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The Risk of Variceal Hemorrhage and Pre-Transplant Mortality in Children with Biliary Atresia

Lee M. Bass[1], Wen Ye[2], Kieran Hawthorne[3], Daniel H. Leung[4], Karen F. Murray[5], Jean P. Molleston[6], Rene Romero[7], Saul Karpen[7], Philip Rosenthal[8], Kathleen M. Loomes[9], Kasper S. Wang[10], Robert H. Squires[11], Alexander Miethke[12], Vicky L. Ng[13], Simon Horslen[14], M. Kyle Jensen[15], Ronald J. Sokol[16], John C. Magee[17] Benjamin L. Shneider[18] on behalf of ChiLDReN

[1]Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (LBass@luriechildrens.org)

[2]Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA (wye@umich.edu)

[3]Arbor Research Collaborative for Health, Ann Arbor, MI, USA (Kieran.Hawthorne@arborresearch.org)

[4]Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA (dhleung@texaschildrens.org)

[5]Department of Pediatrics, Division of Gastroenterology, Hepatology, Seattle Children's Hospital and the University of Washington School of Medicine, Seattle, WA, USA (murrayk5@ccf.org) Currently at Cleveland Clinic Children's Pediatric Institute, Cleveland, Ohio

[6]Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, Riley Hospital for Children, Indiana University, Indianapolis, IN, USA (jpmolles@iu.edu)

[7]Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, Children's Healthcare of Atlanta and Emory University School of Medicine, Atlanta, GA, USA (Rene.Romero@choa.org; saul.karpen@emory.edu)

[8]Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA (prosenth@peds.ucsf.edu)

[9]Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA (loomes@email.chop.edu)

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[10]Department of Pediatric Surgery, Children's Hospital Los Angeles, CA, USA (kwang@chla.usc.edu)
[11]Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh, School of Medicine and Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pittsburgh, PA, USA (Robert.Squires@chp.edu)
[12]Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, University of Cincinnati, OH, USA (Alexander.Miethke@cchmc.org)
[13]Division of GI, Hepatology and Nutrition, Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada (vicky.ng@sickkids.ca)
[14]Department of Pediatrics, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA, USA (simon.horslen@seattlechildrens.org)
[15]Department of Pediatrics, University of Utah, Salt Lake City, UT, USA (kyle.jensen@hsc.utah.edu)
[16]Department of Pediatrics-Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, USA (ronald.sokol@childrenscolorado.org)
[17]Department of Surgery, University of Michigan School of Medicine, Ann Arbor, MI, USA (mageej@umich.edu)
[18] Section of Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital and Baylor College of Medicine, Houston, TX, USA (Benjamin.Shneider@bcm.edu)

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Footnote Page

Corresponding Author
Lee M. Bass, MD
Department of Pediatrics,
Ann & Robert H. Lurie Children's Hospital of Chicago
Northwestern University Feinberg School of Medicine
225 E. Chicago Ave, Box 65
Chicago, IL 60611
Tel: (312) 227-4200
Fax: (312) 227-9645

E-mail: lbass@luriechildrens.org

Abbreviations

ALT = alanine aminotransferase
APRI = aspartate aminotransferase to platelet ratio index
AST = aspartate aminotransferase
BA = biliary atresia
BASIC = The Biliary Atresia Study in Infants and Children
CEPH = clinically evident portal hypertension
ChiLDReN = Childhood Liver Disease Research Network
GGT = gamma-glutamyl transferase
GI = Gastrointestinal
HPE = Hepatoportoenterostomy
INR = international normalized ratio
NIDDK/NIH = National Institute of Diabetes, Digestive and Kidney Diseases/National Institute of Health
PELD =Pediatric End-stage Liver Disease Score
PHT = portal hypertension
TIPS = transjugular intrahepatic portosystemic shunt
VH = variceal hemorrhage

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ABSTRACT-

Background & Aims: The natural history of gastroesophageal variceal hemorrhage (VH) in biliary atresia (BA) is not well characterized. We analyzed risk factors, incidence and outcomes of VH in a longitudinal multi-center study.

Approach & 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 upon gastrointestinal bleeding in the presence of varices accompanied by endoscopic or nontransplant surgical intervention. Cumulative incidence of VH and transplant-free survival was compared based on features of portal hypertension (e.g. splenomegaly and 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 bilirubin, 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, while 10 (12.5%) underwent transplant within six weeks of VH.

