pleural effusion (%)	6 (18.8%)	1 (11.1%)	5 (21.7%)	.648
Cyanosis, (%)	7 (21.9%)	3 (33.3%)	4 (17.4%)	.370
Clubbing, (%)	9 (28.1%)	4 (44.4%)	5 (21.7%)	.383
FEV_1, % pred	80 ± 21.0	82 ± 27.3	80 ± 20.3	.681
FVC, % pred	92 ± 30.3	94 ± 23.3	90 ± 31.2	.541
FEV_1/FVC	.78 ± .048	.78 ± .040	.78 ± .048	.952
TLC, % pred	87 ± 32.5	86 ± 44.8	89 ± 28.5	.822
DL_{CO}, % pred	45 ± 23.0	44 ± 27.8	46 ± 22.8	.964
PaO_2 (mm Hg)	65 ± 19.8	73 ± 30.0	63 ± 19.0	.464
$PaCO_2$ (mm Hg)	34 ± 9.8	38 ± 11.5	33 ± 12.0	.031
Oxygen therapy, (%)	11 (37.9%)	2 (25.0%)	9 (42.9%)	.435

Note: Data are *n* (%) or median ± IQR.

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HCV, hepatitis C virus; IQR, interquartile range; NASH, non-alcoholic steatohepatitis; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; TLC: total lung capacity.

3.2 | Outcome after liver transplantation in those with versus those without concomitant respiratory disease

Table 2 illustrates the disease outcome of HPS patients with concomitant respiratory disease versus those without. The estimated cumulative probability of resolution of oxygen therapy after LT in HPS patients with concomitant respiratory disease versus those without was 50.0% versus 86.3% at 6 months, 62.5% versus 90.9% at 12 months, and 62.5% versus 100% at 18 months (HR 95% CI .140–.995, $p = .040$; Figure 2). The difference in resolution of oxygen therapy was even more evident when comparing those with concomitant COPD or idiopathic interstitial disease (25.0% at 6 and 18 months), those with other concomitant respiratory disease (75.0% at 6 months and 100% at 18 months) versus those without concomitant respiratory disease (86.3% at 6 months and 100% at 18 months), $p = .018$.

Table 3 shows predictive factors for resolution of oxygen therapy with their respective HR 95% CI and p-values. In addition to concomitant respiratory disease (HR 95% CI .140 – .995, $p = .040$), history of smoking (HR 95% CI .103–.751, $p = .012$) and high baseline MAA shunt fraction (≥20%) (HR 95% CI .045–.999, $p = .050$) were significantly associated with resolution of oxygen therapy.

During the study period, 11/31 (35.5%) patients died: four of respiratory failure, two of cancer (bladder and esophagus), one of cerebrovascular accident, one of graft versus host disease, one with graft failure, one of general deterioration, and one due to sudden death.

TABLE 2 Disease outcomes after liver transplantation of patients with HPS and concomitant respiratory disease versus those without ($n = 31$).

Characteristic	Total study population ($n = 31$)	HPS with concomitant respiratory disease ($n = 8$)	HPS without concomitant respiratory disease ($n = 23$)	p-value
Oxygen therapy, months	2.5 ± 5.00	5.8 ± 48.00	2.5 ± 4.00	.095
Hospital stay, days	17.0 ± 9.00	20.0 ± 9.00	15.0 ± 9.00	.325
On ventilator, days	1.5 ± 5.00	1.3 ± 4.75	2.0 ± 5.00	.792
ICU stay, days	8.0 ± 8.00	9.0 ± 10.00	7.0 ± 8.00	.434
30-day postoperative mortality	2 (.1)	0 (.0)	2 (.9)	.389
Survival, years	7.8 ± 6.00	4.7 ± 4.00	8.6 ± 7.00	.072

Note: Data are *n* (%) or median ± IQR.
Abbreviations: HPS, hepatopulmonary syndrome; ICU, intensive care unit; IQR, interquartile range.

