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## Longitudinal Outcomes in Young Patients with Alpha-1-Antitrypsin Deficiency with Native Liver Reveal that Neonatal Cholestasis is a Poor Predictor of Future Portal Hypertension

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## Abstract

**Objectives**—To identify predictors of portal hypertension, liver transplantation, and death in North American youth with alpha-1-antitrypsin (AAT) deficiency, and compare with AAT deficiency patients elsewhere.

**Study design**—The Childhood Liver Disease Research Network Longitudinal Observational Study of Genetic Causes of Intrahepatic Cholestasis is a prospective, cohort study of pediatric cholestatic liver diseases, including AAT deficiency, enrolling PIZZ and PISZ subjects 0-25 years of age seen since November 2007 at 17 tertiary care centers in the US and Canada. Data from standard-of-care baseline and annual follow-up visits were recorded from medical records, history, physical examination, and laboratory studies. Participants with portal hypertension were identified based on data collected.

**Results**—We enrolled 350 participants (60% male) with a native liver; 278 (79%) entered the cohort without portal hypertension and 18 developed portal hypertension during follow-up. Thirty participants required liver transplantation; 2 patients died during 1077 person-years of follow-up. There was no difference in participants with or without preceding neonatal cholestasis progressing to transplantation or death during the study (12% vs 7%;  $P = .09$ ), or in experiencing portal hypertension (28% vs 21%;  $P = .16$ ); the hazard ratio for neonatal cholestasis leading to portal hypertension was  $P = .04$ . Development of portal hypertension was associated with a reduced height Z-score.

**Conclusions**—Portal hypertension in youth with AAT deficiency impacts growth measures. Progression to liver transplantation is slow and death is rare, but the risk of complications and severe liver disease progression persists throughout childhood. A history of neonatal cholestasis is a weak predictor of severe disease.

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Alpha-1-antitrypsin (AAT) deficiency occurs in 1 in 2000-3500 births in North American and European populations.<sup>1,2</sup> It is associated with chronic liver disease, cirrhosis, and hepatocellular carcinoma. The Z mutant allele of the AAT gene is associated with the vast majority of AAT liver disease, either as the classical form of homozygous ZZ AAT deficiency, or as the SZ compound heterozygous form, which also has an increased risk of liver disease.<sup>1</sup>

The most common childhood presentation of AAT deficiency is neonatal cholestasis<sup>1,2</sup> Although the cholestasis often resolves spontaneously, a minority of these children go on to develop cirrhosis and portal hypertension in the first few years of life. Children with AAT less commonly present at later ages with signs or symptoms of liver disease or are diagnosed during family testing. A minority of children with AAT progress to liver failure and liver transplantation or death. The factors influencing liver disease are not known, and it is not possible to predict which patients will progress to severe liver disease.

The mechanism of the liver injury in AAT deficiency involves the accumulation within hepatocytes of the AAT mutant Z protein, which triggers hepatocellular death, compensatory regeneration and, in some patients, hepatic fibrosis.<sup>1,3-5</sup> However, given the wide variability in clinical course, an important role for genetic and environmental modifiers is likely.<sup>1,2,6,7</sup> In the early 1970s, a cohort of 127 ZZ AAT-deficient children was identified in Sweden by newborn screening and followed longitudinally.<sup>8-10</sup> This unbiased, population-based cohort had a low rate (<5%) of life-threatening liver disease in childhood, and all patients who developed severe disease had preceding neonatal cholestasis. There was no evidence of liver injury or complications of liver disease from the second through the fourth decades of life. This finding is in contrast with other single-center retrospective reports from more genetically mixed groups of patients in North America and Western Europe that report a wider range of liver complications with progression throughout childhood, sometimes without preceding neonatal cholestasis.<sup>1,2,11-14</sup> It maybe that some complications of liver disease, or progressive disease in childhood, are too infrequent to be detected in the Swedish cohort of 127 individuals. However, it is also possible that a different set of disease modifiers, associated with more severe disease, are found outside of Sweden.

The Childhood Liver Disease Research Network is a National Institutes of Health-supported consortium of pediatric tertiary care centers in North America, 17 of which collected data during this study period, focused on the study of rare pediatric liver diseases, as described.<sup>15-19</sup> The Longitudinal Observational Study of Genetic Causes of Intrahepatic Cholestasis (NCT00571272) is a study conducted by this network with the goal of describing the natural history and genetic and environmental modifiers of a group of metabolic-cholestatic liver diseases, including AAT deficiency. We hypothesized that the prospective study of a cohort of children and young adults with AAT deficiency would provide insight into the natural history and clinical variability. The goal of this analysis was to evaluate undefined predictors of portal hypertension, liver transplantation, and death in North American youth with AAT deficiency, and determine how they differ from other AAT deficiency patients around the world.

## Methods

### Population and Assessments

This report includes participants with AAT deficiency with their native livers enrolled into Longitudinal Observational Study of Genetic Causes of Intrahepatic Cholestasis from November 30, 2007, through November 30, 2017.<sup>15-18</sup> Institutional review board approvals and consents were obtained at each site. Eligibility for enrollment of AAT participants in the Longitudinal Observational Study of Genetic Causes of Intrahepatic Cholestasis study include PIZZ or PISZ serum protein phenotype or genotype, with a corresponding low serum level of AAT protein (defined as less than the laboratory wild-type reference range), age birth to 25 years, and evidence of liver disease as defined by documentation of one of the following: neonatal cholestasis (conjugated hyperbilirubinemia and jaundice within the first 3 months of life); 1.25 or more times the upper limit of normal alanine transaminase, aspartate transaminase (AST), or gamma-glutamyl transpeptidase (GGTP); chronic hepatomegaly; clinical findings or complications of portal hypertension or cirrhosis;

impaired liver synthetic function; or abnormal liver biopsy histology, other than globular inclusions of AAT, showing liver injury (inflammation, fibrosis, or necrosis), as described.<sup>19</sup>

