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Prevalence and Predictors of Pulmonary Hypertension in Children with Portal Hypertension: A Single Center Study

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ABSTRACT

Purpose: This study aimed to estimate the prevalence and predictors of portopulmonary hypertension (POPH) in children with portal hypertension.
Methods: We recruited children of both sexes aged 3–15 years with portal hypertension that was clinically suspected and confirmed by the presence of varices on esophagogastroduodenoscopy (EGD). The participants underwent clinical examination, 6-min walk distance (6-MWD), and echocardiography.
Results: We enrolled 94 children with portal hypertension: 26.6% with pre-hepatic causes and 73.4% secondary to chronic liver disease. Among our participants, 13.8% had one or more cardiac manifestations, such as exercise intolerance, dyspnea on exertion, cyanosis, or orthopnea, whereas 86.2% were asymptomatic. EGD examination revealed grade I varices in 54.3% of cases, grade II–III in 43.6%, and grade IV in 2.1%. Pulmonary hypertension (>35 mmHg) was detected in 30.9% of cases using echocardiography; two of them were >45 mmHg. Patients with POPH had significantly more frequent dyspnea on exertion, lower O_2 saturation, and more severe variceal grades than those with normal pulmonary artery pressure. Five (6.9%) cases had <300 m 6-MWD, with no significant difference between patients with normal and those with elevated pulmonary artery pressure. The duration of portal hypertension and 6-MWD were correlated significantly with the echocardiographic measures. High-grade varices (p=0.04) and low O_2 saturation (p=0.03) were identified as risk factors for POPH.
Conclusion: POPH was detected in 30.9% of our study group. High-grade varices and low O_2 saturation are predictors of POPH. Echocardiography screening is crucial for the early detection of cases.

Keywords: Child; Echocardiography; Esophageal and gastric varices; Hypertension, pulmonary and hypertension, portal; Exercise test

INTRODUCTION

Portopulmonary hypertension (POPH) is a rare and fatal complication of end-stage liver disease. It is defined as the development of pulmonary arterial hypertension in cases of

Conflict of Interest
The authors have no financial conflicts of interest.

portal hypertension, regardless of the liver condition. In addition, POPH is classified as group I pulmonary hypertension [1]. Pulmonary hypertension is identified when the mean pulmonary artery (MPA) pressure exceeds 20 mmHg at rest, the average wedge pressure is <15 mmHg, and pulmonary vascular resistance is >3 Wood units×m^2 [2].

Elevated portal pressure increases cardiac output, pulmonary blood flow, and endothelial damage by releasing humoral mediators, cytokines, and endotoxins. Increased vascular resistance is caused by vasoconstriction, pulmonary vascular remodeling, and pulmonary arterial endothelial cell proliferation, resulting in pulmonary hypertension [3].

Cardiac catheterization is the gold standard for the diagnosis and treatment monitoring of pulmonary arterial hypertension. However, catheterization in children is mainly performed under general anesthesia, making follow-up repetition difficult [4]. Conventional 2-D transthoracic echocardiography remains one of the most widely used tools to diagnose pediatric pulmonary arterial hypertension and is noninvasive, widely available, safe, and feasible [5].

As most patients with POPH have no cardiac symptoms and may remain undiagnosed for a long time, echocardiography screening is recommended for all liver transplant candidates and symptomatic patients with cirrhosis and portal hypertension [6]. Advanced POPH progresses rapidly, leading to deterioration in the child's functional status, and may preclude liver transplantation owing to the unacceptably high operative mortality rate [7]. The survival rate of this high-risk group is poor, with only 14% survival in five years in post-transplant candidates [8]. In mild-to-moderate POPH, liver transplantation is indicated after careful multidisciplinary evaluation with adjuvant medical treatments, including prostacyclin analogs, endothelial receptor antagonists, and phosphodiesterase-5 inhibitors [9]. Most authorities recommend liver transplantation in patients with POPH if the mean pulmonary arterial pressure is >35 mmHg (Grade II-2/3) [10].

The 6-minute walk test (6-MWT) is an excersise test that clinically assesses functional exercise capacity. It measures a patient's walking distance in 6 min [11]. A 6-minute walking distance (6-MWD) ≤300 m is indicated as a risk factor for pediatric pulmonary hypertension by the American Heart Association and American Thoracic Society. They reported that pediatric patients with pulmonary hypertension with a 6-MWD >500 m had a good prognosis [12]. The 6-MWD correlates well with the World Health Organization (WHO) functional classification and hemodynamic parameters [13]. Unfortunately, the 6-MWT has not been well-validated in young children, and additional parameters are required to monitor disease severity, prognosis, and treatment efficacy.

