

Evaluation of Predisposing Metabolic Risk Factors for Portopulmonary Hypertension in Patients with NASH Cirrhosis

Fatih Türker¹, Tolga Sahin², Alihan Oral², Erdem Koçak³, Betül Çavuşoğlu Türker⁴, Adil Niğdelioğlu², Hayriye Esra Ataoğlu¹

¹University of Health Sciences, Haseki Health Training and Research Hospital, Internal Medicine Clinic, İstanbul, Turkey; ²Demiroğlu Bilim University, Florence Nightingale Hospital Internal Medicine Clinic, İstanbul, Turkey; ³Istinye University, Liv Hospital Vadi İstanbul, Gastroenterology, İstanbul, Turkey; ⁴University of Health Sciences, Taksim Health Training and Research Hospital, Internal Medicine Clinic, İstanbul, Turkey

Correspondence: Fatih Türker, Aksaray, Dr. Adnan Adıvar Cd, No: 9, İstanbul, Tel +0905364721656, Fax +0212 453 20 00, Email fatihturker1985@hotmail.com

Purpose: Metabolic parameters are important for the development of portopulmonary hypertension (PoPH) during nonalcoholic steatohepatitis (NASH)-associated cirrhosis. This study evaluated patients with NASH-associated cirrhosis to determine metabolic risk factors for portopulmonary hypertension.

Patients and Methods: Data on 171 patients (120 men and 51 women) with NASH-associated cirrhosis who were seen in Florence Nightingale Hospital's gastroenterology Clinic from 2009 to 2018 was obtained from the Hospital database. A pulmonary artery systolic pressure >35 mmHg was defined as PH (pulmonary hypertension) according to standard transthoracic echocardiography. Portal hypertension was diagnosed from clinical symptoms and dilated portal veins shown by abdominal ultrasound or computed tomography (CT). Pulmonary patients with portal hypertension were diagnosed with portopulmonary hypertension (PoPH).

Results: A total of 171 patients with NASH-associated cirrhosis were included in this study. Of these, 43 patients had PoPH. These patients had increased TSH ($p=0.004$), bilirubin ($p=0.023$) and triglyceride ($p=0.048$) levels, higher MELD scores ($p=0.018$) and decreased hemoglobin ($p=0.05$). MELD score and hemoglobin, total bilirubin, TSH, and triglyceride levels were all included in a multivariate logistic regression model and TSH levels were independently associated with increased risk of PoPH.

Conclusion: Increased TSH is an independent risk factor for PoPH.

Keywords: pulmonary hypertension, portopulmonary hypertension, NASH cirrhosis

Introduction

Portopulmonary hypertension (PoPH) is defined as pulmonary arterial hypertension (PAH) associated with cirrhotic or noncirrhotic portal hypertension.¹ Pulmonary hypertension is classified into five groups, and portopulmonary hypertension (PoPH) is included in the first group because of hemodynamic similarities to other causes of precapillary pulmonary hypertension. Thus, transthoracic echocardiography (TTE) should be performed to screen cirrhotic patients for systolic pulmonary arterial pressure (sPAP). TTE is a reliable screening tool to estimate cardiac function. Systolic pulmonary arterial pressure is calculated by measuring the velocity of the tricuspid regurgitation jet to estimate the tricuspid pressure gradient during systole and calculating pressure using the modified Bernoulli equation, to which an estimate of right atrial pressure is added.

A strong correlation between sPAP and PAP obtained by right-heart catheterization has been shown in the general population.² A pulmonary artery systolic pressure >35 mmHg was defined as pulmonary hypertension (PH) using standard echocardiography.³ PH is confirmed when right heart catheterization demonstrates that pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest with a normal pulmonary artery wedge pressure ≤ 15 mmHg.⁴ Right-heart catheterization is the gold standard for a “definitive diagnosis” of PH. While the mechanism of PoPH is similar to

other forms of pulmonary arterial hypertension (PAH), the exact pathophysiology remains unclear and the prevalence of PoPH has ranged from 0.5% and 5% among patients with portal hypertension in prior studies.^{5–7}

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of chronic hepatic steatosis and inflammation in the absence of excessive alcohol consumption and is associated with metabolic comorbidities, such as obesity, diabetes mellitus, and dyslipidemia.^{8,9} NAFLD progresses to non-alcoholic steatohepatitis (NASH) and has the potential to progress further into cirrhosis. Several studies have shown that the prevalence of thyroid dysfunction is significantly higher in patients with NAFLD.¹⁰ This may be explained by the strong association between thyroid hormone levels and metabolic syndrome as well as the disturbance of lipid metabolism.¹¹ However, few studies have characterized predisposing metabolic risk factors including thyroid hormone levels in cirrhotic patients with PoPH. The aim of the current study was to evaluate the association between PoPH and risk factors in patients with NASH-associated cirrhosis.

