Mortality, Risk Factors and Disparities Associated with Esophageal Variceal Bleeding in Children's Hospitals in the US

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Objectives To use a large administrative database to determine the mortality, risk factors, and comorbidities of esophageal variceal bleeding in children.

Study design Retrospective cohort study using Pediatric Health Information System data from 50 tertiary children's hospitals in the US. *International Classification of Diseases* (ICD) codes (FY 2020 ICD-10 update and revision 10 of ICD-9) from 2004 through 2019 identified children 18 years and younger with variceal bleeding and complications. Univariate analyses used the Student *t* -test for continuous variables (age) and the χ^2 test for categorical variables (all others). A mixed-effects linear regression was performed for multiple variables.

Results There were 1902 patients who had 3399 encounters for esophageal variceal bleeding. The mortality rate for variceal bleeding was 7.3%, increasing to 8.8% by 6 weeks; any mortality during the study was 20.1%. Transfusion was required in 54.7% of encounters, and 42.6% were admitted to the intensive care unit. Variceal bleeding encounters were complicated by peptic ulcer disease (6.9%), bacteremia (11.4%), acute renal failure (5.1%), mechanical ventilation (18%), ascites (21.3%), and peritonitis (3.3%). Multivariable mixed-effects logistic regression showed that Black race (OR, 2.59; $P < .001$) or Hispanic ethnicity (OR, 2.31; $P = .001$), but not sex, household income, or insurance type, were associated with increased mortality. Bacteremia, peritonitis, mechanical ventilation, acute renal failure, and transfusion were associated with higher mortality (ORs of 2.29, 2.18, 1.93, 6.33, and 1.81, respectively; $P < .001$, .005, .011, <.001, and .005, respectively).

Conclusions The 6-week mortality rate for variceal bleeding in children is 8.8%. Black or Hispanic children are at higher risk of dying. Serious morbidities associated with variceal hemorrhage impact mortality. These data can inform consideration of prophylactic or therapeutic interventions for children at risk. *(J Pediatr 2021;232:176-82)*.

Variceal bleeding, a dreaded complication of portal hypertension, may result from cirrhosis or portal vein thrombosis. Because mortality in adults ranges from 15% to 30% at 6 weeks, interventions to prevent bleeding and decrease mortality have been studied, including medications to decrease portal flow and variceal band ligation/sclerotherapy to obliterate varices.[1-7] In adults with medium to large varices on screening endoscopy, primary prophylaxis to prevent bleeding is life-saving and decreases morbidity.[8,9]

Because variceal bleeding is rare in children, morbidity and mortality are not well-studied; screening endoscopy and primary prophylaxis are advocated by some investigators, but are not standard of care.[10-16] The potential value of screening endoscopy depends in part on the risk of bleeding, the mortality, and the effectiveness of interventions to prevent bleeding. In published series of 20-150 children, the mortality rate varied from 0% to 20%; in a Childhood Liver Disease Research Network abstract, risk of variceal bleeding in almost 600 children with portal hypertension was 8% at 5 years with no mortality.[16-23]

We studied children from the Pediatric Health Information System (PHIS) database, hypothesizing that the mortality of variceal bleeding in children would be low and that clinical variables associated with more severe liver disease would increase mortality.

Methods

Data for this study were obtained from the PHIS, an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation encounter-level data from more than 52 not-for-profit, tertiary care pediatric

CPT	Current Procedural Technology
EGD	Esophagogastroduodenoscopy
ICU	Intensive care unit
ICD	*International Classification of Diseases*
PHTN	Portal hypertension
PHIS	Pediatric Health Information System

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hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Lenexa, Kansas). Data quality and reliability are ensured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by IBM Watson Health (Ann Arbor, Michigan). For the purposes of external benchmarking, participating hospitals provide discharge and encounter data including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource use data (eg, pharmaceuticals, imaging, and laboratory) into PHIS. Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. For this study, data from 50 hospitals were included.

Specific Data Elements Obtained

We searched PHIS from 2004 to 2019 (inclusive) for cases using the following criteria: (1) age 18 years or younger, (2) inpatient or observation encounters, and (3) any *International Classification of Diseases* (ICD)-9 or ICD-10 code for bleeding esophageal varices associated with that encounter (456.0, 456.20, I85.01, I85.11).

