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Risk Factors and Impact of Chronic Obstructive Pulmonary Disease in Candidates for Liver Transplantation

Debbie Rybak[1], **Michael B. Fallon**[3], **Michael J. Krowka**[4], **Robert S. Brown Jr**[1], **Jenna Reinen**[1], **Linda Stadheim**[4], **Dorothy Faulk**[3], **Carrie Nielsen**[5], **Nadine Al-Naamani**[1], **Kari Roberts**[6], **Steven Zacks**[5], **Ted Perry**[7], **James Trotter**[7], and **Steven M. Kawut**[1,2] **for the Pulmonary Vascular Complications of Liver Disease Study Group**

[1] Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY

[2] Department of Epidemiology, Joseph L. Mailman School of Public Health, Columbia University, New York, NY

[3] Department of Medicine, University of Alabama, Birmingham, AL

[4] Department of Medicine, Mayo Clinic, Rochester, MN

[5] Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC

[6] Department of Medicine, Tufts–New England Medical Center, Boston, MA

[7] Department of Medicine, University of Colorado, Denver, CO

Abstract

Chronic obstructive pulmonary disease (COPD) may cause significant symptoms and have an impact on survival. Smoking is an important risk factor for COPD and is common in candidates for liver transplantation; however, the risk factors for and outcomes of COPD in this population are unknown. We performed a prospective cohort study of 373 patients being evaluated for liver transplantation at 7 academic centers in the United States. COPD was characterized by expiratory airflow obstruction and defined as follows: prebronchodilator forced expiratory volume in 1 second/forced vital capacity < 0.70. Patients completed the Liver Disease Quality of Life Questionnaire 1.0, which included the Short Form-36. The mean age of the study sample was 53 ± 9 years, and 234 (63%) were male. Sixty-seven patients (18%, 95% confidence interval 14%–22%) had COPD, and 224 (60%) had a history of smoking. Eighty percent of patients with airflow obstruction did not previously carry a diagnosis of COPD, and 27% were still actively smoking. Older age and any smoking (odds ratio = 3.74, 95% confidence interval 1.94–7.23, $P < 0.001$) were independent risk factors for COPD. Patients with COPD had worse New York Heart Association functional class and lower physical component summary scores on the 36-Item Short Form but had short-term survival similar to that of patients without COPD. In conclusion, COPD is common and often undiagnosed in candidates for liver

Address reprint requests to Steven M. Kawut, M.D., M.S., Division of Pulmonary, Allergy, and Critical Care Medicine, College of Physicians and Surgeons, Columbia University, 622 West 168th Street, PH 8E, Room 101, New York, NY 10032. Telephone: 212-305-7771; FAX: 212-342-5382; sk2097@columbia.edu.

The Pulmonary Vascular Complications of Liver Disease Study Group also includes the following: Jeffrey Okun, B.A., Daniel Rabinowitz, Ph.D., Evelyn M. Horn, M.D., Lori Rosenthal, N.P., and Sonja Olsen, M.D., from Columbia University; Vijay Shah, M.D., and Russell Wiesner, M.D., from the Mayo Clinic; J. Stevenson Bynon, M.D., Devin Eckhoff, M.D., Harpreet Singh, Rajasekhar Tanikella, Raymond L. Benza, M.D., and Keith Wille, M.D., from the University of Alabama; Lisa Forman, M.D., and David Badesch, M.D., from the University of Colorado; Roshan Shrestha, M.D., from The University of North Carolina at Chapel Hill; Darren B. Taichman, M.D., Ph.D., Vivek Ahya, M.D., Harold Palevsky, M.D., and Rajender Reddy, M.D., from the University of Pennsylvania; and Neil Kaplowitz, M.D., and James Knowles, M.D., Ph.D., from the University of Southern California.

transplantation. Older age and smoking are significant risk factors of COPD, which has adverse consequences on functional status and quality of life in these patients.

