Published in final edited form as:

Hepatology. 2008 July ; 48(1): 196–203. doi:10.1002/hep.22275.

Clinical Risk Factors for Portopulmonary Hypertension

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Abstract

Portopulmonary hypertension affects up to 6% of patients with advanced liver disease, but the predictors and biologic mechanism for the development of this complication are unknown. We sought to determine the clinical risk factors for portopulmonary hypertension in patients with advanced liver disease. We performed a multicenter case-control study nested within a prospective cohort of patients with portal hypertension recruited from tertiary care centers. Cases had a mean pulmonary artery pressure >25 mm Hg, pulmonary vascular resistance >240 dynes · second · cm^{-5}, and pulmonary capillary wedge pressure ≤ 15 mm Hg. Controls had a right ventricular systolic pressure < 40 mm Hg (if estimable) and normal right-sided cardiac morphology by transthoracic echocardiography. The study sample included 34 cases and 141 controls. Female sex was associated with a higher risk of portopulmonary hypertension than male sex (adjusted odds ratio =2.90, 95% confidence interval 1.20-7.01, $P = 0.018$). Autoimmune hepatitis was associated with an increased risk (adjusted odds ratio = 4.02, 95% confidence interval 1.14-14.23, $P = 0.031$),

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Potential conflict of interest: Dr. Taichman received grants from Actelion. Dr. Trotter received grants from Roche, Debivision, and Wyeth. He is on the speakers' bureau of Salix and Astellis. He consults for and received grants from Novartis. Dr. Kawut is a consultant for Encysive. He is a consultant for, advises, is on the speakers' bureau of, and received grants from Gilead. He is on the speakers' bureau of and received grants from Pfizer and Actelion. He is a consultant for and received grants from United Therapeutics. He is on the speakers' bureau of INO Therapeutics. He received grants from Lung Rx. Dr. Badesch is a consultant for, is on the speakers' bureau of, advises, and received grants from GlaxoSmithKline, United Therapeutics/Lung Rx, Actelion/CoTehrix, Encysive, Pfizer, and Gilead/Myogen. He also received grants from Lilly/ICOS. He is a consultant for and advises Mondo-Biotech and Biogen IDEC.

Published online in Wiley InterScience (www.interscience.wiley.com).

and hepatitis C infection was associated with a decreased risk (adjusted odds ratio =0.24, 95% confidence interval 0.09-0.65, *P* =0.005) of portopulmonary hypertension. The severity of liver disease was not related to the risk of portopulmonary hypertension.

Conclusion—Female sex and autoimmune hepatitis were associated with an increased risk of portopulmonary hypertension, whereas hepatitis C infection was associated with a decreased risk in patients with advanced liver disease. Hormonal and immunologic factors may therefore be integral to the development of portopulmonary hypertension.

Pulmonary arterial hypertension (PAH) is a progressive disease which is characterized by elevated pulmonary vascular resistance, right heart failure, exercise limitation, and an increased risk of death. Histopathologic examination reveals intimal proliferation, medial hypertrophy, and adventitial fibrosis in the small muscular pulmonary arteries. Plexiform lesions and *in situ* thrombosis are also commonly seen. Most commonly idiopathic, PAH may also be associated with portal hypertension, termed portopulmonary hypertension (PPHTN). McDonnell et al. showed a prevalence of histopathologic changes of PAH in 0.61% of autopsies of patients with cirrhosis, and PPHTN was the third most common form of PAH in a population-based epidemiologic study in France.[1,2] Recent cohort studies showed a prevalence of PPHTN of 5%-6% in patients presenting for liver transplant evaluation.[3-5] Patients with PPHTN have an increased risk of death, even with specific PAH treatment.[4,6] In many cases, PPHTN greatly complicates or precludes liver transplantation, significantly affecting the course of hepatic failure in these patients.[7,8]

There are no known clinical factors which determine the risk of PPHTN in patients with advanced liver disease. Similarly, the mechanism for pulmonary vascular obliteration in patients with portal hypertension (characterized by systemic vasodilation) is unknown. It follows that the identification of patient characteristics that increase or decrease the probability of developing PPHTN might not only be clinically useful, but could also shed light on the etiology of this relatively common comorbidity of portal hypertension. Therefore, we studied whether demographics, type and severity of underlying liver disease, or other patient factors were associated with the risk of PPHTN.

