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Portal Hypertension in Children: A Tertiary Center Experience in Turkey

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ABSTRACT

Purpose: Portal hypertension (PH) and its complications have a significant impact on morbidity and mortality. This study aimed to evaluate the etiology; clinical, laboratory, and endoscopic findings; treatment approaches; long-term outcomes; and prognosis of pediatric PH.
Methods: This retrospective study included 222 pediatric patients diagnosed with PH between 1998 and 2016, and data encompassing clinical, laboratory, and radiological features; treatments; and complications were analyzed.
Results: The most common causes of PH were portal vein thrombosis (20.3%), progressive familial intrahepatic cholestasis (18.9%), and biliary atresia (12.2%). Among the enrolled patients, 131 (59.0%) were included in the cirrhotic group and 91 (41.0%) in the non-cirrhotic group. Hepatomegaly and increased transaminase levels were more frequent in the cirrhotic group than in the non-cirrhotic group. Additionally, portal gastropathy, esophageal varices, and variceal bleeding were more frequent in the non-cirrhotic group, whereas ascites, hepatopulmonary syndrome and hepatic encephalopathy were more common in the cirrhotic group. The incidence of hepatomegaly was higher in the presinusoidal group than in the prehepatic group (p<0.001). Hyperbilirubinemia was more frequent in the prehepatic group (p=0.046). The frequency of esophageal varices was similar between the prehepatic and presinusoidal groups; however, variceal bleeding was more frequent in the prehepatic group (p=0.002).
Conclusion: Extrahepatic portal vein obstruction, genetic-metabolic diseases, and biliary atresia were the most prevalent causes of PH in our country. In patients with PH, hepatomegaly, increased transaminase levels, and synthesis dysfunction were suggestive of cirrhotic PH. Notably, PH in patients without cirrhosis might be more severe than that in those with cirrhosis.

Keywords: Portal hypertension; Child; Esophageal and gastric varices; Liver cirrhosis; Hypertension

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INTRODUCTION

Portal hypertension (PH) is defined as an increase in the pressure of the portal vein (PV) or the pressure difference between the PV and inferior vena cava [1]. The common causes of PH in children include extrahepatic portal vein obstruction (EHPVO), biliary atresia, alpha 1 antitrypsin deficiency, and autoimmune hepatitis [2]. However, the etiology varies from country to country. While intrahepatic causes, such as biliary atresia, are prevalent in developed countries, extrahepatic causes, such as EHPVO, are more common in developing countries [3].

PH and its complications have a significant impact on morbidity and mortality. Esophageal varices and variceal bleeding are crucial complications of PH [4,5]. The presence of varices is the most important factor in determining the treatment for PH. Regardless of the etiology, beta-blockers and endoscopic modalities are frequently used to treat esophageal varices. Surgical shunt procedures are used in patients with prehepatic and presinusoidal PH who are unresponsive to medical and endoscopic treatments. In patients with end-stage liver disease, liver transplantation is the primary treatment option [6].

Most data related to the etiology, clinical features, diagnosis, management, and outcomes of PH are primarily obtained from adult studies [7,8]. Notably, few fundamental differences exist between PH in children and adults. First, liver disease in children begins early and progresses rapidly, leading to cirrhosis and PH. In most cases, split-organ transplants are required to manage this condition. Second, the etiology of PH in children involves prehepatic and presinusoidal diseases, which can have different effects on the management and outcomes of PH [9].

Considering the limited available data on PH in children, in this study, we aimed to evaluate the etiology; clinical, laboratory, and endoscopic findings; treatment approaches; long-term outcomes; and prognosis of PH in pediatric patients.

MATERIALS AND METHODS

This retrospective study included patients ≤18 years who were diagnosed with PH at the Gazi University Faculty of Medicine, Department of Pediatric Gastroenterology between January 1, 1998 and December 31, 2016. Information on clinical, laboratory, and radiologic findings; therapies; and complications of the patients were obtained from the medical records.

The etiology of PH in the patients was recorded, and the patients were categorized into cirrhotic and non-cirrhotic groups based on clinicopathological criteria. Additionally, anatomical subgroups were formed, including prehepatic, hepatic (presinusoidal, sinusoidal, postsinusoidal), and posthepatic groups. Comparative analyses between these groups, along with an assessment of clinical, laboratory, endoscopic, and radiological factors facilitated subgroup differentiation and identification of factors affecting prognosis.