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation that is not fully reversible. The physiologic changes associated with COPD lead to dyspnea, exercise limitation, susceptibility to infections and exacerbations, and significant morbidity and mortality. Patients with advanced liver disease have well-known abnormalities in pulmonary function. Lung volumes are commonly decreased by hepatomegaly, ascites, basal atelectasis, or pleural effusions.[1–5] Screening studies of patients with chronic liver disease have demonstrated arterial blood gas abnormalities in as many as 45%.[2] However, little is known about the prevalence, risk factors, and impact of COPD in patients with advanced liver disease considered for liver transplantation (LT).

Smoking is the most important risk factor for COPD in the general population and is commonly reported by patients with advanced liver disease. Smoking may also contribute to the severity of various liver diseases and hepatocellular carcinoma.[6–8] Smoking and COPD may be particularly important in patients with advanced liver disease being evaluated for LT, for whom perioperative outcomes and postoperative recovery could be compromised and long-term interactions with immunosuppression are unknown.

Therefore, we aimed to determine the prevalence and predictors of COPD in patients with advanced liver disease evaluated for LT. We hypothesized that smoking would be not only common but also a strong predictor of COPD. We also aimed to determine the impact of COPD on functional status, health-related quality of life, and overall survival.

PATIENTS AND METHODS

Study Design and Study Sample

The Pulmonary Vascular Complications of Liver Disease study enrolled a cohort of 536 patients evaluated for LT at 7 centers in the United States between 2003 and 2006.[9] The cohort included patients with clinical portal hypertension and excluded patients who had evidence of active infection or recent (<2 weeks) gastrointestinal bleeding or who had previously undergone liver or lung transplantation. The sample for this study included newly evaluated patients in the cohort with available prebronchodilator spirometry and data regarding smoking status.

Data Collection

Demographic information was collected from each patient; age was categorized by quartiles for the analysis. Data regarding the etiology of underlying liver disease, past medical history, and social history were recorded. Patients underwent a physical examination that included anthropometry and blood pressure measurements and underwent a laboratory assessment. The Model for End-Stage Liver Disease (MELD) score was calculated.[10]

Chest radiography was interpreted locally at each center. Spirometry, lung volumes, and diffusing capacity for carbon monoxide were measured; results are expressed with standard gender- and race-specific prediction equations where appropriate.[11–13] Arterial blood gas sampling was performed on room air in the seated position. Contrast transthoracic echocardiography was performed and interpreted at each center. Agitated saline was injected via a peripheral vein during imaging. The appearance of microbubbles in the left heart after 3 or more cardiac cycles (late) after venous injection of agitated saline was considered to indicate intrapulmonary shunting. The appearance of microbubbles in the left heart after fewer than 3 cardiac cycles (early) after venous injection was considered to indicate intracardiac shunting.

The presence of hepatopulmonary syndrome was defined by (1) contrast echocardiography with late appearance of microbubbles after venous injection of agitated saline and (2) an alveolar-arterial oxygen gradient ≥ 15 mm Hg (or ≥ 20 mm Hg if age > 64 years).[14] Significant pulmonary hypertension was defined as right ventricular systolic pressure (RVSP) > 50 mm Hg by echocardiography (if estimable).

We administered the Liver Disease Quality of Life Questionnaire 1.0.[15] This is a validated questionnaire that not only includes questions specific to advanced liver disease but also includes the Medical Outcomes Study Short Form-36 (SF-36; version 2.0).[16] Patients either completed the questionnaire during their visit to the clinical center or returned the questionnaire by mail.

The study was approved by the institutional review board of each center, and patients provided informed consent before undergoing study procedures.

COPD Definition

COPD was defined with modified Global Initiative on Obstructive Lung Disease criteria as follows: prebronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) < 0.70.[17] Mild COPD was defined as FEV1 % predicted ≥ 80%, moderate as FEV1 % predicted ≥ 50% and < 80%, severe as FEV1 % predicted ≥ 30% and < 50%, and very severe as FEV1 % predicted < 30%.