Patients and Methods

Study Design and Study Sample

The Pulmonary Vascular Complications of Liver Disease (PVCLD) Study prospectively enrolled a cohort of 536 patients evaluated for liver transplantation or pulmonary hypertension at seven centers in the United States between 2003 and 2006. The only inclusion criterion was the presence of clinical portal hypertension with or without intrinsic liver disease. We excluded patients with evidence of active infection or recent (less than 2 weeks) gastrointestinal bleeding, or who had undergone liver or lung transplantation. Patients in the prospective cohort were newly referred for evaluation for liver transplantation or pulmonary hypertension. We also included patients in the cohort who had been diagnosed with PPHTN and treated before the beginning of the study (“prevalent” patients).

We performed a case-control study nested within the prospectively-assembled PVCLD cohort. The study sample included newly referred patients who were evaluated with transthoracic echocardiography (routinely performed for pretransplant evaluation) during the study period. “Prevalent” patients who met the case definition (see below) were also included. We excluded patients with significant obstructive lung disease, defined as forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.70 with FEV1 percent predicted <80%, and patients with a significant restrictive ventilatory defect, defined as FVC percent predicted and (if performed) total lung capacity percent predicted < 70%. Patients

who otherwise fulfilled the case definition (see below) without available pulmonary function testing were included if chest radiography showed neither significant hyperinflation nor interstitial lung disease; controls without pulmonary function testing were excluded. The study sample also excluded patients with human immunodeficiency virus infection or the presence of more than moderate aortic or mitral stenosis or regurgitation or significant left ventricular dysfunction determined by transthoracic echocardiography.

Case and Control Definitions

Cases with PPHTN met the following criteria at initial evalution: (1) mean pulmonary artery pressure >25 mm Hg, pulmonary capillary wedge pressure (or left ventricular end-diastolic pressure) ≤ 15 mm Hg, and pulmonary vascular resistance > 240 dynes · second · cm^{-5} measured by right heart catheterization, and (2) no other etiology for pulmonary hypertension. Controls met the following echocardiographic criteria at entry into the cohort: (1) right ventricular (RV) systolic pressure < 40 mm Hg (if estimable) and (2) absence of right atrial or ventricular dilation, hypertrophy, or dysfunction. Data from the initial evaluation (before treatment) were used in analysis of “prevalent” cases. It was recommended that right heart catheterization should be performed for patients with RV systolic pressure > 50 mm Hg with abnormal RV morphology by echocardiography.

Sensitivity analyses included both patients who met the case definition but who had pulmonary capillary wedge pressure between 16 and 19 mm Hg as cases and patients who met the control definition but who had abnormal right atrial or ventricular morphology and/or RV systolic pressure < 50 mm Hg (if estimable) as controls. We also performed a subset analysis with cases who presented for their initial evaluation during the study period.

Potential Predictors

Data were collected from the patients and from the medical record. The etiology of underlying liver disease (or portal vein thrombosis), past medical history, and social history were recorded. Patients underwent a physical examination that included anthropometry, blood pressure measurements, and laboratory assessment. The Model for End-Stage Liver Disease (MELD) score was calculated.[9]

Other Variables

Chest radiography and computed tomography were interpreted locally at each center. The results of the abdominal imaging study closest to the day of initial evaluation (computed tomography, magnetic resonance imaging, or ultrasound) were recorded. Spirometry, lung volumes, and diffusing capacity for carbon monoxide were measured; results are expressed using standard sex-specific and race-specific prediction equations, where appropriate.[10-12] Arterial blood gas was obtained, and the alveolar-arterial oxygen gradient was calculated. Transthoracic echocardiography was interpreted at each center. Injection of agitated saline was performed through a peripheral vein; an intrapulmonary shunt was considered present if appearance of micro-bubbles in the left atrium occurred three or more cardiac cycles after opacification of the right side of the heart. The study was approved by the Institutional Review Board of each center, and patients provided informed consent before undergoing study procedures.

