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Predictive factors of morbidity associated with esophageal variceal bleeding in children with portal hypertension

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HIGLIGHTS

- Most data on the natural history of portal hypertension come from studies in adults.
- The morbidity rate of upper gastrointestinal bleeding in children with portal hypertension tend to be underestimated.
- This study showed the relevance of morbidity rates after variceal hemorrhage in pediatric patients, especially those with cirrhosis.
- Patients with hemodynamic instability requiring blood transfusion or expansion on admission are at increased risk of complications secondary to upper gastrointestinal bleeding and should be closely monitored.

ABSTRACT – Background – Most data on the natural history of portal hypertension come from studies in adults. The morbidity rate of upper gastrointestinal bleeding (UGIB) in children with portal hypertension has not been systematically characterized. **Objective –** To describe the morbidity and mortality of UGIB in pediatric patients with portal hypertension and identify predictive factors for the occurrence of its main complications. **Methods –** This retrospective study included pediatric patients with cirrhotic portal hypertension or with extrahepatic portal vein obstruction (EHPVO). Mortality and UGIB complications within a period of up to 6 weeks of the bleeding were investigated. To determine the predictive factors of morbidity, a multivariate analysis was performed using logistic regression; all results were considered significant at $P<0.05$. **Results –** A total of 86 patients (51.2% with EHPVO and 48.8% with cirrhosis) had 174 bleeding events. Ascites was the most common complication (43.1% of all cases), being more prevalent in patients with cirrhosis ($P<0.001$). Cirrhosis was a predictor of the occurrence of any morbidity (OR 20.3). The need for blood transfusion was predictor of at least one complication (OR 5.8), ascites (OR 7.2) and infections (OR 3.8) in the general group and at least one complication (OR 11.3) and ascites (OR 5.8) in cirrhotic patients. The need for expansion was a predictor of any morbidity (OR 4.6) and infections (OR 3.9) in the general group, in addition to being predictor of infection in cirrhotic patients (OR 5.4). There were no deaths from UGIB in the six weeks post-bleeding. **Conclusion –** The study showed the relevance of morbidity after UGIB in pediatric patients with portal hypertension, especially in those with cirrhosis. The patients with hemodynamic instability requiring blood transfusion or expansion on admission are at increased risk of complications related to upper gastrointestinal bleeding and should be closely monitored.

Keywords – Portal hypertension; acute variceal bleeding; esophageal varices; morbidity; children.

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INTRODUCTION

Esophageal variceal (EV) bleeding is a major cause of morbidity and mortality in adults with chronic liver disease. Approximately half the adults with cirrhosis have EV, with mortality from upper gastrointestinal bleeding (UGIB) ranging between 14–30%[1-4]. Morbidity and mortality due to bleeding are related to secondary complications such as ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hemorrhagic shock, infections, and others[5]. Furthermore, complications like ascites and encephalopathy should be considered in the context of advances of cirrhosis or may occur concomitant or subsequent to development of UGIB[3].

Most data on the natural history of portal hypertension come from studies in adults. Cirrhosis is the leading cause of portal hypertension in adults. In studies on pediatric patients, a considerable number of patients have extrahepatic portal vein obstruction (EHPVO), in which, the mechanism of developing portal hypertension is different and liver function is preserved[6]. Consequently, the mortality rate of UGIB in patients with EHPVO is lower, ranging from 0–2%[7,8].

More recent studies have separated intrahepatic (cirrhosis) from extrahepatic causes (EHPVPO) of portal hypertension. Cirrhosis has a higher mortality rate than EHPVO in children, ranging from 0–8%, which is still lower than that in adults with cirrhosis; however the morbidity associated has not been systematically characterized[6-9]. These issues could influence decisions regarding primary prophylaxis and need to be properly studied. Primary prophylaxis of variceal hemorrhage, while recommended for adults, has not been endorsed by Baveno Consensus for children[10,11]. However, new studies have shown the relevance of morbidity rates in children with portal hypertension, with significant complications occurring in up to 57% of UGIB cases[5,6].