There are only a limited number of case reports and studies on children with POPH; therefore, its prevalence has not been accurately determined in the pediatric age group [14]. Thus, we aimed to estimate the prevalence of pulmonary hypertension in children with portal hypertension (pre-hepatic and hepatic causes) and assess its predictors.

MATERIALS AND METHODS

We present an observational, analytical, and cross-sectional study of children with portal hypertension from attendees of the hepatology unit at the Pediatric Hospital, Cairo

University, Egypt. The participants were evaluated in the cardiology unit for the detection of pulmonary hypertension. The Research Ethics Committee of the Cairo University Faculty of Medicine approved the study protocol. Informed consent was obtained from one parent before enrollment. The patients were enrolled between June 2021 and October 2022.

Children aged 3–15 years of both sexes who had portal hypertension due to hepatic or pre-hepatic causes were included. A diagnosis of portal hypertension was confirmed based on the presence of varices during esophagogastroduodenoscopy (EGD) in children with splenomegaly [15].

Patients with known cardiac affection, congenital, or syndromic hepatic disease were excluded.

Cases were subjected to noting down of medical history, emphasizing the age at portal hypertension diagnosis, and manifestations related to hematemesis or melena. The duration of portal hypertension was calculated from the time of diagnosis of portal hypertension upon EGD examination, to the timing of echocardiography. We also asked about manifestations suggestive of cardiac diseases such as dyspnea, syncopal attacks, cyanosis, or exercise intolerance.

Weight was measured using a stadiometer, and body mass index was calculated as follows: weight (kg)/height (cm^2). Anthropometric Z-scores were calculated using the WHO application [16]. Vital signs were assessed, and O_2 saturation was measured. The patients were examined for clubbing, organomegaly, and systemic affection. We also obtained complete blood counts and liver function tests from the patient files.

Anemia was defined as a hemoglobin level below the mean level for the patient's age. The severity of anemia was defined as mild when the hemoglobin level was between 10 gm/dL and the lower limit of normal, moderate when it was between 8 and 10 gm/dL, and severe when it was <8 gm/dL [16].

Echocardiography was performed using a device equipped with Vivid Probes 6S and 3S (GE Healthcare). In the apical 4-chamber view, a tricuspid regurgitation (TR) signal was obtained using color Doppler.

We used continuous-wave (CW) Doppler of the TR to measure the pressure gradient between the right ventricle (RV) and the right atrium (RA). We calculated this pressure difference using the peak TR velocity and the simplified Bernoulli equation. End-systolic pulmonary artery pressure (ESPAP) was calculated by adding the right atrial pressure to the obtained pressure gradient.

A pulmonary regurgitation (PR) signal was obtained from the parasternal short-axis view using color Doppler. CW Doppler was used to measure the peak PR velocity and the Bernoulli equation was used to calculate the pressure difference. We then added the pressure difference to the RA pressure to calculate the end-diastolic pulmonary artery pressure (EDPAP).

RV dilatation assessment: Using the M mode, we measured the right ventricular end-diastolic diameter (RVEDD) and left ventricular end-diastolic diameter (LVEDD) in the parasternal long-axis view. We then calculated the RVEDD Z-score and RV/LV ratio [17,18].

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Assessment of RA dilatation: Using 2D echo in the apical 4-chamber view, we measured the RA area using planimetry at the end of the ventricular systole, the largest volume, tracing the RA cavity.

In addition, using 2D echo in the parasternal short-axis view, we measured the MPA diameter at the level of the pulmonary valve.

Assessment of RV systolic function: The 2D tricuspid annular plane systolic excursion (TAPSE) was measured by obtaining an apical four-chamber view, followed by M-mode tracing of the lateral tricuspid valve annulus and measurement of the distance between the end-systole and end-diastole.

The right ventricular outlet tract (RVOT) acceleration time was measured using color and pulsed-wave Doppler in the left parasternal short-axis view at the level of the pulmonary artery. A mid-systolic notching or RVOT time <100 ms was considered an indicator of pulmonary hypertension [19].

