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# Risk of variceal hemorrhage and pretransplant mortality in children with biliary atresia

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## Abstract

**Background and Aims:** The natural history of gastroesophageal variceal hemorrhage (VH) in biliary atresia (BA) is not well characterized. We analyzed

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risk factors, incidence, and outcomes of VH in a longitudinal multicenter study.
**Approach and Results:** Participants enrolled in either an incident
(Prospective Database of Infants with Cholestasis [PROBE]) or prevalent
(Biliary Atresia Study of Infants and Children [BASIC]) cohort of BA were
included. Variceal hemorrhage (VH) was defined based on gastrointestinal
bleeding in the presence of varices accompanied by endoscopic or nontrans-
plant surgical intervention. Cumulative incidence of VH and transplant-free
survival was compared based on features of portal hypertension (e.g., spleno-
megaly, thrombocytopenia) and clinical parameters at baseline in each cohort
(PROBE: 1.5 to 4.5 months after hepatoportoenterostomy [HPE]; BASIC: at
enrollment > 3 years of age). Analyses were conducted on 869 children with
BA enrolled between June 2004 and December 2020 (521 in PROBE [262
(51%) with a functioning HPE] and 348 in BASIC). The overall incidence of
first observed VH at 5 years was 9.4% (95% CI: 7.0–12.4) in PROBE and 8.0%
(5.2–11.5) in BASIC. Features of portal hypertension, platelet count, total bili-
rubin, aspartate aminotransferase (AST), albumin, and AST-to-platelet ratio
index at baseline were associated with an increased risk of subsequent VH
in both cohorts. Transplant-free survival at 5 years was 45.1% (40.5–49.6) in
PROBE and 79.2% (74.1–83.4) in BASIC. Two (2.5%) of 80 participants who
had VH died, whereas 10 (12.5%) underwent transplant within 6 weeks of VH.
**Conclusions:** The low risk of VH and associated mortality in children with
BA needs to be considered in decisions related to screening for varices and
primary prophylaxis of VH.

# INTRODUCTION

Biliary atresia (BA) is a progressive chronic liver dis-
ease resulting from fibro-obliteration of bile ducts,
which can lead to cirrhosis and end-stage liver dis-
ease. Hepatoportoenterostomy (HPE), also known as
the Kasai procedure, provides a means of relieving ex-
trahepatic biliary obstruction and permitting bile flow.
However, HPE is not a curative procedure, and most
patients will require liver transplantation in childhood
secondary to progression to cirrhosis and end-stage
liver disease. BA is the leading indication for liver trans-
plantation in the pediatric population.[1–3] Cirrhosis in
BA leads to the development of portal hypertension
(PHT) with an attendant risk of development of esoph-
ageal and gastric varices. Gastroesophageal variceal
hemorrhage (VH) can lead to mortality and morbidity,
including decompensation in hepatic function and ac-
celerated need for liver transplantation.[4–7] The mag-
nitude of these effects from VH is not well delineated.

The course of BA following HPE is highly depen-
dent on the re-establishment of bile flow in the months
following HPE.[3] Infants who have poor bile drainage
following HPE develop end-stage liver disease requir-
ing liver transplantation before 2 to 3 years of age.

Meanwhile, infants who survive with their native liver
beyond age 3 will typically follow a different course,
with PHT and cirrhosis as the major drivers of com-
plications in this population.[2] One must acknowledge
that the presentation of complications from BA, includ-
ing VH, may differ between these two separate popu-
lations. Many of the existing studies reporting VH in BA
are retrospective, single-center, and span over large
time periods.[4,8,9] The natural history of VH in BA is not
well defined, and systematic evaluation of risk factors
for VH in BA requires further evaluation. Because of a
lack of an evidence base,[10] there remains consider-
able variation in the surveillance for and management
of varices in pediatric PHT.[11,12]

The Childhood Liver Disease Research Network
(ChiLDReN) is a National Institute of Diabetes,
Digestive and Kidney Diseases (NIDDK)/National
Institute of Health–funded cooperative research con-
sortium of 16 clinical sites in the United States and
Canada. Its goal is to advance understanding of the eti-
ology, pathogenesis, course, and outcomes of BA and
other pediatric cholestatic conditions. The Prospective
Database of Infants with Cholestasis (PROBE; Clinical
Trials.gov: NCT00061828) is designed to acquire lon-
gitudinal, prospective, clinical, and laboratory data in a

standardized fashion at defined time points to enable definitive studies of natural history of cholestatic liver diseases in infants and early childhood. The Biliary Atresia Study in Infants and Children (BASIC; Clinical Trials.gov: NCT00345553) is a second ChiLDReN longitudinal study, in which participants with BA not enrolled in PROBE are enrolled at any time after age 6 months following their BA diagnosis, either before or after liver transplantation. The ChiLDReN's research approach, which combines both incident and prevalent cohorts of children with BA, permits a unique and powerful ability to study the natural history and risk factors for VH in BA, which may then inform future medical, endoscopic, and surgical management of children with this disease.

## PATIENTS AND METHODS

### Study populations

Data from PROBE and BASIC were analyzed in parallel. PROBE (NCT00061828)[1,3] examines incident cases of BA through a prospective longitudinal study of neonatal cholestasis. Study visits are coordinated with routine clinical care at 1, 2, 3, and 6 months after HPE, at 12, 18, and 24 months of age and yearly thereafter. BASIC (NCT00345553)[2] includes annual follow-up of a prevalent cohort of children at least 6 months of age with BA. In this analysis, PROBE was used to assess the early (i.e., age < 3 years) variceal bleeding natural history of BA, while BASIC data were analyzed for patients who enrolled at age > 3 years, denoting a large cohort of patients surviving past infancy with their native liver. Patients with polysplenia or asplenia were excluded from this analysis, given the reliance on spleen size and platelet count to determine clinically evident portal hypertension (CEPH).[13] PROBE participants were dichotomized according to successful post-HPE bile drainage as determined by achievement of total serum bilirubin less than 2 mg/dl in the first 3 months after HPE, as previously described.[3]

All participating ChiLDReN centers had institutional review board and/or research ethics approval for this study. Written informed consent was obtained from parents and/or guardians, and assent obtained from children ≥ 7 years old.