Statistical Analysis

Continuous data were summarized as mean ± standard deviation or median (interquartile range). Categorical variables were summarized as n (%). Unpaired Student *t* tests, Wilcoxon rank sum tests, chi-square tests, and Fisher's exact tests were used as appropriate. Bivariate logistic regression was performed with COPD status as the dependent variable and potential predictors as independent variables, with results expressed as odds ratios (ORs). Multivariate logistic regression was performed, including all variables that had *P* values < 0.20 on bivariate analysis or were hypothesized to predict case status. With the number of cases, we determined that the final multivariate model should include 4 or fewer predictors to prevent overfitting. The final multivariate model was assessed with the Hosmer-Lemeshow goodness-of-fit test; dbetas were calculated to assess influential subjects. Proportional hazards regression models were used for survival analyses.

All analyses were performed with Stata/IC version 10.0 (StataCorp, College Park, TX). A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Of 536 patients in the entire cohort, 473 (88%) patients were undergoing a new evaluation for LT. Of these, 373 (79%) had pulmonary function testing and available smoking history recorded, and they composed the study sample. The study sample was similar to the excluded patients [new LT evaluations without pulmonary function or smoking data (n = 100)] in terms of age, gender, and MELD score (data not shown). Excluded patients were more likely to be non-Hispanic white (92%) than included patients (79%).

The mean age of the study sample was 53 ± 9 years, and 234 (63%) were male. Two hundred ninety-three (79%) were non-Hispanic white, 39 (10%) were Hispanic, and 22 (6%) were non-Hispanic black. Sixty-seven patients [18%, 95% confidence interval (CI) 14%–22%] had COPD. Eighteen (29%) had mild COPD, 39 (58%) had moderate COPD, 8 (12%) had severe COPD, and 2 (3%) had very severe COPD. Patients with COPD were somewhat older than

patients without COPD and tended to be male (Table 1). COPD patients were somewhat less likely to be Hispanic white.

There were significant differences in the etiology of liver disease between patients with and without COPD (Table 1); patients may have had more than 1 etiology of liver disease. Patients with COPD were significantly more likely than those without it to have alcohol-related liver disease. Those without COPD tended to have more nonalcoholic fatty liver disease, primary sclerosing cholangitis (PSC), or primary biliary cirrhosis (PBC) in comparison with those with COPD. The groups were similar in terms of hepatitis C infection and alpha-1-antitrypsin deficiency–related liver disease. We had available genotyping on 5 patients with reported alpha-1-antitrypsin deficiency (all non-COPD), which showed the ZZ genotype in only 1 patient. The severity of liver dysfunction appeared similar between the groups, as reflected by the MELD score, and the median time from diagnosis of liver disease to referral for LT evaluation was 3 years in both groups.

Patients with COPD were more likely to have a history of ascites than those without COPD ($P = 0.018$; Table 2). Other liver disease complications and the prevalence of diabetes, hypertension, coronary artery disease, and other medical comorbidities were not different between the groups (data not shown). Notably, 80% of patients with COPD by spirometry had this diagnosis first made at the time of LT evaluation.

Eighty-one percent of patients with COPD had ever smoked versus 56% of those without COPD ($P = 0.001$; Table 2). Of the COPD patients who were ever-smokers, more than one-quarter (27%) reported active smoking at the time of their LT evaluation. For those who were ever smokers with available pack-year data (n = 131), 20 pack years or more of smoking was associated with a dramatically increased risk of COPD in comparison with those with a lesser smoking history (OR = 4.17, 95% CI 1.12–15.47, $P = 0.033$). For all patients with smoking status and pack-year data (n = 280), 20 pack years or more of smoking continued to show a very significant increased risk of COPD versus fewer pack years or no smoking history (OR = 6.09, 95% CI 2.97–12.48, $P = 0.001$). Alcohol use was also associated with an increased risk of COPD ($P = 0.008$).

Patients with COPD had a significantly lower body mass index in comparison with patients without COPD (27 ± 6 kg/m^2 versus 29 ± 6 kg/m^2, respectively, $P = 0.004$; Table 3). There were no other differences in physical examination or laboratory values.