Statistical Analyses

Continuous data were summarized using mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were summarized using n (%). Bivariate logistic regression was performed with case/control 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 which had *P* value < 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 four or fewer predictors to prevent overfitting. Unpaired Student *t* tests, Wilcoxon rank sum tests, chi-squared tests, and Fisher's exact tests were used for other analyses, as appropriate.

The final multivariate model was assessed using the Hosmer-Lemeshow goodness-of-fit test; dbetas were calculated to assess for influential subjects. All analyses were performed with available data without imputation using Stata/IC version 10.0 (StataCorp, College Park, TX). A two-sided *P* value of < 0.05 was considered statistically significant.

Results

There were 34 cases and 141 controls in the study sample. The mean age of the patients was 53 ± 9 years, and 44% were female. A total of 76% were non-Hispanic white, 13% were Hispanic white, and 5% were non-Hispanic black. Patients with PPHTN had a mean right atrial pressure of 10 ± 7 mm Hg, a mean pulmonary artery pressure of 49 ± 9 mm Hg, and pulmonary capillary wedge pressure (or left ventricular end-diastolic pressure) of 10 ± 3 mm Hg by right heart catheterization. The mean cardiac output was 5.4 ±1.8 L/minute, the cardiac index was 2.8 ± 0.9 L/minute/m^2, and the pulmonary vascular resistance was 696 ± 397 dynes · second · cm^{-5}. Mean pulmonary artery oxygen saturation was 65 ±11% (N = 31).

Bivariate Analyses

Cases and controls were similar in terms of age and race/ethnicity (Table 1). Cases with PPHTN were significantly more likely to be female than liver disease controls (OR = 3.98, 95% confidence interval 1.77-8.98, *P* = 0.001). Almost half of the cases and controls had liver disease attributable to alcohol use. Cases with PPHTN were significantly less likely than liver disease controls to be infected with hepatitis C, whereas they were significantly more likely to have autoimmune hepatitis (both $P \leq 0.001$). Patients with PPHTN were also somewhat more likely to have primary biliary cirrhosis than controls, however, this was not statistically significant. There was no association between case/control status and the prevalence of nonalcoholic fatty liver disease, hepatitis B infection, primary sclerosing cholangitis, or cryptogenic cirrhosis. There were fewer than three patients in each group with primary portal vein thrombosis (one case), alpha-1 antitrypsin deficiency (one case, two controls), biliary atresia (one control), or sarcoid (one case). Patients in the study sample may have had more than one etiology of liver disease. One patient with PPHTN (3%) was receiving interferon therapy as were five (4%) liver disease controls (*P* = 1.0).

The median time from diagnosis of the underlying liver disease to evaluation at the study center was 6 years for cases and 3 years for controls (*P* = 0.04, N = 162). The mean MELD score was 12 ± 4 and 13 ± 5 in cases and controls, respectively (*P* = 0.81). A total of 34% of PPHTN cases and 36% of controls had mild liver disease (MELD score ≤ 10), and there was no association between the presence of mild liver disease and PPHTN case status (*P* = 1.0). Similarly, there were no associations between mean pulmonary artery pressure or pulmonary vascular resistance and age, sex, or MELD score in patients with PPHTN (data not shown).

Cases with PPHTN were less likely than liver disease controls to have a history of ascites and possibly less likely to have a history of encephalopathy, but there were no differences between the groups in terms of other complications of liver disease or portal hypertension (Table 2). A transjugular intrahepatic portosystemic shunt (or surgical shunt) was placed in 3% of cases and 6% of controls (*P* = 0.53) The prevalence of chronic obstructive pulmonary disease, diabetes mellitus, hypertension and other medical conditions were similar between

the groups. Most cases and controls had a history of smoking and chronic alcohol use, whereas controls were somewhat more likely than cases to have used intravenous drugs.