The objective of this study was to describe the mortality and morbidity related to UGIB events in pediatric patients with portal hypertension and to identify predictive factors for the occurrence of its main complications.

METHODS

This was a retrospective study on children and adolescents with portal hypertension who had at least one variceal UGIB event treated at a tertiary Pediatric Hepatology Service.

The inclusion criteria were children and adolescents with cirrhotic portal hypertension or EHPVO, aged up to 18 years, who had at least one UGIB event from September 1990 to May 2021. The exclusion criteria was UGIB events not well documented due to occurring outside the service.

A UGIB event was defined as the occurrence of hematemesis and/or melena requiring expansion with intravenous fluid or blood transfusion in a patient admitted to the Emergency Care Unit of the Service, with the presence of varicose veins without another probable cause of bleeding being confirmed by gastrointestinal endoscopy. Each patient's first bleeding event and all other subsequent bleeding events were documented as long as they met the above criteria.

The etiology of cirrhosis was confirmed by clinical, laboratory, histopathological, and/or radiological investigations. EHPVO was diagnosed by clinical–laboratory suspicion and confirmed by ultrasound.

This project was approved by Ethics Committee (CAAE:60087316.2.0000.5149). The Informed Consent Form was signed by parents or guardians and the Informed Assent Form was signed by children and adolescents, when indicated.

Descriptive factors (such as sex, age at first UGIB event, portal hypertension etiology), endoscopic findings, hospital approach to UGIB, laboratory tests on admission, mortality and UGIB complications within a period of up to 6 weeks of the bleeding were investigated in the medical records.

Some definitions related to the bleeding event and complications (outcomes) were necessary, such as:

- Time zero was defined as the moment of hospital admission; the period for the acute bleeding event was 120 hours (5 days);
- The period to define mortality due to acute variceal bleeding was 6 weeks;
- Failure to control bleeding was defined as bleeding persistence or need for new intervention within 5 days of hospital admission[11];

- Rebleeding was defined as rebleeding 5 days and up to 6 weeks after hospital admission, 3 g/dL drop in hemoglobin, need for transfusion, or death;
- The presence or absence of ascites was assessed by through physical examination or ultrasound; it was considered only documented ascites occurring or worsening after UGIB.
- Hepatic encephalopathy was determined by the Pediatric Acute Liver Failure Study classification for children under four years of age[12] and by the West Haven classification system for children over four years of age[13];
- Acute kidney injury was defined as a 0.3 mg/dL increase in serum creatinine within 48 hours or a 1.5 times increase from the baseline value within 7 days, or urine volume <0.5 mL/kg/h for 6 hours[14];
- Sepsis was defined according to the International Consensus on Pediatric Sepsis as evidence of temperature abnormality (fever or hypothermia) or specific white blood cell count abnormality for the age and one of the following: tachycardia, bradycardia, acute respiratory disease, or pulmonary condition requiring mechanical ventilation associated with at least one positive blood culture (BC)[15];
- Occult bacteremia was defined as fever associated with positive BC that did not meet sepsis criteria;
- Infections were defined by the need to use antibiotics during hospital stay, regardless of bacteremia and sepsis criteria. Infections events previous to UGIB were excluded.

The database was analyzed using the SPSS v20.0 software®. Descriptive analysis was performed using absolute (n) and relative (%) frequencies and median to describe the variables analyzed. Continuous variables with non-normal distribution were expressed as median and interquartile range 25–75% (IQ25–75%) and the non-parametric Kruskal–Wallis test was used to compare the cirrhosis and EHPVO groups. Continuous variables with normal distribution were expressed as mean and standard deviation and compared using the Student's *t*-test. Dichotomous variable comparisons were analyzed by the chi-square test with Yates correction or by the Fisher's exact test, two-tailed if necessary.