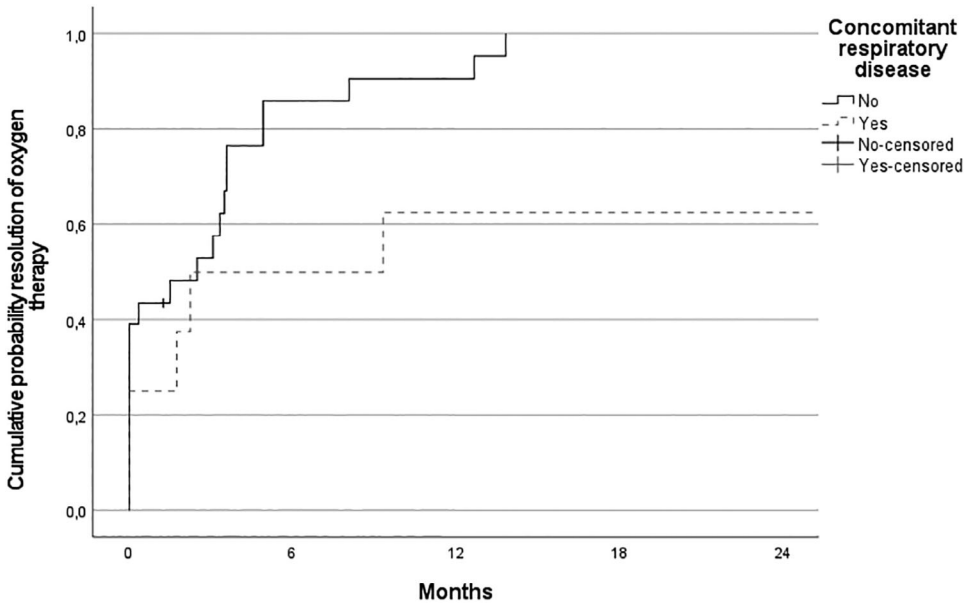

FIGURE 2 Cumulative probability of resolution of oxygen therapy in hepatopulmonary syndrome patients with concomitant respiratory disease versus those without ($n = 31$). The estimated cumulative probability of resolution of oxygen therapy after liver transplantation in hepatopulmonary syndrome patients with concomitant respiratory disease versus those without was 50.0% versus 86.3% at 6 months, 62.5% versus 90.9% at 12 months and 62.5% versus 100% at 18 months (hazards ratio 95% confidence interval .140–.995, $p = .040$). Person-years were censored on the date of liver-related event, death or the last outpatient clinic visit, whichever came first.

There was no difference in mortality due to respiratory failure between patients with versus without concomitant respiratory disease (1/4 (25.0%) vs. 3/7 (42.9%), $p = .554$). Characteristics of the 11 patients who died are depicted in Table S1.

The 5 years cumulative probability of mortality after liver transplantation in HPS patients with concomitant respiratory disease versus those without was 50.0% versus 22.7% (HR 95% CI .416–6.867, $p = .463$). The difference in 5 years mortality was even more evident when comparing those with concomitant COPD or idiopathic interstitial disease (66.7%), those with other concomitant respiratory disease (33.3%) and those without concomitant respiratory disease (22.7%), $p = .589$.

4 | DISCUSSION

This study represents the first series to date focusing on the clinical outcomes after LT for HPS patients with versus without concomitant respiratory disease. Several observations are of potential importance. First, our study shows that concomitant respiratory disease was not uncommon in HPS patients who underwent LT. Second, overall the presence of concomitant respiratory disease did not affect the immediate postoperative outcome. Third, the need for supplemental oxygen therapy post-LT was longer for those HPS patients with versus those without concomitant respiratory disease. Finally, compared to patients without concomitant respiratory disease, HPS patients with

TABLE 3 Predictive factors for resolution of oxygen therapy after liver transplantation ($n = 31$).

Predictive factors	HR 95% CI	*p*-value
Concomitant respiratory disease (yes vs. no)	.140–.995	.040
Age, years	.995–1.079	.082
Male sex (yes vs. no)	.472–2.241	.943
History of smoking (yes vs. no)	.103–.751	.012
BMI ≥ 30 kg/m^2 (yes vs. no)	.324–1.696	.478
Child–Pugh score	.965–1.348	.123
MELD score	.998–1.147	.056
Ascites (yes vs. no)	.668–2.996	.364
Pleural effusion (yes vs. no)	.656–5.441	.239
Cyanosis (yes vs. no)	.306–1.922	.572
Clubbing (yes vs. no)	.289–1.656	.409
MAA shunt fraction ≥ 20% (yes vs. no)	.045–.999	.050
FEV_1, % pred	.983–1.044	.402
FVC, % pred	.973–1.014	.535
FEV_1/FVC	.704–1.039	.116
TLC, % pred	.966–1.008	.211
DL_{CO}, % pred	.967–1.034	.985
$PaO_2 \leq 60$ mm Hg (yes vs. no)	.157–4.843	.330
$PaCO_2$, mm Hg	.936–1.051	.786
Baseline oxygen therapy (yes vs. no)	.296–1.393	.262

Abbreviations: BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HR, hazards ratio; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; TLC, total lung capacity.

concomitant respiratory disease had a worse 5 year survival, especially those with COPD or idiopathic interstitial lung disease.