At enrollment, medical history and physical examination were obtained, including review of available medical records and standard of care laboratories. Updates in medical history and physical examination were documented at annual follow-up visits, and other data collected as previously described.<sup>19</sup>

## Outcomes

Primary outcomes were the onset of either definite, or possible, clinically evident portal hypertension and liver transplantation or death. Definite clinically evident portal hypertension was defined as either ascites (treatment with diuretics for a history of or currently present ascites) or endoscopic evidence of esophageal or gastric varices or clinical findings consistent with portal hypertension. The clinical findings indicating portal hypertension were the presence of both splenomegaly (spleen >2 cm below the costal margin) and thrombocytopenia (platelet count <150 000/mm<sup>3</sup>). Possible clinically evident portal hypertension was used to designate participants with splenomegaly or thrombocytopenia, but not both (definition adapted from<sup>18</sup>). For this analysis, these groups were considered together as definite/possible portal hypertension to increase the power of our conclusions owing to low numbers of severe event outcomes.<sup>18</sup>

Other outcomes assessed were growth and anthropomorphic outcomes, such as weight, height, and weight-for-height Z-scores, body mass index, head circumference, right mid-arm circumference, and right triceps skinfold thickness.

## Statistical Analyses

Descriptive statistics of patient characteristics, follow-up, and longitudinal patterns for outcomes were used to describe the study population and its natural history. Kaplan-Meier methods were used to characterize the time-to-definite/possible portal hypertension and to liver transplantation or death. Last follow-up for those without an event was defined as their last completed clinical visit; thus, participants were censored at the time of liver transplantation, death, drop-out, or last visit for time to definite/possible portal hypertension and were censored at drop-out or last visit for time-to-transplantation or death. (Note that no participants were censored for liver transplantation in this cohort because all transplanted participants experienced definite/possible portal hypertension before transplantation and death.)

To identify potential predictors Cox proportional hazards models were used with either fixed or time-dependent covariates. Time-dependent predictors are those assessed longitudinally at repeated visits (eg, laboratory measures). We examined the relationship between a history of neonatal cholestasis and definite/possible portal hypertension (including those with portal hypertension at study entry and those who developed portal hypertension during the course of the study) in participants with native liver using a  $\chi^2$  test, and assessed time-to-portal hypertension and time-to-liver transplantation, relative to a personal history of neonatal cholestasis, in a Cox model. We also explored the impact of changes in laboratory measures of liver function (albumin, total bilirubin, direct bilirubin, AST, alanine transaminase, GGTP,

platelets, AST/platelets ratio, and international normalized ratio) and changes in growth measures (head circumference Z-score, right mid-arm circumference, right triceps skinfold thickness, body mass index, body mass index Z-score, weight Z-score, and height Z-score) on outcomes. Because of the limited number of events, it was not possible to develop multivariable models to define risk scores for these important outcomes. A *P* value of less than .05 is considered statistically significant.

We used linear mixed models for longitudinal data, adjusted for age, to assess the effect of definite/possible portal hypertension on changes in growth measures. These models were used to predict the average change in anthropometric measures for a participant of average age at baseline with and without portal hypertension; predicted values and 95% CIs are presented graphically for measures that are statistically significant.

## Results

### Demographics and Course of the AAT Liver Disease Cohort

Of 350 participants with their native liver, 60% were male; the median age at baseline enrollment was 4.2 years (IQR, 7.9 years; range, 0.1-24.9 years). The majority of participants were non-Hispanic and white (Table I); 286 participants (90%) were homozygous ZZ and 32 (10%) were SZ.<sup>1,2,8</sup> The median length of follow-up was 2.5 years (range, 0-9.7). Overall, 112 participants (32%) withdrew, were discontinued owing to being followed at noncontinuing centers (grants not renewed), were lost to follow-up, or had other reasons for withdrawal from the study (Table III and Table IV; available at [www.jpeds.com](http://www.jpeds.com)).

Seventy-two participants (21%) had definite/possible clinically evident portal hypertension at entry into the study. Of the 278 participants (79%) who entered the study without portal hypertension, 18 developed definite/possible portal hypertension during follow-up; the incidence rate is 2.1 per 100 person-years of follow-up. Thirty-two participants underwent liver transplantation or died during 1077 person-years of follow-up (annual incidence rate of 3.0 transplants per 100 person-years of follow-up; Table V and Table VI [available at [www.jpeds.com](http://www.jpeds.com)]). One patient died with their native liver with definite/possible portal hypertension and one after transplant. Twenty-nine of the 30 transplanted participants entered the study with definite/possible portal hypertension, and all transplanted participants developed portal hypertension before transplant.

Kaplan-Meier curves for portal hypertension-free survival (Figure 1, A) and liver transplant-free survival (Figure 2) are shown for participants by presence or absence of neonatal cholestasis. We chose to focus on this comparison because neonatal cholestasis, although it only affects a minority of ZZ infants, is by far the most common presentation for AAT deficiency in childhood. Our data show there is no statistically significant difference for either definite/possible portal hypertension-free survival or liver transplant-free survival based on neonatal cholestasis. Prevalent participants with definite/possible portal hypertension at entry into the study are reflected in the drop at time 0. For those without portal hypertension at entry, there is a slow but continued progression; Figure 1, B shows the portal hypertension-free Kaplan-Meier curve for participants without portal hypertension at the time of study entry. For all participants combined at 2 years, the probability of

developing definite/possible portal hypertension is 5% (95% CI, 2%-9%). Similarly, the incidence of liver transplantation or death increases slowly over time, with the 2-year probability of liver transplant or death of all participants estimated to be 8% (95% CI, 5%-11%).