### Outcome and risk factors

The primary outcomes of interest in this analysis were time-to-first observed VH following enrollment and time-to-liver transplant or death (survival with native liver). For the PROBE cohort, the 3-month post-HPE visit was chosen as the baseline visit for this analysis (visit window 1.5–4.5 months) to allow for categorizing a participant as having successful or nonsuccessful bile drainage (based on total serum bilirubin levels up to the 3-month visit[3]). For the BASIC cohort, the first completed visit after enrollment was designated as the baseline visit. VH was operationally defined in this study as gastrointestinal bleeding in the presence of endoscopically identified esophageal or gastric varices, with a defined intervention to treat the varices, including variceal band ligation or injection sclerotherapy, surgical portosystemic shunt, or TIPS. For 7 participants in BASIC for whom variceal hemorrhage episodes did not include a recorded date, the event date was imputed between the index visit date and the previous visit date, evenly distributing the number of bleeds reported throughout the period and taking the imputed date of the first bleed. As a result, for these cases, the interval between variceal hemorrhage and transplant or death could not be determined with complete accuracy. Risk factors of interest included the following parameters: demographic variables (race, sex, and age at enrollment [for BASIC cohort only]), medical history (age at HPE, features of portal hypertension, history of VH, and presence of splenomegaly [based on physical examination]), laboratory measurements (platelet count, total bilirubin [TB], aspartate aminotransferase [AST], alanine aminotransferase [ALT], prothrombin time, international normalized ratio [INR], albumin, gammaglutamyltransferase [GGT], and AST-to-platelet ratio index [APRI]), and growth parameters (height z-score and weight z-score). All laboratory measurements were expressed as continuous variables. Several laboratory variables (TB,[3] GGT, platelet count, albumin, and INR) were also expressed relative to common clinical cutoff points. Sensitivity analyses of predictors of VH were conducted, including cases of gastrointestinal hemorrhage that were followed within 6 weeks by death or liver transplant without the aforementioned operational definition for VH.

The presence of portal hypertension was defined by the presence of complications of portal hypertension, thrombocytopenia, and/or splenomegaly. These parameters are part of a research definition of CEPH (definite, possible, or absent) developed by ChiLDReN.[13] Thrombocytopenia was defined as a platelet count < $150 \times 10^3/\mu L$. Splenomegaly was defined as a spleen palpable more than 2 cm below the left costal margin.

### Statistical analysis

Descriptive statistics were calculated for the total study population. Competing risk models were used to estimate cumulative incidence of VH, for which liver transplant and death were treated as competing events against VH. Gray's test was used to compare cumulative incidence of VH over time between groups. Kaplan-Meier curves were used to estimate

transplant-free survival in the study cohort over time. Log-rank test was used for comparing transplant-free survival between groups. PROBE participants were divided into subgroups according to their TB level in the first 3 months after HPE: Participants who reached TB < 2 mg/dl at any visit up to 3 months following HPE (baseline for this analysis) were defined as having successful bile drainage from a functioning HPE; and participants with TB ≥ 2 mg/dl at all time points during this period were defined as having a nonfunctioning HPE. Univariate cause-specific competing risk models (equivalently Cox proportional hazards models) for baseline covariates were used to study risk factors for VH. Skewed laboratory variables were modeled on the log base 2 scale to improve model fit. All analyses were conducted in SAS 9.4. Due to high correlation among predictors, multivariable modeling was not performed.

## RESULTS

### Study population

A total of 869 participants with BA and their native liver were included in this analysis: 521 from PROBE and 348 children who were >3 years old at enrollment in BASIC (Figure 1). Total enrollment between June 2004 and December 2020 in PROBE and BASIC was 799 and 760 participants, respectively. A total of 117 PROBE and 53 BASIC participants were excluded for not having undergone an HPE. A total of 45 PROBE and 37 BASIC participants were excluded for polysplenia or asplenia. A total of 108 PROBE participants were excluded for lack of baseline information, 77 for absent data, and 31 for study exit before the 3-month post-HPE visit (19 for transplant, 2 for death, and 10 lost to follow-up). There were insufficient follow-up data for 8 PROBE and 75 BASIC participants, who were therefore excluded. The early post-HPE course of BA VH was determined from the PROBE cohort; thus, 221 BASIC participants enrolled at <3 years old were excluded.[2]

Demographic data from PROBE and BASIC for this study were similar with the exception of age at baseline, which was lower for the PROBE cohort by design (PROBE median = 5.0 months, BASIC = 8.5 years) (Table 1). The BASIC cohort had a median follow-up of 4.5 years (maximum of 13.6 years), whereas PROBE participants were followed for a median of 1.3 years (maximum of 15.8 years). Participants in PROBE with a functioning HPE were followed for a median of 3.7 years, while those with a nonfunctioning HPE were followed for a median of 0.4 years. This is due to a significant proportion of these participants having transplant before 2 years of age, and that data after transplant were not included in our analysis. There was a slight predominance of females in both cohorts. Median age

at HPE was similar in both cohorts at approximately 60 days of life.

Baseline clinical features were different between the two cohorts, given the progressive nature of BA as well as a selection bias of survivors with native liver in BASIC (Table 1). Height and weight z-scores were lower in PROBE. A complex and different picture of portal hypertension was observed in these two cohorts. Platelet counts were higher in PROBE, and as such the thrombocytopenia criteria for PHT were less frequently met in PROBE compared with BASIC. When only one feature of PHT was identified, it was typically splenomegaly in PROBE, but was evenly split between splenomegaly and thrombocytopenia in BASIC. Relatively higher platelet counts in PROBE resulted in a lower percentage of participants with two features of PHT in this cohort. Serum markers of hepatobiliary injury tended to be higher in the PROBE cohort along with serum TB levels. A history of prior variceal hemorrhage before the baseline visit in these cohorts was uncommon.

### Transplant-free survival and features of PHT

A total of 282 and 83 liver transplants or death with native liver were observed in the PROBE and BASIC studies, respectively. The 5-year overall transplant-free survival rate was 45.1% (95% CI: 40.5–49.6) for PROBE and 79.2% in BASIC (95% CI: 74.1–83.4) (Table 2). In both cohorts, transplant-free survival was significantly associated with features of PHT at baseline (Figure 2). In PROBE, there was a sharp decline in transplant-free survival immediately after baseline, which leveled off about 2 to 3 years thereafter, which is consistent with the rapid progression of biliary cirrhosis in about half of patients with BA in the first years of life.[1,3] Features of PHT were strongly associated with transplant-free survival in PROBE, regardless of the functional status of the HPE (Figure 3), although overall transplant-free survival more markedly declined in participants with poor bile drainage compared to those with a functioning HPE.