Although HPS is traditionally defined as hypoxia related to pulmonary vascular dilatations in the absence of significant respiratory disease, patients may have concomitant respiratory disease. In our study, 28% of HPS patients who underwent LT had a concomitant respiratory disease. This is in agreement with two previous studies which have shown a high prevalence of concomitant respiratory disease in 38.1% and 46.6% of HPS patients.[9,12] COPD was one of the most common co-existing respiratory disease.

Currently, LT is the only effective therapy for HPS that can lead to resolution of hypoxemia and independence from supplemental oxygen over time. Indeed, oxygen therapy could be stopped in all our patients without a concomitant respiratory disease.

Two HPS patients with concomitant respiratory disease underwent lung-liver transplantation due to hypoxemic respiratory failure. Both patients had idiopathic interstitial lung disease, $DL_{CO} < 45\%$ predicted and required oxygen therapy before transplantation. The clinical setting for lung-transplantation was therefore in line with the consensus statement from the International Society for Heart and Lung transplantation.[21] The COPD patients in our series had only moderate airflow limitation severity based on FEV_1 between 50% and 80%, and accordingly no indication for lung transplantation.

In our descriptive analyses within the HPS group with concomitant respiratory disease, we have found that—in addition to $DL_{CO} < 45\%$ predicted and oxygen therapy before transplantation –MAA shunt fraction ≥ 20%, $FEV_1 < 80\%$ predicted, and $PaO_2 < 60$ mm Hg were among the characteristics associated with a longer demand of oxygen therapy post-LT. These data support previous reports that MAA shunt fraction ≥ 20% and $PaO_2 \leq 50$ mm Hg identify HPS patients with a lower rate of improvement in oxygenation and might increase the risk for mortality after LT.[3–8] Therefore also these parameters might be taken in consideration for a combined lung-liver transplantation among HPS patients with concomitant respiratory disease.

Prior studies among HPS patients but without concomitant respiratory disease have indicated that the main dysfunction in gas exchange was a reduced DL_{CO}. Impaired DL_{CO} may be due to functional (vasodilatation and hyperdynamic circulation) and structural (increased thickness of vessel walls) changes.[22,23] Reversibility of DL_{CO} after LT was illustrated in 38% within 12 months in one study including mainly mild to moderate cases of HPS.[23] Another study did not detect reversibility of DL_{CO} in six patients with HPS more than 3 years after LT.[22] If structural changes predominate in severe cases, it may explain why certain cases are reversible and other cases are not. Considering the absence of standard pulmonary function testing post-LT at our institution, we could not test this hypothesis which would require larger studies.

The association between lower FEV_1 and need for continuous supplemental oxygen therapy may result from progressive airflow limitation of the concomitant respiratory disease.[24]

Resolution of oxygen therapy was observed in 91% at 12 months among our cohort of HPS patients without concomitant respiratory disease and is in line with the reported 94%–100% in earlier studies.[6,9,25–28] This number was only 62.5% at 12 months among HPS with concomitant respiratory disease and even lower among subset of patients with COPD or idiopathic interstitial lung disease. This finding of a lower probability of resolution of oxygen therapy post-LT further supports the importance of identifying HPS patients with concomitant respiratory disease.

Our study has several acknowledged limitations, one of which is its retrospective design. There were no consistent data on patient-reported outcome measures relating to physical, mental and social health. Second, it has a limited sample size and thus limited power like most other published studies in the field of HPS. Third, one should cautiously extrapolate our results as concomitant respiratory disease is a heterogenous group. Our HPS patients with concomitant respiratory disease had comparable PaO2 as to those without and therefore might have not been severe enough to cause hypoxemia. As in previous studies COPD was the most common concomitant respiratory disease.

Although these data need to be validated in future larger cohorts, our study suggests that concomitant respiratory disease is common in

HPS patients who undergo LT. The presence of concomitant respiratory disease is associated with a lower resolution of oxygen therapy after LT. We further specified other characteristics associated with a continuous need of oxygen therapy post-LT which might help the clinician for a better assessment of the long-term outcome of these patients with concomitant respiratory disease. One should include the lower oxygen resolution rate in patients with concomitant respiratory disease in the multidisciplinary decision to progress for combined lung-liver transplantation, liver transplantation or no transplantation.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Proposals should be directed to the corresponding author; to gain access, data requestors will need to sign a data access agreement. Only individual participant data that underlie the results reported in this article, after de-identification, will be shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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