Natural Course of Pediatric Portal Hypertension

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The etiology of portal hypertension (pHTN) in children differs from that of adults and may require different management strategies. We set out to review the etiology, management, and natural history of pHTN at a pediatric liver center. From 2008 to 2018, 151 children and adolescents with pHTN were identified at a free-standing children’s hospital. Patients were stratified by etiology of pHTN (intrahepatic disease [IH], defined as cholestatic disease and fibrotic or hepatocellular disease; extrahepatic disease [EH], defined as hepatic vein obstruction and prehepatic pHTN). Patients with EH were more likely to undergo an esophagoduodenscopy for a suspected gastrointestinal bleed (77% vs. 41%; \( P < 0.01 \)). Surgical interventions differed based on etiology (\( P < 0.01 \)), with IH more likely resulting in a transplant only (65%) and EH more likely to result in a shunt only (43%); 30% of patients with IH and 47% of patients with EH did not undergo an intervention for pHTN. Kaplan-Meier analysis revealed a significant increase in mortality in the group that received no intervention compared to shunt, transplant, or both and lower mortality in patients with prehepatic pHTN compared to other etiologies (\( P < 0.01 \) each). Multivariate analysis revealed increased odds of mortality in patients with refractory ascites (odds ratio [OR], 4.34; 95% confidence interval [CI], 1.00, 18.88; \( P = 0.05 \)) and growth failure (OR, 13.49; 95% CI, 3.07, 58.99; \( P < 0.01 \)). Conclusion: In this single institution study, patients with prehepatic pHTN had better survival and those who received no intervention had higher mortality than those who received an intervention. Early referral to specialized centers with experience managing these complex disease processes may allow for improved risk stratification and early intervention to improve outcomes. (Hepatology Communications 2020;4:1346-1352).
to benefit from liver transplantation. Nonetheless, these scores are imperfect, often times underestimating mortality, nor can they provide specific guidance for the treatment of pHTN. These discrepancies may lead to a delay in life-saving interventions; this emphasizes the need to better define outcomes and predictors of severity in this disease process. Thus, we set out to describe the etiology, management, and natural history of pediatric pHTN. Secondary objectives included understanding the impact of interventions, survival analysis, and determination of predictors of mortality in our patient population.

Participants and Methods

PATIENT POPULATION

A retrospective review was performed of all patients under 18 years of age with newly diagnosed pHTN between 2008 and 2018 at Cincinnati Children's Hospital Medical Center (CCHMC), a free-standing children's hospital with institutional experience caring for children with advanced liver disease as well as a multidisciplinary liver transplant service. Patients were identified using a combination of the International Statistical Classification of Diseases and Related Health Problems (ICD-9 and 10) codes and cross-referenced with a query of an institutional radiology database for "portal hypertension" and variants thereof. Each patient was stratified into one of the following etiologies of pHTN: cirrhosis induced by cholestatic disease (CD; including biliary atresia, neonatal cholestasis, progressive familial intrahepatic cholestasis type 2, total parenteral nutrition induced cholestasis, and Alagille syndrome), fibrotic or hepatocellular disease (HFD; including cystic fibrosis, congenital hepatic fibrosis, and alpha-1 antitrypsin deficiency), hepatic vein obstruction (HVO; including Budd-Chiari and right-sided heart failure), or prehepatic pHTN caused by portal vein obstruction or portal vein sclerosis (PRE). Patients were then grouped into two categories to facilitate analysis of interventions. Patients with intrahepatic disease were comprised of those with CD or HFD, and patients with extrahepatic disease were comprised of those with HVO or PRE. Three patients with portal vein thrombosis were excluded due to confounding diagnoses of hepatoblastoma, acute megakaryocytic leukemia, or short gut syndrome. Appropriate approval from the CCHMC Institutional Review Board (IRB) was obtained before the study (IRB number 2017-6708).