CONCLUSION: 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 disease resulting from fibro-obliteration of bile ducts, which can lead to cirrhosis and end-stage liver disease. Hepatoportoenterostomy (HPE), also known as the Kasai procedure, provides a means of relieving extrahepatic biliary obstruction and permitting bile flow. However, HPE is not a curative procedure and the majority of patients will require liver transplantation in childhood secondary to progression to cirrhosis and end stage liver disease. BA is the leading indication for liver transplantation in the pediatric population [1-3]. Cirrhosis in BA leads to the development of portal hypertension (PHT) with an attendant risk of development of esophageal and gastric varices. Gastroesophageal variceal hemorrhage (VH) can lead to mortality and morbidity, including decompensation in hepatic function and accelerated need for liver transplantation [4-7]. The magnitude of these effects from VH is not well delineated.

The course of BA following HPE is highly dependent upon 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 requiring liver transplantation before two to three years of age. Meanwhile, infants who survive with their native liver beyond age three will typically follow a different course with PHT and cirrhosis as the major drivers of complications in this population [2]. One must acknowledge that the presentation of complications from BA, including VH, may differ between these two separate populations. 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 considerable 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/National Institute of Health (NIDDK/NIH)-funded cooperative research consortium of 16 clinical sites in the United States and Canada. Its goal is to advance understanding of the etiology, 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 longitudinal, 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 six months following their BA diagnosis either prior to, 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.

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 six months of age with BA. In this analysis, PROBE was used to assess the early (i.e. < age three years) variceal bleeding natural history of BA, while BASIC data were analyzed for patients who enrolled at > age three 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 three 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 ≥ age seven years.

Outcome and risk factors

The primary outcomes of interest in this analysis were time-to-first observed variceal hemorrhage (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 non-successful 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 transjugular intrahepatic portosystemic shunt (TIPS). For seven 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, age at enrollment (for BASIC cohort only), medical history (age at HPE, features of portal hypertension, history of VH, the presence of splenomegaly (based upon physical examination), laboratory measurements (platelet count, total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time, international normalized ratio (INR), albumin, gamma-glutamyl transferase (GGT), AST to platelet ratio index (APRI)), and growth parameters (height z-score, 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 cut-off points. Sensitivity analyses of predictors of VH were conducted including cases of gastrointestinal hemorrhage that were followed within six 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 $x10^3$/μl. 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 three months after HPE: participants who reached TB < 2 mg/dl at any visit up to three months post-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 non-functioning 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 > age three 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. 117 PROBE and 53 BASIC participants were excluded for not having undergone an HPE. 45 PROBE and 37 BASIC participants were excluded for polysplenia or asplenia. 108 PROBE participants were excluded for lack of baseline information, 77 for absent data and 31 for study exit prior to the 3-month post-HPE visit (19 for transplant, 2 for death and 10 lost to follow up). There was 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 < age three years 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 13.6 years), while PROBE participants were followed for a median of 1.3 years (maximum 15.8 years). Participants in PROBE with a functioning HPE were followed for a median of 3.7 years while those with a non-functioning HPE were followed for a median of 0.4 years. This is due to a significant proportion of these participants having transplant prior to two years of age and that data after transplant was 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, and also 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 was less frequently met in PROBE compared to 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 total bilirubin levels. A history of prior variceal hemorrhage prior to 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 five-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 2a). 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 two to three years thereafter, which is consistent with the rapid progression of biliary cirrhosis in about half of BA patients 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.

Variceal Hemorrhage 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 five years in PROBE and 8.0% (95% CI: 5.2%-11.5%) at five years in BASIC (Table 2b). 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 five years and 4.6% (95% CI: 1.7%-9.9%) at five years in BASIC. In contrast, in participants with two features of PHT at baseline the cumulative incidence of VH in PROBE was 21.7% (95% CI: 9.1%-37.7%) at five years and 10.6% (95% CI: 5.7%-17.1%) at five 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

2b 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 Variceal Hemorrhage 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 Supplementary Figures 1a and 1b and Supplementary Table 2a and 2b). In both cohorts, decreased albumin, decreased platelet count, increased total bilirubin, 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 of age two months) and the baseline study visit (median age five months) was associated with an increased risk of VH thereafter. A history of VH in BASIC prior to 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. Hazard ratios for the first observed VH by common laboratory value cut-points at baseline are provided in Table 3.