Univariate binary logistic regression was the statistical method used for univariate analysis of factors associated with UGIB complications. Variables with $P<0.4$ were initially used for multivariate analysis. Step by step, the variables with the highest *P*-values were removed until the final model was achieved with an odds ratio (OR) with 95% confidence interval for the variables associated with UGIB events. Continuous variables were dichotomized based on the cutoff points used in the literature. The multivariate logistic regression model was adjusted by the Hosmer and Lemeshow test. The logistic model was also adjusted by the Cox & Snell's and Nagelkerke's pseudo-R^2 to evaluate whether the set of independent variables used to explain a particular dichotomous categorical outcome variable is sufficient or not. All results were considered significant at $P<0.05$.

RESULTS

The study included 86 patients with portal hypertension who had at least one UGIB event in the service between 1990 and 2021, 51.2% with EHPVO and 48.8% with cirrhosis. A total of 174 bleeding events were documented, with a median (Q_1–Q_3) of 2.0 (1.0–3.0) episodes per patient. Most patients were girls (58.1%), with a median (Q_1–Q_3) age of 5 years (2.0–9.0). There was no statistical difference in sex and age between the cirrhosis and EHPVO groups.

The cause of liver disease in patients with cirrhosis was biliary atresia (47.6% of cases), primary sclerosing cholangitis (11.9%), alpha-1 antitrypsin deficiency (9.5%), cryptogenic cirrhosis (9.5%), autoimmune hepatitis (7.1%), choledochal cyst (4.8%), Caroli disease (4.8%), and Budd–Chiari syndrome (4.8%).

There was no statistically significant difference between outcomes between the two eras: between 1990 and 2005 and after 2005 (infection $P=0.38$; ascites $P=0.82$, encephalopathy $P=0.92$, AKI $P=1$, failure to control bleeding $P=0.42$). Octreotide infusion after hospital admission was initiated in 64.9% of all episodes of UGIB; its use was lower in the first era (1990–2005), $P=0.002$, however this was not a significant factor for the occurrence of complications. Antibiotic prophylaxis for spontaneous bacterial pe-

ritonitis was prescribed in 63.8% of bleeding episodes at hospital admission among cirrhotic patients, as recommended to adults.

There were no deaths within 6 weeks after UGIB in any of the bleeding events. Complications of the 174 UGIB events are shown in TABLE 1. At least one relevant complication (ascites, encephalopathy, acute kidney injury (AKI), infection, need for ventilatory support, or failure to control bleeding) was observed in 67.2% of bleeding events, with a higher rate in patients with cirrhosis than in patients with EHPVO (P<0.001). The median (Q_1–Q_3) of relevant complications was 2.0 (1.0–3.3) in patients with cirrhosis and 1.0 (0.8–3.0) in patients with EHPVO (P=0.002). Ascites was the most common complication (43.1% of all cases), being more prevalent in patients with cirrhosis (P<0.001). AKI was the least frequent complication, present in only 2.9% of patients with cirrhosis. Rebleeding was observed in 5.7% of cases, requiring a new endoscopy for control.

Univariate analysis considering the occurrence of at least one complication in the cases with cirrhosis or EHPVO is described in TABLE 2. Multivariate analysis showed that cirrhosis as a cause of portal hypertension, being a boy, and need for blood transfusion and expansion with intravenous fluid were significantly associated with the presence of at least one complication after UGIB.

Predictors of complications were also evaluated in patients with cirrhosis alone (TABLE 3). In this case, multivariate analysis showed that only the need for blood transfusion was a predictor of the occurrence of at least one complication.

Ascites, infections, and encephalopathy were complications analyzed in the total group of patients. Multivariate analysis showed that cirrhosis was a predictor of all complications individually: ascites (OR 12.7, CI95% 5.6–29, P<0.001), infections (OR 4.7, CI95% 2–11, P<0.001), and encephalopathy (OR 7.8, CI95% 2.2–28.1, P=0.002). Need for transfusion remained statistically significant as a predictor of ascites (OR 7.2, CI95% 2.9–18, P<0.001); as for infections, the predictors were need for transfusion (OR 3.8, CI95% 1.4–10.5, P=0.009), need for expansion (OR 3.9, CI95% 1.7–9, P=0.009), and failure to control bleeding (OR 3.7, CI95% 1.5–9.3, P=0.005); and for encephalopathy, failure to control bleeding (OR 6, CI95% 2.3–15.6, P<0.001).