There were no differences between cases and controls in terms of vital signs and signs of portal hypertension and hepatic dysfunction by physical examination, other than there being a lower probability of ascites in patients with PPHTN (Table 3). Hemoglobin was slightly higher in cases than controls. However, white blood cell count, platelet count, and the international normalized ratio were similar. There were no differences in total bilirubin or total protein, although cases had a higher mean serum albumin and lower aminotransferase levels compared to controls.

Chest radiography showed cardiomegaly and large pulmonary arteries more commonly in the patients with PPHTN than in liver disease controls (Table 4). There were no differences in spirometric measures between cases and controls; however, cases had lower diffusing capacity for carbon monoxide (corrected for hemoglobin) percent predicted. Cases had slightly higher arterial pH, lower arterial partial pressure of oxygen, and higher alveolar-arterial oxygen gradient. Abdominal imaging confirmed a lower prevalence of ascites in cases compared to controls; most patients in both groups had splenomegaly.

Patients with PPHTN had characteristic right-sided findings on transthoracic echocardiography; liver disease controls (by definition) did not show right-sided abnormalities (Table 5). Cases had somewhat more left ventricular hypertrophy, however, left atrial size was similar between the groups. Pericardial effusion was more common in patients with PPHTN (22%) compared to liver disease controls (6%) ($P = 0.011$). Intrapulmonary shunting was significantly less common in cases (30%) than in controls (56%) ($P = 0.02$).

Multivariate Analysis

We assessed the variables from Tables 1 and 2 in multivariate logistic regression (Table 6). Female sex and autoimmune hepatitis were independently associated with an increased risk of PPHTN. On the other hand, hepatitis C infection was associated with a lower risk of PPHTN. Other demographics, anthropomorphics, MELD score, and medical comorbidities were not significant predictors in the multivariate model. Model fit was adequate by the Hosmer-Lemeshow goodness-of-fit test ($P =0.62$), and there were no overly influential subjects.

An analysis incorporating patients who met the criteria for PPHTN except for having a pulmonary capillary wedge pressure between 16 and 19 mm Hg (N = 3) showed similar results. Inclusion of patients with abnormal right-sided echocardiographic results as controls similarly did not alter the conclusions. A subset analysis excluding “prevalent” case patients (N = 15) produced results consistent with the final logistic model.

Discussion

This is the first multicenter epidemiologic study of the clinical risk factors for PPHTN in patients with severe liver disease and portal hypertension. Using a case-control design (well-suited to study this rare disease), we have demonstrated that females with liver disease have a higher risk than males of developing PPHTN. We have also shown that the etiology of liver disease is important in determining the risk of this serious pulmonary vascular complication. Patients with autoimmune hepatitis have a higher risk and patients with hepatitis C infection have a lower risk of PPHTN than patients with other etiologies of liver disease. Previously hypothesized factors, such as age, severity of liver disease, and medical comorbidities, were not associated with the risk of PPHTN. Patients with PPHTN also had

characteristic radiographic, arterial blood gas, and echocardiographic findings and were less likely than controls to have intrapulmonary shunting.

The idiopathic and familial forms of PAH are well-known to occur more commonly in women than in men.[13,14] However, this is the first form of PAH related to an associated condition shown to have an increased risk in women compared to men. Although PAH associated with connective tissue disease frequently occurs in women, such diseases are as a whole more common in women, and sex is not thought to affect the risk of PAH in this setting.[15] Prior retrospective studies of PPHTN have shown a possible overrepresentation of women compared to men (considering the underlying demographic of portal hypertension), but the absence of appropriate control groups has prevented a definitive statement until this point.[5,16] For example, Krowka et al. compared patients with PPHTN to liver disease patients with pulmonary hypertension by echocardiography which did not meet the criteria for PPHTN. These authors found no significant differences in demographics or other variables between these two groups of patients. The discrepancy between these authors' conclusions and ours is likely explained by differences between the control group in the study of Krowka et al. (patients with liver disease with pulmonary hypertension determined by echocardiography) and the control group of our study (patients with liver disease with normal right heart morphology determined by echocardiography).