Risk factors in PROBE were also analyzed stratified by functional status of the HPE (Supplementary Figures 2a and 2b). Spleen size, platelet count, albumin level at baseline were noted to be risk factors independent of HPE status, while in participants with a functioning HPE, elevated alkaline phosphatase, elevated total bilirubin 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 six weeks of gastrointestinal hemorrhage but which otherwise did not meet the research definition of VH (Supplemental Table 3).

Mortality/Transplant Risk after VH

Two PROBE participants died within six weeks of VH (2/52=3.8%), one at seven months of age with a nonfunctioning HPE performed at 115 days of life, the other with a functioning HPE who also died at seven months of age (Supplemental Table 4). This latter participant appears to have had a significant hepatic decompensation co-incident with the VH. Relevant characteristics of the 10 total participants (10/80=12.5%) who underwent liver transplant within six weeks of VH include: 1) Seven had non-functioning HPE, 2) Eight were less than two years of age at VH and transplant, 3) Eight were listed for transplant prior to VH, 4) Natural PELD scores exceeded 20 in 6 of 10 at transplant and six 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 six weeks after VH and 28 underwent liver transplant more than six weeks after VH, while in BASIC 1 of 28 died more than six weeks after VH and 14 underwent liver transplant more than six weeks after VH. (Supplemental Figure 3a; 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 non-functioning HPE group and 1.51 years for participants with a functioning HPE (Supplemental Figure 3b).

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 upon 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 upon 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 two or three years of age. Children with BA and bile drainage following HPE and who survive with their native liver beyond three 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, two-year native liver survival was approximately 50% and was distinctly related to functionality of the HPE, with rare native liver survival beyond two years of age in those with poor bile drainage post HPE. Amongst the survivors greater than three years of age at baseline in BASIC, native liver survival was 87% and 80% at two and five 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 non-functioning 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 x 10^3/mm^3 [14].

The overall cumulative incidence of VH was relatively low at approximately 8-9% after five 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 the majority of patients reported were from prior to the year 2000. The differences in the reported incidence may be secondary to era-specific differences in the approach to a non-functioning HPE and pre-emptive utilization 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 three months following Kasai was a significant risk factor for transplant or death by age two years [3]. Lampela and colleagues noted that increased serum bilirubin at three months after portoenterostomy was a significant risk factor for 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 and colleagues showed that INR was an independent risk factor for increased waiting 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 cut-points provided additional insights into the potential use of routine laboratory parameters as risk predictors of VH. Stepwise increase in risk was observed in both cohorts

for progressively lower serum albumin cut-points. Albumin, in conjunction with total bilirubin 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 of <3.5 g/dL has been identified as a risk factor for lower two-year survival in infants post HPE [30]. Therefore, incorporation of serum albumin levels will be useful in prognostic model development and identifying the cohort of BA patients 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 amongst 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 six 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 six weeks of the event, without an intervening procedure to identify varices and/or treat varices or portal hypertension. One could argue 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 six weeks of VH could not be confirmed. In the PROBE cohort, there were only two deaths within six 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 post VH was excellent when compared to the 19% mortality rate reported historically [5, 33] or the more recent Pediatric Health Information System report of an 8.8% six-week

mortality in 1902 children following variceal hemorrhage [7]. An interesting sub-analysis of this latter cohort revealed a mortality rate of only 1.7% amongst 410 bleeds which were treated with transfusion and endoscopic band ligation therapy, similar to our data. The interpretation of liver transplantation within six 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 MELD or PELD scores suggesting a high likelihood of imminent transplant. Transplant-free survival after VH in infants with a non-functioning 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].

CONCLUSIONS:

In this large prospective multi-center study, the risk of VH was approximately 8-9% over five 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].