### VH and features of PHT

A total of 52 and 28 VH events were observed in the PROBE and BASIC cohorts, respectively. The overall incidence of first observed VH was 9.4% (95% CI: 7.0–12.4) at 5 years in PROBE and 8.0% (95% CI: 5.2–11.5) at 5 years in BASIC (Table 3). In participants with no features of PHT at baseline, the cumulative incidence of VH in PROBE was 7.0% (95% CI: 4.3–10.5) at 5 years and 4.6% (95% CI: 1.7–9.9) at 5 years in BASIC. In contrast, in participants with two features of PHT at baseline, the cumulative incidence of VH in PROBE
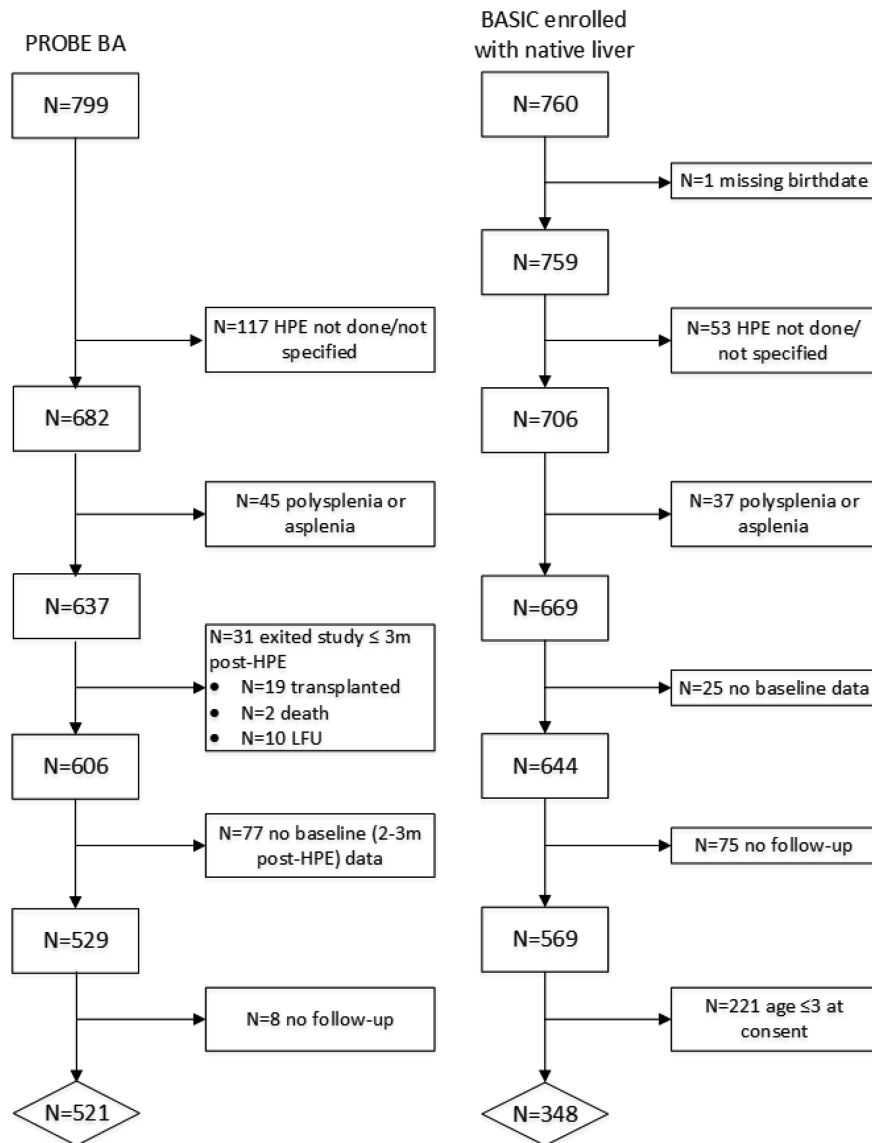
**FIGURE 1** Flow chart for participants in both BASIC and PROBE. Abbreviation: LFU, long-term follow-up

was 21.7% (95% CI: 9.1–37.7) at 5 years and 10.6% (95% CI: 5.7–17.1) at 5 years in BASIC. Transplant and death were both treated as competing events in this analysis. Patients with more features of PHT at baseline tended to have higher risk of VH, but the association was not found to be statistically significant (Table 3 and Figure 4A). However, in PROBE when stratified by bile drainage, features of PHT were associated with the cumulative incidence of VH (Figure 4B).

## Predictors of VH in BA

Univariate analysis for the risk for VH was performed separately for each cohort. Risk factors at baseline significantly associated with VH at $p < 0.05$ in at least one study are shown in Figure 5 (full results in Supporting Figure S1A,B and Supporting Table S2A,B). In both

cohorts, decreased albumin, decreased platelet count, increased TB, increased APRI, increased AST, and the presence of two features of PHT at baseline were all associated with a significantly increased risk of VH. A history of VH in between the time of HPE in PROBE (median age of 2 months) and the baseline study visit (median age of 5 months) was associated with an increased risk of VH thereafter. A history of VH in BASIC before baseline visit was not significantly associated with subsequent VH. However, a history of VH was uncommon in both PROBE ($n$ = 5) and BASIC ($n$ = 11). Increased spleen size, the presence of one feature of PHT, elevation of alkaline phosphatase, and increased AST/ALT ratio at baseline were all associated with significantly increased risk of VH in PROBE but not in BASIC. HRs for the first observed VH by common laboratory value cutoff points at baseline are provided in Table 4.

**TABLE 1** Baseline characteristics

| Variable | | PROBE (n = 521) | | BASIC (n = 348) | |
| --- | --- | --- | --- | --- | --- |
| | | N | n (%) or median (IQR) | N | n (%) or median (IQR) |
| Age at baseline[a] visit (years) | | 521 | 0.4 (0.4, 0.5) | 348 | 8.5 (5.5, 12.9) |
| Age at baseline[a] visit (months) | | 521 | 5.0 (4.4, 5.5) | | |
| Age at HPE (days) | | 521 | 62 (45,74) | 339 | 56 (42, 73) |
| Sex | Female | 521 | 284 (54.5%) | 348 | 189 (54.3%) |
| Race | | 507 | | 345 | |
| | Black | | 71 (14.0%) | | 40 (11.6%) |
| | Non-Black, Non-White | | 140 (27.6%) | | 74 (21.4%) |
| | White | | 296 (58.4%) | | 231 (67.0%) |
| PHT features | | 521 | | 348 | |
| | 0 features | | 312 (59.9%) | | 133 (38.2%) |
| | 1 feature | | 176 (33.8%) | | 94 (27.0%) |
| | Splenomegaly only | | 153 (29.4%) | | 48 (13.8%) |
| | Thrombocytopenia only | | 23 (4.4%) | | 46 (13.2%) |
| | 2 features | | 33 (6.3%) | | 121 (34.8%) |
| History of VH before baseline | | 521 | 5 (1.0%) | 348 | 11 (3.2%) |
| Height z-score | | 506 | −1.01 (−1.72, −0.23) | 338 | −0.04 (−0.77, 0.70) |
| Weight z-score | | 514 | −1.28 (−1.95, −0.53) | 342 | 0.37 (−0.36, 0.98) |
| Spleen size (cm below costal margin) | | 482 | 2.0 (0.0, 3.0) | 303 | 3.0 (0.0, 6.0) |
| Platelet count ($10^3/mm^3$) | | 439 | 262 (188, 347) | 287 | 129 (79, 217) |
| AST (U/L) | | 501 | 148 (102, 211) | 321 | 65 (43, 117) |
| ALT (U/L) | | 508 | 112 (76, 173) | 324 | 63 (35, 108) |
| AST/ALT | | 501 | 1.32 (1.03, 1.66) | 321 | 1.12 (0.84, 1.42) |
| GGT (U/L) | | 450 | 776 (337, 1,344) | 286 | 76 (33, 188) |
| Alkaline phosphatase (U/L) | | 500 | 533 (390, 729) | 309 | 303 (208, 449) |
| Total bilirubin (mg/dl) | | 509 | 2.5 (0.7, 9.0) | 318 | 0.7 (0.5, 1.3) |
| Functioning HPE[b] | | 514 | 262 (51.0%) | | |
| INR | | 397 | 1.1 (1.0, 1.3) | 271 | 1.1 (1.0, 1.2) |
| Albumin (g/dl) | | 504 | 3.7 (3.2, 4.0) | 316 | 4.2 (3.7, 4.5) |
| APRI | | 430 | 1.4 (0.9, 2.4) | 279 | 1.4 (0.7, 2.7) |

Abbreviation: IQR, interquartile range.