Diagnosis of pulmonary hypertension was reached when ESPAP was ≥35 mm Hg. The selected cutoff had a sensitivity of 100% and a specificity of 96% in previous pediatric studies [20,21].

6-MWT

The 6-MWT was used to assess exercise intolerance in the study group [22]. The patient started the test after at least 10 min of rest. To determine the 6-MWD, we measured the patient's heart rate, blood pressure, and oxygen saturation, and determined the levels of tiredness and dyspnea before and after the test [23]. A 6-MWD <300 m was considered a high risk for pulmonary hypertension according to the AHA guidelines [12].

Statistics

Sample size calculation

The sample size was calculated based on our primary outcome, which was the percentage of pulmonary hypertension among children with chronic liver disease, using the open Epi version 3 software.

We used the following equation: sample size n=[DEFF*Np (1-p)]/[(d2/Z21-α/2 *(N-1)+p*(1-p)]. The minimum sample size required was 82, with a 95% confidence interval (CI) and 80% power.

Statistical analysis

We used IBM SPSS software, version 25 (IBM Co.) Qualitative data were presented as numbers (percentages). We verified the normality of the distribution of variables using the Kolmogorov–Smirnov test. We described the quantitative data using the mean (standard deviation), median (interquartile range), minimum, and maximum. We determined the significance of the results obtained at the 5% level.

We used the chi-square test to compare different categorical variables and Monte Carlo for chi-square correction when >20% of the cells had an expected count <5.

To compare more than two quantitative variables, we used the ANOVA test for normally distributed variables and the Kruskal–Wallis test for abnormally distributed variables.

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The Marginal Homogeneity Test was used to analyze the significance of the different stages. The Wilcoxon signed-rank test, Student's *t*-test, and Mann–Whitney U-test were used to compare abnormally distributed quantitative variables between the two groups. Pearson's and Spearman's correlations were used to test for a linear association between echocardiographic results and patient characteristics. Statistical significance was set at $p<0.05$.

RESULTS

We included 94 children with portal hypertension. Their ages ranged from 3–15 years, with a mean age of 7.7±3.4 years and a male-to-female ratio of 1.2:1. Among the participants, 86.2% had no cardiac manifestations, and 13.8% had one or more symptoms. Patient characteristics and endoscopic findings are presented in **Table 1**. The median duration of portal hypertension from diagnosis until study enrollment was 4 years.

Table 1. Characteristics of the studied children with portal hypertension (N=94)

Variable	Value
Age (yr)	7.7±3.4 (3–15)
Sex	
Male	52 (55.3)
Female	42 (44.7)
Cardiac manifestations	
Exercise intolerance	11 (11.7)
Dyspnea on exertion	3 (3.2)
Cyanosis	2 (2.1)
Orthopnea	1 (1.1)
Patient diagnoses	
Pre-hepatic portal hypertension	25 (26.6)
Portal hypertension on top of chronic liver disease	69 (73.4)
Biliary atresia, post-Kasai operation	24 (25.5)
Congenital hepatic fibrosis	15 (15.9)
Progressive familial intrahepatic cholestasis	14 (14.8)
Cryptogenic cirrhosis	8 (8.4)
Autoimmune hepatitis	3 (3.3)
Chronic hepatitis cryptogenic	2 (2.2)
Glycogen storage disease, type IV	1 (1.1)
Caroli disease	1 (1.1)
Cystic fibrosis	1 (1.1)
Endoscopic findings	
Mild varices group (small veins or grade I)	51 (54.3)
Moderate group (grade II and III)	41 (43.6)
Severe group (grade IV)	2 (2.1)
Duration of portal hypertension (yr)	4 (2–6)
Anthropometric measures	
Weight (kg)	24.8±11.2
Weight for age Z-score	−0.8 (−1.7 to −0.2)
Underweight (<−2 Z-score)	19 (20.2)
Height (cm)	118±20.97
Height Z score	−1.5 (−2.5 to −0.6)
Stunted (<−2 Z-score)	32 (34)
BMI (kg/m^2)	16.9±2.5
BMI Z score	0.09 (−0.5 to 0.6)
Wasted (<−2 Z-score)	1 (1.1)

Values are presented as mean±standard deviation (range), number (%), or median (interquartile range).
BMI: body mass index.