Statistical analyses

Normally distributed continuous variables were expressed as mean±standard deviation, and non-normally distributed continuous variables were expressed as median (25–75%). Paired group comparisons for continuous variables were conducted using the Student's *t*-test

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for normally distributed data and the Mann–Whitney U-test for non-normally distributed data. Categorical data were evaluated using the chi-square or Fisher's exact tests. Statistical significance was set at $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Co.).

Ethical approval for the study was granted by the Gazi University Ethics Committee at a meeting dated March 7, 2017, numbered 03, and research code 2017-113. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. As this was a retrospective study, the requirement for informed consent was waived.

RESULTS

A total of 222 patients were included in the study. Demographic, clinical, and laboratory characteristics of the patients are summarized in **Table 1**. The most common causes of PH were portal vein thrombosis in 45 (20.3%), progressive familial intrahepatic cholestasis (PFIC) in 42 (18.9%), and biliary atresia in 27 (12.2%) patients (**Fig. 1**).

Non-cirrhotic group vs. cirrhotic group

In the cirrhotic group, the median age at presentation was 54.9 (14.1–134.9) months, which was significantly lower than that in the non-cirrhotic group (100 [44.1–174.1] months) ($p<0.001$). Although the frequency of hepatomegaly was significantly higher in the cirrhotic group than in the non-cirrhotic group ($p<0.001$), the frequency of splenomegaly was similar in both the groups. However, the spleen z-score was higher in the non-cirrhotic group ($p=0.022$) than in the cirrhotic group. Leukopenia ($p<0.001$) and thrombocytopenia ($p<0.001$) were significantly more prevalent in patients with non-cirrhotic PH, whereas

Table 1. Demographic, clinical, and laboratory characteristics of all patients

Features	All patients (N=222)	Cirrhotic group (N=131)	Non-cirrhotic group (N=91)	*p*-value
Sex, male	133 (59.9)	72 (54.9)	61 (67.0)	0.071
Age at presentation (mo)	61.5 (14–143)	24 (6–120)	96 (35–167)	<0.001
Age at diagnosis (mo)	76.9 (27–154.1)	54.9 (14.1–134.9)	100 (44.1–174.1)	<0.001
Follow-up (mo)	21 (7–54)	24 (6.2–64.7)	20 (7–45)	0.380
Clinical features				
Hepatomegaly	145 (65.3)	111 (84.7)	34 (37.8)	<0.001
Splenomegaly	200 (90.1)	120 (91.6)	80 (88.9)	0.641
Spleen z-score	4.6 (2.8–7.9)	4.5 (2.4–5.2)	5.1 (3.3–7.2)	0.022
Laboratory features				
Leukopenia	52/218 (40.6)	18/128 (14.1)	34/90 (37.8)	<0.001
Anemia	119/218 (54.6)	72/128 (56.3)	47/90 (52.2)	0.556
Thrombocytopenia	137/218 (62.8)	68/128 (53.1)	69/90 (76.7)	<0.001
Elevated transaminase	150/216 (69.4)	112/127 (88.2)	38/89 (42.7)	<0.001
Hyperbilirubinemia	96/215 (44.6)	83/127 (65.4)	13/88 (14.8)	<0.001
Hypoalbuminemia	20/216 (9.2)	17/127 (13.4)	3/89 (3.4)	0.012
Prolonged coagulation	97/213 (45.5)	68/127 (53.5)	29/86 (33.7)	0.004
Portal hypertension complications				
Ascites	31 (13.9)	25 (19.1)	6 (6.6)	0.001
Portal gastropathy	92 (41.4)	39 (41.5)	53 (61.6)	0.007
Esophagus varices	143 (64.4)	59 (67)	84 (96)	<0.001
Variceal bleeding	75 (33.8)	19 (14.5)	56 (61.5)	<0.001
Hepatopulmonary syndrome	8 (3.6)	8 (6.1)	0 (0.0)	0.022
Hepatorenal syndrome	2 (0.9)	2 (1.5)	0 (0.0)	0.514
Hepatic encephalopathy	7 (3.1)	7 (5.3)	0 (0.0)	0.043
Portal biliopathy	2 (0.9)	0 (0.0)	2 (1.4)	0.167

Values are presented as number (%) or median (interquartile range).