Hormone profile, pregnancy, and a tendency toward autoimmune processes are three mechanistic factors which may explain the female sex predilection for PAH. Interestingly, the female sex predominance in our study was independent of the underlying etiology of liver disease, indicating that this finding was not accounted for by a predisposition to autoimmune liver disease. These findings indicate that the biologic components of sex differences may be an important starting point from which to understand why patients with liver disease develop PPHTN.

Several lines of investigation have suggested that PAH has an immune etiology. First, individuals with certain human leukocyte antigen subtypes have a higher risk of PAH than do those with other subtypes.[17,18] Second, connective tissue diseases are a well-established risk factor for PAH. Third, antinuclear antibody titers are frequently elevated in patients with PAH.[19,20] Last, immune-mediated diseases of other organs (for example, thyroid) are common in patients with PAH.[21] We found that autoimmune hepatitis (and possibly primary biliary cirrhosis) was associated with an increased risk of PPHTN. Therefore, in some cases, PPHTN may be attributable not only to the presence of portal hypertension, but also to the autoimmune process resulting in liver disease, consistent with a "two-hit" hypothesis.

Patients with hepatitis C infection were less likely to suffer from PPHTN, even after consideration of the demographics and medical and social histories of these patients. There may be some characteristic of the treatment for hepatitis C–associated liver disease which decreases the risk in this population. However, we did not find differences between cases and controls in the use of interferon at the time of evaluation, although we did not have available data on all treatments received previously. Alternatively, there could be a direct effect of the virus which is protective to the pulmonary vasculature. The basis of this novel association is unknown.

The American Association for the Study of Liver Diseases currently recommends that all patients being evaluated for liver transplantation undergo screening with transthoracic echocardiography, due to the greatly increased perioperative risk of death for a liver transplant recipient with untreated PPHTN.[22] However, it is not established whether patients with liver disease who are not transplant candidates warrant screening for this condition. Given the relatively low specificity of echocardiography (that is, high false-positive rate)

and the lack of well-studied therapies for PPHTN with documented efficacy,[23-25] it is likely premature to recommend screening for patients with liver disease who are not transplant candidates, even if they fall into the "high-risk" subgroups in our study. On the other hand, clinicians should have a low threshold to obtain echocardiography in patients with portal hypertension with symptoms suggestive of PPHTN.

Certain factors that have been postulated to be linked to PPHTN were not associated with case status in our study. Age and race/ethnicity did not differ between the groups. Cases with PPHTN (which included prevalent patients) may have had a longer duration of liver disease, however, there were no differences between cases and controls in terms of severity of liver disease (that is, MELD score and previous hepatic complications, except for ascites and encephalopathy). The placement of a portosystemic shunt or performance of splenectomy did not affect the risk of PPTHN. Smoking and chronic alcohol use were common in both groups.

Levels of liver aminotransferases were somewhat lower in cases than in controls, and albumin levels were higher. However, other markers of liver function were similar between the groups. These differences possibly reflect the different types of liver disease represented in the two populations. The lower diffusing capacity for carbon monoxide, acid-base abnormalities, and higher alveolar-arterial oxygen gradient in the absence of significant differences in spirometric measures confirm other studies which have shown these abnormalities in patients with PPHTN.[26] These findings likely result from the vascular arteriopathy and ventilation:perfusion mismatch which characterize PAH.

Patients with PPHTN had pericardial effusions more commonly than did controls. The presence of a pericardial effusion is associated with worse survival in idiopathic PAH[20,27]; the clinical implications of a pericardial effusion in PPHTN are unknown. Intrapulmonary shunting was less common (although still relatively frequent) in cases with PPHTN than in the liver disease controls. Pulmonary vasodilation is common in patients with advanced liver disease and portal hypertension, and when accompanied by abnormal arterial partial pressure of oxygen, defines hepatopulmonary syndrome. Considering the hemodynamic profile of PPHTN, less pulmonary vasodilation would be expected in these patients; however, the relationship of these two opposing pulmonary vascular syndromes seen in the setting of portal hypertension remains to be clarified.