The assessment of predictors of ascites, infection, and encephalopathy in the group of patients with cirrhosis is shown in TABLE 4. In multivariate analysis, only blood transfusion was a predictor of ascites,

TABLE 1. Complications of the 174 episodes of variceal bleeding among cirrhosis and extrahepatic portal vein obstruction (EHPVO) group.

Variables	Cirrhosis (%) N=94	EHPVO (%) N=80	Total (%)	*P*
At least one complication*	79 (84)	38 (47.5)	117 (67.2)	<0.001
Ascites	61 (64.9)	14 (17.5)	75 (43.1)	<0.001
Encephalopathy	23 (24.5)	3 (3.8)	26 (14.9)	<0.001
Sepsis	11 (11.8)	3 (3.8)	14 (8)	0.052
Bacteremia	9 (9.6)	3 (3.8)	12 (6.9)	0.131
Infection	39 (41.5)	15 (18.8)	54 (31)	0.001
Acute kidney injury	5 (5.3)	0 (0)	5 (2.9)	0.063
Ventilatory support				
Noninvasive oxygen support	12 (12.8)	7 (8.8)	19 (10.9)	0.209
Invasive ventilation	15 (16)	7 (8.8)	22 (12.6)	
Failure to control bleeding	22 (23.4)	11 (13.8)	33 (19)	0.105

*At least one relevant complication: ascites, encephalopathy, acute kidney injury, infection, need for ventilatory support, or failure to control bleeding.

TABLE 2. Univariate and multivariate analysis of predictor factors of at least one complication after acute variceal bleeding among all the 174 episodes of acute variceal bleeding.

Predictor factors	Complications		*P*	OR	CI95%
	Yes (117) N (%)	No (57) N (%)			
Group Cirrhosis EHPVO	79 (84.0) 38 (47.5)	15 (16.0) 42 (52.5)	<0.001	5.8 1.0	2.9–11.8
Sex Female Male	49 (55.1) 68 (80.0)	40 (44.9) 17 (20.0)	0.001	1.0 3.3	1.7–6.4
Age Median (Q_1–Q_3)	7.0 (3.5–10.0)	6.0 (3.0–11.0)	0.878	1.0	0.90–1.1
Site of bleeding Esophageal varices Gastric varices No identified	71 (62.8) 36 (76.6) 9 (69.2)	42 (37.2) 11 (23.4) 04 (30.8)	0.651 0.589	0.8 1.5 1.0	0.2–2.6 0.4–5.7
Need for blood transfusion	94 (77.0)	28 (23.0)	<0.001	4.2	2.1–8.4
Need for intravenous fluid	65 (77.4)	19 (22.6)	0.007	2.5	1.3–4.8
Failure to control bleeding	33 (100.0)	0 (0.0)	0.001	–	–
Hemoglobin <8 g/dL	63 (70.0)	27 (30.0)	0.561	1.2	0.6–2.3
Platelets /mm^3 Median (Q_1–Q_3)	112000 (77000–169000)	119000 (68500–159500)	0.440	1.0	1.0–1.0
AST >40 UI/L	56 (76.7)	17 (23.3)	0.027	2.4	1.1–5.4
ALT >56 UI/L	33 (75.0)	11 (25.0)	0.273	1.6	0.7–3.7
Total bilirubin >1.2 mg/dL	27 (90.0)	3 (10.0)	0.042	3.9	1.1–14.4
Direct bilirubin >0.40 mg/dL	35 (89.7)	04 (10.3)	0.014	4.4	1.3–14.2
INR >1.0	100 (69.9)	43 (30.1)	0.813	1.2	0.3–4.1
Albumin <3.5 g/dL	55 (84.6)	10 (15.4)	<0.001	8.9	2.9–27.1
Creatine >1.2 mg/dL	6 (100.0)	0 (0.0)	0.001	–	–
Sodium >135 mEq/L	44 (81.5)	10 (18.5)	0.374	0.6	0.2–2.0
Potassium <3.5 mEq/L	12 (100.0)	0 (0.0)	0.001	–	–
GGT >30 UI/L	51 (87.9)	07 (12.1)	<0.001	7.3	2.7–19.9
Predictor factors	**Multivariate analysis**				
	ß	**chi-squared (Wald)**	***P***	**OR**	**CI95%**
Cirrhosis	3.011	30.881	<0.001	20.3	7.0–58.7
Male Sex	1.641	13.083	<0.001	5.2	2.1–12.6
Need for blood transfusion	1.765	14.290	<0.001	5.8	2.3–14.6
Need for intravenous fluid	1.535	10.842	0.001	4.6	1.9–11.6