We then gathered the following data for each case: hospital, patient age, sex, ethnicity (Hispanic or non-Hispanic), race (White, Black, Asian, or other), estimated household income by median for zip code of residence, insurance type (commercial, Medicaid, or other), length of stay, pediatric intensive care unit (ICU) use, packed red blood cell transfusion, inpatient mortality during the same encounter, inpatient mortality within 6 weeks, and any mortality for the patients found in PHIS through 2019. We calculated mortality by encounter, as well as by patient.

Additionally, we determined the presence or absence of specific ICD-9 and ICD-10 diagnostic and procedure codes associated with each case: any esophagogastroduodenoscopy (EGD) performed (45.16, 0DJ08ZZ), EGD with banding or sclerotherapy (42.33, 42.91, 06L38CZ), cirrhosis (571.5, 571.6, K71.7, K74.3, K74.4, K74.5, K74.60, K74.69, P78.81), portal hypertension (572.3, K76.6), portal venous thrombosis (452, I81), peptic ulcer disease (538, 528.01, 531.XX-533.XX, K25.X-K28.X), bacteremia or sepsis (790.7, 771.81, 995.91, 995.92, A40.8, A40.9, A41.XX, B37.7, P36.2, P36.9, P36.2, P36.9, R65.2X, R78.81), ascites (789.5, 789.59, R18.8), acute renal failure (584.X, N17.X), peritonitis (567.XX, K65.X), and the use of mechanical ventilation (96.70, 96.71, 96.72, 5A1935Z, 5A1945Z, or 5A1955Z, or a charge mapped to a clinical transaction classification code 521166 or 521169). We also determined whether liver transplant (50.51, 50.59, 0FY00Z0) was performed within the study period and the duration of time from first recorded variceal bleed until transplant.

Data were then stored on a secure server compliant with the Health Insurance Portability and Accountability Act (Box Health, www.box.com/industries/healthcare) before and during subsequent analyses. All data were anonymized before the PHIS query, and no protected health information was used during the duration of the analysis. The Indiana University Institutional Review Board approved this study with exempt status before pulling data or performing analyses.

Statistical Analyses

Univariate analyses were performed using the Student *t* test for continuous variables (age) and the χ^2 test for categorical variables (all others). Mixed-effects linear regression was then performed using hospital as a random effect, and age, sex, race, ethnicity, income, insurance type, ICU status, transfusion status, and diagnostic/procedural variables (banding, mechanical ventilation, portal venous thrombosis, peptic ulcer disease, bacteremia/sepsis, peritonitis, transfusion of packed red blood cells, acute renal failure, and ascites) modeled as fixed effects. Income was transformed into a categorical variable as noted in **Table I**. We built multiple models to determine if any terms interacted. The goodness of fit was comparable for most models, so we elected to report the results from the full model with all variables. We used the R software package (r-project.org) with the "lme4" package to build each regression model.

We subsequently constructed survival curves for all patients, as well as stratified survival curves by race. Time to event was calculated as either any mortality coded in PHIS, age 18, or the last quarter of 2019. Patients that reached age 18 without mortality were censored in the survival curve model. All survival analysis was performed using the R package "survival." On the stratified survival curve by race, we performed Cox regression. We computed 95% CIs, and the significance on Cox regression and mixed-effects logistic regression was determined at a *P* value of less than .05.

Results

We found 1902 patients who had at least 1 encounter for bleeding esophageal varices; the mortality rate for variceal bleeding was 7.3%, with an increase in mortality to 8.8% by 6 weeks (**Table I**). The rate of any mortality (per patient) during the study period was 20.1%. The per-patient 6-week mortality rate for those with a diagnosis of cirrhosis was 8.4%, and for those with portal vein thrombosis was 5.4%; these differences were not statistically different rates by univariate comparison ($P = .08$). Taking liver transplantation into consideration, the rate of mortality or transplantation was 10.1% at 6 weeks and 26.9% over the entire study period. In addition, we assessed a subgroup of patients who had a single admission for variceal bleeding in our dataset, as an estimate of a "first bleed." The mortality rate for these 1202 patients was 8.7% at 6 weeks (data not shown), which was similar to the mortality for our overall cohort (8.8%).