### Predictors of Future Severe Disease and Disease Associations

Prospective standard of care physical examination and laboratory factors were analyzed for their ability to predict the development of portal hypertension (Table II) or liver transplantation or death (Table VI; available at [www.jpeds.com](http://www.jpeds.com)). We found no statistically significant associations of anthropometric and growth measurements with risk of future portal hypertension. Over time, participants with increasing total bilirubin, AST, GGTP, and AST/platelet ratio, along with decreasing platelet count, were associated with increased risk of future portal hypertension. Owing to small numbers of events, neither a single measure nor a group of measures, could be found with useful predictive specificity for the development of portal hypertension. However, when a plot of absolute GGTP values vs age was constructed, many of the relatively few participants who developed definite/possible portal hypertension (Figure 3 [available at [www.jpeds.com](http://www.jpeds.com)], red dots, n = 11 participants with GGTP values recorded) had higher GGTP values, especially among those 3 years of age or younger. Decreasing serum albumin and platelet count, and increasing total bilirubin, direct bilirubin, AST, and international normalized ratio were univariately associated with future liver transplant or death (Table VII).

We also examined whether development of definite/possible portal hypertension affected subsequent growth measures, after adjusting for age. Smaller changes in height Z-score (estimate = -0.21), triceps skinfold thickness (estimate = -0.17, log scale), and mid-arm circumference (estimate = -0.06, log scale) were found in children with, than in those without, definite/possible portal hypertension ( $P < .05$  for each). Figure 4 (available at [www.jpeds.com](http://www.jpeds.com)) represents the predicted average differences of these anthropometric measures for a representative AAT participants from our study (6 years old).

Twenty-eight percent of participants with a history of neonatal cholestasis had definite/possible portal hypertension (at entry or during follow-up) compared with 21% without a history of neonatal cholestasis ( $P = .16$ ); the hazard ratio in those with neonatal cholestasis history relative to those without is 3.70 (95% CI, 1.06-12.87;  $P = .04$ ). Twelve percent of participants with a history of neonatal cholestasis were transplanted or died during the follow-up period compared with 7% without neonatal cholestasis history; the hazard ratio for liver transplantation or death for those with neonatal cholestasis history relative to those without is 1.93 (95% CI, 0.89-4.17;  $P = .09$ ).

We found that 50 of 350 participants reported asthma or similar respiratory difficulties. There were no other clear associations in AAT participants between medical histories, medications, or other diagnoses reported in the cohort and the development of portal hypertension, death, or need for transplantation.

## Discussion

We chose to focus on portal hypertension as one of our most important outcomes for children with AAT deficiency, because it is the most common severe liver disease outcome seen in children with this disease. Furthermore, it is common for AAT-deficient children with portal hypertension to remain stable for many years before decompensating to liver transplantation, which made it more likely we would capture a larger number of events than if we focused solely on the outcome of liver transplantation. The finding that the rate of definite/possible portal hypertension was 2.1 per 100 person-years is consistent with previous studies, suggesting that a large portion of patients with AAT deficiency are asymptomatic and well throughout childhood, and likely go unrecognized. This interpretation of the genetic prevalence data has been common. However, symptomatic North American children with AAT deficiency tend to be identified early in life during workup for signs or symptoms of liver disease, most commonly the neonatal cholestasis syndrome. Therefore, our reported cohort is representative of the currently diagnosed body of young patients in the US and Canada. We followed a broad age range of individuals at multiple sites for long periods of time, including some for a decade. Our cohort's characteristics are consistent with the known North-West European genetic origin of this disease, but are also likely to reflect the mixed gene pool of the US and Canada, which is hypothesized to have an important impact on outcomes.<sup>1,2,8</sup>

Our study highlights that most children with AAT-associated neonatal cholestasis do not develop portal hypertension within the current cohort follow-up period. Furthermore, most of our North American AAT participants did well, and the neonatal cholestasis resolved spontaneously, which is consistent with reports from other countries. We recognize that more patients left the study than we anticipated, which is a limitation; 16% were lost to follow-up, and another 13% exited the study because they were originally enrolled at study sites that were discontinued owing to grants not renewed. Although the existing follow-up data on these subjects was analyzed, there were likely events following discontinuation that were not captured.

From our analysis, it is evident that progression to portal hypertension or liver transplantation is not limited to those with a history of neonatal cholestasis and that the absence of neonatal cholestasis does not rule out the possibility of the future development of severe disease. This observation has been reported anecdotally, but has sometimes been questioned owing to a lack of systematic data collection.<sup>2,12,14</sup> This finding is in contrast with the Swedish birth cohort, in which 100% of the severe disease participants had a history of neonatal cholestasis. It should be noted, however, that some of our potential participants might have had neonatal cholestasis and gone on to liver transplantation, before enrollment, and were therefore missed. In that case, this current report would underestimate the predictive value of neonatal cholestasis. Taken together, these data support the practice of continuing to monitor young patients with AAT for the development of portal hypertension, or other complications of liver disease, and to provide anticipatory guidance for health maintenance in the setting of increased risk of liver disease. For example, maintaining a healthy weight, administration of hepatitis A and B vaccines, counseling about the use of potentially hepatotoxic medications or supplements, counseling for strict avoidance of



smoking or second-hand smoke, and nonsteroidal anti-inflammatory drug avoidance if portal hypertension is suspected.

Our cohort is selected for the presence of liver disease and identified a wider range of disease courses. The development of definite/possible portal hypertension was documented, and liver transplants occurred throughout childhood. This factor strengthens our study, in that nearly all reported outcomes in childhood of this disease are captured. However, the fact that this is not an unbiased birth cohort limits our ability to be specific about the frequency of these events in the population of asymptomatic, undiagnosed patients.