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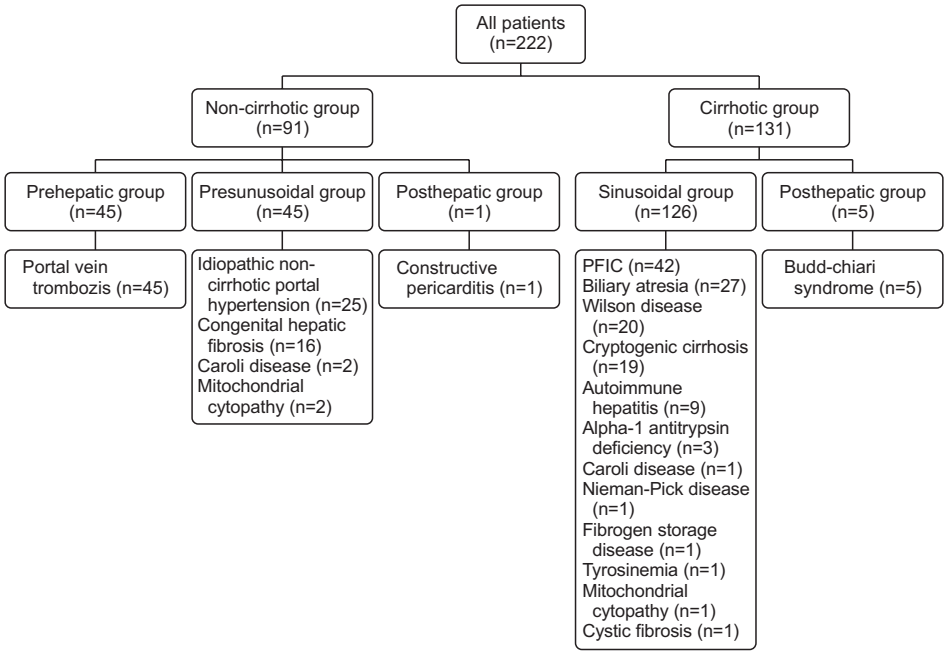

Fig. 1. Distribution of portal hypertension causes according to portal hypertension types.
PFIC: progressive familial intrahepatic cholestasis.

elevated transaminase levels (p<0.001), hypoalbuminemia (p=0.012), hyperbilirubinemia (p<0.001), and frequency of prolonged coagulation (p=0.004) were more common in the patients with cirrhotic PH (**Table 1**).

On evaluating the complications of patients with cirrhotic and non-cirrhotic PH, we observed that portal gastropathy (p=0.007), esophageal varices (p<0.001), and variceal bleeding (p<0.001) were significantly frequent in the non-cirrhotic group, whereas ascites (p=0.001), hepatopulmonary syndrome (p=0.022), and hepatic encephalopathy (HE) (p=0.043) was more common in the cirrhotic group (**Table 1**).

The treatments used for primary prophylaxis were similar between the two groups. Endoscopic treatment (band ligation and sclerotherapy) (p<0.001) and shunt surgery (p<0.001) were performed more frequently in the non-cirrhotic group, and liver transplantation (p<0.001) was performed more frequently in the cirrhotic group (**Table 2**).

Prehepatic group vs. presinusoidal group

The patients in the non-cirrhotic group were anatomically categorized into prehepatic (45 patients), presinusoidal (45 patients), and posthepatic (1 patient) groups. In the cirrhotic group, 126 patients had sinusoidal PH and 5 had posthepatic PH. No patients had postsinusoidal PH (**Fig. 1**). When patients with non-cirrhotic portal PH were anatomically grouped, only the prehepatic and presinusoidal groups were compared (**Table 3**) because of the insufficient number of patients in the posthepatic group (n=1) for a statistical comparison.

Significant differences were observed between the anatomically classified groups in terms of age at presentation and frequency of hepatomegaly. Although the age at onset was lower in the prehepatic group (p=0.004), the frequency of hepatomegaly was higher in the presinusoidal group (p<0.001). The laboratory findings differed only in terms

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Table 2. Prophylaxis and treatment characteristics of patients