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Consanguinity was detected in 42 (44.6%) patients. The primary presenting manifestations of our studied children were abdominal distention in 84 (89.4%), jaundice in 29 (30.9%), clubbing in 29 (30.9%), hematemesis or melena in 28 (29.8%), pruritus in 20 (21.3%), bleeding tendency or ecchymosis in 15 (16%), ascites in 5 (8.5%), and lower limb edema in 5 (5.3%). None of the patients experienced syncopal attacks. All patients had a palpable spleen and 55 (58.5%) had a palpable liver.

In the study group, 70 (74.5%) patients underwent interventions for esophageal varices, including band ligation in 67 (95.7%) and injection sclerotherapy in 3 (4.3%).

Anemia was observed in 50 (53.1%) patients, graded as mild in 32 (34%) and moderate to severe in 18 (19.1%). Moreover, platelet count <150,000 was observed in 58 (61.7%) patients and leucocyte count <4,500 in 31 (32.9%). Abnormalities in the liver function were observed as follows: elevated ALT in 56 (59.6%) patients, elevated AST in 67 (71.3%), hyperbilirubinemia in 27 (28.7%), hypoalbuminemia in 15 (15.9%), and prolonged prothrombin time in 61 (64.9%).

Vitals of the group showed that 5 (5.3%) patients had tachycardia, one had tachypnea, and one patient with congenital hepatic fibrosis and polycystic kidney disease had hypertension for height. The standing O_2 saturation of the cases ranged from 87-100%, with a mean of 98.7±2.2, whereas the supine O_2 saturation of the cases ranged from 88–100% with a mean of 98.8±1.9, with no significant difference. Two patients (2.1%) had O_2 saturation <92%, and none had platypnea orthodeoxia.

In **Table 2**, we present the echocardiographic findings and results of 6-MWD in our study group. The echocardiographic assessment revealed that 29 (30.9%) patients had pulmonary hypertension with ESPAP >35 mmHg, and 2 (2.1%) of them had significant elevation at >45 mmHg.

Table 2. Echocardiographic findings and 6-min walk distance results of the studied children with portal hypertension

Variable	Value
Echocardiographic findings (N=94)	
ESPAP (mmHg)	31.8±5.1
ESPAP ≥35 mmHg	29 (30.85)
EDPAP (mmHg)	14±2.9
MPA Z score	0.26 (0–0.62)
RVEDD/LVEDD ratio	0.4±0.1
RVEDD Z-score	1.7 (1.4–2)
RVEDD Z-score (>2 z score)	11 (11.7)
RA area Z-score	0.4 (0.07–0.9)
TAPSE (mm)	24.7±2.4
TAPSE Z score	2.9 (1.7–3.96)
RVOT acceleration time (ms)	127.6±16.4
RVOT acceleration time <100 (ms)	1 (1.1)
6-min walk distance in m (N=72)	
Mean±standard deviation (range)	372±67.3 (150–550)
<300 m	5 (6.94)

Values are presented as mean±standard deviation (range), number (%), or median (interquartile range).
EDPAP: estimated diastolic pulmonary artery pressure, LV: left ventricle, MPA: mean pulmonary artery, RA: right atrium, RVEDD/LVEDD: right ventricular end-diastolic diameter/left ventricular end-diastolic diameter ratio, RVEDD: right ventricular end-diastolic diameter, RVOT: right ventricular outflow tract, TAPSE: tricuspid annular plane systolic excursion.

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Table 3. Comparison between cases with normal and high estimated systolic pulmonary artery pressure (N=94)

Variable	Estimated systolic pulmonary artery pressure		*p*-value
	Normal (<35 mmHg) (N=65)	Pulmonary hypertension (≥35 mmHg) (N=29)	
Age (yr)	7.6±3.6	7.8±3.1	0.6
Sex			0.6
Male	37 (56.9)	15 (51.7)	
Female	28 (43.1)	14 (48.3)	
Duration of portal hypertension (yr)	3.5 (0.5–13)	5 (0.5–12.5)	0.09
Cardiac manifestations			
Exercise intolerance	7 (10.8)	4 (13.8)	0.7
Dyspnea on exertion	0	3 (10.3)	0.03*
Cyanosis	0	2 (6.9)	0.09
Orthopnea	0	1 (3.4)	0.3
Endoscopic findings			
Mild (grade I)	40 (61.5)	11 (37.9)	
Moderate (grade II–III)	24 (36.9)	17 (58.6)	
Severe (grade IV)	1 (1.5)	1 (3.4)	0.03*
O_2 saturation	99.1±1	97.7±3.5	0.04*
6-min walk distance (m) (N=72)	372.4±64.5	371.3±74.6	0.9

Values are presented as mean±standard deviation (range), number (%), or median (interquartile range).
*p-value was considered significant at $p<0.05$.