Modifier genes are likely to play an important role in progression to severe AAT disease, and it is possible that populations in different regions of the world have different sets of modifier genes. As our analysis continues, we have embarked on an ambitious genetic analysis of the cohort in an effort to identify disease modifiers whose physiologic relevance can be examined and possibly leveraged to find to new therapies.

Throughout the process of building and analyzing this cohort, we have sought to identify clinical markers obtained during routine care that would help physicians and families to identify patients at high risk of progression to severe liver disease. Although the development of an algorithm with useful specificity for predicting the hepatic prognosis of youth with AAT is not yet possible from these data, some features portending a poor prognosis were evident. First, very high GGTP levels in the first few years of life were commonly seen in participants with portal hypertension. In general, worsening liver chemistries tended to be seen as portal hypertension developed. However, no specific cut-off values with predictive significance have yet been found.

Our study does have limitations. First, it is a liver disease cohort, not an unbiased birth cohort, as noted, and the participants were mostly, but not exclusively, evaluated and managed at tertiary care centers. Also, this is a slowly progressive disease, and a large proportion of the cohort has been followed for only a few years. Therefore, conclusions about the disease risk or health of the pool of asymptomatic or undiagnosed AAT patients cannot be made.

Patient samples linked to the database are under study in an attempt to identify AAT disease-specific biomarkers, different from typical clinical tests that would be obtained during routine care, that might be used to predict progression to portal hypertension, liver transplant, and other complications. This type of new, powerful biomarker determination is only made possible by our combination of detailed, prospective data collection and continued long-term follow-up, with links to a biospecimen repository. ■

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## Appendix

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**Table III.**

## Patient disposition

Disposition	No. (%)	Median length of follow-up, <sup>*</sup> years (range)
Active with native liver	206 (58.9)	3.45 (0.00-9.74)
Death or transplant	32 (9.1)	1.64 (0.00-7.76)
Withdrawn	10 (2.9)	2.03 (0.00-4.05)
Lost to follow-up	57 (16.3)	1.13 (0.00-5.20)
Other <sup>†</sup>	45 (12.9)	2.17 (0.00-6.11)
Total	350 (100.0)	2.47 (0.00-9.74)

<sup>\*</sup>From baseline visit to either transplant or death (for those with an event), or last known follow-up.

<sup>†</sup>Other reasons for study removal included: Completed study, noncontinuing site, transferred to adult care, or moved out of network.

**Table IV.**

## Demographics and baseline characteristics by clinical outcome

Characteristics	Survival with native liver (n = 208)	Died or underwent liver transplantation (n = 32)	Censored <sup>*</sup> (n = 110)
Age at visit (years)			
N	208	32	110
Mean (SD)	5.0 (4.7)	5.8 (4.7)	8.1 (6.5)
Median (Q1, Q3)	3.2 (1.2, 7.5)	4.6 (1.6, 9.1)	6.9 (2.1, 13.0)
Min, Max	0.1 (18.6)	0.3 (15.2)	0.1 (24.9)
Sex			
Female	89 (43%)	10 (31.3%)	39 (35.5%)
Male	118 (57%)	22 (68.8%)	71 (64.5%)
Race			
Black	1 (0.5%)	2 (6.5%)	0 (0%)
Other	11 (5.4%)	1 (3.2%)	7 (6.4%)

Characteristics	Survival with native liver (n = 208)	Died or underwent liver transplantation (n = 32)	Censored* (n = 110)
White	191 (94.1%)	28 (90.3%)	103 (93.6%)
Ethnicity			
Hispanic	10 (4.9%)	2 (6.5%)	9 (8.3%)
Non-Hispanic	196 (95.1%)	29 (93.5%)	99 (91.7%)
Neonatal cholestasis			
No	84 (44.2%)	9 (28.1%)	45 (42.1%)
Yes	106 (55.8%)	23 (71.9%)	62 (57.9%)
Incident dpCEPH	10 (4.8%)	3 (9.4%)	5 (4.5%)
Time to incident dpCEPH, median years (Q1, Q3)	2.1 (1.9, 4.0)	0.7 (0.4,1.1)	2.4 (1.9, 2.8)

*ChiLDRen*, Childhood Liver Disease Research Network; *dpCEPH*, definite, or possible, clinically evident portal hypertension.

\* Participants were censored if they were lost to follow-up, withdrew from the study, transferred care to a non-*ChiLDRen* hospital, or were at a discontinued *ChiLDRen* site.

**Table V.**

Longitudinal patterns for clinical outcomes

Outcomes	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
dpCEPH										
No. at risk	350	196	151	121	93	65	48	39	23	10
Cumulative no. of events	72	76	82	85	87	88	88	89	90	90
KM estimate (95% CI)	1.00	0.78 (0.74-0.82)	0.75 (0.70-0.80)	0.74 (0.69-0.79)	0.72 (0.67-0.77)	0.71 (0.66-0.77)	0.71 (0.66-0.77)	0.70 (0.63-0.76)	0.68 (0.61-0.75)	0.68 (0.61-0.75)
Person-years (time on study)	0	211	384	519	623	698	753	798	829	846
Transplant or death										
No. at risk	350	249	193	155	120	83	63	51	25	11
Cumulative no. of events	0	11	20	23	28	30	31	31	32	32
KM estimate (95% CI)	1.00	0.96 (0.94-0.98)	0.92 (0.89-0.95)	0.91 (0.87-0.94)	0.87 (0.83-0.92)	0.86 (0.80-0.91)	0.84 (0.79-0.90)	0.84 (0.79-0.90)	0.82 (0.75-0.89)	0.82 (0.75-0.89)
Person-years (Time on study)	0	266	485	658	793	888	959	1017	1058	1077

*dpCEPH*, definite, or possible, clinically evident portal hypertension; *KM*, Kaplan-Meier.