STUDY VARIABLES AND DEFINITIONS

Etiology, disease course, and interventions were assessed. Study variables included age at diagnosis, duration of follow-up, presence of refractory ascites, surgical and endoscopic interventions, development, and mortality. Refractory ascites was assessed using hepatology notes indicating failure of medical management and need for recurrent paracentesis. Endoscopic analysis included pre-operative esophagogastroduodenoscopy (EGD) for suspected gastrointestinal bleed, findings of pre-operative gastrointestinal bleed, mean number of EGDs, endoscopic intervention (such as banding or sclerotherapy), mean number of interventions, and presence of varices. Surgical
interventions were categorized as orthotopic liver transplantation, shunt creation, transplantation after shunt creation, or no intervention. Abnormal development and cognitive delay were evaluated in the clinic setting and based on reaching age-appropriate milestones. Growth failure was determined as having height and/or weight below the second percentile according to the Centers for Disease Control and Prevention Clinical Growth Charts for children ages 2 and older.\textsuperscript{(8,9)} Given the variation in time of presentation, variation in imaging, and retrospective nature of the study, laboratory values and measurement of splenomegaly were not evaluated.

OUTCOMES AND STATISTICAL ANALYSIS

The primary outcome was overall survival. Secondary outcomes included determination of the impact of invasive interventions or medical management. Outcomes were assessed based on etiology and mortality. Continuous variables are represented as median and interquartile range (IQR). Categorical variables are represented as a percentage of the population (n, %). Analysis was performed using Fisher’s exact test for categorical variables and Kruskal-Wallis test for continuous variables. Statistical significance was set at $P < 0.05$. Time-to-event (death) analyses were performed with the use of Kaplan-Meier estimates and were compared with the use of the log-rank test. Multivariable logistic regression was used to evaluate predictors of mortality. The following characteristics were considered for inclusion in the final model: age, sex, race, refractory ascites, pre-operative EGD, varices, intervention type, growth failure, abnormal development, cognitive delay, and pHTN etiology.

Results

DEMOGRAPHICS

Between 2008 and 2018, 151 patients were diagnosed with pHTN (Table 1). Criteria for diagnosis included upper gastrointestinal bleed with presence of varices, presence of ascites, or splenomegaly on physical examination or imaging without a hemato logic cause. The median age of diagnosis was 0.5 years (IQR, 0.1-1.4). Of these patients, 71 (47%) were male patients and 103 (68.2%) were white, 25 (16.6%) were black, 13 (8.6%) were Hispanic, and 10 (6.6%) were Asian. CD was the most common etiology of pHTN and was seen in 105 (69.5%) patients, followed by PRE (26, 17.2%), HFD (16, 10.6%), and HVO (4, 2.6%). In the entire cohort, 81 (53.6%) patients eventually underwent a transplant, 14 (9.3%) underwent a shunt, 6 (4%) underwent both a transplant and shunt, and 50 (33.1%) did not undergo any surgical intervention associated with pHTN. Twenty-two patients (14.6%) died during the study period.

ANALYSIS BY ETIOLOGY

We next examined differences in treatment and outcomes based on each etiology. Patients were stratified as having intrahepatic (CD or HFD) or extrahepatic (HVO or PRE) disease. There were no differences in sex, race, or years of follow-up between groups (Table 1). Patients who had intrahepatic disease (0.4 years at diagnosis; IQR, 0.1-1.0) as the etiology of pHTN were diagnosed with pHTN earlier in life than those with extrahepatic disease (2.9 years at diagnosis; IQR, 0.9-6.0; $P < 0.01$). Patients with intrahepatic disease (n = 41, 33.9%) were also more likely to have refractory ascites than those with extrahepatic disease (n = 4, 13.3%; $P = 0.03$). No differences were found between groups regarding growth failure, abnormal development, or cognitive delay.

Endoscopic and operative interventions varied based on etiology. Twenty-three (76.7%) patients in the extrahepatic group underwent an EGD for a suspected upper gastrointestinal bleed compared to 50 (41.3%) in the intrahepatic group ($P < 0.01$). Patients in the extrahepatic group also underwent more endoscopic interventions compared to patients in the intrahepatic group (2 vs. 0; $P < 0.01$) and were more likely to have esophageal varices (75% vs. 40.5%; $P < 0.01$). More patients with extrahepatic disease were found to have gastrointestinal bleeding (53.3% vs. 32.2%; $P = 0.04$). Eventually, the etiology of disease led to variations in surgical intervention. Seventy-nine (65.3%) patients with intrahepatic disease required a transplant alone compared to 2 (6.7%) patients with extrahepatic disease (secondary to a vascular anomaly of the liver or idiopathic end-stage liver disease) ($P < 0.01$). In contrast, 43.3% (n = 13) of patients with extrahepatic disease underwent an operative shunt.
Thirty-six (29.8%) patients with intrahepatic disease and 14 (46.7%) patients with extrahepatic disease did not undergo any intervention.