Table 3 compares cases of pulmonary hypertension and those with normal pulmonary arterial pressure. Patients with pulmonary hypertension had more frequent dyspnea on exertion, lower O_2 saturation, and more severe variceal grades than those with normal pulmonary artery pressure. There were no statistically significant differences in the other cardiac manifestations between the groups.

Comparison of cases of portal hypertension due to a pre-hepatic cause and those secondary to chronic liver disease showed no significant difference in terms of the measured echocardiographic findings.

Table 4 presents the correlations between the echocardiographic results and age, duration of portal hypertension, and 6-MWD. Patient age was positively correlated with the RVEDD/LVEDD ratio and negatively correlated with the TAPSE Z-score. The duration of portal hypertension positively correlated with the RVEDD Z-score and negatively correlated with the TAPSE Z-score. In addition, the 6-MWD correlated negatively with EDPAP, RVEDD/LVEDD ratio, and RVEDD Z-score, but positively with RVOT.

The predictors of PH development in our study group were tested using univariate and multivariate regression analyses, as shown in **pghn-28-101**. High-grade varices (p=0.04; odds ratio [OR], 2.618; 95% CI) and low O_2 saturation (p=0.03; OR, 0.717; 95% CI) were predictors for developing pulmonary hypertension.

Table 4. Correlations between patient characteristics and 6-min walk distance with echocardiographic findings (N=94)

Variable	EPASP		EDPAP		RVEDD/LVEDD ratio		RVEDD Z-score		RA area Z-score		MPA Z-score		TAPSE Z-score		RVOT	
	r	*p*-value	r	*p*-value	r_s	*p*-value	r_s	*p*-value	r_s	*p*-value	r	*p*-value	r_s	*p*-value	r	*p*-value
Age (yr)	−0.1	0.5	−0.04	0.7	0.3	0.009*	0.1	0.2	−0.1	0.3	−0.2	0.08	−0.4	<0.001*	0.2	0.2
Duration of Portal hypertension (yr)	0.1	0.3	0.1	0.6	0.1	0.2	0.2	0.048*	0.04	0.7	0.06	0.6	−0.4	<0.001*	−0.1	0.6
6-min walk distance (m)	−0.2	0.05	−0.3	0.004*	−0.3	0.02*	−0.4	0.001*	−0.003	0.9	−0.2	0.2	0.03	0.8	0.2	0.04*

ESPAP: estimated systolic pulmonary artery pressure, EDPAP: estimated diastolic pulmonary artery pressure, RVOT: right ventricular outflow tract, LVEDD: left ventricular end-diastolic diameter, RVEDD: right ventricular end-diastolic diameter, RA: right atrium, MPA: mean pulmonary artery, TAPSE: tricuspid annular plane systolic excursion, r: Pearson coefficient, r_s: Spearman coefficient.
*p-value was considered significant at $p<0.05$.

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Table 5. Univariate and multivariate linear regression analysis for the different parameters affecting estimated systolic pulmonary artery pressure (N=94)

Variable	Univariate		Multivariate	
	p-value	OR (95% CI)	*p*-value	OR (95% CI)
Sex	0.6	1.233 (0.51–2.97)		
Age (yr)	0.8	1.015 (0.89–1.15)		
Duration of portal hypertension (yr)	0.15	1.115 (0.96–1.29)		
Moderate and severe grade of varices	0.04*	2.618 (1.06–6.45)	0.02*	3.099 (1.18–8.13)
Clubbing				
Grade 2	0.1	2.611 (0.74–9.16)		
Grade 3	0.9	1.088 (0.34–3.53)		
6-min walk distance (m)	0.9	1.000 (0.99–1.01)		
O_2 saturation	0.03*	0.717 (0.54–0.96)	0.02*	0.695 (0.51–0.94)
Dyspnea	0.99	-		
Exercise intolerance	0.67	1.326 (0.36–4.94)		
Orthopnea	0.9	-		
Cyanosis	0.9	-		

CI: confidence interval, OR: odds ratio.
*p-value was considered significant at $p<0.05$

Two of our patients had ESPAP >45 mmHg and were candidates for sildenafil. The first case was an 11-year-old female diagnosed with portal hypertension at age 2.5 years with grade III esophageal varices. She developed dyspnea on exertion and exercise intolerance at age 8 years. She had grade IV clubbing and her O_2 saturation was 88%. Her 6-MWD was 178 m, with an N-terminal pro-brain natriuretic peptide level of 845 pg/mL. The ESPAP was 50 mmHg, EDPAP was 30 mmHg, RVEDD Z-score was 5.4, RVEDD/LVEDD ratio was 0.64, RVOT acceleration time was 96 ms, and TAPSE Z-score was 0.41.