By definition, pulmonary function varied significantly between the 2 groups (Table 4). Patients with COPD had significantly lower FEV1 % predicted, FEV1/FVC, and (in whom it was measured) diffusing capacity for carbon monoxide and higher alveolar-arterial oxygen gradients (all $P < 0.05$). Chest radiography and most echocardiographic measurements were similar between the 2 groups (Table 5). However, patients with COPD had significantly higher estimated RVSP than patients without COPD and more commonly had significant pulmonary hypertension [RVSP > 50 mm Hg; COPD = 9 (24%) versus no COPD = 20 (10%), $P = 0.02$, n = 230]. Imputing low RVSP estimates for those patients with transthoracic echocardiography with missing RVSP estimates did not change these findings (data not shown). Approximately 60% of both COPD and non-COPD patients demonstrated intrapulmonary shunting; 3 (27%) patients with COPD and 69 (33%) patients without COPD (with complete data) had hepatopulmonary syndrome ($P = 1.0$, n = 218).

Multivariate Analysis

We assessed variables from Tables 1 and 2 in multivariate logistic regression. Older age and any smoking were independently associated with an increased risk of COPD (Table 6). Alcohol use and etiology of liver disease were no longer associated with the risk of COPD in our

adjusted model and were likely confounded by smoking. Race/ethnicity and gender were not found to be predictors of COPD in our study sample. There were no significant interactions between the final factors in the model. The model fit was adequate ($P = 0.51$), and there were no particularly influential subjects.

Functional Status, Quality of Life, and Socioeconomic Status

Overall, patients with COPD had worse New York Heart Association functional class than patients without COPD (Table 7). Of the 373 patients in the study sample, 214 completed the Liver Disease Quality of Life Questionnaire 1.0. Patients who returned the questionnaire were similar to those from the study sample who did not in terms of age, gender, race/ethnicity, MELD score, smoking, and probability of COPD (data not shown). There were no differences in the liver disease–specific scales between patients with and without COPD (data not shown). However, patients with COPD scored lower than non-COPD patients on the physical component summary score of the SF-36 questionnaire, indicating worse quality of life (31 ± 10 versus 35 ± 12, respectively, $P = 0.047$, n = 209) Adjustment for age did not affect these results. There were no differences in marital status, educational status, or income between the 2 groups (data not shown).

LT and Survival

Two hundred four patients in the study sample were listed for LT. Patients with COPD were significantly less likely to be listed for LT than patients without COPD [28 (42%) versus 176 (58%), respectively, $P = 0.019$]. Of the patients with COPD who were listed for LT, 39% had mild COPD, 50% had moderate COPD, 11% had severe COPD, and none had very severe COPD. Patients with COPD who were denied listing for LT had significantly more severe disease than patients with COPD who were listed ($P = 0.01$). One hundred thirteen (30%) patients in the study sample underwent LT; there were no differences in performance of LT between patients with and without COPD (data not shown).

All patients were followed until December 31, 2006; there were no patients lost-to follow-up. The 1-year survival of the entire cohort was 87% (95% CI 83%–90%), and there were 81 deaths overall. The median follow-up time was 601 days (interquartile range, 390–1319 days). Patients with COPD had a survival similar to that of patients without COPD overall (hazard ratio = 1.0, 95% CI 0.50–1.70, $P = 0.89$); adjustment for the performance of LT did not change this result. The severity of COPD was not associated with the risk of death in the study sample (data not shown). We found no difference between groups in post-LT survival (hazard ratio = 0.50, 95% CI 0.06–3.70, $P = 0.48$). Similarly, there was no association between smoking and overall or posttransplant mortality (data not shown).

DISCUSSION

To the best of our knowledge, this is the largest prospective, multicenter cohort study of lung function ever performed in candidates for LT. We have shown that 18% of new patients undergoing LT evaluation in the United States have COPD. Older age and any history of smoking increase the risk of COPD in this population. Notably, 27% of patients with COPD reported active smoking, and 80% had the diagnosis of COPD made for the first time during their LT evaluation. In addition, COPD was associated with a worse New York Heart Association functional class and with a worse quality of life in terms of physical limitations. Despite the impact on functional status and quality of life, COPD did not significantly affect survival.