Materials and Methods

Study Participants

This study was approved by the Ethics Committee of Florence Nightingale Hospital, University of Bilim, Istanbul, Turkey, and the clinical research ethics committee at Florence Nightingale Hospital (approval number 2019–16-03; approved on 8 June 2019) and performed in accordance with National Institute of Health guidelines. The study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All data were collected anonymously without including patient-identifying information, and consent to review patient medical records was not required by the Ethics Committee of Florence Nightingale Hospital. Patients >18 years of age with cirrhosis resulting from nonalcoholic steatohepatitis (NASH) who had pulmonary artery systolic pressure >35 mmHg measured by TTE were included in the study. Patients ≤18 years, with cardiovascular disease (congenital heart disease, valvular heart disease, or coronary heart disease), severe lung disease, thromboembolism, kidney disease, or active infection were excluded.

Patients with NASH-associated cirrhosis were Child B and Child C patients from whom a biopsy was contraindicated. Those with NASH-associated liver cirrhosis who did not have excessive alcohol intake (considered as an average daily consumption of alcohol >30 g/day in men and >20 g/day in women), negative test results for hepatitis B surface antigen and hepatitis C virus antibody, and no drug treatments known to cause liver steatosis, such as corticosteroids and estrogens, were included. In total, 171 patients (120 men and 51 women) with NASH-associated cirrhosis who were seen in Florence Nightingale Hospital's gastroenterology clinic from 2009 to 2018 were included in the study. Ultrasonography and CT were performed on all NASH patients. A pulmonary artery systolic pressure >35 mmHg was defined as PH using standard TTE. Data for the study analyses was obtained from dispensing records and profile data in the electronic hospital management system at Florence Nightingale Hospital. Patient demographic information, medical history, TTE, abdominal ultrasound, and laboratory examination data were obtained through standardized data collection. Demographic data, medical history, vital signs at admission, medications, and final diagnosis were obtained from electronic patient medical records.

Laboratory Measurements

Routine blood samples were drawn between 6 and 7 am after a 12-hour fast and immediately analyzed. Liver and kidney function, blood glucose, serum lipid, hemogram, and inflammatory markers like sedimentation and C-reactive protein (CRP) were measured in the Department of Laboratory Medicine at Florence Nightingale Hospital, University of Bilim. Laboratory data were obtained from the hospital's electronic patient medical records. Biochemical parameters were measured for all participants.

sPAP was calculated by measuring the velocity of the tricuspid regurgitation jet to estimate the tricuspid pressure gradient during systole and calculating pressure using the modified Bernoulli equation, to which an estimate of right atrial pressure is added.

Portal hypertension was diagnosed using clinical symptoms (ascites, history of gastrointestinal hemorrhage, abdominal wall varicose veins, and splenomegaly) and expanded portal veins were determined by abdominal ultrasound or CT.

A pulmonary artery systolic pressure >35 mmHg was defined as pulmonary hypertension (PH). PH patients with portal hypertension were diagnosed with PoPH. Based on diagnosis, patients were divided into those with or without portopulmonary hypertension. Biochemical and metabolic parameters were compared between the two groups.

Statistical Analysis

Data are expressed as the mean \pm standard deviation and statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Basic descriptive statistics were measured including the means, standard deviations, ranges, and percentages. The normality of the distribution was examined using the Kolmogorov–Smirnov test. Mean values between two independent groups were compared using the Mann–Whitney *U*-test for continuous variables and the χ^2 test for categorical parameters and comparisons between three or more subgroups were performed using ANOVA and Kruskal–Wallis *h*-tests. Bivariate correlations were assessed by Pearson's (continuous variables). Differences were considered statistically significant if the two-tailed *P* value was <0.05 .

Results

In total, 171 patients with NASH-associated cirrhosis were included in this study, of whom 29% were female, and the median age of the patients was 55.9 years. Most patients ($N=155$) were complicated with portal hypertension and 46 and 43 patients had PH and PoPH, respectively. The patient demographics and biochemical parameters are shown in Table 1. Higher body mass index was associated with PoPH ($p=0.005$) and there was no significant difference in CHILD PUGH scores ($p=0.344$) or albumin, liver, and renal function test results between patients with and without PoPH (Table 1). PoPH patients had a higher MELD score ($p=0.018$), higher total bilirubin ($p=0.023$) and triglyceride ($p=0.048$) levels, and lower hemoglobin ($p=0.05$) than patients without PoPH. Patients with PoPH were significantly older than those without. There was no significant difference between cardiac function and ejection fraction (EF) (59.7 ± 3.7 vs 58.8 ± 4.8 , $p=0.174$), or levels of tumor markers (eg, AFP, CEA, CA19-9 and PoPH) between the groups (Table 1). Higher TSH was associated with an increased risk of PoPH. However, there was no significant difference in FreeT3 and FreeT4 levels between patients with and without PoPH.