The other patient was an 11-year-old female who was diagnosed with portal hypertension at age 5 years and had grade IV esophageal varices. She developed dyspnea on exertion and exercise intolerance at age 9 years and subsequently developed orthopnea. She had grade III clubbing and her O_2 saturation was 96%. Her 6-MWD was 274 m, with an N-terminal pro-brain natriuretic peptide level of 1,280 pg/mL. Her ESPAP was 48 mmHg, EDPAP was 25 mmHg, RVEDD Z-score was 3.69, RVEDD/LVEDD ratio was 0.48, RVOT acceleration time was 110 ms, and TAPSE Z-score was –1.05.

DISCUSSION

This observational cross-sectional study included 94 children with portal hypertension from attendees of a tertiary center. Their ages ranged between 3–15 years, with a mean age of 7.7±3.4 years and a male-to-female ratio of 1.2:1. We aimed to assess the prevalence of POPH, a rare but devastating long-term complication of portal hypertension that has been poorly studied, and identify its clinical predictors in this high-risk group.

In our study, 29 (30.8%) patients had elevated ESPAP ≥35 mmHg; of these, ESPAP was between 35–45 mmHg in 27 (28.7%) patients and >45 mmHg in 2 (2.1%). The rates obtained in our study are much higher than those previously reported. A systematic review noted that 0.5% of children with portal hypertension and 0.9% of children with end-stage liver disease awaiting liver transplantation had POPH, which was confirmed by cardiac catheterization [24]. The prevalence of POPH in children is unknown, and the disease has been primarily reported in case series. Savale et al. [9] reported that patients with POPH represent 5–15% of

pulmonary hypertension patients. Besides, POPH was detected using morphological criteria in a pediatric autopsy population in 5.3% of all cases of portal hypertension [25].

Regarding manifestations in our study, 3.2% of cases had dyspnea on exertion, 2.1% had cyanosis, and 11.7% had exercise intolerance, whereas only one patient had orthopnea. All patients with dyspnea on exertion had an ESPAP >35 mmHg. Similarly, studies have reported that dyspnea at rest or during exercise is the most common presenting symptom in patients with POPH. Additional symptoms included palpitations, fatigue, chest pain, and syncope [26].

In our study, cases of extrahepatic portal vein obstruction and those secondary to chronic liver disease were comparable in terms of echocardiographic findings. There are limited case reports on children with POPH, including those with biliary atresia, portal vein thrombosis, focal nodular hyperplasia, and congenital hepatic fibrosis [3].

From our observations, the median duration from portal hypertension diagnosis to pulmonary pressure assessment was 4 years. The duration of portal hypertension was longer in patients with pulmonary pressure >35 mmHg than in those with normal pressure; however, the difference was not statistically significant. Duration showed a positive correlation with RVEDD and a negative correlation with the TAPSE Z-score. In contrast, Kawut et al. [27] observed a longer duration of underlying liver disease (6 years) before the detection of POPH during their case-control study, and performed pre-transplantation transthoracic echocardiography for enrolled cases.

In our cohort, the varices of II–IV grade were predictors for the presence of pulmonary hypertension (p=0.04; OR, 2.618; 95% CI). In addition, 58.6% of cases with ESPAP ≥35 mmHg had moderate grades of varices (grades II–III). In contrast, Ekmen and Cifci [28] reported no significant differences between the grades of esophageal varices and pulmonary artery pressure. They detected grade III varices in 70.3% of the patients with POPH.

Our results showed that O_2 saturation was significantly lower in patients with ESPSP ≥35 mmHg than in those with average measures. Low O_2 saturation was observed as a predictor for elevated ESPSP ≥35 mmHg (p=0.03; OR, 0.717; 95% CI). In Shao et al. [29], 28 (14.8%) out of 188 portal hypertension cases were diagnosed with POPH. They included cases with fingertip O_2 saturation <95%.