Of the patients who underwent a shunt, 8 underwent a mesorex shunt, 3 a distal splenorenal shunt, 2 a mesocaval shunt, and 1 a transjugular intrahepatic portosystemic shunt (TIPS). Of the patients who underwent a transplant after shunt, 2 of these patients underwent a portocaval shunt, 2 a mesorex shunt, 1 a distal splenorenal shunt, and 1 a TIPS. Outcomes and analysis of this cohort at our institution have been published.\(^{(10)}\)

**TABLE 1. DEMOGRAPHICS AND ANALYSIS OF OUTCOMES BASED ON ETIOLOGY OF pHTN**

|                           | Intrahepatic | Extrahepatic | P Value* |
|---------------------------|--------------|--------------|----------|
| Total patients            | 151 (121)    | 30           |          |
| Age at Dx (years)         | 0.5 (0.1-1.4) | 0.4 (0.1-1.0) | <0.01    |
| Male                      | 71 (47%)     | 58 (47.9%)   | 0.69     |
| Years of follow-up        | 4.7 (2.1-7.4) | 5.1 (2.5-7.5) | 0.06     |
| Race                      |              |              | 0.72     |
| White                     | 103 (68.2%)  | 84 (69.4%)   |          |
| Black                     | 25 (16.6%)   | 20 (16.5%)   |          |
| Hispanic                  | 13 (8.6%)    | 9 (7.4%)     |          |
| Asian                     | 10 (6.6%)    | 8 (6.6%)     |          |
| Etiology                  |              |              | <0.01    |
| Cholestatic disease       | 105 (69.5%)  | 105 (86.8%)  |          |
| Hepatocellular/fibrotic   | 16 (10.6%)   | 16 (13.2%)   |          |
| Hepatic vein obstruction  | 4 (2.7%)     | 0 (0%)       |          |
| Prehepatic disease        | 26 (17.2%)   | 0 (0%)       |          |
| Refractory ascites        | 45 (29.8%)   | 41 (33.9%)   | 0.03     |
| Growth failure            | 22 (16.5%)   | 20 (18.9%)   | 0.24     |
| Normal development        | 87 (73.1%)   | 21 (72.4%)   | 1.00     |
| Cognitive delay           | 32 (27.1%)   | 10 (34.5%)   | 0.49     |
| EGD for suspected GI bleed| 50 (41.3%)   | 23 (76.7%)   | <0.01    |
| GI bleed                  | 39 (32.2%)   | 16 (53.3%)   | 0.04     |
| Median number EGDs        | 0 (0-1.5)    | 2 (1-3)      | <0.01    |
| Required banding/sclerotherapy | 29 (26.6%) | 7 (24.1%) | 1.00 |
| Median number banding/ sclerotherapy | 0 (0-1) | 0 (0-0.5) | 0.79 |
| Varices                   | 45 (40.5%)   | 21 (75.0%)   | <0.01    |
| Intervention              |              |              | <0.01    |
| Transplant                | 81 (53.6%)   | 79 (65.3%)   | 2 (6.7%) |
| Shunt                     | 14 (9.3%)    | 1 (0.8%)     | 13 (43.3%) |
| Transplant and shunt      | 6 (4%)       | 5 (4.1%)     | 1 (3.3%)  |
| No intervention           | 50 (33.1%)   | 36 (29.8%)   | 14 (46.7%) |
| Died                      | 22 (14.6%)   | 20 (16.5%)   | 2 (6.7%)  | 0.25 |

*P < 0.05 considered significant.
Abbreviations: Dx, diagnosis; GI, gastrointestinal.