Complications associated with cirrhosis in patients with and without PoPH are shown in Table 2. There was no significant difference in portal vein thrombosis, esophageal varices, hepatic encephalopathy, or spontaneous bacterial peritonitis between the two groups. Ascites was more common in patients with PoPH ($p=0.008$). Age, MELD score, and Hb, total bilirubin, TSH, ascites, and triglyceride levels were included in a multivariate logistic regression model, and only increased TSH level was independently associated with an increased risk of PoPH (Table 3).

Discussion

This study investigated the risk factors of PoPH in patients with NASH-associated cirrhosis. A total of 171 patients were included in the study, 43 of whom were diagnosed with PoPH. Patients with PoPH exhibited higher levels of TSH, total bilirubin, and triglycerides, higher MELD scores, higher incidence of ascites, and lower levels of hemoglobin than those without. All these parameters were included in a multivariate logistic regression model and higher TSH levels were independently associated with an increased risk of PoPH. Few studies have measured an association between patients with cirrhosis and PoPH. Li et al¹² investigated the prognosis and prevalence of PoPH in liver transplantation recipients in China and demonstrated that low hemoglobin level was an independent risk factor for PoPH and screening for PoPH was essential for patients with advanced liver disease. The current study found an association between TSH level and PoPH in patients with cirrhosis that was not seen previously.

PoPH occurs in 7–10% of patients with PAH. Symptoms of PoAH are generally non-specific, and patients are often asymptomatic at the time of diagnosis.^{13–15} Studies have indicated that right heart dysfunction progresses with the development of PoPH and aggravates congestion as liver disease worsens.¹⁵ Of the laboratory parameters examined in this study, patients with PoPH had higher hemoglobin levels, MELD scores, and total bilirubin than patients without PoPH, reflecting more serious liver disease.

TTE is a reliable screening tool to estimate cardiac function. Pulmonary artery systolic pressure >35 mmHg was defined as pulmonary hypertension (PH) using standard echocardiography. PH is confirmed when right heart

Table 1 Demographics and Biochemical Parameters of the Study Patients

Variables	PoPH	nonPoPH	P value
Age	58±8	53±11	0.033*
Gender M/F	27/16	93/35	0.221
MELD score	17.5±5.1	15.6±4.3	0.018*
CHILD PUGH score	8.8±1.9	8.5±1.9	0.344
BMI	29.7±5.6	27.9±5.2	0.05*
Hemoglobin (g/dl)	10.8±1.5	11.4±1.9	0.05*
Platelet (10 ³ /μL)	92,116±64,305	94,378±64,305	0.911
INR	1.7±0.3	1.6±0.4	0.958
Fasting Glucose (mg/dl)	111±34	120±46	0.219
Creatinine (mg/dl)	1.1±0.5	0.9±0.5	0.053
Bilirubin (mg/dl)	4.8±6.8	3.8±4.6	0.023
AST (U/L)	61.8±50.6	61.1±56.8	0.922
ALT (U/L)	39.1±33.8	39.4±34.7	0.621
Albumin (g/dL)	2.8±0.5	3.0±0.5	0.138
TSH (mIU/L)	3.5±3.32	2.3±1.75	0.004*
Free T3 (mIU/L)	3.1±0.9	3.2±0.8	0.525
Free T4 (mIU/L)	13.2±7.6	12.3±6.7	0.486
Cholesterol (mg/dl)	119±40	130±42	0.253
Triglyceride (mg/dl)	103.1±104.6	81.6±34.4	0.048*
AFP	4.8±12.5	4.56±8.78	0.897
CEA	3.69±2.48	3.58±1.79	0.764
CA19-9	57.2±90.1	38.82±46.4	0.112

Note: *Statistically significant variables ($p < 0.05$).

Abbreviations: PoPH, portopulmonary hypertension; nonPoPH, nonportopulmonary hypertension; BMI, body mass index; AFP, alpha-fetoprotein; CEA, carcinoembryonic Antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TSH, thyroid stimulating hormone; INR, international normalized ratio.