Appendix

Members of ChiLDReN:

Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL (supported by NIDDK DK62436 and NCATS UL1TR001422): Estella Alonso, MD; Lee Bass, MD; Susan Kelly, RN, BSN; Mary Riordan, CCRP; Hector Melin-Aldana, MD

Cincinnati Children’s Hospital Medical Center, Cincinnati, OH (supported by NIDDK DK62497 and NCATS UL1TR000077): Jorge Bezerra, MD; Kevin Bove, MD; James Heubi, MD; Alexander Miethke, MD; Greg Tiao, MD; Julie Denlinger, BSN, RN; Erin Chapman

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Texas Children's Hospital, Houston, TX (supported by NIDDK DK103149): Benjamin Shneider, MD; Sanjiv Harpavat, MD; Paula Hertel, MD; Daniel Leung, MD; Mary Tessier, MD; Deborah Schady, MD; Laurel Cavallo; Diego Olvera; Christina Banks; Cynthia Tsai

King's College Hospital, London, UK: Richard Thompson, BM, BCh, MRCP, MRCPCH

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Sherry Hall, MS

Scientific Data Coordinating Center, Ann Arbor, MI (supported by NIDDK DK62456): John Magee, MD; Robert Merion, MD, FACS; Cathie Spino, DSc; Wen Ye, PhD

Figure Legends:

Figure 1: Flow chart for participants in both BASIC and PROBE

Figure 2: Kaplan-Meier curve for transplant-free survival in each cohort based on number of features of PHT

Figure 3: Kaplan-Meier curve demonstrating transplant free survival in PROBE by functioning vs. non-functioning HPE, based on number of features of PHT

Figure 4: 4a) Cumulative incidence curve for first observed VH in BASIC and PROBE based on number of features of PHT. 4b) Cumulative incidence curve for first observed VH in PROBE by functioning vs non-functioning HPE based on number of features of PHT

Figure 5: Risk factors at baseline significantly associated with VH in both BASIC and PROBE

Supplementary Figures

Supplementary Figure 1a. Risk factors at baseline in PROBE participants. Forest plot with 95% confidence intervals indicated by horizontal line.

Supplementary Figure 1b. Risk factors at baseline in PROBE participants. Forest plot with 95% confidence intervals indicated by horizontal line.

Supplementary Figure 2a. Risk factors at baseline in PROBE participants with a functioning hepatoportoenterostomy. Forest plot with 95% confidence intervals indicated by horizontal line.

Supplementary Figure 2b. Risk factors at baseline in PROBE participants with a non-functioning hepatoportoenterostomy. Forest plot with 95% confidence intervals indicated by horizontal line.

Supplementary Figure 3a. Cumulative incidence curve for death with native liver or transplant after variceal hemorrhage in PROBE (left panel) and BASIC (right panel) participants.

Supplementary Figure 3b. Cumulative incidence curve for death with native liver or transplant after variceal hemorrhage in PROBE participants with a non-functioning (left panel) and functioning (right panel) hepatoportoenterostomy.

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Table 1. Baseline characteristics

Variable		PROBE (N=521) N	PROBE (N=521) n (%) or median (IQR)	BASIC (N=348) N	BASIC (N=348) n (%) or median (IQR)
Age at baseline* visit (years)		521	0.4 (0.4,0.5)	348	8.5 (5.5,12.9)
Age at baseline* 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%)
	Nonblack, Nonwhite		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 prior to 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)
GGTP (U/L)		450	776 (337,1344)	286	76 (33,188)