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; INR: international normalised ratio.

TABLE 3. Univariate and multivariate analysis of predictor factors of at least one complication of acute variceal bleeding among cirrhotic patients.

Predictor factors	Complications		Univariate analysis		
	Yes (79) N (%)	No (15) N (%)	*P*	OR	CI95%
Sex					
Female	40 (76.9)	39 (92.9)			
Male	12 (23.1)	3 (7.1)	0.046	3.9	1.0–14.9
Age Median (Q_1–Q_3)	8.0 (4.0–10.0)	9.0 (5.0–11.0)	0.343	0.9	0.80–1.1
Site of bleeding					
Esophageal varice	46 (79.3)	12 (20.7)	0.850	0.9	0.2–4.5
Gastric varice	23 (95.8)	1 (4.2)	0.205	5.1	0.4–63.6
No identified	9 (81.8)	2 (18.2)		1.0	
Need for blood transfusion	62 (95.4)	3 (4.6)	<0.001	14.6	3.7–57.7
Need for intravenous fluid	39 (100)	0 (0.0)	0.001	–	–
Failure to control bleeding	22 (100.0)	0 (0.0)	0.001	–	–
Hemoglobin <8 g/dL	37 (94.9)	2 (5.1)	0.034	5.4	1.1–25.8
Platelets /mm^3	117.000	111.500			
Median (Q_1–Q_3)	(81.000–180.000)	(61.000–147.250)	0.209	1.0	1.0–1.0
AST >40 UI/L	47 (87.0)	7 (13.0)	0.723	0.7	0.1–6.1
ALT >56 UI/L	32 (82.1)	7 (17.9)	0.133	0.2	0.0–1.7
Total bilirubin >1.2 mg/dL	26 (92.9)	2 (7.1)	1.000	1.0	0.1–7.6
Direct bilirubin >0.40 mg/dL	34 (91.9)	3 (8.1)	0.698	0.6	0.1–6.5
INR >1.0	67 (85.9)	11 (14.1)	0.863	1.2	0.1–11.4
Albumin <3.5 g/dL	41 (95.3)	2 (4.7)	0.025	13.7	1.4–134.1
Creatine >1.2 mg/dL	6 (100.0)	0 (0.0)	0.001	–	–
Sodium >135 mEq/L	32 (94.1)	2 (5.9)	0.829	0.7	0.1–8.9
Potassium <3.5 mEq/L	7 (100.0)	0 (0.0)	0.001	–	–
GGT >30 UI/L	48 (90.6)	5 (9.4)	0.232	4.8	0.4–62.8
Predictor factors	**Multivariate analysis**				
	ß	**chi-squared (Wald)**	***P***	**OR**	**CI95%**
Need for blood transfusion	2.429	11.175	0.001	11.3	2.7–47.1

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; INR: international normalised ratio.

TABLE 4. Univariate and multivariate analysis of predictor factors of ascites, infection and encephalopathy among cirrhotic patients.