Table 2 Association Between Complications of Cirrhosis and Portopulmonary Hypertension

Variables	PoPH (n:43)	nonPoPH (n:129)	P value
Spontan Bacterial Peritonitis	3 (%8.1)	10 (%8.9)	0.878
Hepatic Encephalopathy	19 (%47.5)	72 (%58.1)	0.242
Esophageal Varices	16 (%39)	44 (%35.2)	0.658
Ascites	42 (%97.7)	104 (%81.3)	0.008*
Portal Vein Thrombosis	5 (%11.6)	6 (%4.7)	0.109

Note: *Statistically significant variables ($p < 0.05$).

Abbreviations: PoPH, portopulmonary hypertension; nonPoPH, nonportopulmonary hypertension.

Table 3 Results of Multivariate Logistic Regression Analysis

Variable	P	OR	%95 CI
Age	0.194	0.030	0.985–1.078
TSH (mIU/L)	0.041*	0.181	1.007–1.428
Bilirubin (mg/dl)	0.709	−0.019	0.886–1.086
MELD	0.137	0.093	0.971–1.240
BMI	0.448	0.029	0.955–1.110
Hemoglobin (g/dl)	0.153	−0.166	0.675–1.063
Triglyceride (mg/dl)	0.332	0.004	0.996–1.012

Note: *Statistically significant variables ($p < 0.05$).

Abbreviations: BMI, body mass index; TSH, thyroid stimulating hormone.

catheterization demonstrates that pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest with normal pulmonary artery wedge pressure ≤ 15 mmHg. Although right heart catheterization is recommended for the definitive diagnosis of pulmonary hypertension, many studies show that patients in this group can be diagnosed with echocardiography by using an sPAP value instead of invasive catheterization in order to avoid invasive interventions and associated complications such as bleeding, thromboembolism, and infection that may develop in chronic liver patients. Calle et al reported that the NPV and PPV of sPAP values >30 mm/Hg were $>55\%$ and 100% , respectively.^{16,17} Liberal et al reported that the sensitivity and specificity of sPAP values >38 mm/Hg were 100% and $>80\%$, respectively.¹⁵ In the current study, patients with sPAP >35 mm/Hg values were enrolled from patient medical record data collected prospectively.

The thyroid is one of the most important organs responsible for regulating hemodynamics in the human body. The liver plays an important role in thyroid hormone metabolism by controlling peripheral deiodination of thyroid hormones, producing carrier proteins like thyroxine-binding globulin, transthyretin, and albumin and playing a role in the clearance of thyroid hormones.¹⁸ Some studies show that Free T3 (FT3) and Free T4 (FT4) levels are significantly lower and TSH levels are significantly higher in liver cirrhosis patients.^{19–24} An association between thyroid disorder and PH has been reported,²⁵ but few studies have evaluated the association between thyroid function and PoPH. In the current study, patients with PoPH had higher TSH levels than those without, while Free T3 and Free T4 were in the normal range. Thus, these patients were characterized as having subclinical hypothyroidism. Hypothyroidism has an influence on the cardiovascular system as a result of increased systemic vascular resistance and diastolic blood pressure.^{26,27} An increase in cardiac afterload affects the renin–angiotensin axis and reduces cardiac output, leading to higher pressure in the pulmonary veins. Hypothyroidism can also increase the oxidation of LDL.^{28,29} Thus, the presence of oxidative-LDL and hypothyroidism can increase vascular systemic and pulmonary resistance. Findings from this study showed a significant difference in the average age of patients in the two groups. Elevated TSH, total bilirubin, and triglyceride levels in PoPH patients may represent the severity of liver disease progression with age. As a result, L-thyroxine treatment for TSH may have a beneficial effect on NASH and PoPH patients. L-thyroxine treatment could reorganize the hemodynamics of the human body and reduce complications in patients with NASH cirrhosis. Findings from this study also showed that elevated TSH was an independent risk factor for PoPH irrespective of these cardiac and vascular alterations. Thus, TSH and thyroid hormone levels should be routinely monitored, especially in patients with NAFLD and cirrhosis.

This study also found that high BMI and triglyceride levels were associated with PoPH. Increased body weight can increase systemic vascular inflammation,^{30,31} which can, in turn, cause angioproliferative alterations in the pulmonary vascular bed and pulmonary hypertension.

This study has some limitations. It is a retrospective study and pulmonary hypertension cannot be confirmed with right heart catheterization even though RHC is the gold standard for diagnosing PoPH. PH was diagnosed using standard echocardiography.

Conclusion

Elevated TSH, total bilirubin and triglyceride levels, and decreased hemoglobin levels were strongly associated with the development of PoPH in patients with NASH-related cirrhosis. Moreover, elevated TSH was shown to be an independent risk factor for the development of PoPH. Future investigation should focus on the role of thyroid hormone in the development of PoPH in patients with NASH-related cirrhosis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The author reports no conflicts of interest in this work.

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