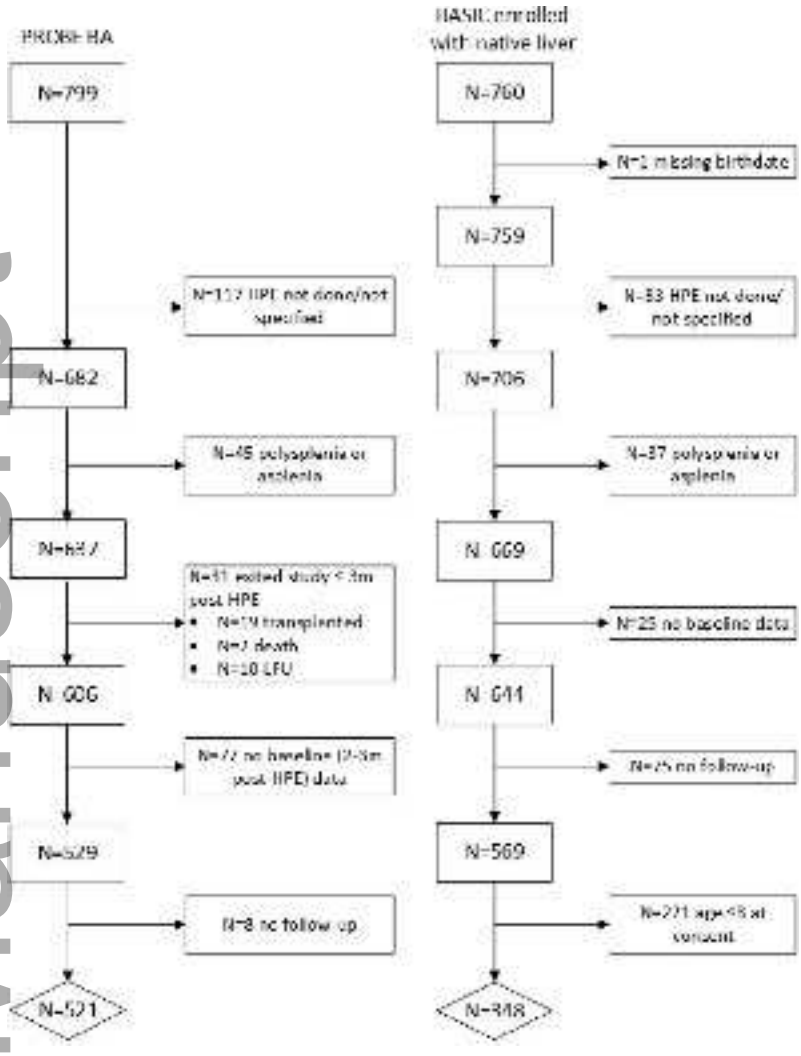
Alkaline phosphatase (U/L)	500	533 (390,729)	309	303 (208,449)
Total bilirubin (mg/dl)	509	2.5 (0.7,9.0)	318	0.7 (0.5,1.3)
Functioning HPE**	514	262 (51.0%)		
INR	397	1.1 (1.0,1.3)	271	1.1 (1.0,1.2)
Albumin (g/dl)	504	3.7 (3.2,4.0)	316	4.2 (3.7,4.5)
APRI	430	1.4 (0.9,2.4)	279	1.4 (0.7,2.7)

*Baseline for PROBE participants is at 2-3 months post-HPE

**Total bilirubin <2mg/dl at any point up to 3 months post-HPE

Table 3. Hazard ratios for first VH by lab value cutpoints

		PROBE (N=521)			BASIC (N=348)		
Variable		N	HR (95% CI)	P-value	N	HR (95% CI)	P-value
Total Bilirubin (mg/dl)	≤2	242	(ref)		264	(ref)	
	>2	267	3.19 (1.75-5.84)	<.001	54	4.34 (1.98-9.52)	<.001
GGTP (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)	<.001	4	25.33 (7.29-87.98)	<.001
	≥3	429	(ref)		302	(ref)	
	<3	75	4.54 (2.27-9.07)	<.001	14	21.62 (8.11-57.61)	<.001
	≥3.5	303	(ref)		273	(ref)	
	<3.5	201	3.82 (2.17-6.75)	<.001	43	5.31 (2.37-11.90)	<.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)	



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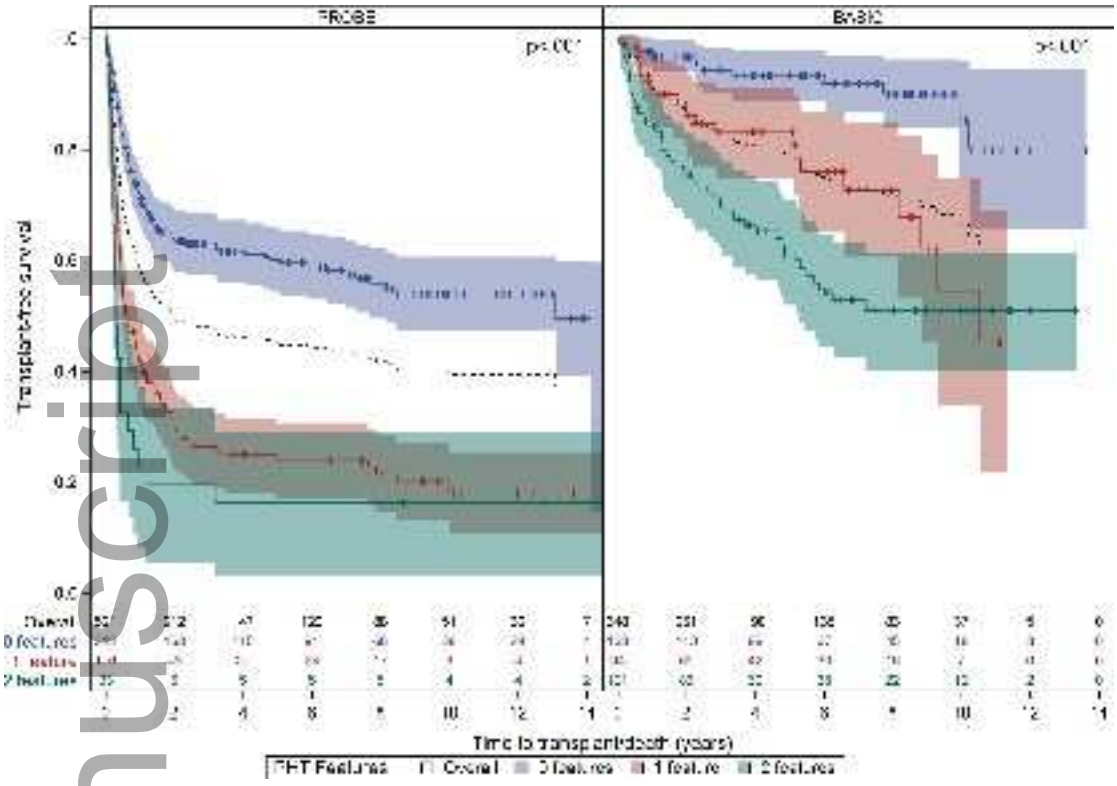