There are some limitations to our study. This is one of the largest samples of patients with PPHTN with detailed phenotyping ever collected; however, there was a relatively small number of cases. The predictors we describe had large effect sizes and were highly significant, and our final multivariate model was robust to alterations in case and control definitions, deletion of potentially influential subjects, and exclusion of prevalent subjects. It is however possible that risk factors with smaller effect sizes may not have been detected in our study. Information bias is possible, but we used standard data collection forms for all patients. Although this could still be a problem (because some data were collected after case/control status was established), the predictors in our final model (that is, sex and liver disease diagnosis) are not easily affected by such bias. We specifically avoided inclusion of factors which could be affected by PPHTN, such as radiographic and laboratory findings, in our final explanatory multivariate model. Selection bias and exchangeability are always a concern in case-control studies. However, it would appear that the liver disease controls at each center came from the same source population as the cases by design, and the severity of liver disease (reflected by MELD) was virtually identical between the groups, assuring the comparability of the two groups. Echocardiography and right heart catheterization results were interpreted locally; measurement error and misclassification are possible. However, such misclassification would have led to bias to the null, unless such error was systematic

and related to the risk factors demonstrated, which was unlikely. We recorded a variety of potential risk factors for PPHTN; nonetheless, our findings could be accounted for by another confounding variable or residual confounding.

In summary, sex and type of liver disease affect the risk of PPHTN. These are the first clinical predictors of PPHTN ever defined. The mechanistic role of these factors in the evolution of PPHTN in patients with portal hypertension should be examined in future studies.

Appendix

The Pulmonary Vascular Complications of Liver Disease Study Group also includes: Columbia University: Jenna Reinen, BA, Jeffrey Okun, BA, Daniel Rabinowitz, PhD, Debbie Rybak, BA; Mayo Clinic: Linda Stadheim, RN, Vijay Shah, MD, Russell Wiesner, MD; University of Alabama: Dottie Faulk, J. Stevenson Bynon, MD, Devin Eckhoff, MD, Harpreet Singh, Rajasekhar Tanikella; University of Colorado: Ted Perry, Lisa Forman, MD; The University of North Carolina at Chapel Hill: Carrie Nielsen, RN, Roshan Shrestha, MD; University of Pennsylvania: Vivek Ahya, MD, Harold Palevsky, MD, Rajender Reddy, MD; University of Southern California: James Knowles, MD, PhD.

Acknowledgments

Funded by National Institutes of Health grants DK064103, DK065958, RR00645, RR00585, RR00046, RR00032, and HL67771.

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Abbreviations

FEV1	forced expiratory volume in one second
FVC	forced vital capacity
MELD	Model for End-Stage Liver Disease
OR	odds ratio
PAH	pulmonary arterial hypertension

PPHTN	portopulmonary hypertension
PVCLD	Pulmonary Vascular Complications of Liver Disease
RV	right ventricular

Table 1

Demographics and Liver Disease Variables

Variable	N	Cases	Controls	OR	95% CI	*P* Value
Age, years	175	53 ± 10	53 ± 9	1.0	0.97–1.05	0.62
Gender, female	175	24 (71%)	53 (38%)	3.98	1.77–8.98	0.001
Race/Ethnicity	175					
Non-Hispanic white		29 (85%)	104 (74%)	1.0	—	—
Hispanic white		2 (6%)	21 (15%)	0.34	0.08–1.54	0.16
Non-Hispanic black		0	9 (6%)	—	—	—
Other		3 (9%)	7 (5%)	1.54	0.37–6.31	0.5
Etiology of cirrhosis/portal hypertension	175					
Alcohol		14 (41%)	61 (43%)	0.92	0.43–1.96	0.83
Hepatitis C infection		6 (18%)	75 (53%)	0.19	0.07–0.48	0.001
Autoimmune hepatitis		9 (26%)	5 (4%)	9.79	3.03–31.65	< 0.001
Nonalcoholic fatty liver disease		1 (3%)	12 (9%)	0.33	0.04–2.60	0.29
Hepatitis B infection		1 (3%)	8 (6%)	0.50	0.06–4.17	0.53
Primary sclerosing cholangitis		1 (3%)	9 (6%)	0.44	0.05–3.63	0.45
Primary biliary cirrhosis		4 (12%)	5 (4%)	3.63	0.92–14.31	0.07
Cryptogenic cirrhosis		2 (6%)	8 (6%)	1.04	0.21–5.13	0.96
MELD score	172	12 ± 4	13 ± 5	1.0	0.91–1.07	0.81