[a]Baseline for PROBE participants is at 2–3 months following HPE.

[b]Total bilirubin < 2mg/dl at any point up to 3 months following HPE.

Risk factors in PROBE were also analyzed stratified by functional status of the HPE (Supporting Figure S2A,B). Spleen size, platelet count, and albumin level at baseline were noted to be risk factors independent of HPE status, whereas in participants with a functioning HPE, elevated alkaline phosphatase, elevated TB, and increased AST/ALT ratio were also significant risk factors. The risk factors for VH were unchanged if one includes VH event of participants (n = 7) who died or underwent transplant within 6 weeks of gastrointestinal hemorrhage, but which otherwise did not meet the research definition of VH (Supporting Table S3).

## Mortality/transplant risk after VH

Two PROBE participants died within 6 weeks of VH (2 of 52 = 3.8%), 1 at 7 months of age with a nonfunctioning HPE performed at 115 days of life, and the other with a functioning HPE who also died at 7 months of age (Supporting Table S4). This latter participant appears to have had a significant hepatic decompensation co-incident with the VH. Relevant characteristics of the 10 total participants (10 of 80 = 12.5%) who underwent liver transplant within 6 weeks of VH include the following: (1) 7 had nonfunctioning HPE; (2) 8 were less than 2 years of age at VH and transplant; (3) 8 were

**TABLE 2** Estimated transplant-free survival by number of PHT features

| PHT features | Years since baseline | PROBE (n = 521) | | | BASIC (n = 348) | | |
|---|---|---|---|---|---|---|---|
| | | No. of events | No. at risk | Survival estimates (95% CI) | No. of events | No. at risk | Survival estimates (95% CI) |
| Overall | 1 | 211 | 283 | 58.5% (54.0%–62.6%) | 31 | 298 | 91.0% (87.5%–93.6%) |
| | 2 | 251 | 212 | 49.7% (45.2%–54.1%) | 44 | 261 | 86.9% (82.7%–90.1%) |
| | 3 | 258 | 179 | 48.0% (43.5%–52.4%) | 55 | 220 | 83.0% (78.4%–86.7%) |
| | 5 | 268 | 137 | 45.1% (40.5%–49.6%) | 64 | 162 | 79.2% (74.1%–83.4%) |
| 0 features | 1 | 86 | 207 | 71.6% (66.2%–76.4%) | 4 | 123 | 97.0% (92.1%–98.8%) |
| | 2 | 107 | 163 | 64.0% (58.2%–69.2%) | 4 | 113 | 97.0% (92.1%–98.8%) |
| | 3 | 109 | 137 | 63.2% (57.4%–68.5%) | 7 | 100 | 94.3% (88.3%–97.2%) |
| | 5 | 115 | 108 | 60.1% (54.1%–65.7%) | 8 | 80 | 93.3% (87.1%–96.6%) |
| 1 feature | 1 | 100 | 69 | 41.8% (34.3%–49.1%) | 8 | 76 | 91.3% (83.3%–95.6%) |
| | 2 | 118 | 43 | 30.0% (23.2%–37.2%) | 11 | 65 | 87.4% (78.4%–92.9%) |
| | 3 | 123 | 36 | 26.5% (19.9%–33.6%) | 14 | 50 | 83.1% (73.0%–89.7%) |
| | 5 | 126 | 24 | 24.0% (17.5%–31.0%) | 14 | 37 | 83.1% (73.0%–89.7%) |
| 2 features | 1 | 25 | 7 | 22.8% (10.2%–38.4%) | 19 | 99 | 84.2% (76.4%–89.6%) |
| | 2 | 26 | 6 | 19.6% (8.1%–34.8%) | 29 | 83 | 75.4% (66.5%–82.2%) |
| | 3 | 26 | 6 | 19.6% (8.1%–34.8%) | 34 | 70 | 70.5% (61.2%–78.0%) |
| | 5 | 27 | 5 | 16.3% (6.0%–31.0%) | 42 | 45 | 61.5% (51.4%–70.1%) |

listed for transplant before VH; (4) natural Pediatric End-Stage Liver Disease (PELD) scores exceeded 20 in 6 of 10 at transplant, and 6 had approved exception requests; and (5) technical variants (n = 4) and living donor (n = 2) transplants were common. During the follow-up, an additional 1 of 52 PROBE participants died more than 6 weeks after VH, and 28 underwent liver transplant more than 6 weeks after VH, whereas in BASIC 1 of 28 died more than 6 weeks after VH and 14 underwent liver transplant more than 6 weeks after VH (Supporting Figure S3A; 1 BASIC participant had no follow-up after VH). The median transplant-free survival after VH was 0.48 years in PROBE and 2.36 years in BASIC. Median transplant-free survival after VH in PROBE was 0.20 years for the nonfunctioning HPE group and 1.51 years for participants with a functioning HPE (Supporting Figure S3B).

## DISCUSSION

In this study, prospectively collected data from the natural history of over 800 children with BA, accumulated by 16 centers over 16 years, was used to determine the frequency, predictors, and outcomes of VH, one of the most serious complications of portal hypertension in children. An operational research definition of VH, dependent on a relevant intervention for bleeding, was applied to standardize this data element. BA is often treated as a single entity, although its natural history suggests that there are distinct phenotypic differences depending on the outcome of the HPE. The

early course of BA is highly dependent on whether there is restitution of bile flow after HPE. Those infants who have poor drainage develop rapidly progressive liver disease requiring liver transplantation for survival beyond 2 or 3 years of age. Children with BA and bile drainage following HPE and who survive with their native liver beyond 3 years of age typically have cirrhosis and associated portal hypertension, but demonstrate a slower course of progression and complications.[2] The current study permitted distinct analyses of both the earlier and later course of BA via the incident PROBE cohort and the cross-sectional survivor analysis in BASIC, respectively.