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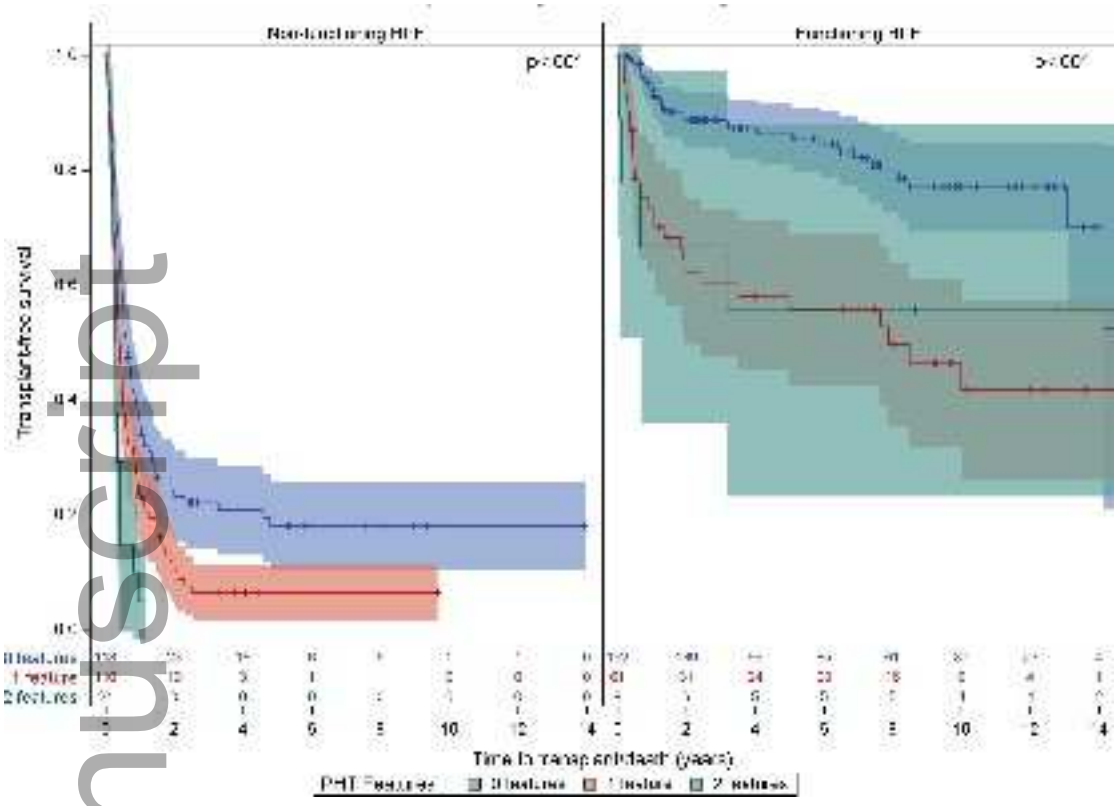