Data are shown as mean ± standard deviation or n (%). MELD = Model for End-stage Liver Disease

Table 2

Past Medical History

Variable	N	Cases	Controls	OR	95% CI	*P* Value
Ascites	175	12 (35%)	86 (61%)	0.35	0.16–0.76	0.008
Variceal bleeding	175	8 (24%)	27 (19%)	1.30	0.53–3.18	0.57
Encephalopathy	174	9 (26%)	62 (44%)	0.45	0.20–1.04	0.06
Spontaneous bacterial peritonitis	173	1 (3%)	10 (7%)	0.39	0.05–3.16	0.38
Hepatocellular carcinoma	174	1 (3%)	21 (15%)	0.17	0.02–1.32	0.09
Hepatic hydrothorax	175	2 (6%)	2 (1%)	4.34	0.59–32.01	0.15
Transjugular intrahepatic portosystemic shunt	175	1 (3%)	8 (6%)	0.50	0.06–4.17	0.53
Chronic obstructive pulmonary disease	174	3 (9%)	7 (5%)	1.84	0.45–7.51	0.40
Interstitial lung disease	174	0	6 (4%)	—	—	—
Venous thromboembolism	174	2 (6%)	9 (6%)	1.0	0.21–5.09	0.97
Diabetes mellitus	173	7 (21%)	40 (29%)	0.64	0.26–1.59	0.34
Hypertension	174	12 (35%)	37 (26%)	1.52	0.68–3.37	0.31
Hypercholesterolemia	174	3 (9%)	7 (5%)	1.84	0.45–7.52	0.40
Coronary artery disease	174	0	3 (2%)	—	—	1.0
Hypothyroidism	173	2 (6%)	10 (7%)	0.84	0.17–4.02	0.83
Hyperthyroidism	173	1 (3%)	1 (1%)	4.34	0.26–71.31	0.30
Splenectomy	174	0	4 (3%)	—	—	—
Smoking	175	22 (65%)	86 (61%)	1.17	0.54–2.56	0.69
Chronic alcohol use	170	20 (65%)	100 (72%)	0.71	0.31–1.62	0.41
Intravenous drug use	168	2 (6%)	28 (20%)	0.27	0.06–1.19	0.08
Blood transfusion	142	15 (47%)	41 (37%)	1.48	0.67–3.29	0.33

Data are shown as n (%).

Table 3

Physical Examination and Laboratory Results

Variable	N	Cases	Controls	*P* Value
Physical examination				
Body mass index, kg/m^2	175	29 ± 5	28 ± 6	0.78
Pulse, beats per minute	175	78 ± 15	75 ± 12	0.22
Systolic blood pressure, mm Hg	173	115 ± 17	119 ± 17	0.23
Diastolic blood pressure, mm Hg	173	68 ± 9	70 ± 11	0.34
Room air oxygen saturation, %	158	95 ± 4	95 ± 3	0.30
Ascites	172	5 (16%)	55 (39%)	0.01
Lower extremity edema	174	18 (53%)	67 (48%)	0.60
Clubbing	172	1 (3%)	9 (7%)	0.69
Asterixis	173	2 (6%)	3 (2%)	0.25
Spider angiomata	168	7 (21%)	39 (29%)	0.38
Laboratory results				
Blood urea nitrogen, mg/dL	173	14 [10–19]	14 [10–18]	0.95
Creatinine, mg/dL	174	0.9 [0.8–1.1]	0.9 [0.7–1.1]	0.78
Hemoglobin, g/dL	173	14 ± 2	13 ± 2	0.05
Platelet count, 10^9/L	170	82 [66–103]	90 [67–137]	0.19
International normalized ratio	174	1.3 [1.2–1.4]	1.2 [1.1–1.4]	0.49
Alanine aminotransferase, U/L	174	28 [23–54]	49 [31–79]	0.002
Aspartate aminotransferase, U/L	174	44 [35–61]	74 [47–110]	< 0.001
Total bilirubin, mg/dL	174	1.8 [1.1–2.7]	1.9[1.3–2.9]	0.67
Alkaline phosphatase, U/L	172	114 [96–164]	140 [100–203]	0.045
Total protein, g/dL	165	7.3 ± 0.8	7.2 ± 0.9	0.28
Albumin, g/dL	167	3.7 ± 0.4	3.2 ± 0.7	< 0.001