The clinical characteristics at baseline and the transplant-free survival differed according to the BA cohort. In PROBE, 2-year native liver survival was approximately 50% and was distinctly related to functionality of the HPE, with rare native liver survival beyond 2 years of age in those with poor bile drainage following HPE. Among the survivors greater than 3 years of age at baseline in BASIC, native liver survival was 87% and 80% at 2 and 5 years, respectively. Features of PHT were relevant in all of the BA cohorts, with significantly worse survival in those who had thrombocytopenia and/or splenomegaly at baseline. Surprisingly, these features were prognostic even in those infants with a nonfunctioning HPE. It was interesting to note that isolated splenomegaly was the sole finding of PHT in many infants with BA, consistent with our finding that some infants with PHT do not present with thrombocytopenia, at least as defined by a value less than $150 \times 10^3/mm^3$.[14]
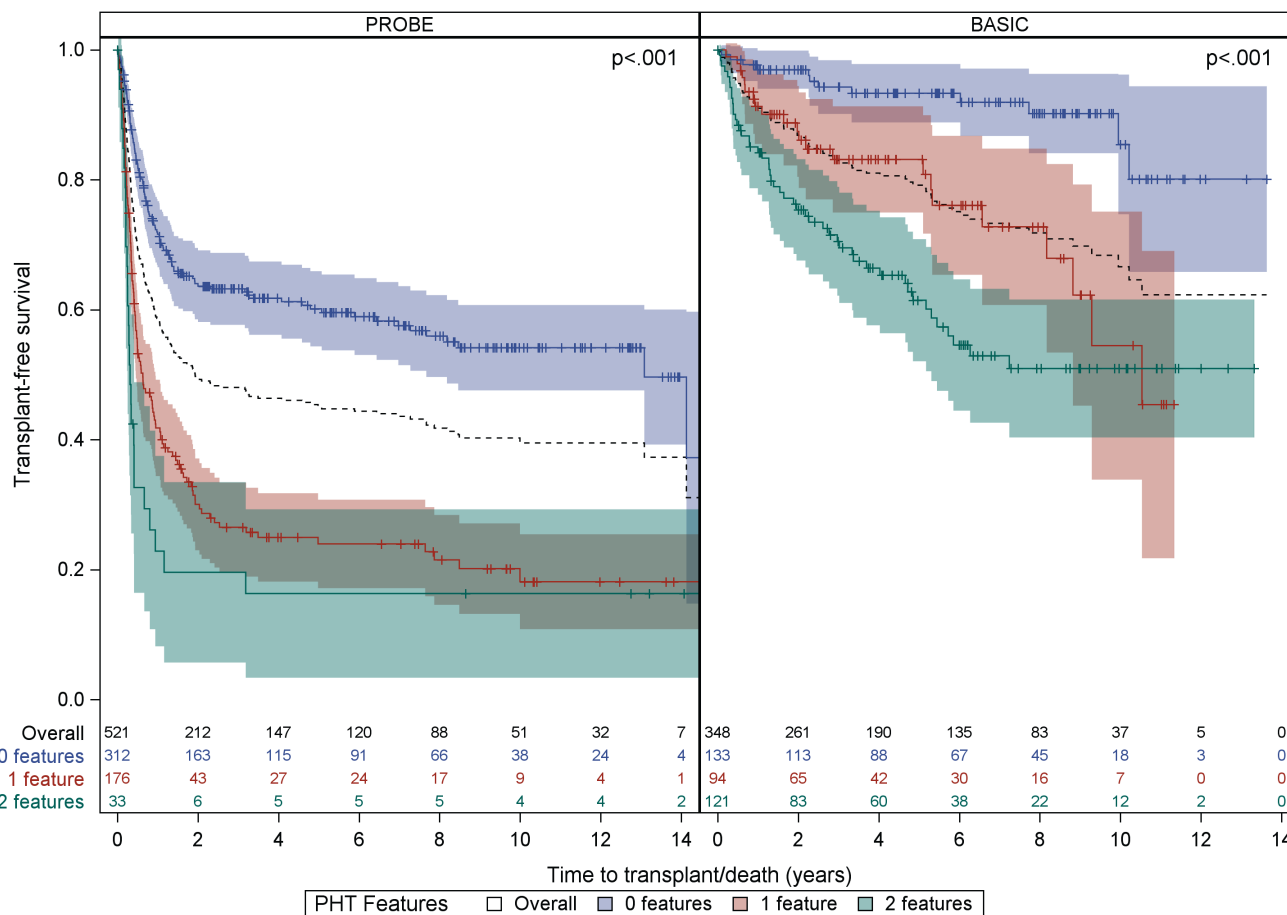
**FIGURE 2** Kaplan-Meier curve for transplant-free survival in each cohort based on number of features of PHT

The overall cumulative incidence of VH was relatively low at approximately 8%–9% after 5 years and surprisingly similar in both the PROBE and BASIC cohorts. The incidence that we recorded is lower than reports from other countries,[4,15] of which most patients reported were from before the year 2000. The differences in the reported incidence may be secondary to era-specific differences in the approach to a nonfunctioning HPE and pre-emptive use of technical variants and living donor transplantation. In infancy, especially in the context of poor bile flow after HPE, liver transplantation can be a major competing risk for VH. In the PROBE cohort, features of PHT significantly increased the risk for VH in those with and without good bile flow after HPE. Despite different baseline characteristics in PROBE and BASIC cohorts, platelet count, TB, AST, albumin, and APRI were predictive risk factors for subsequent VH in both cohorts. Elevation of TB has long been noted as a poor prognostic sign in BA. In a ChiLDReN cohort with BA followed prospectively from the time of HPE, a TB that did not fall below 2 mg/dl by 3 months following Kasai was a significant risk factor for transplant or death by 2 years of age.[3] Lampela et al. noted that increased serum bilirubin at 3 months after portoenterostomy was a significant risk factor for

gastrointestinal (GI) bleeding in BA.[9] Thus, elevated TB represents higher susceptibility to complications of cirrhosis and end-stage liver disease, including GI bleeding. It is not surprising that platelet count is predictor of risk of VH, although in 87% of the PROBE cohort the absolute platelet counts were ≥150,000, yet still were predictive of VH. This suggests that the clinically relevant "normal" range of platelets may be higher in infants with BA.

This study confirms the predictive value of an INR > 1.5 for clinical decompensation (i.e., VH in this study) in infants with chronic cholestasis. In a study of alpha-1 antitrypsin deficiency performed within ChiLDReN, elevated INR was more prevalent in participants who had PHT compared to those without PHT[16]. Elevated INR has been demonstrated to be an independent risk factor for liver-related events (including VH) in a Korean study of children with BA.[17] Furthermore, Pugliese et al. showed that INR was an independent risk factor for increased wait-list mortality in children with chronic liver failure[18]. Thus, INR as a biomarker for clinical disease progression should be monitored sequentially.