Predictor factors	Univariate analysis								
	Ascites			Infection			Encephalopathy		
	P	OR	CI95%	*P*	OR	CI95%	*P*	OR	CI95%
Male sex	0.235	1.7	0.7–4.0	0.549	0.8	0.3–1.8	0.119	2.2	0.8–6.1
Age median	0.693	1.0	0.9–1.1	0.065	0.91	0.81–1.01	0.865	1.0	0.9–1.1
Site of bleeding									
Esophageal varice	0.260	2.1	0.6–7.8	0.922	1.1	0.3–4.1	0.001	–	–
Gastric varice	0.095	3.6	0.8–16.2	0.454	1.8	0.4–7.6	0.001	–	–
No identified		1.0			1.0			1.0	
Need for blood transfusion	<0.001	6.9	2.6–18.2	0.008	4.0	1.4–11.0	0.043	3.9	1.0–14.2
Need for intravenous fluid	0.108	2.1	0.9–5.1	<0.001	6.5	2.6–16.1	0.033	2.9	1.1–7.5
Failure to control bleeding	0.888	0.9	0.3–2.5	0.019	3.3	1.2–8.9	<0.001	6.7	2.3–19.1
Hemoglobin <8	0.258	1.7	0.7–4.1	0.842	1.1	0.5–2.5	0.409	1.5	0.6–3.9
Platelets median	0.088	1.0	1.0–1.0	0.512	1.00	1.00–1.00	0.541	1.0	1.0–1.0
AST >40	0.103	0.17	0.02–1.43	0.084	4.2	0.8–21.2	0.139	5.0	0.6–42.2
ALT >56	0.027	0.2	0.1–0.9	0.189	2.0	0.7–5.8	0.062	3.3	0.9–11.4
Total bilirubin >1.2	0.771	0.8	0.3–2.6	0.004	0.8	1.7–16.5	0.012	5.2	1.4–18.9
Direct bilirubin >0.40	0.638	0.7	0.2–2.5	0.002	0.7	2.1–28.7	0.015	13.7	1.7–113.8
INR >1.0	0.948	1.1	0.2–6.2	0.627	1.5	0.3–8.9	0.628	1.7	0.2–15.7
Albumin <3.5	0.036	11.6	1.2–115.6	0.001	–	–	0.458	2.4	0.2–23.1
Creatine >1.2	0.001	1.0	–	0.375	0.4	01–2.7	0.286	2.5	0.5–14.0
Sodium >135	0.752	0.8	0.2–2.9	0.277	1.8	0.6–5.5	0.399	1.7	0.5–5.3
Potassium <3.5	0.885	0.9	0.2–5.1	0.396	0.5	0.1–2.5	0.776	0.8	0.1–4.4
GGT >30	0.851	1.3	0.1–15.0	0.001	1.3	0.1–15.0	0.001	–	–
Predictor factors	**Multivariate analysis**								
	Ascites			Infection			Encephalopathy		
	P	OR	CI95%	*P*	OR	CI95%	*P*	OR	CI95%
Need for blood transfusion	<0.001	5.8	2.2–15.6	–	–	–	–	–	–
Need for intravenous fluid	–	–	–	<0.001	5.4	2.1–13.7	–	–	–
Failure to control bleeding	–	–	–	–	–	–	<0.001	9.1	2.8–29.7

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; INR: international normalised ratio.

need for expansion was a predictor of infections, and failure to control bleeding was a predictor of encephalopathy in patients with cirrhosis.

DISCUSSION

Data on the natural history and morbidity of variceal UGIB in the pediatric age group are scarce in scientific literature. Recent studies have shown the relevance of complication rates in children with cirrhosis with non-negligible mortality rates[5,6,16]. The present study showed that the rate of complications related to UGIB events is high in patients with cirrhosis and EHPVO. Complications occurred in 67.2% of the bleeding cases, which corroborates the study by Moura et al.[5], who presented the first detailed study

assessing morbidity and mortality. They retrospectively evaluated 70 UGIB events in 57 children and adolescents with portal hypertension aged under 18 years admitted between 2000 and 2015, 58% with cirrhosis and 30% with EHPVO. Significant morbidity occurred in 57% of patients in all UGIB events, a rate very similar to the one found in the present study.