**Table VI.**

## Longitudinal pattern for incident dpCEPH

Variables	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
No. at risk	278	196	151	121	93	65	48	39	23	10
Cumulative no. of events	0	4	10	13	15	16	16	17	18	18
KM estimate (95% CI)	1.00	0.98 (0.96-1.00)	0.95 (0.91-0.98)	0.93 (0.89-0.97)	0.91 (0.87-0.95)	0.90 (0.85-0.95)	0.90 (0.85-0.95)	0.88 (0.81-0.94)	0.85 (0.77-0.93)	0.85 (0.77-0.93)
Person-years (Time on study)	0	211	384	519	623	698	753	798	829	846

dpCEPH, definite, or possible, clinically evident portal hypertension; KM, Kaplan-Meier.

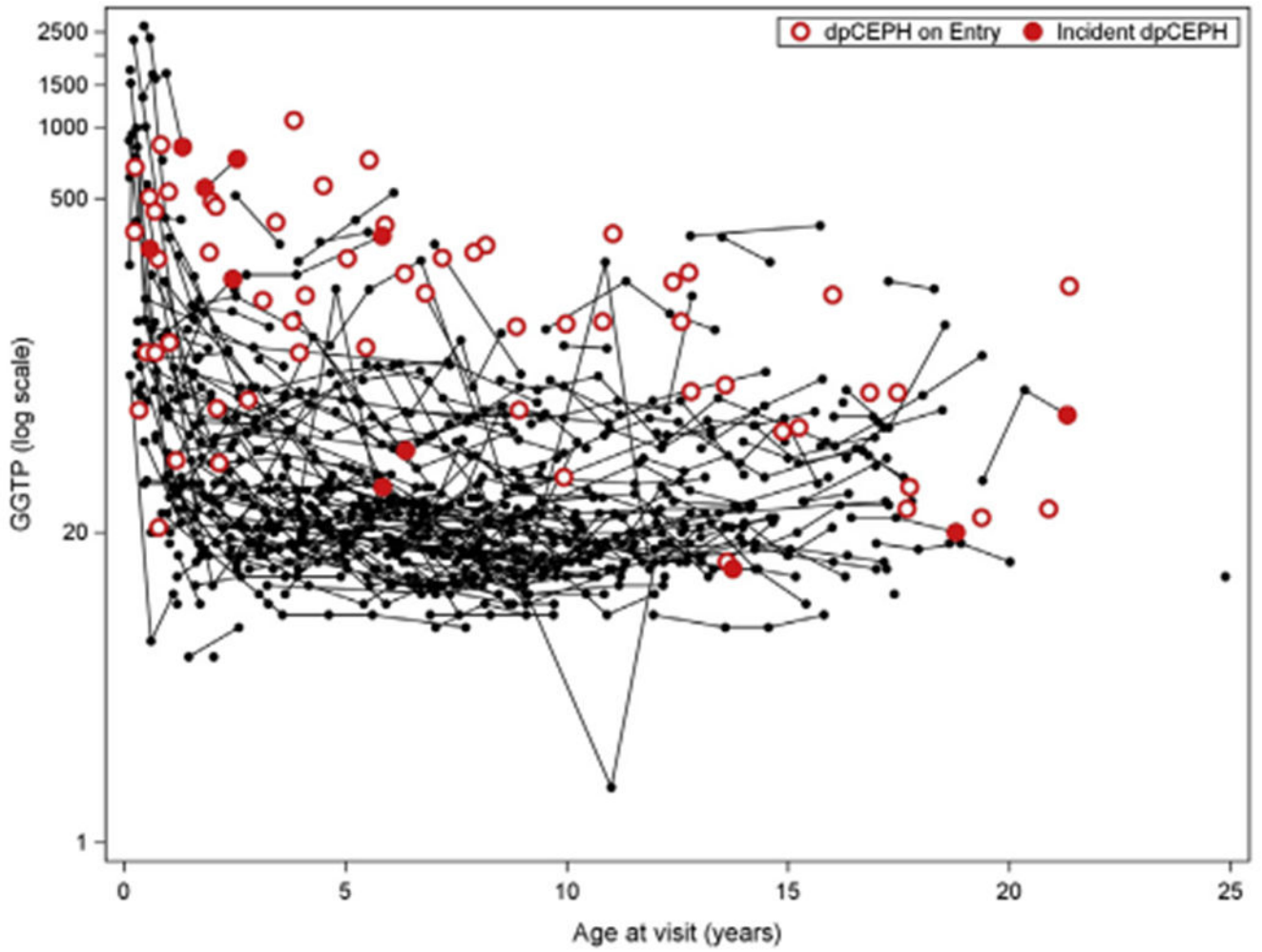
**Table VII.**

## Univariate predictors of time-to-transplant/death: All participants

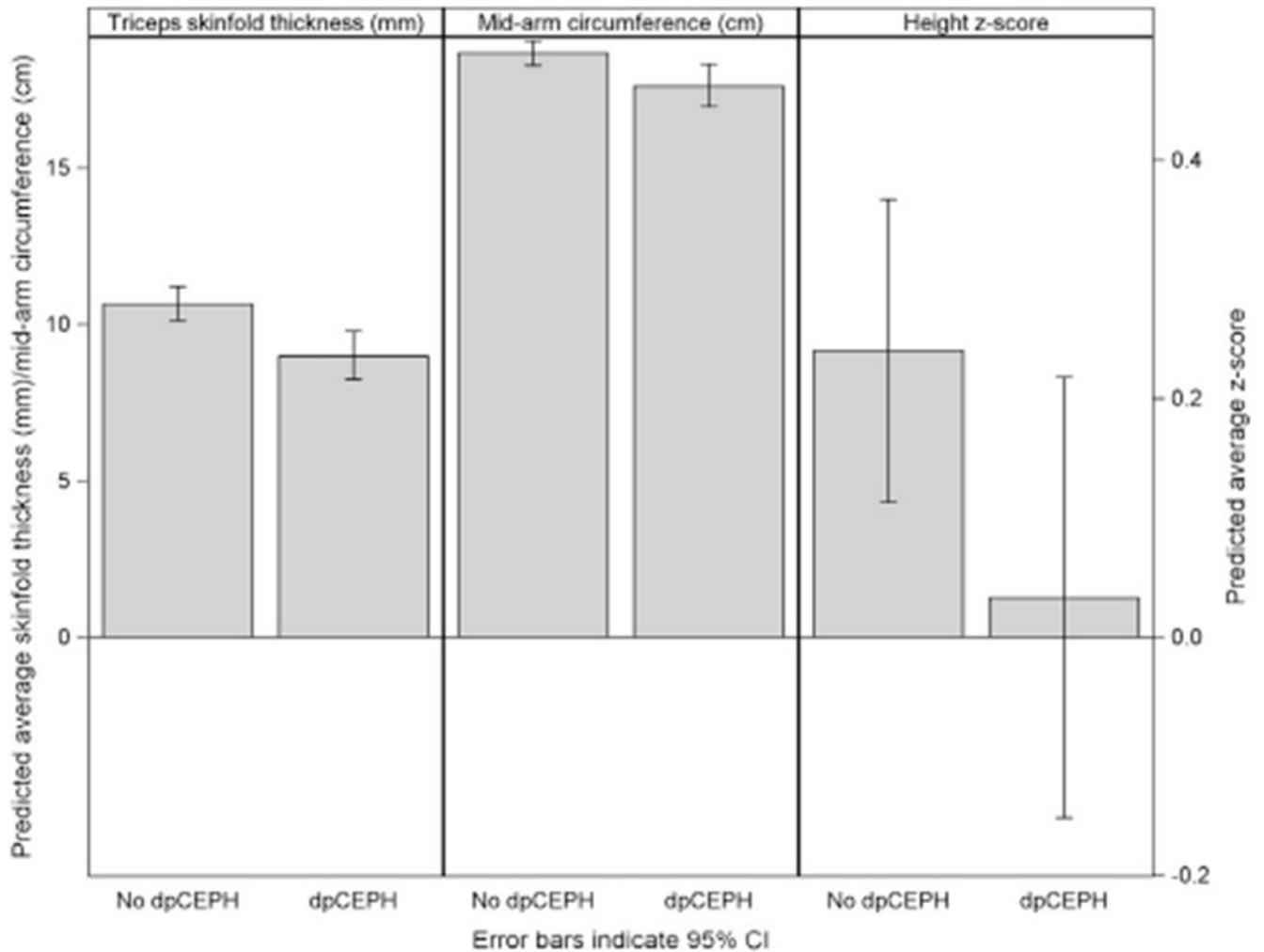
Predictor	HR	95% CI	P Value
Head circumference Z-score	0.76	0.15-3.74	.73
Right mid-arm circumference	0.75	0.53-1.07	.11
Right triceps skinfold thickness	0.81	0.56-1.18	.27
BMI	1.00	0.93-1.08	.91
BMI Z-score	1.49	0.45-4.94	.51
Weight Z-score	0.58	0.28-1.21	.15