The application of cutoff points provided additional insights into the potential use of routine laboratory parameters as risk predictors of VH. Stepwise increase
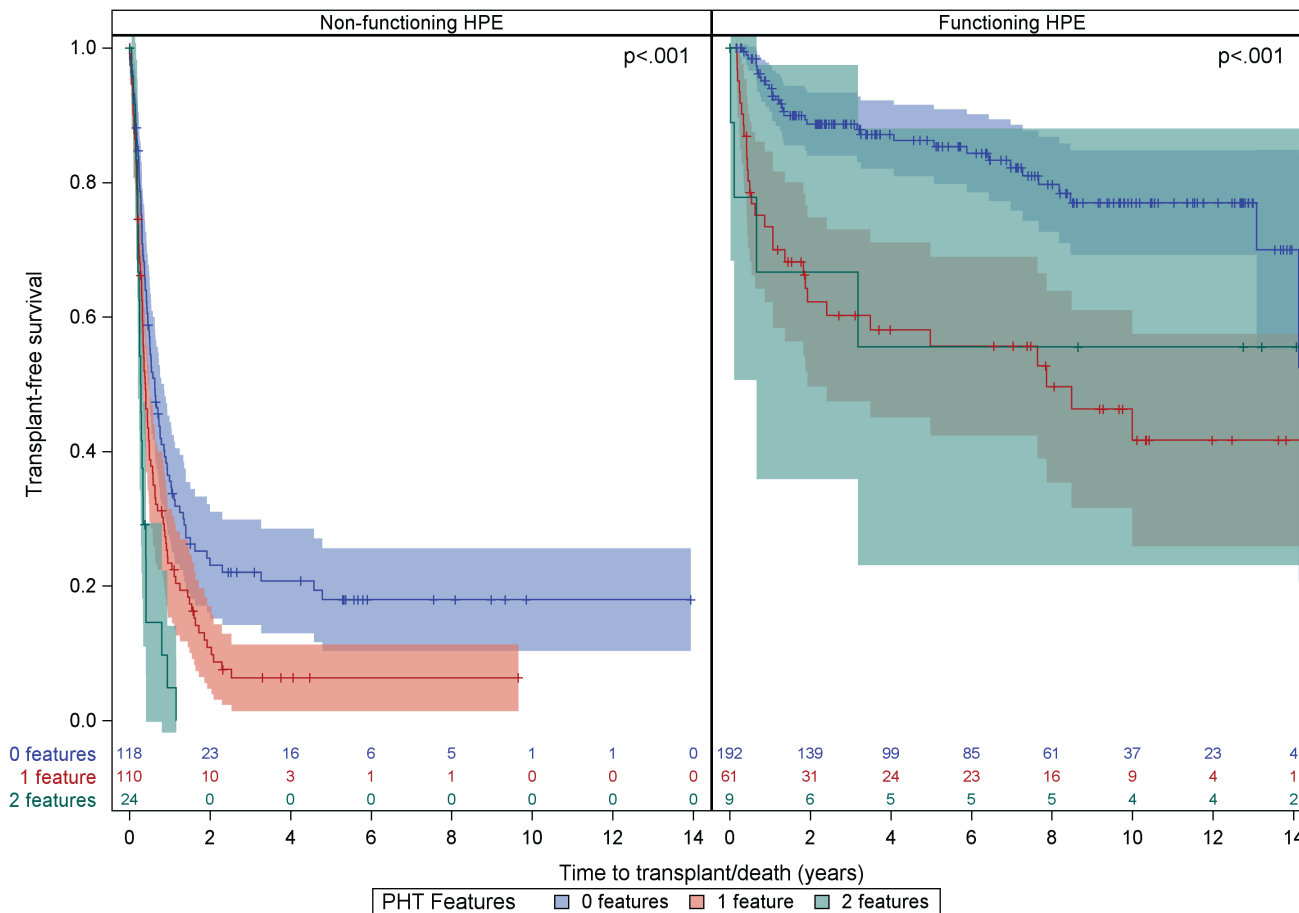
**FIGURE 3**    Kaplan-Meier curve demonstrating transplant-free survival in PROBE by functioning versus nonfunctioning HPE, based on number of features of PHT

in risk was observed in both cohorts for progressively lower serum albumin cutoff points. Albumin, in conjunction with TB, has been demonstrated to be useful in adults as an indicator of clinically significant portal hypertension, high-risk esophageal varices, as well as mortality.[19–23] Serum albumin level is correlated with hepatic venous pressure gradient in adult patients with cirrhosis.[24] Low serum albumin was found in children with BA and with definite clinically evident PHT,[14] and it has been reported that lower albumin correlated with increased severity of liver disease in cystic fibrosis.[25] Several variceal prediction rules in children with PHT correlated albumin with the presence of varices.[26–28] Low albumin has been noted in children with evidence of portal hypertensive gastropathy.[29] Moreover, serum albumin level < 3.5 g/dl has been identified as a risk factor for lower 2-year survival in infants following HPE.[30] Therefore, incorporation of serum albumin levels will be useful in prognostic model development and identifying the cohort of patients with BA with findings of PHT who have the highest risk for VH. Measurement of spleen size on ultrasound and transient elastography was not regularly performed in our cohort. Transient elastography in BA is a focus of our research consortium moving

forward,[31] and future investigations may provide further information on its impact on predicting VH.

Understanding the morbidity and mortality after VH should influence the consideration of endoscopic primary prophylaxis in BA. In this 16-year prospective study conducted by 16 hepatology-focused centers, there were only 80 episodes of observed first VH in 3,481 total person-years of observation among 869 children with BA followed for a median of 2.5 years. This low prevalence of VH, despite over 250 center-years of investigation, precludes careful evaluation of its consequences and efficacy of interventions.[6] The Baveno criteria classify any death with 6 weeks of variceal hemorrhage as related to the bleeding event.[32] One potential limitation in the existing medical literature for assessment and reporting of VH in children is a lack of a consistent definition for VH. We included an operational research definition including documentation of endoscopic evidence of varices and an intervention to treat those varices. In a few cases, gastrointestinal hemorrhage was followed by death or transplant within 6 weeks of the event, without an intervening procedure to identify varices and/or treat varices or portal hypertension. One could argue