On the other hand, Duche et al.[16] analyzed the history of 141 cirrhotic children with UGIB between 1989 and 2014 with the main objective of describing the service's experience with primary prophylaxis, but also presenting a brief description of morbidity and mortality data from UGIB events. The authors defined a life-threatening event as one resulting in death or requiring emergency transplantation, including refractory bleeding, hepatic decompensation, hepatorenal syndrome, or severe hepatic encephalopathy. These events occurred in 19.1% of patients. There was no detailing of each complication. As more serious outcomes resulting from UGIB were reported, the rate found was lower than the one described in the present study and in the one by Moura et al[5].

Ascites was the most common complication (43.1%), being more prevalent in patients with cirrhosis, as expected. This demonstrates the relevance of UGIB as a triggering event for other complications in the natural history of decompensated cirrhosis[3]. The rate of occurrence of ascites in this study corroborates the study by Moura et al. (34%), but is higher than the one reported by Molleston and Bennett (21.3%), whose study involved the analysis of databases of 50 tertiary pediatric hospitals in the USA[6], with the risk of losing and omitting more detailed data, although with a significant number of cases (1,902 patients with at least one variceal UGIB event, totaling 3,399 events). In any case, the morbidity observed in these studies is not negligible.

The rate of infections requiring the use of antimicrobials was the second most frequent complication corroborating the one reported by Moura et al. (30%)[5]. Encephalopathy was also a relevant complication (14.9%), mainly in patients with cirrhosis (24.5%), as this group has hepatocellular involvement. Moura et al.[5] reported lower rates (7%), including in non-cirrhotic patients. The severity of cirrhosis in the two studies may account for these differences, but the available data do not allow such a comparison. AKI was found only in patients with cirrhosis in this study (5.4%), similar to the study by Moura et al.[5] (6%) and Molleston and Bennett[6] (5.1%).

Cirrhosis, as expected, was a predictor of the occurrence of at least one complication (OR 20.3), ascites (OR 12.7), encephalopathy (OR 7.8), and infections (OR 4.7). Patients with EHPVO have preserved liver function and present a significantly lower risk of complications than patients with cirrhosis, but still have significant complication rates (47.5% overall, 17.5% ascites, 18.8% infections).

The need for blood transfusion was a predictor of complications (OR 5.8), ascites (OR 7.2), and infections (OR 3.8) in the general group. In patients with cirrhosis, it was also a predictor of complications in general (OR 11.3) and ascites (OR 5.8). The need for expansion was a predictor of the occurrence of any complications (OR 4.6) and of infections (OR 3.9) in the general group, in addition to being a predictor of infections in cirrhotic patients (OR 5.4). The need for blood transfusion or expansion shows that patients with hemodynamic instability are at greater risk of tissue hypotension, and may predict complications secondary to UGIB in patients with portal hypertension[15].

In the only study published to date assessing predictive factors for complications, Carneiro de Moura et al.[5] found only Pediatric End-Stage Liver Disease (PELD) as a predictor of ascites. The authors were stricter in relation to the statistical analysis, considering only a $P<0.01$ as statistically significant. Factors such as age, laboratory tests on admission, endoscopy findings and antimicrobial use were studied, but not associated with any complications[5]. In the present study, laboratory tests on admission were not good predictors of complications. There was a loss of laboratory data in the analysis of medical records.

No deaths due to UGIB were observed within 6 weeks of bleeding. Bass et al.[17] and Luoto et al.[18] also reported zero mortality. The studies reported extremely variable rates, justified in part by their different methodologies and primary objectives. Studies prior to 2010, such as the one by Eroglu et al.[19] and Poddar et al.[20] reported much higher mortality rates of 26.7% and 29.6%, respectively, in patients with cirrhosis. More recent studies such as the ones by

Carneiro de Moura et al.[5] and Molleston and Bennett[6] reported a mortality rate up to 6 weeks after a bleeding event of 8.0% and 8.8%, respectively, showing a possible temporal effect, with a tendency to decreased rates in the last decade as a result of the development of established care protocols.