**SURVIVAL ANALYSIS**

There was no significant difference when evaluating patients based on intrahepatic versus extrahepatic disease (\(P = 0.25\)). However, there was a significant difference in overall survival based on stratified etiology. No patients with PRE died compared to 15.2% (n = 16) of patients with CD, 25% (n = 4) with HFD, and 50% (n = 2) with HVO (death secondary to reversal of flow leading to bowel ischemia in 1 patient and respiratory failure while awaiting transplant for cholangitis lenta in another) (\(P = 0.01\)) (Fig. 1). Based on surgical intervention for
pHTN, patients who had no intervention had lower survival compared to those who underwent a transplant, shunt, or both ($P < 0.01$) (Fig. 2). There were no differences in mortality based on age of diagnosis, sex, race, pre-operative comorbidities, or endoscopic interventions or findings (Table 2). Patients identified with abnormal development based on not meeting developmental milestones for age had higher mortality ($n = 12, 28.6\%$) compared to those identified as having normal development ($n = 13, 1.6\%; P < 0.01$). For patients over the age of 2 who died, $71.4\%$ ($n = 5$) exhibited growth failure ($P < 0.01$) and all had decompensated end-stage liver disease at the time of death.

Based on multiple logistic regression to determine predictors of mortality, patients with refractory ascites had an increased risk of death (odds ratio [OR], 4.34; 95% confidence interval [CI], 1.00, 18.88; $P = 0.05$). Similarly, patients with growth failure had significantly increased risk of death (OR, $13.49$; 95% CI, $3.07, 58.99$; $P < 0.01$).

**TABLE 2. ANALYSIS OF CHARACTERISTICS BASED ON MORTALITY**

|                          | Alive | Died |
|--------------------------|-------|------|
|                          | n (%) | n (%) |
|                          | (IQR) | (IQR) | $P$ Value* |
| Total patients           | 129   | 22   |
| Age of Dx (years)        | 0.5 (0.1-2.0) | 0.7 (0.1-1.0) | 0.87 |
| Follow-up (years)        | 5.3 (2.7-7.6) | 0.6 (0.3-1.4) | <0.01 |
| Male                     | 63 (48.8%) | 8 (36.4%) | 0.36 |
| Race                     |       |      | 0.75 |
| White                    | 89 (69.0%) | 14 (63.6%) |
| Black                    | 21 (16.2%) | 4 (18.2%) |
| Hispanic                 | 10 (7.8%) | 3 (13.6%) |
| Asian                    | 9 (7.0%) | 1 (4.6%) |
| Refractory ascites       | 36 (27.9%) | 9 (40.9%) | 0.22 |
| Growth failure (n = 133) | 17 (13.5%) | 5 (71.4%) | <0.01 |
| Abnormal development     | 30 (23.3%) | 9 (47.4%) | 0.01 |
| Cognitive delay          | 35 (27.1%) | 7 (38.9%) | 0.41 |
| EGD                      | 66 (51.2%) | 7 (31.8%) | 0.11 |
| GI bleed                 | 47 (36.4%) | 9 (40.9%) | 0.64 |
| Median number EGDs       | 1 (0-2) | 0 (0-1) | 0.10 |
| Required banding/ sclerotherapy | 32 (24.8%) | 4 (23.5%) | 1.00 |
| Median number banding/ sclerotherapy | 0 (0-1) | 0 (0-0.5) | 0.73 |
| Varices                  | 60 (46.5%) | 6 (27.3%) | 0.31 |
| Intervention             |       |      | <0.01 |
| Transplant               | 75 (58.1%) | 6 (27.3%) |
| Shunt                    | 14 (10.9%) | 0 (0%) |
| Transplant and shunt     | 6 (4.7%) | 0 (0%) |
| No intervention          | 34 (26.4%) | 16 (72.7%) |

* $P < 0.05$ considered significant.

Abbreviations: Dx, diagnosis; GI, gastrointestinal.

**SUBSET ANALYSIS AMONG COHORT WHO UNDERWENT NO INTERVENTION**

Fifty patients in our cohort did not undergo any surgical intervention for pHTN. Of the 16 patients who...
died without intervention, 6 patients died while listed for transplant, 4 patients were not candidates due to progression of disease, and 6 patients had clinical deterioration before the workup was completed. Of the 34 patients who were alive at the time of this report and had not undergone intervention, 25 were being medically managed, 6 were wait-listed for organs, and 3 were not candidates for intervention due to severity of disease.