Height Z-score	0.60	0.29-1.24	.17
Albumin (per 1 g/dL increase)	0.09	0.03-0.29	<.0001
Total bilirubin (per 1 mg/dL increase)	1.31	1.17-1.47	<.0001
Direct bilirubin (per 1 mg/dL increase)	3.56	1.58-8.01	.0021
AST (per 10 U/L increase)	1.18	1.09-1.26	<.0001
ALT (per 10 U/L increase)	1.00	1.00-1.01	.48
Platelets ( $10^3/\text{mm}^3$ )	0.99	0.98-1.00	.0128
AST/platelets	1.05	0.98-1.14	.18
INR (per 0.1)	1.83	1.32-2.54	.0003
Neonatal cholestasis	1.93	0.89-4.17	.0941

ALT, alanine transaminase; BMI, body mass index; HR, hazard ratio; INR, international normalized ratio; KM, Kaplan-Meier.

Model: Cox proportional hazards model with time-varying covariates (except for Neonatal Cholestasis, which is fixed).



**Figure 3.**  
Relationship of GGTP, age, and definite/possible clinically evident portal hypertension (dpCEPH): all participants.



**Figure 4.** Predicted anthropometric outcomes at age 6 by definite/possible clinically evident portal hypertension (dpCEPH) vs no dpCEPH: all participants.