Although with a significant sample, this study has limitations due to its retrospective design, with data loss, especially of laboratory tests due to the lack of information in medical records. On the other hand, few pediatric studies analyze the predictors of UGIB complications, which can help and direct care on admission of these patients. In addition, patients with cirrhosis were separated from the ones with EHPVO, which has a different pathophysiology and outcomes and should be treated differently.

In conclusion, although we report no mortality at 6 weeks, our results demonstrate a high rate of complications related to variceal bleeding in children and adolescents with portal hypertension, especially in those with cirrhosis. The patients with hemodynamic instability requiring blood transfusion or expansion on admission are at increased risk of complications secondary to UGIB and should be closely monitored. Although there are not enough data in the literature on the efficacy of primary UGIB prophylaxis in children, these results should be considered in the evaluation of its indication in this age group as a motivation for well-conducted multicenter studies.

Authors' contribution

Fagundes EDT and Ferreira AR: conceptualized the work and obtained ethics committee approval. Gama MCFLR: conceptualized the work, collected the data, analyzed and interpretated of data and drafted the initial manuscript. Queiroz TCN and Rodrigues AT: collected the data, supported data curation and revision of the manuscript. Vieira LC: collected the data, analyzed of data and revision of the manuscript. Fagundes EDT and Ferreira AR: supported supervision of all stages, reviewed and edited the manuscript. All authors approved the final version as submitted.

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Gama MCFLR, Fagundes EDT, Queiroz TCN, Rodrigues AT, Vieira LC, Ferreira AR. Fatores preditivos de morbidade associada à sangramento de varizes esofágicas em crianças com hipertensão porta. Arq Gastroenterol. 2023;60(2):247-56.

RESUMO – Contexto – A maioria dos dados sobre a história natural da hipertensão porta provém de estudos em adultos. A morbidade associada à hemorragia digestiva alta (HDA) em crianças com hipertensão porta ainda não foi sistematicamente estudada. **Objetivo –** Descrever a morbimortalidade da HDA em pacientes pediátricos com hipertensão porta e identificar fatores preditivos para a ocorrência de suas principais complicações. **Métodos –** Este estudo retrospectivo incluiu pacientes pediátricos com hipertensão porta cirrótica ou com obstrução extra-hepática da veia porta (OEHVP). A mortalidade e as complicações da HDA foram estudadas até seis semanas após o sangramento. Para determinar os fatores preditivos de morbidade, foi realizada análise multivariada por meio de regressão logística; todos os resultados foram considerados significativos com $P<0,05$. **Resultados –** Oitenta e seis pacientes (51,2% com OEHVP e 48,8% com cirrose) tiveram 174 eventos hemorrágicos. A ascite foi a complicação mais comum (43,1% de todos os casos), sendo mais prevalente em pacientes com cirrose ($P<0,001$). A cirrose foi preditor da ocorrência de pelo menos uma complicação (OR 20,3). A necessidade de transfusão sanguínea foi preditora de pelo menos uma complicação (OR 5,8), ascite (OR 7,2) e infecções (OR 3,8) no grupo geral e pelo menos uma complicação (OR 11,3) e ascite (OR 5,8) nos cirróticos. A necessidade de expansão foi preditor de qualquer morbidade (OR 4,6) e infecções (OR 3,9) no grupo geral, além de ser preditor de infecção em cirróticos (OR 5,4). Não houve óbitos por HDA nas 6 semanas pós-sangramento. **Conclusão –** O estudo mostrou a relevância da morbidade após HDA em pacientes pediátricos com hipertensão porta, principalmente naqueles com cirrose. Os pacientes com instabilidade hemodinâmica que necessitam de transfusão de sangue ou expansão na admissão têm risco aumentado de complicações relacionadas à hemorragia digestiva alta e devem ser monitorados de perto.

Palavras-chave – Hipertensão porta; hemorragia digestiva; varizes esofágicas; morbidade; crianças.

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