Overall, 86.4% of patients had a diagnostic code for portal hypertension, 20.2% were coded as portal vein thrombosis, and 62 patients (3%) who had undergone prior liver transplantation subsequently developed variceal bleeding; 80%

Table I. Patient characteristics

Characteristics	No. of patients (out of 1902)	Percentage of patients
Female sex (n)	955	50.2%
Race		
White	1268	66.7%
Black	211	11.1%
Asian	83	4.4%
Other	264	13.9%
Unknown	76	4.0%
Ethnicity		
Hispanic	493	25.9%
Non-Hispanic	942	49.5%
Unknown	467	24.6%
Insurance		
Commercial	701	36.9%
Medicaid	992	52.2%
Other	195	10.3%
Unknown	14	0.7%
Income		
<25k	118	6.2%
25-50k	1170	61.5%
50k-75k	445	23.4%
75k-100k	98	5.2%
>100k	19	1.0%
Unknown	52	2.7%
Medical history		
Cirrhosis	684	36.0%
Portal hypertension	1643	86.4%
Portal venous thrombosis	385	20.2%
History of liver transplant	62	3.3%
No. of admissions		
Mean	1.79	
Median	1	
1 admission	1202	63.2%
2 admissions	382	20.1%
3 admissions	151	7.9%
4 admissions	69	3.6%
≥5 admissions	98	5.2%
Mortality		
During any bleeding encounter	138	7.3%
6-week mortality	168	8.8%
Any mortality	383	20.1%
Mean time to mortality (days)	351.8	
Median time to mortality (days)	0	
Liver transplantation	628	33%

of the patients had 1 or 2 admissions for bleeding esophageal varices. Most patients were White and non-Hispanic, and receiving public insurance. Most patients had an estimated household income between US$25 000 and US$75 000 per year.

From 2004 to 2019, there were 33 885 encounters for portal hypertension in 9545 patients in the PHIS data base; there were 4297 encounters with portal venous thrombosis in 2265 patients and 14 173 encounters for cirrhosis in 6175 patients. Thus, 19.9% of patients with portal hypertension had an admission for bleeding esophageal varices during the study period.

A total of 628 patients (33%) in our cohort eventually underwent liver transplant. The mean time to transplant from initial bleed was 457.2 ± 804 days (range, 0-4269 days) and the median time was 128 days (IQR, 40-476 days). Eight patients underwent liver transplantation during the same admission as the variceal bleed.

Table II shows descriptive statistics by encounter. We found 3399 encounters for bleeding esophageal varices. Mortality for any individual encounter for variceal bleeding was 4.1%, with mortality increasing to 4.9% by 6 weeks. Transfusion was performed in 54.7% of encounters and 42.6% of patients were admitted to the ICU. Variceal bleeding encounters were complicated by a diagnosis of peptic ulcer disease in 6.9%, bacteremia in 11.4%, acute renal failure in 5.1%, mechanical ventilation in 18%, ascites in 21.3% and peritonitis in 3.3% of patients.

Endoscopies were coded in 76% of the encounters. In most encounters, it was not possible to differentiate between therapeutic interventions of banding vs sclerotherapy; among 362 records where Current Procedural Technology (CPT) codes were provided, 250 underwent banding and 112 underwent sclerotherapy.

To examine the mortality of a "typical encounter" of variceal bleeding, we assessed 410 encounters where both transfusion and endoscopic band ligation were documented; for this small subgroup, the mortality rate was 1.7% (data not shown).

On mixed-effects logistical regression analysis (performed by encounter), Black race (OR, 2.59; $P < .001$) and Hispanic ethnicity (OR, 2.31; $P = .001$) but not sex, household income, or insurance type were associated with an increased mortality rate (Table III). Bacteremia, peritonitis, mechanical ventilation, acute renal failure and transfusion were associated with higher mortality (OR, 2.29, 2.18, 1.93, 6.33, and 1.81, respectively, with $P < .001$; $P = .005$; $P = .011$; $P < .001$, and $P = .005$, respectively). Portal vein thrombosis was associated with lower mortality (OR, 0.58; $P = .027$).

The Figure shows survival curves by the overall mortality rate, stratified by race. Cox regression analysis showed a

Table II. Encounter characteristics

Characteristics	No. of encounters (n = 3399)	Percentage of encounters
Age at admission (years)		
Mean	7.8	
Median	6.9	
Length of stay (days)		
Mean	15.2	
Median	5	
Mortality		
Same encounter	138	4.1%
6-week mortality	168	4.9%
Mean time to mortality (days)	491.4	
Median time to mortality (days)	86	
ICU admissions	1448	42.6%
Need for PRBC transfusion	1860	54.7%
EGD with biopsies	890	26.2%
Banding/sclerotherapy	2310	68.0%
EGD only	278	8.2%
Either EGD or banding	2588	76.1%
Peptic ulcer disease	235	6.9%
Bacteremia	389	11.4%
Peritonitis	112	3.3%
Acute renal failure	173	5.1%
Ascites	723	21.3%
Mechanical ventilation	612	18.0%

PBRC, packed red blood cells.