Prophylaxis and treatment	All patients (N=222)	Cirrhotic group (N=131)	Non-cirrhotic group (N=91)	*p*-value
Primer prophylaxis				
Propranolol	54 (24.3)	31 (23.6)	23 (25.2)	0.789
Endoscopic band ligation	2 (0.9)	0 (0.0)	2 (2.2)	0.086
Endoscopic sclerotherapy	0 (0.0)	0 (0.0	0 (0.0)	-
Secondary prophylaxis				
Propranolol	68 (30.6)	15 (11.5)	53 (58.2)	0.354
Endoscopic treatment	45 (20.3)	9 (6.9)	36 (39.6)	<0.001
Band ligation	37 (16.7)	8 (6.1)	29 (31.9)	<0.001
Sclerotherapy	11 (5.0)	1 (0.8)	10 (11.0)	0.001
Radiological and surgical treatments				
TIPS	2 (0.9)	2 (1.5)	0 (0.0)	0.514
Shunt surgery	38 (17.1)	0 (0.0)	38 (41.8)	<0.001
Distal splenorenal shunt	20 (9.0)	0 (0.0)	20 (22.0)	<0.001
Proximal splenorenal shunt	18 (8.1)	0 (0.0)	18 (19.8)	<0.001
Liver transplantation	32 (14.4)	31 (23.7)	1 (1.1)	<0.001

Values are presented as number (%).
TIPS: transjugular intrahepatic portosystemic shunt.

of hyperbilirubinemia, which was more frequent in the prehepatic group than in the presinusoidal group (p=0.046) (**Table 3**).

The frequency of esophageal varices was similar between the prehepatic and presinusoidal groups (p>0.05); however, variceal bleeding was more common in the prehepatic group (p=0.002) (**Table 3**).

The median follow-up period was 21 (7–54) months, and 118 patients underwent follow-up. During the follow-up period, 6.7% (3/45) patients with prehepatic PH, 4.4% (2/45) patients with presinusoidal PH, and 9.2% (12/131) of patients with cirrhotic PH succumbed

Table 3. Demographic, clinical, and laboratory characteristics of patients with prehepatic and presinusoidal PH

Features	Prehepatic group (N=45)	Presinusoidal group (N=45)	*p*-value
Sex, male	32 (71.1)	29 (64.4)	0.413
Age at presentation (mo)	62 (31–112)	147 (62–181)	0.004
Follow-up (mo)	23 (4–47)	15.5 (8–41)	0.850
Clinical features			
Hepatomegaly	8 (18.2)	25 (55.6)	<0.001
Splenomegaly	37 (84.1)	43 (95.6)	0.192
Spleen z-score	4.7 (2.3–7.7)	5.1 (3.4–7.2)	0.552
Laboratory features			
Leukopenia	16 (35.6)	18 (40.0)	0.787
Anemia	22 (48.9)	25 (55.6)	0.680
Thrombocytopenia	32 (71.1)	37 (82.2)	0.387
Elevated transaminase	18 (40.0)	19 (42.2)	0.877
Hyperbilirubinemia	9 (20.0)	3 (6.7)	0.046
Hypoalbuminemia	2 (4.4)	1 (2.2)	0.608
Prolonged coagulation	16 (35.8)	13 (29.5)	0.402
Portal hypertension complications			
Ascites	4 (8.9)	2 (4.4)	0.434
Portal gastropathy	25 (55.6)	28 (62.2)	0.905
Esophagus varices	42 (93.3)	42 (93.3)	>0.999
Variceal bleeding	35 (77.8)	21 (46.7)	0.002
Hepatopulmonary syndrome	0 (0.0)	0 (0.0)	-
Hepatorenal syndrome	0 (0.0)	0 (0.0)	-
Hepatic encephalopathy	0 (0.0)	0 (0.0)	-
Portal biliopathy	1 (2.2)	1 (2.2)	>0.999

Values are presented as number (%) or median (interquartile range).
PH: portal hypertension.

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to death. The cause of death in the prehepatic group was tuberculous meningitis (n=1), hepatoblastoma (n=1), and post-liver transplant complications due to Budd–Chiari syndrome (n=1). In the presinusoidal group, one patient died due to pulmonary hemorrhage (who was also being followed-up for Osler–Weber–Rendu), and the other died due to diffuse mesenteric ischemia, secondary to vasculitis (n=1).

DISCUSSION

In the present study, approximately 50% of the patients exhibited sinusoidal PH, followed prehepatic and presinusoidal PH. EHPVO, idiopathic non-cirrhotic PH, and congenital hepatic fibrosis constituted the major causes of non-cirrhotic PH. In addition, PFIC was the most common cause of cirrhotic PH. Studies have shown that EHPVO and biliary atresia are the most common causes of PH in children [10]. The etiologies of PH in our country differ from those in other developed countries. In addition to EHPVO and biliary atresia, genetic diseases, such as PFIC, Wilson's disease, and congenital hepatic fibrosis were among the major and common causes of PH. This may be attributed to the relatively high frequency of consanguineous marriages in our country compared to developed countries [11,12].