The prevalence of COPD in the LT candidates in our study was greater than the prevalence in the general population found in some studies and similar to that found in others.[18–20] The

COPD prevalence in our study was greater than that found in older, smaller studies performed in LT candidates; however, differences between our study population and the others may explain these findings. In 1991, Hourani et al.[2] published a study of 116 consecutive patients admitted for evaluation for LT and found that 7% had obstruction by spirometry (defined as FEV1/FVC less than 2 standard deviations below the predicted value). Although 55% of these patients were current or former smokers, the mean age was 45 years, and most patients were female, in contrast to our cohort, which was some 10 years older on average and mostly male. In addition, only 8% of the study population of Hourani et al. had cirrhosis due to alcohol; this was a much lower prevalence than that in our study. Another study found a prevalence of obstruction of 12% by spirometry in 58 patients listed for LT.[4] Of note, this study excluded symptomatic patients and patients who were evaluated but not listed for LT. This cohort had a smoking prevalence of 29%, included mostly females, and included mostly patients with PBC and PSC. Krowka et al.[3] studied 95 patients who underwent LT who had preoperative and postoperative pulmonary function testing. Although 75% of these patients had either PBC or PSC, these investigators found that 17% had an FEV1/FVC ratio <75%, which did not change after LT.

It may be difficult to generalize the prevalence and risk factors for COPD from these studies. The most common modern indications for LT evaluation are alcohol-related liver disease and hepatitis C infection, which affect very different populations in terms of age and gender in comparison with those included in these older studies. Importantly, gender and alcohol use are tightly related to smoking, so our results are likely much more applicable to the LT population evaluated in the United States in the modern era.

Patients with advanced liver disease commonly demonstrate coexistent restriction due to hepatomegaly and ascites, which could increase the FEV1/FVC ratio.[1,2,5] Therefore, it is possible that we have underestimated the actual prevalence of COPD in our cohort. On the other hand, some studies have shown that diuresis or large-volume paracentesis in patients with tense ascites increases FEV1 and FVC in parallel with an unchanged FEV1/FVC ratio.[21,22] Less than 50% of patients in our study had detectable ascites by physical examination, and this makes it less likely that this had a significant impact on our conclusions.

The most important contributor to the increased prevalence of COPD in this population was smoking, which was reported by 81% of the patients with COPD and 56% of the study sample overall. Others have shown virtually identical frequencies of smoking in patients with advanced liver disease.[2,23] These smoking rates are significantly higher than those seen in the general population, and this is likely attributable to the association between smoking and other habits predisposing to advanced liver disease, such as chronic alcohol use and intravenous drug use. The increased risk for older patients in our study may be due to either age-related changes in lung function or residual confounding by pack years (that is, older age potentially represents more years of smoking). Although we recorded collected information on pack years, these data were incomplete and may suffer from misclassification.

In addition to the impact of smoking on COPD, studies have also shown that tobacco use is associated with increased severity of liver fibrosis,[6] hepatocellular carcinoma,[7] and hepatic lesions in patients with hepatitis C infection.[8] There is also evidence to indicate that patients with a history of smoking have an increased risk for posttransplant complications.[23] We did not find differences in overall survival or post-transplant survival by smoking status; however, we neither assessed perioperative outcomes (such as length of stay) nor had sufficient numbers of transplanted patients and length of follow-up to assess post-LT complications, such as neoplasm. Studies have found increased risks of various cancers in patients with alcohol-related liver disease undergoing LT in comparison with others.[24,25] This association may very well be confounded by smoking, which is more likely responsible for many of these cancers.

Patients with COPD had higher RVSP by transthoracic echocardiography and more commonly had significant pulmonary hypertension in comparison with patients without COPD. This may be explained by ventilation-perfusion mismatch and local hypoxic vasoconstriction, hypoxia-related pulmonary vascular remodeling, parenchymal destruction, or elevated cardiac output or pulmonary venous pressure. Although there were no differences between COPD and non-COPD patients in terms of the partial pressure of oxygen or oxygen saturation in arterial blood, there was a significant difference in the alveolar-arterial oxygen gradient. Because right heart catheterization was not routinely performed in these patients, it is difficult to know whether the pulmonary hypertension in these patients was attributable to the lung disease itself or to a cardiac etiology. It is certainly possible, however, that the pulmonary hypertension in patients with COPD contributed to the functional limitation, although there were no differences in right-sided cardiac morphology attributable to COPD. It should be noted that it is unknown whether these patients had portopulmonary hypertension, which requires invasive hemodynamic measurement and the absence of other significant cardiac or pulmonary disease for diagnosis.