Table III. Mixed effects logistical regression results

Variables	OR	*P* value	Lower	Upper
Sex				
Female	–	–	–	–
Male	1.36	.094	0.95	1.96
Ethnicity				
Non-Hispanic	–	–	–	–
Hispanic	2.31	.001	1.38	3.87
Race				
White				
Asian	0.63	.425	0.21	1.94
Black	2.59	<.001	1.53	4.36
Other	1.09	.752	0.65	1.83
Income				
25-50k	–	–	–	–
<25k	1.18	.627	0.61	2.26
50k-75k	0.95	.835	0.58	1.55
75k-100k	0.68	.508	0.22	2.13
>100k	0.00	.916	0.00	Inf
Insurance type				
Commercial	–	–	–	–
Medicaid	1.38	.172	0.87	2.20
Other	1.21	.601	0.59	2.48
ICU	3.52	<.001	2.16	5.74
Clinical features				
Portal venous thrombosis	0.58	.027	0.35	0.94
Banding	0.70	.062	0.48	1.02
Mechanical ventilation	1.93	.005	1.22	3.05
Peptic ulcer disease	0.63	.229	0.30	1.34
Bacteremia	2.29	<.001	1.51	3.49
Peritonitis	2.18	.011	1.19	3.98
Transfusion	1.81	.005	1.20	2.72
Acute renal failure	6.33	<.001	3.96	10.12
Ascites	1.48	.052	1.00	2.19

significant difference between Black and White patients ($P = .0465$), but no difference between Asian and White patients ($P = .5279$). We performed a survival analysis on patients with cirrhosis vs portal vein thrombosis, and although patients with portal vein thrombosis had lower overall mortality throughout the time course of the analysis, this difference was not statistically significant ($P = .072$ by Cox regression).

Discussion

The mortality rates we report can be used to inform guidelines and individual decisions about primary prophylaxis and other clinical decision-making in children with portal hypertension. When assessed endoscopically, varices have been reported to be present in more than 66% of children with portal hypertension, in the context of either cirrhosis, extrahepatic portal hypertension, or other causes.[11,20,24,25] Our study is in line with previous reports: nearly 20% of patients in the PHIS database with portal hypertension had an encounter for variceal bleeding.[11,18,20,24-27] The mortality rate associated with variceal bleeding in pediatric patients has been reported, often without a described timeframe, or sometimes within 6 weeks of bleeding. This can range up to 20% in the literature; pediatric mortality has usually been reported to be lower than that reported in adults.[2-7,16-23]

An analysis of the PHIS database allows characterization of variceal bleeding in a large number of children at 50 tertiary American children's hospitals. The limitations of this administrative database make it difficult to ascertain the true percentage of children with chronic hepatocellular liver disease or cirrhosis vs those with isolated extrahepatic portal hypertension. Many children required multiple admissions for variceal bleeding, and blood transfusions and ICU admission were often required. Hospitalizations were frequently complicated by ascites, mechanical ventilation, bacteremia, acute renal failure, and spontaneous bacterial peritonitis. These data suggest the potential value of prophylactic antibiotics, which are standard of care in adults with variceal bleeding. They also demonstrate the frequency of important comorbidities. It is notable that one-third of these patients underwent liver transplantation, within a median of 128 days (range, 0-4269 days) of the initial gastrointestinal bleed.

Acute variceal bleeding is managed with volume resuscitation, blood products, and circulatory support. Often, somatostatin analogues are used to constrict the splanchnic circulation, although there are limited data available in children.[17,28,29] Endoscopy with variceal band ligation or sclerotherapy is a mainstay of treatment, usually requiring 3 or more additional sessions after initial presentation.[12,21,30] In our report, nearly 2600 endoscopies were reported; in 890 of those, only EGD without mention of therapeutic intervention was reported, and 811 hospitalizations did not report an endoscopy CPT code, because these events are not captured well within PHIS. Because it is likely that endoscopy occurred during most of these hospitalizations, incomplete coding is likely. We cannot be certain whether control of bleeding was attempted in those patients who underwent EGD only, and codes to differentiate between band ligation and sclerotherapy were not commonly provided. Of note, in almost 400 patients who had CPT codes to differentiate the 2 procedures, mortality was not significantly different in children who underwent banding vs sclerotherapy.