**TABLE 3** Cumulative incidence of first VH by number of PHT features

| PHT features | Years Since baseline | PROBE (n = 521) | | | BASIC (n = 348) | | |
|---|---|---|---|---|---|---|---|
| | | No. of events | No. at risk | Cumulative incidence function estimates (95% CI) | No. of events | No. at risk | Cumulative INCIDENCE function estimates (95% CI) |
| Overall | 1 | 26 | 273 | 5.1% (3.4%–7.3%) | 8 | 292 | 2.3% (1.1%–4.3%) |
| | 2 | 37 | 203 | 7.5% (5.4%–10.1%) | 15 | 253 | 4.5% (2.7%–7.2%) |
| | 3 | 40 | 171 | 8.3% (6.0%–11.0%) | 20 | 212 | 6.3% (4.0%–9.3%) |
| | 5 | 44 | 132 | 9.4% (7.0%–12.4%) | 24 | 156 | 8.0% (5.2%–11.5%) |
| 0 features | 1 | 10 | 202 | 3.3% (1.7%–5.8%) | 1 | 123 | 0.8% (0.1%–3.8%) |
| | 2 | 16 | 158 | 5.5% (3.3%–8.6%) | 1 | 113 | 0.8% (0.1%–3.8%) |
| | 3 | 17 | 134 | 5.9% (3.6%–9.1%) | 3 | 99 | 2.5% (0.7%–6.7%) |
| | 5 | 19 | 106 | 7.0% (4.3%–10.5%) | 5 | 78 | 4.6% (1.7%–9.9%) |
| 1 feature | 1 | 10 | 65 | 5.8% (2.9%–10.0%) | 1 | 76 | 1.1% (0.1%–5.2%) |
| | 2 | 15 | 40 | 9.0% (5.2%–14.0%) | 4 | 63 | 4.9% (1.6%–11.3%) |
| | 3 | 17 | 32 | 10.4% (6.3%–15.8%) | 6 | 48 | 7.7% (3.1%–15.1%) |
| | 5 | 18 | 22 | 11.2% (6.9%–16.7%) | 7 | 34 | 9.8% (4.2%–18.4%) |
| 2 features | 1 | 6 | 6 | 18.4% (7.2%–33.7%) | 6 | 93 | 5.0% (2.0%–10.0%) |
| | 2 | 6 | 5 | 18.4% (7.2%–33.7%) | 10 | 77 | 8.5% (4.3%–14.5%) |
| | 3 | 6 | 5 | 18.4% (7.2%–33.7%) | 11 | 65 | 9.5% (5.0%–15.7%) |
| | 5 | 7 | 4 | 21.7% (9.1%–37.7%) | 12 | 44 | 10.6% (5.7%–17.1%) |
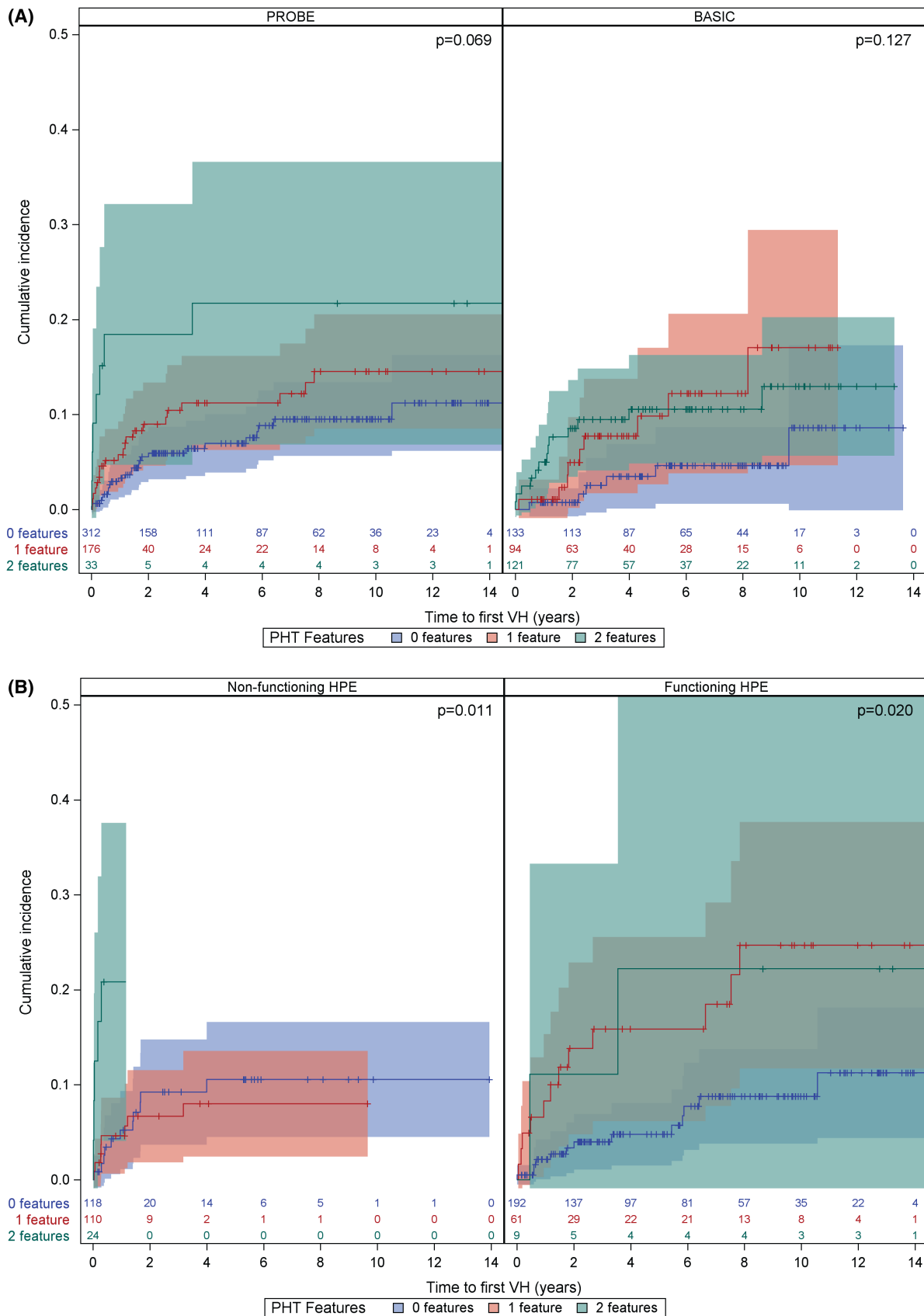
**FIGURE 4** (A) Cumulative incidence curve for first observed VH in BASIC and PROBE based on number of features of PHT. (B) Cumulative incidence curve for first observed VH in PROBE by functioning versus nonfunctioning HPE based on number of features of PHT
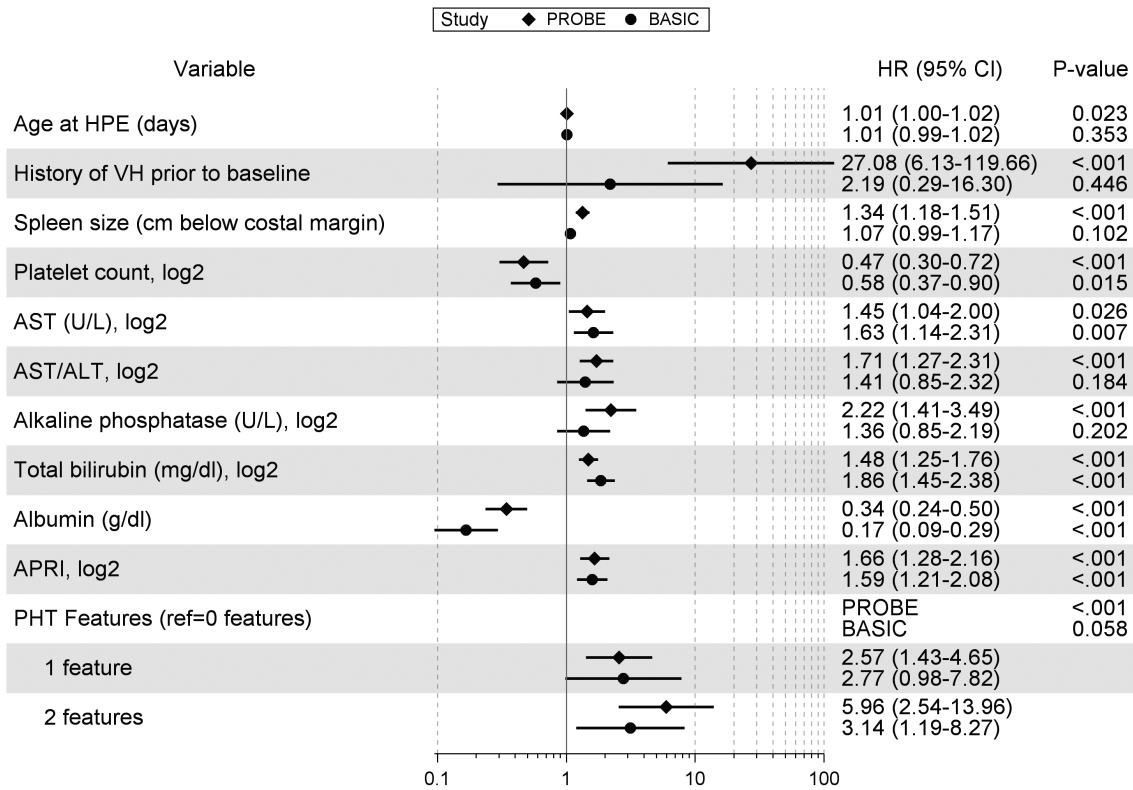
**FIGURE 5** Risk factors at baseline significantly associated with VH in both BASIC and PROBE