Splenomegaly detected incidentally in children is one of the most common findings of pediatric PH [13]. In our study, 90% of the patients exhibited splenomegaly. Similar to a previous study [14], no difference in the frequency of splenomegaly was observed between the groups; however, the spleen sizes were more extensive in the non-cirrhotic group than in the cirrhotic group. Regarding hepatomegaly, the frequency of hepatomegaly was higher in the cirrhotic group than in the non-cirrhotic group. Anatomically, the frequency of hepatomegaly increased from the prehepatic group to the presinusoidal group. Considering that the patients in the cirrhotic group had intrahepatic and posthepatic etiologies, whereas those in the non-cirrhotic group had prehepatic and presinusoidal etiologies, hepatomegaly was expected to be more common in the cirrhotic group.

Cytopenia, especially thrombocytopenia, is frequently observed as a manifestation of hypersplenism in PH. Hypersplenism decreases the production of erythropoietin and thrombopoietin synthesized in the liver, and blood loss resulting from bleeding plays a role in the pathogenesis of cytopenia [15]. The frequencies of leukopenia and thrombocytopenia were higher in the non-cirrhotic group than in the cirrhotic group. Similar to the relationship between spleen size and PH severity, leukopenia and thrombocytopenia are hypothesized to be associated with PH severity.

In patients with PH, liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], Gamma glutamyltransferase [GGT], and alkaline phosphatase [ALP]) and synthesis functions (bilirubin, albumin, prothrombin time [PT], and INR) constitute an essential part of laboratory examinations. Most patients with non-cirrhotic PH exhibit normal liver function test results; however, some patients may display abnormalities in liver enzyme levels, PT, and albumin levels [16,17]. Peter et al. [14] observed that ALT, AST, ALP, and bilirubin levels are higher, whereas albumin levels are lower in children with cirrhosis than in those without cirrhosis.

In our study, the proportion of patients with elevated transaminase levels, hypoalbuminemia, hyperbilirubinemia, and coagulation disorders was significantly higher among those with

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cirrhosis than in those without cirrhosis. Hepatocellular damage was expected to be more common in patients with cirrhotic PH than in those with non-cirrhotic PH, resulting in elevated transaminase levels and impaired synthesis functions. In chronic liver diseases, hepatocellular synthesis dysfunction leads to decreased production of anticoagulant factors and albumin [18], and PT and INR are directly proportional to hepatocellular damage [19]. In patients with cirrhotic PH, coagulant and anticoagulant factors decrease and PT and INR values are prolonged [18-20].

PH can give rise to various complications, including esophageal varices and secondary bleeding to varices, hypersplenism, ascites, hepatorenal syndrome, HE, and pulmonary and biliary complications [21]. Esophageal varices and gastrointestinal bleeding secondary to the varices are key findings in patients with PH [22]. Although mortality associated with gastrointestinal bleeding is lower in children than that in adults, acute gastrointestinal bleeding due to varicose veins is a critical emergency condition [23]. In our study, esophageal varices were detected in approximately 75% of the patients, and gastrointestinal bleeding secondary to the varices developed in approximately 50% of the patients with esophageal varices. Gugig and Rosenthal [24] reported that the risk of gastrointestinal bleeding is 22% in cirrhotic children and 15–25% in patients with biliary atresia. Studies conducted involving patients with EHPVO have revealed a varying history of gastrointestinal bleeding ranging from 40% to 90%. In our study, varicose bleeding rates were similar to those reported in the literature for both the cirrhotic and non-cirrhotic groups [25-27]. The varicose bleeding rates were higher in the non-cirrhotic group than in the cirrhotic group in the current study. The activation of compensatory mechanisms against PH due to a chronic process in the cirrhotic group may explain the severity of the complications observed in the non-cirrhotic PH.

Portal gastropathy is histologically defined as a macroscopic alteration of the gastric mucosa, characterized by mucosal and submucosal vascular ectasia and dilatation without inflammatory changes [28,29]. A study investigating the presence of portal gastropathy in children with PH reported no difference in the frequency of portal gastropathy between patients with cirrhosis (61%) and those without cirrhosis (54%), after 2-year follow-up [30]. In another study, no association was observed between the frequency of portal gastropathy and causes of PH [31]. In our study, the incidence of portal gastropathy was higher in patients with non-cirrhotic PH than in those with cirrhotic PH (p=0.007). The difference between our results and the literature may be related to differences in PH severity among the subgroups.