As reported in the pediatric literature, almost 7% of children undergoing endoscopy for variceal bleeding had peptic ulcer disease. This consideration is important when gastrointestinal bleeding occurs in a child with known portal hypertension because different endoscopic or medication interventions might be implemented.

Mixed-effects logistical regression analysis permitted an evaluation of the risk factors for death associated with an admission for bleeding esophageal varices. The identification of risk factors might be used to identify children at higher risk of death from bleeding—these individuals might be selected for primary prophylaxis, shunting, or transplantation. Portal vein thrombosis as a cause of portal hypertension was associated with a lower mortality risk. Children who were transfused, had bacteremia, spontaneous bacterial peritonitis, renal failure, or mechanical ventilation had a significantly higher risk of death, although these are all components of multisystem organ failure and are associated with higher mortality in most disease cohorts.

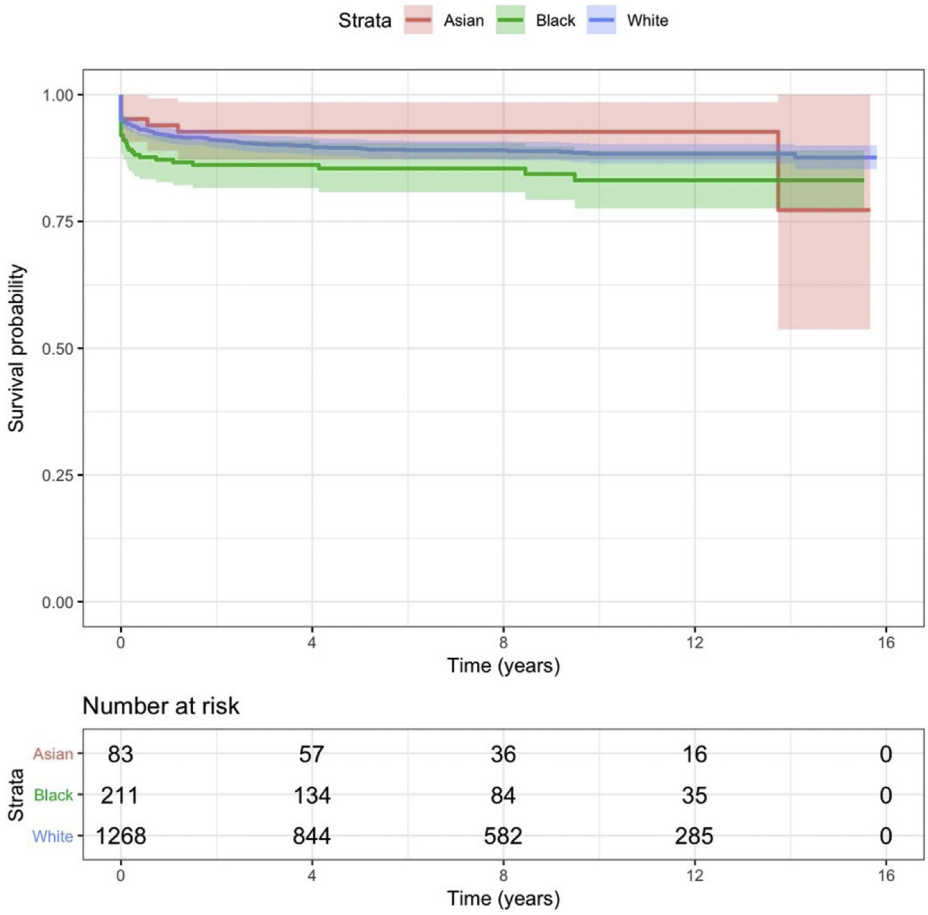

Figure. Survival curve, all patients and stratified by race compared with a survival curve by overall mortality. Shaded areas show the 95% CI. Cox regression was performed on the survival curve and showed a significant difference between black and with patients (P = .0465), but no difference between Asian and White patients (P = .5279).