**TABLE 4** HRs for first VH by Lab value cutoff points

| Variable | | PROBE (*n* = 521) | | | BASIC (*n* = 348) | | |
|---|---|---|---|---|---|---|---|
| | | N | HR (95% CI) | *p* value | N | HR (95% CI) | *p* value |
| TB (mg/dl) | ≤ 2 | 242 | (ref) | | 264 | (ref) | |
| | >2 | 267 | 3.19 (1.75–5.84) | <0.001 | 54 | 4.34 (1.98–9.52) | <0.001 |
| GGT (U/L) | ≤ 100 | 30 | (ref) | | 160 | (ref) | |
| | >100 | 420 | 2.95 (0.41–21.51) | 0.285 | 126 | 2.09 (0.88–4.99) | 0.095 |
| Platelet count | ≥50 | | | | 268 | (ref) | |
| | <50 | | | | 19 | 3.58 (1.05–12.19) | 0.042 |
| | ≥100 | 426 | (ref) | | 186 | (ref) | |
| | <100 | 13 | 3.76 (0.90–15.78) | 0.070 | 101 | 1.45 (0.64–3.30) | 0.374 |
| | ≥150 | 383 | (ref) | | 120 | (ref) | |
| | <150 | 56 | 3.16 (1.56–6.38) | 0.001 | 167 | 2.06 (0.89–4.80) | 0.092 |
| | ≥200 | 312 | (ref) | | 80 | (ref) | |
| | <200 | 127 | 2.16 (1.20–3.88) | 0.010 | 207 | 2.65 (0.91–7.75) | 0.074 |
| Albumin (g/dl) | ≥2.5 | 474 | (ref) | | 312 | (ref) | |
| | <2.5 | 30 | 6.84 (2.82–16.57) | <0.001 | 4 | 25.33 (7.29–87.98) | <0.001 |
| | ≥3 | 429 | (ref) | | 302 | (ref) | |
| | <3 | 75 | 4.54 (2.27–9.07) | <0.001 | 14 | 21.62 (8.11–57.61) | <0.001 |
| | ≥3.5 | 303 | (ref) | | 273 | (ref) | |
| | <3.5 | 201 | 3.82 (2.17–6.75) | <0.001 | 43 | 5.31 (2.37–11.90) | <0.001 |
| INR | ≤ 1 | 161 | (ref) | | 83 | (ref) | |
| | >1 | 236 | 2.38 (1.28–4.44) | 0.006 | 188 | 0.94 (0.42–2.10) | 0.872 |
| | ≤ 1.5 | 350 | (ref) | | 269 | (ref) | |
| | >1.5 | 47 | 2.69 (1.02–7.12) | 0.046 | 2 | 17.08 (2.21–131.88) | 0.007 |

these circumstances could be added to a research definition of VH. Including these events in a sensitivity analysis in the PROBE subset of our study did not change our results. Due to the annual nature of data collection in the BASIC study, death within 6 weeks of VH could not be confirmed. In the PROBE cohort, there were only two deaths within 6 weeks of the first observed VH, yielding a mortality rate of 3.8%. This low mortality rate occurred in the context of centers that generally do not perform screening endoscopy or primary prophylaxis of varices in BA.[14] Survival after VH was excellent when compared with the 19% mortality rate reported historically[5,33] or the more recent Pediatric Health Information System report of an 8.8% 6-week mortality in 1,902 children following variceal hemorrhage.[7] An interesting subanalysis of this latter cohort revealed a mortality rate of only 1.7% among 410 bleeds, which were treated with transfusion and endoscopic band ligation therapy, similar to our data. The interpretation of liver transplantation within 6 weeks of VH in this cohort is more likely to be related to the underlying liver disease severity of the individual patient, as many of those transplanted were already listed for transplantation with Model for End-Stage Liver Disease or PELD scores suggesting a high likelihood of imminent transplant. Transplant-free survival after VH in infants with a nonfunctioning HPE is very short and suggests that transplantation had already been selected as the primary therapeutic approach for these patients. Survival with native liver after variceal hemorrhage in older children is more prolonged and likely relates to the underlying status of the liver, which can be captured by TB at the time of the bleed.[5]

In this large prospective multicenter study, the risk of VH was approximately 8%–9% over 5 years in children with BA. Six-week mortality was 3.8% after the observed first VH in the PROBE subset of this cohort, although the competing event of liver transplantation may account for this low rate. Predictors at baseline of higher risk of VH include elevated TB, thrombocytopenia, and hypoalbuminemia. This information may aid clinicians in providing effective anticipatory guidance, and help inform decision making regarding timing of liver transplantation. The low rate of VH events will make it difficult to perform definitive randomized clinical trials to assess approaches to primary prophylaxis of variceal hemorrhage in children with BA.[34]

## CONFLICT OF INTEREST

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*Manuscript draft critical revision for important intellectual content:* Lee M. Bass, Wen Ye, Kieran Hawthorne, Daniel H. Leung, Karen F. Murray, Jean P. Molleston, Rene Romero, Ronald J. Sokol, Saul Karpen, Philip Rosenthal, Kathleen M. Loomes, Kasper S. Wang, Robert H. Squires, Alexander Miethke, Vicky L. Ng, Simon Horslen, M. Kyle Jensen, John C. Magee, and Benjamin L. Shneider.

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## DATA AVAILABILITY STATEMENT

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

## APPENDIX

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