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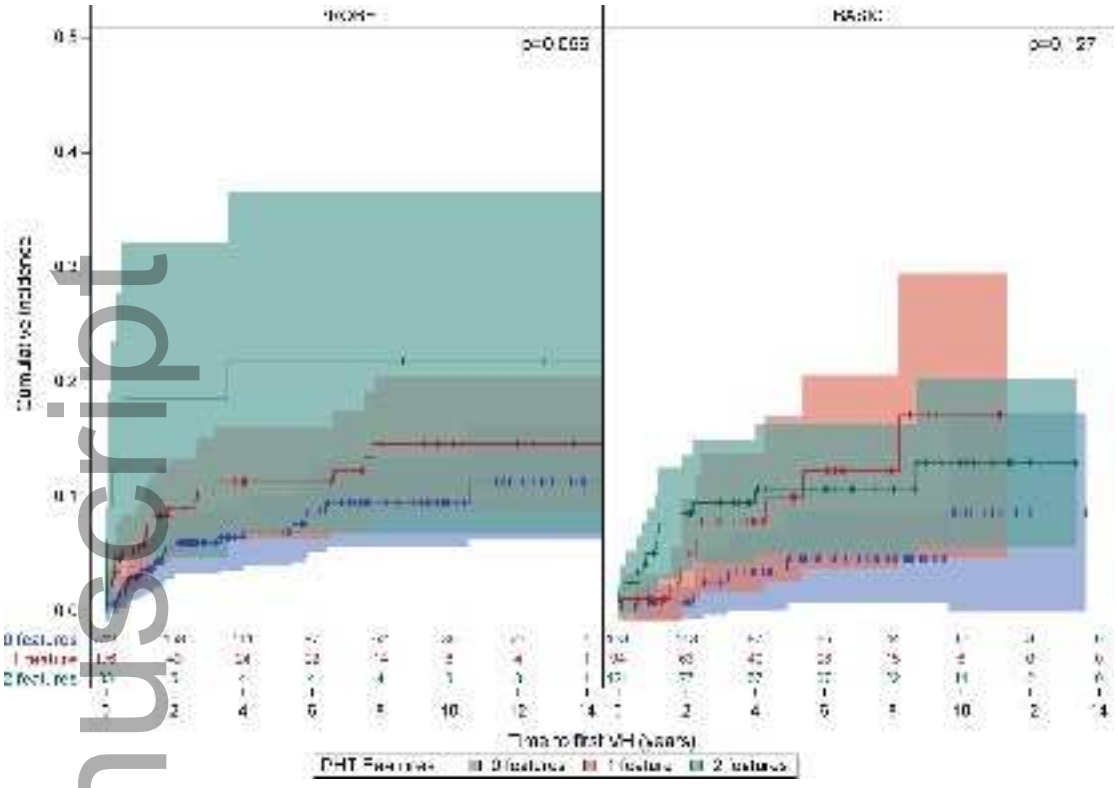

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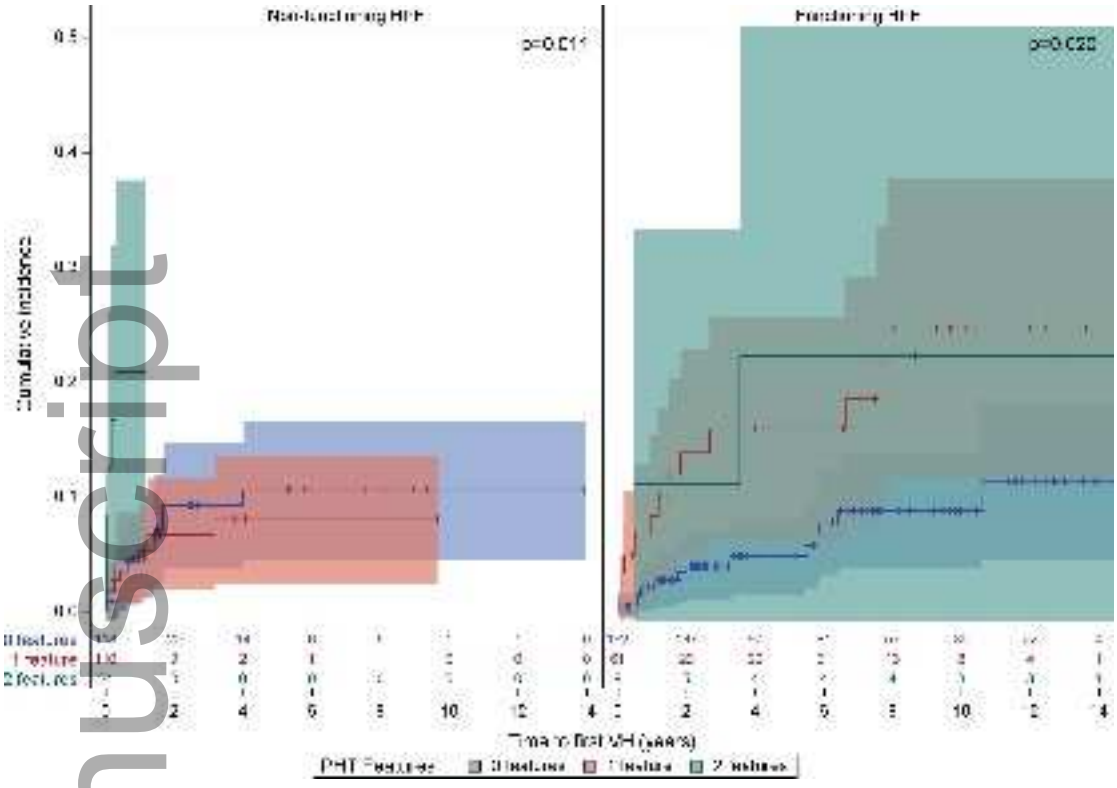