Discussion

In this single institution study, we examined the etiology, management, and disease course of pHTN in children. While the cause of pHTN differed compared to the adult population, we found that most patients in our study presented with end-stage liver disease. However, unlike the adult population, the next most common cause of pHTN in the pediatric population was pre-hepatic pHTN. In our cohort, management strategies involving endoscopic and surgical interventions differed based on etiology of pHTN, with more endoscopic interventions in patients with PRE and more transplants in patients with CD. Patients with PRE had lower mortality compared to those with other etiologies. Multivariate analysis found that patients with growth failure and refractory ascites had higher odds of mortality. These findings reinforce the importance of growth failure in the prognosis of pHTN given the difficulty in management of the disease once it has progressed.

Our findings emphasize the differences in the etiology of pHTN between pediatric and adult populations. Cirrhosis caused by alcohol, hepatitis B and C, and nonalcoholic steatohepatitis lead to the majority of cases of pHTN in adults, whereas extrahepatic portal vein obstruction has been reported to be the most common presenting etiology of pHTN in the pediatric population. In our study, we found that PRE and CD predominated as the leading etiologies of pHTN. The high proportion of patients with CD in our cohort may be due to our role as a tertiary care center. Due to the differing etiologies of pHTN in adult and pediatric populations, deriving management practices from adult studies may not adequately address the needs of pediatric patients.

The management of pHTN has evolved over the past few decades as endoscopic interventions have increased and survival has improved for liver transplantation. Multiple studies have sought to determine predictors of requiring surgery in this disease process while minimizing invasive procedures. Di Giorgio et al. analyzed comorbidities and features of 187 pediatric patients with portal vein thrombosis and found that variceal bleeding was associated with an eventual need for surgery. Another study found that nearly one third of children with pHTN and esophageal varices underwent a shunt and another one third underwent liver transplantation, but no patients died from an acute variceal bleed. This finding differed from a study that analyzed 26 patients with noncirrhotic pHTN and found that the majority did well in the long term without surgical intervention. In our study, the majority of patients who had an intervention underwent a transplantation and only a portion of these patients had a pre-operative gastrointestinal bleed. While variceal bleeding may be associated with confirmed gastrointestinal bleeding on endoscopy in patients with PRE who undergo a shunt, it was a poor predictor for undergoing surgical intervention for pHTN in this study. Additionally, while patients in other studies may have done well without intervention, our study showed higher mortality in patients who did not undergo surgical intervention compared to those who underwent transplant or shunt.

Few studies have been devoted to determining predictors of overall mortality in children with pHTN. Unlike previous studies in the pediatric population, our study found refractory ascites to be a predictor of mortality. The management of ascites for pediatric patients is largely inferred from literature in the adult population. Despite medical interventions and lifestyle modifications, many patients ultimately progress toward refractory ascites requiring frequent paracentesis for control. Once patients progress to this stage, their disease is likely severe enough to necessitate intervention, but refractory ascites is not included in the process for determining disease severity for pediatric transplantation. While ascites has long been used in the adult population as a component of the Child-Turcotte-Pugh score, it has been largely criticized for being easily manipulated given its subjectivity. The PELD score uses bilirubin, international normalized ratio, albumin level, growth failure, and age to estimate disease severity in patients under the age of 12, but it does not include ascites as a factor. A study found that although Child scores correlated with PELD scores, PELD was a better predictor for mortality after liver transplantation.
of refractory ascites in a pediatric-specific score may address the mortality associated with pHTN by better highlighting the severity of disease.

Our study has limitations. First, this is a single institution study. As such, this limits the generalizability of our work. Additionally, our center serves as a tertiary referral center and treats a high volume of patients with complex hepatobiliary disease, which may limit the interpretation of our survival analysis. While the adult population with this disease process undergoes imaging and endoscopy more consistently, the conscious effort to reduce invasive procedures and radiation in the pediatric population may limit the ability to determine the presence and severity of varices. Finally, given the variations in time of presentation after diagnosis and types of imaging used, we did not evaluate laboratory values or measurements on imaging regarding splenomegaly.

In summary, we report a large single-center series evaluating the progression of pHTN in the pediatric population while also addressing the predictors of mortality. Further work should be done to understand the long-term outcomes in this population as they transition to adulthood. A multi-institutional collaboration may also allow for better determination of predictors of mortality and criteria for intervention and create a better understanding of the progression of this disease.

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