## Glossary

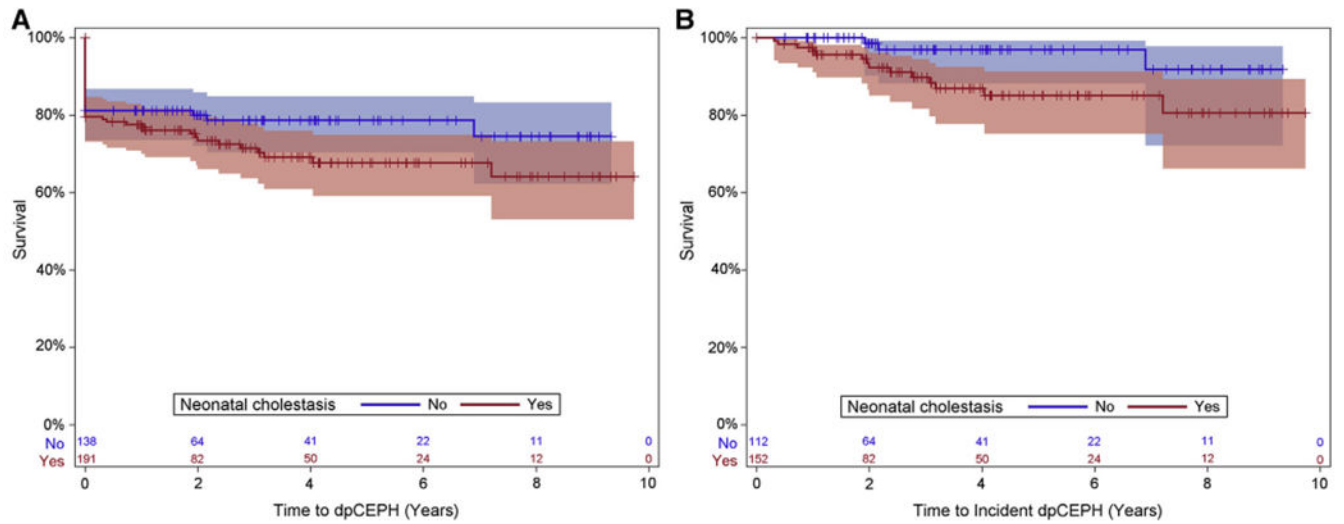
<b>AAT</b>	Alpha-1-antitrypsin
<b>AST</b>	Aspartate transaminase
<b>GGTP</b>	Gamma-glutamyl transpeptidase

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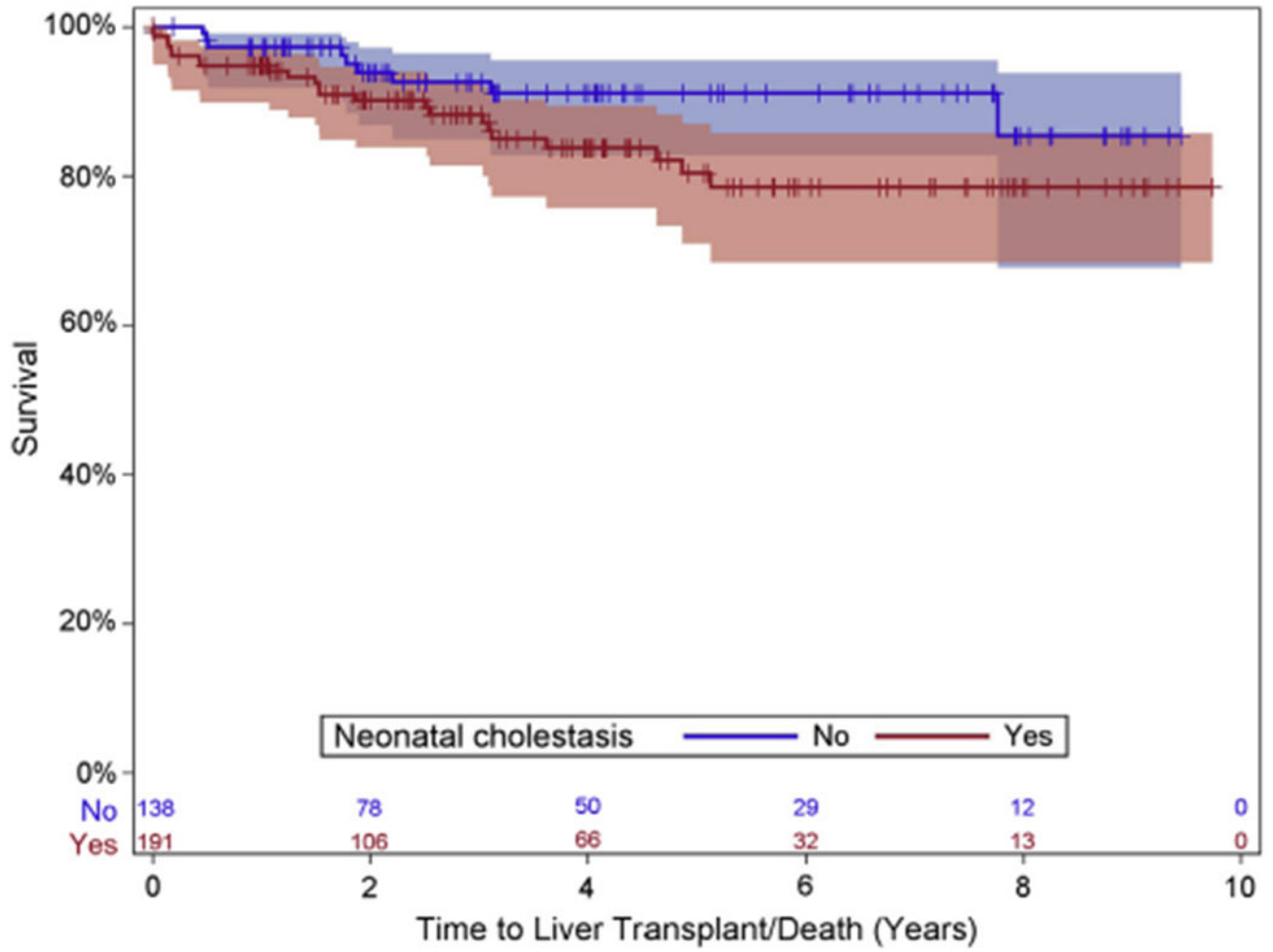
**Figure 1.** **A**, Definite/possible clinically evident portal hypertension (dpCEPH)-free Kaplan-Meier curve: all participants by neonatal cholestasis status. **B**, dpCEPH-free Kaplan-Meier curve: incident dpCEPH cases only.

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**Figure 2.** Liver transplant-free survival Kaplan-Meier curve. All participants by neonatal cholestasis status.