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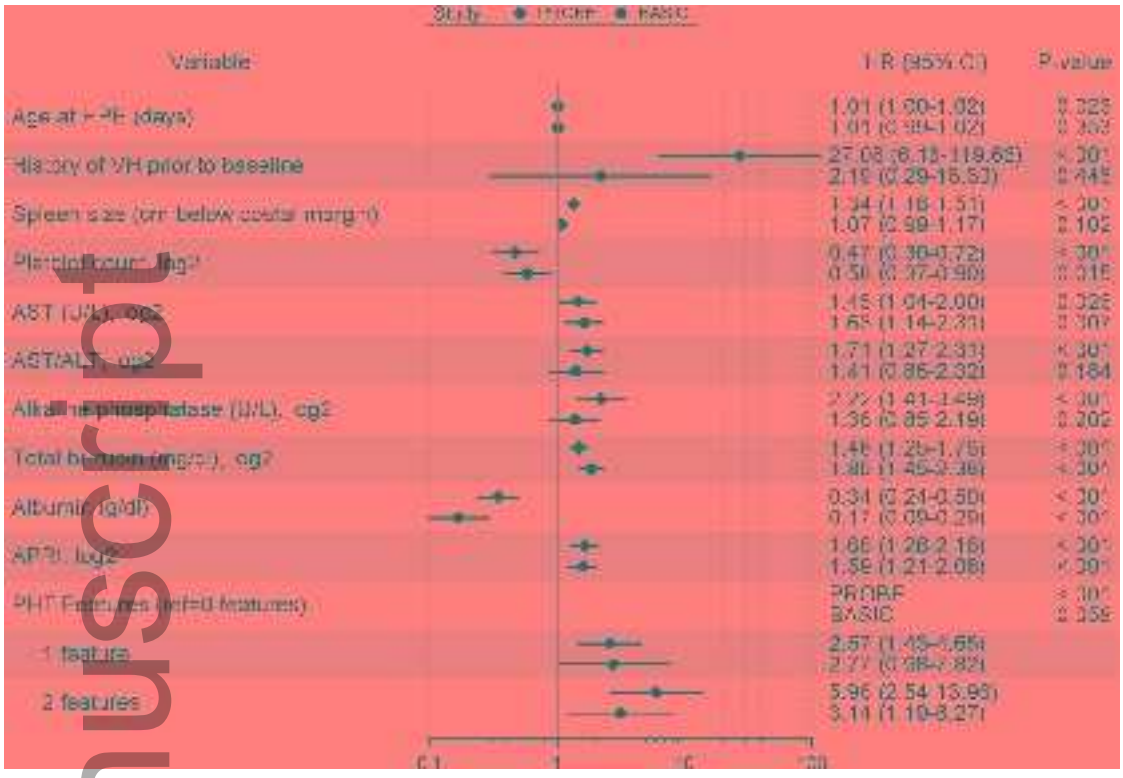

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