Chronic liver disease is associated with reduced quality of life, notwithstanding other comorbid conditions.[26] Even so, COPD had a significant additional negative impact not only on functional class but also on quality of life in our cohort. LT candidates with COPD had more impairment in the performance of usual physical activities, as reflected by the SF-36 physical component score. Considering this already severely compromised patient population, we believe that the treatment of COPD and smoking cessation are likely important for a positive impact on patients' physical functioning and quality of life both before and after LT.

Although 18% of our study patients were found to have COPD as defined by prebronchodilator FEV1/FVC < 0.70, 80% of these patients did not have a previous clinical diagnosis of COPD. It may be reasonable, therefore, for all patients evaluated for LT to undergo screening spirometry. The diagnosis of unsuspected COPD in the LT candidate presents an important opportunity for a smoking cessation intervention by transplant health professionals. The risks of respiratory tract cancers, particularly in the setting of posttransplant immunosuppression, make this an important part of the pretransplant evaluation. Lastly, the impact on functional status and physical activity–related quality of life makes diagnosis and treatment of COPD (including smoking cessation) potentially clinically important interventions in a candidate for LT.

There are some limitations to our study. Our study sample included only patients who were evaluated for LT and only those with pulmonary function testing and a provided smoking history. This may have resulted in a selection bias. Although postbronchodilator spirometry is the gold standard for diagnosing COPD, only prebronchodilator spirometry data were available. Thus, we may have included patients with other types of obstructive disease (such as asthma) in our diseased group. We recorded a variety of potential risk factors for COPD; nonetheless, our findings could be accounted for by another confounding variable or by residual confounding. Given the relatively small size of our study sample, there was limited power to detect weaker risk factors for COPD; however, this is the largest study of lung function ever performed in LT candidates.

In summary, older age and smoking were independently associated with an increased risk of COPD in patients with advanced liver disease undergoing LT evaluation. Screening and intervention may be warranted to minimize the short- and long-term impact of COPD in this patient population.

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Abbreviations

CI	confidence interval
COPD	chronic obstructive pulmonary disease
$DLCO_{corr}$	diffusing capacity for carbon monoxide corrected for hemoglobin
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
LT	liver transplantation
MELD	Model for End-Stage Liver Disease
OR	odds ratio
PBC	primary biliary cirrhosis
pCO_2	partial pressure of carbon dioxide
pO_2	partial pressure of oxygen
PSC	primary sclerosing cholangitis
RVSP	right ventricular systolic pressure
SF-36	Medical Outcomes Study Short Form-36

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TABLE 1

Demographics and Liver Disease Variables

Variable	n	COPD	No COPD	OR	95% CI	*P* Value
Age, years	373					
18–47		11 (16%)	70 (23%)	1.0	—	—
48–53		13 (19%)	87 (28%)	0.95	0.40–2.25	0.91
54–59		18 (27%)	71 (23%)	1.61	0.71–3.66	0.25
60–79		25 (37%)	78 (26%)	2.03	0.94–4.45	0.07
Gender, male	373	48 (72%)	186 (61%)	1.62	0.91–2.91	0.10
Race/ethnicity	373					0.47
Non-Hispanic white		60 (90%)	233 (76%)	1.0	—	—
Hispanic white		3 (5%)	36 (12%)	0.32	0.10–1.09	0.07
Non-Hispanic black		3 (5%)	19 (6%)	0.61	0.18–2.14	0.44
Other		1 (2%)	18 (6%)	0.22	0.03–1.65	0.14
Etiology of liver disease	373					
Alcohol		38 (57%)	116 (38%)	2.15	1.26–3.67	0.005
Hepatitis C infection		32 (48%)	138 (45%)	1.11	0.66–1.89	0.69
Autoimmune hepatitis		1 (2%)	12 (4%)	0.37	0.05–2.90	0.35
Nonalcoholic fatty liver disease		3 (5%)	36 (12%)	0.35	0.10–1.18	0.09
Hepatitis B infection		2 (3%)	15 (5%)	0.60	0.13–2.67	0.50
Alpha-1 antitrypsin deficiency		1 (2%)	9 (3%)	0.50	0.06–4.01	0.51
Primary sclerosing cholangitis		1 (2%)	16 (5%)	0.27	0.04–2.11	0.21
Primary biliary cirrhosis		1 (2%)	12 (4%)	0.37	0.05–2.90	0.35
Cryptogenic cirrhosis		6 (9%)	29 (9%)	0.94	0.37–2.36	0.89
MELD score	371	14 ± 5	13 ± 5	1.02	0.98–1.07	0.34