**Table 1.**

Patient characteristics at study entry and during follow-up

Characteristic	Statistic	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
Participants	N	350	229	179	151	102	73	56	47	37	18
Visits per participant	Mean (SD)	3.55 (2.48)	-	-	-	-	-	-	-	-	-
	Median (IQR)	3 (4)	-	-	-	-	-	-	-	-	-
	Min, max	1, 11	-	-	-	-	-	-	-	-	-
Phenotype	SZ	32 (10.1%)	-	-	-	-	-	-	-	-	-
	ZZ	286 (89.9%)	-	-	-	-	-	-	-	-	-
Age (years)	N	350	229	179	151	102	73	56	47	37	18
Age group (years)	Mean (SD)	6.05 (5.49)	6.82 (5.09)	7.31 (4.87)	8.91 (4.99)	9.83 (4.85)	9.99 (4.21)	10.86 (4.04)	11.52 (3.75)	12.96 (3.97)	13.24 (4.24)
	Median (IQR)	4.23 (7.98)	5.59 (7.38)	5.93 (6.38)	7.7 (7.07)	8.64 (7.27)	9.04 (5.3)	9.94 (5.58)	10.72 (4.49)	12.79 (4.76)	12.13 (4.25)
	Min, max	0.12, 24.87	0.96, 22.48	1.77, 22.85	2.78, 23.9	4.05, 24.96	4.95, 25.97	6.06, 24.54	7.35, 25.79	8.25, 26.88	9.77, 28.07
	0-<5	191 (54.6%)	107 (46.7%)	77 (43%)	42 (27.8%)	13 (12.7%)	1 (1.4%)	-	-	-	-
	5-<10	83 (23.7%)	70 (30.6%)	60 (33.5%)	56 (37.1%)	47 (46.1%)	43 (58.9%)	28 (50%)	20 (42.6%)	11 (29.7%)	2 (11.1%)
	10-<15	43 (12.3%)	31 (13.5%)	25 (14%)	31 (20.5%)	26 (25.5%)	23 (31.5%)	21 (37.5%)	20 (42.6%)	18 (48.6%)	13 (72.2%)
	15-<20	28 (8%)	17 (7.4%)	13 (7.3%)	17 (11.3%)	12 (11.8%)	4 (5.5%)	5 (8.9%)	5 (10.6%)	6 (16.2%)	2 (11.1%)
20-<25	5 (1.4%)	4 (1.7%)	4 (2.2%)	5 (3.3%)	4 (3.9%)	1 (1.4%)	2 (3.6%)	1 (2.1%)	1 (2.7%)	-	
Ethnicity	25	-	-	-	-	-	1 (1.4%)	-	1 (2.1%)	1 (2.7%)	1 (5.6%)
	Hispanic	21 (6.1%)	15 (6.6%)	13 (7.3%)	9 (6%)	8 (7.8%)	5 (6.8%)	3 (5.4%)	4 (8.5%)	3 (8.1%)	3 (16.7%)
Sex	Non-Hispanic	324 (93.9%)	212 (93.4%)	165 (92.2%)	141 (94%)	94 (92.2%)	68 (93.2%)	53 (94.6%)	43 (91.5%)	34 (91.9%)	15 (83.3%)
	Male	211 (60.5%)	144 (62.9%)	112 (62.6%)	86 (57%)	61 (59.8%)	39 (53.4%)	32 (57.1%)	22 (46.8%)	20 (54.1%)	11 (61.1%)
Race	Female	138 (39.5%)	85 (37.1%)	67 (37.4%)	65 (43%)	41 (40.2%)	34 (46.6%)	24 (42.9%)	25 (53.2%)	17 (45.9%)	7 (38.9%)
	White	322 (93.6%)	210 (92.5%)	167 (93.3%)	140 (92.7%)	96 (94.1%)	70 (95.9%)	52 (92.9%)	43 (91.5%)	34 (91.9%)	17 (94.4%)
Other	Black	3 (0.9%)	3 (1.3%)	1 (0.6%)	1 (0.7%)	-	-	-	-	-	-
	Other	19 (5.5%)	14 (6.2%)	11 (6.1%)	10 (6.6%)	6 (5.9%)	3 (4.1%)	4 (7.1%)	4 (8.5%)	3 (8.1%)	1 (5.6%)

**Table II.**

Univariate predictors of time-to-dpCEPH: Incident dpCEPH cases only

Predictor	HR	95% CI	P value
Head circumference Z-score	0.65	0.42-1.00	.051
Right mid arm circumference	0.93	0.2-1.07	.32
Right triceps skinfold thickness	1.05	0.97-1.13	.27
BMI	0.89	0.68-1.17	.40
BMI Z-score	0.61	0.32-1.14	.12
Weight Z-score	0.66	0.43-1.03	.07
Height Z-score	0.67	0.42-1.07	.09
Albumin (per 1 g/dL increase)	0.52	0.23-1.16	.11
Total bilirubin (per 1 mg/dL increase)	1.97	1.33-2.90	.0007
Direct bilirubin (per 1 mg/dL increase)	0.32	0.76-2.28	.32
AST (per 10 U/L increase)	1.06	1.01-1.10	.01
ALT (per 10 U/L increase)	1.00	1.00-1.01	.25
GGTP (per 100 U/L increase)	1.20	1.10-1.31	<.0001
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	0.99	0.98-1.00	.04
INR (per 0.1)	1.21	0.95-1.54	.12
AST/platelets	5.93	2.30-15.33	.0002
Neonatal cholestasis	3.70	1.06-12.87	.04

ALT, alanine transaminase; BMI, body mass index; dpCEPH, definite or possible clinically evident portal hypertension; HR, hazard ratio; INR, international normalized ratio; KM, Kaplan-Meier.

Model: Cox proportional hazards model with time-varying covariates (except for neonatal cholestasis, which is fixed).