Ascites is characterized by the accumulation of serous fluid in the peritoneal cavity and is usually observed in patients who develop PH due to cirrhosis [2]. Gugig et al. [24] reported that the frequency of ascites in pediatric patients with PH is 7–21%. Consistent with the previously reported rates, the frequency of ascites in our study was approximately 14%, which was significantly higher in the cirrhotic group than in the non-cirrhotic group. Peter et al. [14] reported that the frequency of ascites is higher in pediatric patient with cirrhosis than in those with extrahepatic PH. Goel et al. [32] reported ascites in 22.7% of patients with non-cirrhotic intrahepatic PH and in 40% of patients with cirrhotic intrahepatic PH.

The treatment of PH includes treatment of the underlying cause and managing its complications. Since the treatment of the underlying cause is beyond the scope of our study, it is not discussed here. Esophageal varices and variceal bleeding are among the most common complications and form the basis of PH management [2]. Medical, endoscopic, radiological, and surgical treatments were administered to our patients for managing esophageal varices (**Table 2**).

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Propranolol and, on rare occasions, endoscopic band ligation are used for primary prophylaxis, whereas propranolol and endoscopic and surgical treatments are preferred for secondary prophylaxis. In our study, hemorrhage recurred in 50% of the patients after propranolol administration and endoscopic treatments. Beta-blockers are not recommended for pediatric use due to insufficient evidence regarding their appropriate dose, efficacy, and safety [33-36]. However, many clinicians consider primary prophylaxis a high risk of death due to variceal bleeding. We observed that propranolol was administered for primary prophylaxis in 24.3% of the patients and endoscopic band ligation was used in only two patients with non-cirrhotic PH (**Table 2**). Conversely, an evidence-based consensus is available concerning the indications for endoscopic methods for secondary prophylaxis in children with cirrhosis [37]. Our study, revealed that band ligation treatment was more frequently used than sclerotherapy for secondary prophylaxis. However, in young children, in whom tape devices cannot be used with small pediatric endoscopes, sclerotherapy is the only viable option for the management of large varicose veins [38]. Recently, varicose band ligation has become more popular, which does not involve injecting sclerosing agents into or around the varicose veins for detecting endoscopic obliteration and is considered superior to sclerotherapy in terms of efficacy and safety [38,39]. Therefore, band ligation is often recommended as primary and secondary prophylaxis [35].

Considering the surgical treatments administered to our study patients, liver transplantation was opted for patients with cirrhosis, whereas selective portosystemic shunt surgeries were preferred for those without cirrhosis. Selective portosystemic shunt surgery (distal and proximal splenorenal shunts) is recommended in patients with non-cirrhotic PH who have variceal bleeding, hypersplenism, and a risk of splenic rupture unresponsive to medical and endoscopic treatments [40]. In our study, approximately 50% of the patients with non-cirrhotic PH underwent shunt surgery during long-term follow-up, and 23.6% of our patients with cirrhosis underwent liver transplantation. This prevalence may be related to the fact that our clinic serves as a reference center.

The prognoses for patients with non-cirrhotic PH were better than those with cirrhotic PH with similar portal venous pressure values. This is because of the longer preservation of liver functions in patients without cirrhotic PH than in those without non-cirrhotic PH [17]. In our study, 6.7%, 4.4%, and 9.2% of patients with prehepatic, presinusoidal, and cirrhotic PHs, respectively, succumbed to death; the mortality rate was higher in the cirrhotic group than in the non-cirrhotic group.

In the existing literature, data on PH in children are limited. With this retrospective study, we aimed to investigate the demographic, clinical, laboratory, and treatment characteristics of pediatric patients diagnosed with PH at a tertiary center. In conclusion, EPHVO, genetic-metabolic diseases, and biliary atresia were the most common causes of PH in our country. In patients with PH, hepatomegaly, increased transaminase levels, and synthesis dysfunction were suggestive of cirrhotic PH. Finally, complications of PH, such as esophageal varices, variceal bleeding, and portal gastropathy, as well as the requirements endoscopic and shunt surgery treatment were more common in the non-cirrhotic group than in the cirrhotic group. In light of this information, it can be inferred that PH-related complications manifest more severely in patients with non-cirrhotic PH than in those with cirrhotic PH. In addition, mortality and liver transplantation were more frequent in patients with cirrhotic PH, indicating a less favorable prognosis for these patients.

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