NOTE: Data are shown as mean ± standard deviation or n (%).

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

TABLE 2

Past Medical History

Variable	n	COPD	No COPD	OR	95% CI	*P* Value
Ascites	371	48 (73%)	173 (57%)	2.03	1.13–3.67	0.018
Variceal bleeding	372	14 (21%)	69 (22%)	0.90	0.47–1.72	0.76
Encephalopathy	371	29 (44%)	138 (45%)	0.95	0.55–1.62	0.85
Spontaneous bacterial peritonitis	372	3 (5%)	22 (7%)	0.60	0.18–2.08	0.40
Hepatocellular carcinoma	372	5 (8%)	28 (9%)	0.80	0.30–2.14	0.70
Hepatic hydrothorax	373	3 (5%)	14 (5%)	0.98	0.27–3.50	0.97
Transjugular intrahepatic portosystemic shunt	372	5 (8%)	22 (7%)	1.04	0.38–2.84	0.94
Smoking	373					
Never		13 (19%)	136 (44%)	1.0	—	—
Past or current		54 (81%)	170 (56%)	3.32	1.74–6.34	0.001
Chronic alcohol use	370					
Never		12 (18%)	103 (34%)	1.0	—	—
Past or current		55 (82%)	200 (66%)	2.36	1.21–4.60	0.01
Intravenous drug use	364	12 (19%)	52 (17%)	1.08	0.54–2.15	0.84
Blood transfusion	318	22 (37%)	99 (38%)	0.93	0.52–1.67	0.81

NOTE: Data are shown as n (%).

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

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TABLE 3

Physical Examination and Laboratory Results

Variable	n	COPD	No COPD	*P* Value
Physical examination				
Body mass index, kg/m^2	373	27 ± 6	29 ± 6	0.007
Pulse, beats per minute	372	75 ± 14	77 ± 14	0.41
Systolic blood pressure, mm Hg	373	123 ± 19	120 ± 18	0.26
Diastolic blood pressure, mm Hg	373	70 ± 11	70 ± 11	0.82
Room air oxygen saturation, %	218	97 ± 4	97 ± 3	0.84
Ascites	368	31 (48%)	113 (37%)	0.12
Lower extremity edema	368	32 (49%)	165 (54%)	0.44
Clubbing	363	6 (9%)	26 (9%)	0.90
Asterixis	366	4 (6%)	19 (6%)	0.96
Spider angiomata	356	25 (40%)	102 (35%)	0.46
Laboratory results				
Blood urea nitrogen, mg/dL	365	16 ± 9.0	16 ± 12	0.60
Creatinine, mg/dL	373	1.2 ± 1.0	1.0 ± 1.0	0.37
Hemoglobin, g/dL	370	12.4 ± 2.2	12.6 ± 2.0	0.46
Platelet count, 10^9/L	368	117 ± 63	124 ± 89	0.55
International normalized ratio	371	1.4 ± 0.3	1.3 ± 0.3	0.24
Alanine aminotransferase, U/L	372	48 ± 35	55 ± 42	0.18
Aspartate aminotransferase, U/L	372	71 ± 50	76 ± 48	0.41
Total bilirubin, mg/dL	373	2.5 ± 2.6	2.8 ± 3.0	0.63
Alkaline phosphatase, U/L	369	146 ± 70	172 ± 149	0.72
Total protein, g/dL	358	7.1 ± 0.8	7 ± 0.8	0.52
Albumin, g/dL	365	3.1 ± 0.6	3.1 ± 0.7	0.60

NOTE: Data are shown as mean ± standard deviation or n (%).