Black race and Hispanic ethnicity had a significant impact on mortality, with an increased odds of death of 2.59 and 2.31, respectively, after controlling for household income and insurance status. Racial disparities in Black adults with liver disease, including higher rates of hepatocellular carcinoma in hepatitis C, longer waits for endoscopy, and lower rates of transplantation, have been reported.[31-33] Racial and socioeconomic disparities in liver transplant outcomes have also been described in children and young adults.[34] Increased mortality in Black patients has been reported in other conditions as well, with a recent focus on racial disparities in coronavirus disease.[35] Such a significant increase in the odds of death in Black or Hispanic children after the acute event of a variceal hemorrhage is noteworthy. The National Institute on Minority Health and Health Disparities Research Framework identifies biological, behavioral, environmental, and sociocultural factors, as well as the health care system as domains of determinants of health.[36] Potential causes of increased mortality in Black children with variceal bleeding could include environmental factors, poor access to medical care, or an implicit bias on the part of health care providers. Potential actions to decrease this gap might include anticipatory guidance to families regarding variceal bleeding, planning regarding emergency response to hemorrhage episodes, and the education of pediatricians and subspecialists regarding mortality and risk factors in Black and Hispanic children.

A large retrospective cohort study such as this has many advantages; however there are important but expected limitations: low sensitivity (although relatively high specificity) of ICD codes, omitted data, possible era effect and the possibility of mortality or other interventions occurring in non-PHIS hospitals.[37] ICD-9 and -10 coding accuracy has been assessed in PHIS for a number of conditions, including febrile infants, *Clostridium difficile* infection, and sepsis, but not specifically for gastrointestinal bleeding.[38-40] Coding accuracy has been assessed for gastrointestinal bleeding in adults, although not within PHIS specifically. Sensitivity tended to be moderate (70%-80%), but specificity high (>90%), as is the case for most assessments of ICD-9 and -10 coding accuracy.[37,41] We may have missed variceal bleeding not coded specifically as such, and it is possible that a prophylactically scheduled endoscopy could have been coded as "variceal bleeding." Because information regarding laboratory

data and outpatient medication management are not included, we were unable to assess the effect of prophylaxis or outpatient endoscopic management. Because the PHIS only reflects data from hospitalizations and procedures in participating hospitals, it thus does not include events at outside hospitals, including deaths at home or in local hospitals. Therefore, we may have under-reported the mortality rate, although it could be argued that children with chronic liver disease are likely to return to the tertiary care hospital where they are followed. Similarly, we could have underestimated other diagnoses if they were not coded. Although the mortality rate was lower (1.7%) in a smaller "typical" subgroup with both transfusion and band ligation coded, we assume that the mortality and comorbidities are at least what is reported in PHIS.

These rich data on mortality in almost 2000 children with variceal bleeding can be used in a number of ways. High mortality has been used as an argument for screening endoscopy and primary prophylaxis in children.[11,21] Neither screening nor primary prophylaxis are included in standard of care protocols in the US, although they may be recommended in other countries.[11,12,42] High mortality rates would also lower the threshold for other interventions such as transjugular intrahepatic portosystemic shunts, surgical shunts, and liver transplantation. High mortality rates should lead to enhanced education of families. Clearly, there will be individual, cultural, and national differences in risk tolerance and what is considered "low" mortality when using these data. In an era when the 1-year survival after liver transplantation greatly exceeds 90%, accurate mortality data are vital. Our finding that Black and Hispanic children have a much higher mortality rate makes individualized counseling, consideration of prophylactic interventions, and risk stratification essential.

Clearly, more study is needed on the management of variceal bleeding in children with liver disease. There are extensive data in adults, but they cannot easily be extrapolated to children given physiologic differences in young children and more comorbidities in adults, potentially influencing mortality. The present report provides more robust mortality data that can impact future multicenter study design. The Childhood Liver Disease Research Network (NCT00571272, NCT00345553, NCT00061828) is following hundreds of children with biliary atresia, α_1-antitrypsin deficiency, Alagille syndrome, and progressive familial intrahepatic cholestasis longitudinally, and will provide more carefully curated data. The Pediatric Baveno group is also planning a prospective registry of children with portal hypertension, which will provide further insights.

In conclusion, variceal bleeding has a lower mortality in children when compared with adult reports but remains substantial at nearly 9%. Black and Hispanic children are at higher risk of dying with variceal bleeding and these disparities should be addressed. Serious comorbidities are commonly associated with variceal hemorrhage and impact mortality. These data can be used when prophylactic or therapeutic interventions are considered for children at risk for variceal bleeding. ■

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