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

Table 4

Chest Radiography, Pulmonary Function Testing, Arterial Blood Gas Results, and Abdominal Imaging

Variable	N	Cases	Controls	*P* Value
Chest radiography				
Cardiomegaly	167	14 (45%)	7 (5%)	< 0.001
Large pulmonary arteries	167	13 (42%)	1 (1%)	< 0.001
Interstitial lung disease	167	0	4 (3%)	1.0
Hyperinflation	167	0	1 (1%)	1.0
Pleural effusion	167	2 (6%)	13 (10%)	0.74
Pulmonary function testing				
FVC, % predicted	162	85 ± 16	88 ± 15	0.38
FEV1, % predicted	162	83 ± 15	88 ± 14	0.14
FEV1/FVC	162	0.77 ± 0.07	0.78 ± 0.06	0.54
$DLCO_{corr}$, % predicted	153	53 ± 11	62 ± 15	0.009
Arterial blood gas				
pH	147	7.46 ± 0.03	7.43 ± 0.04	0.009
pCO_2, mm Hg	147	32 ± 4	35 ± 5	0.02
pO_2, mm Hg	147	76 ± 16	87 ± 15	0.006
Alveolar-arterial oxygen gradient, mm Hg	147	29 [14–41]	13 [6–20]	0.007
Abdominal imaging				
Splenomegaly	163	20 (80%)	103 (75%)	0.57
Ascites	173	4 (15%)	66 (48%)	0.002
Portal vein thrombosis	174	1 (4%)	7 (5%)	1.0

Data are shown as mean ± standard deviation, median [interquartile range], or n (%). Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; $DLCO_{corr}$, diffusing capacity for carbon monoxide corrected for hemoglobin.

Table 5

Echocardiography Results

Variable	N	Cases	Controls	*P* Value
Right atrial dilation	162	24 (77%)	0	< 0.001
Right ventricular dilation	167	28 (82%)	0	< 0.001
Right ventricular hypertrophy	166	13 (41%)	0	< 0.001
Right ventricular dysfunction	167	20 (61%)	0	< 0.001
Paradoxical septal motion	152	7 (23%)	0	< 0.001
Tricuspid regurgitation	166	31 (97%)	111 (83%)	0.049
Estimated right ventricular systolic pressure, mm Hg	91	77 ± 25	30 ± 5	< 0.001
Pulmonic regurgitation	129	23 (82%)	38 (38%)	< 0.001
Left atrial size, cm	137	4.1 [3.5–5.5]	4 [3.5–4.3]	0.16
Left ventricular hypertrophy	173	11 (32%)	25 (18%)	0.06
Pericardial effusion	166	7 (22%)	8 (6%)	0.011
Shunting	144			0.02
None		13 (57%)	45 (37%)	
Intrapulmonary		7 (30%)	68 (56%)	
Intracardiac		2 (9%)	8 (7%)	
Indeterminate		1 (4%)	0	

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

Table 6

Multivariate Logistic Regression

Variable	OR	95% CI	*P* Value
Female gender	2.90	1.20–7.01	0.018
Autoimmune hepatitis	4.02	1.14–14.23	0.031
Hepatitis C infection	0.24	0.09–0.65	0.005