Abbreviation: COPD, chronic obstructive pulmonary disease.

TABLE 4

Pulmonary Function Testing and Arterial Blood Gas Results

Variable	n	COPD	No COPD	*P* Value
Pulmonary function testing				
Forced vital capacity, % predicted	373	85 ± 19	85 ± 16	0.71
Forced expiratory volume in 1 second, % predicted	373	69 ± 19	86 ± 16	<0.0001
Forced expiratory volume in 1 second/forced vital capacity	373	62 ± 8	79 ± 5	<0.0001
$DLCO_{corr}$, % predicted	355	55 ± 13	60 ± 17	0.02
Arterial blood gas				
pH	333	7.44 ± 0.03	7.44 ± 0.04	0.79
pCO_2, mm Hg	333	34 ± 5	35 ± 5	0.69
pO_2, mm Hg	333	81 ± 12	85 ± 16	0.11
Oxygen saturation, %	326	94 ± 3	95 ± 4	0.72
Alveolar-arterial oxygen gradient, mm Hg	333	24 (13–31)	15 (7–26)	0.003

NOTE: Data are shown as mean ± standard deviation, median (interquartile range), or n (%).

Abbreviations: COPD, chronic obstructive pulmonary disease; $DLCO_{corr}$, diffusing capacity for carbon monoxide corrected for hemoglobin; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

TABLE 5

Echocardiography and Chest Radiography Results

Variable	n	COPD	No COPD	*P* Value
Chest radiography				
Cardiomegaly	351	8 (13%)	30 (10%)	0.60
Large pulmonary arteries	351	2 (3%)	7 (2%)	0.67
Interstitial lung disease	351	2 (3%)	9 (3%)	1.0
Hyperinflation	351	2 (3%)	3 (1%)	0.22
Pleural effusion	351	7 (11%)	46 (16%)	0.33
Echocardiography				
Right atrial dilation	332	10 (17%)	52 (19%)	0.66
Right ventricular dilation	344	20 (32%)	88 (31%)	0. 95
Right ventricular hypertrophy	343	12 (19%)	57 (20%)	0.82
Right ventricular dysfunction	346	6 (9%)	15 (5%)	0.24
Paradoxical septal motion	324	1 (2%)	2 (1%)	0.47
Right ventricular systolic pressure, mm Hg	230	44 ± 19	37 ± 13	0.01
Left atrial size, cm	309	4 ± 1	4 ± 1	0.63
Left ventricular hypertrophy	349	15 (24%)	91 (32%)	0.24
Pericardial effusion	341	8 (13%)	33 (12%)	0.81
Shunting	307			0.46
None		17 (32%)	91 (36%)	
Intrapulmonary		31 (58%)	150 (59%)	
Intracardiac		5 (9%)	13 (5%)	

NOTE: Data are shown as mean ± standard deviation or n (%).

Abbreviation: COPD, chronic obstructive pulmonary disease.

TABLE 6

Multivariate Logistic Regression

Variable	OR	95% CI	*P* Value
Age			
18–47	1.0	—	—
48–53	0.84	0.35–2.03	0.71
54–59	1.69	0.73–3.90	0.22
60–79	2.27	1.02–5.06	0.044
Smoking (past or current versus never)	3.74	1.94–7.23	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 7

New York Heart Association Functional Class: COPD Versus No COPD (n = 372)

Class	COPD	No COPD
I	12 (18%)	88 (29%)
II	29 (43%)	138 (45%)
III	25 (37%)	66 (22%)
IV	1 (2%)	13 (4%)

NOTE: Wilcoxon rank sum test, $P = 0.03$.

Abbreviation: COPD, chronic obstructive pulmonary disease.