The mean 6-MWD of our study group was 372±67.3 m, and five (6.94%) cases had test results <300 m. The 6-MWD was slightly lower in patients with a high ESPSP >35 mmHg. In addition, the 6-MWD was positively correlated with RVOT and negatively correlated with the EDPAP, RVEDD/LVEDD ratio, and RVEDD Z-score. Our 6-MWD results were shorter than the 6-MWD mean of 342±91 m reported by the Dutch national network [30]. A decline in 6-MWD in adults with pulmonary artery hypertension predicts future clinical worsening of cardiac problems with high specificity [31].

Our patients with moderate-to-severe POPH who received treatment had high NT-proBNP levels of 845 pg/mL and 1,280 pg/mL. Dasgupta et al. [32] recommended NT-proBNP as a valuable adjunct diagnostic tool for pulmonary hypertension in the pediatric population. In their study, NT-pro BNP correlated negatively with the TAPSE Z-score, right ventricular fractional area change, and pulmonary artery acceleration time.

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We used an echocardiographic ESPAP cutoff value of 45 mmHg to define moderate-to-severe pulmonary hypertension. Additional findings, such as dyspnea on exertion, right ventricular dilatation, decreased RVOT acceleration time, high NT-pro BNP, and low 6-MWD, were used to decide on pharmacological therapy initiation. Similarly, using a cutoff value of 50 mmHg for RSVP has considerable sensitivity of 97% and specificity of 77% for identifying patients with moderate-to-severe POPH [33].

In our studied cases with moderate-to-severe pulmonary hypertension (ESPAP >45 mmHg), we initiated phosphodiesterase-5 inhibitor at a dose of 0.25 mg/kg/ds as a monotherapy. No satisfactory clinical or echocardiographic improvement was observed. The failure to achieve a good response can be attributed to late-stage liver disease, multiple comorbidities, or the need for a combined drug regimen. The 6th World Symposium on Pulmonary Hypertension underlined the residual role of monotherapy with phosphodiesterase-5 inhibitors in a subset of patients, including those with POPH. These medications are usually selected because they do not cause hepatotoxicity [9].

Two patients with ESPAP >45 mmHg died within the study period despite an evidence-based approach to care owing to complications of long-standing liver disease and portal hypertension. Tingo et al. [34] also reported a high mortality rate during follow-up (3 of 5 mortality cases). The severity of underlying liver disease determines the survival of patients with POPH [9].

The sequence from hepatopulmonary syndrome to POPH was observed in patients with cirrhosis and those with portal vein obstruction [35]. Portosystemic shunts, rather than portal hypertension, are key risk factors for POPH development. They also support the role of an injured pulmonary artery endothelium secondary to an increase in pulmonary blood flow, which increases the risk of pulmonary hypertension as described in Eisenmenger syndrome [36]. POPH precession was reported in 6 of 98 patients with liver disease who presented with an episode of hypoxemia due to hepatopulmonary syndrome in childhood [24].

Screening for POPH using transthoracic echocardiography is recommended by The American Association for the Study of Liver Diseases and the European Respiratory Society/European Society of Cardiology for all patients evaluated for liver transplantation and symptomatic cirrhotic patients with portal hypertension. The screening age was not precisely defined; however, POPH has been reported in children as young as 2.5 years [6,37]. Early diagnosis and management of POPH are essential to improve the survival rate and increase the chances of successful liver transplantation.

The limitations of this study included its single-center design with a limited number of cases and the unfeasibility of performing the 6-MWD in infants and young children.

In conclusion, pulmonary hypertension was detected in 30.8% of children with portal hypertension, of whom 2.1% were candidates for treatment. The duration since the diagnosis of portal hypertension was longer in patients with pulmonary hypertension than in those with normal pressure, and it correlated positively with RVEDD and negatively with the TAPSE Z-score. The 6-MWD is an excellent indicator of a patient's functional status; it correlated positively with RVOT and negatively with the EDPAP, RVEDD/LVEDD ratio, and RVEDD Z-score. The NT-pro BNP level was high in patients with moderate-to-severe pulmonary hypertension. Moderate-to-severe esophageal varices (grades II-IV) and low O_2 saturation were significant clinical predictors of pulmonary hypertension.

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