Assessing the Validity of Adult-derived Prognostic Models for Primary Sclerosing Cholangitis Outcomes in Children

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Validity of adult-derived prognostic models for primary sclerosing cholangitis outcomes in children

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Abstract: (266 words)

Background:

Several natural history models for PSC have been derived from adult patient data, but none have been validated in children. It is unclear how accurate such models are for pediatric-onset PSC patients, given that children have lower rates of dominant stricture and cholangiocarcinoma, and higher rates of autoimmune hepatitis overlap and small duct phenotype compared to adult PSC patients.

Methods:

We utilized patient data from the pediatric PSC consortium in three adult-based models: the Revised Mayo Clinic, the Amsterdam-Oxford and the Boberg models. We risk-stratified patients and calculated predicted survival with native liver probabilities for each patient according to each model. We evaluated model discrimination with the c-statistic. We compared predicted to observed probabilities graphically. We evaluated risk-stratification with the Logrank test.

Results:

The Mayo model had good discrimination (c-statistic 0.78), and provided reasonably accurate survival probabilities. Risk-stratification was excellent, with most children correctly stratified as low risk. The Amsterdam-Oxford model had fair discrimination (c-statistic 0.69), and provided reasonably accurate survival probabilities through 5 years, but not to 10 years. Risk-stratification was poor, with most children incorrectly labelled as high risk. The Boberg model offered excellent discrimination (c-statistic 0.87) of one-year outcomes, but the worst survival prediction.

Conclusion:

The best balance of discrimination, prediction and risk-stratification was provided by the Mayo model. None of the models accounted for the high prevalence of features of autoimmune hepatitis overlap in children and the associated biochemical profile. A pediatric-specific natural history model, with weighting of predictors that accounts for the unique features of children is likely to yield more useful and accurate predictions and risk-stratification for pediatric-onset PSC.

Introduction:

Several natural history models have been derived from clinical data in adult populations with primary sclerosing cholangitis (PSC) (1-10). No consensus exists regarding the optimal model (11), and none have been validated for use in children. Important clinical differences exist between pediatric and adult-onset PSC patients. At PSC diagnosis, dominant strictures are present in 4% of children (12, 13), compared to 45% of adults (14). Similarly, cholangiocarcinoma is rare in pediatric-onset PSC, occurring in 1% of children by 10 years (12, 13), compared to at least 7-13% of adults (15-17). A small duct phenotype is present in 20% of children (12, 13), but only 10% of adults (18, 19). Features of autoimmune hepatitis overlap with PSC are present in over 33% of children (12, 13), but only 7% of adults with PSC (20, 21). With these clinical differences, it is unclear how well risk models derived from adult patient data are generalizable to children.

The most widely-used model to estimate transplant-free patient survival is the Revised Natural History Model for PSC, from a group at the Mayo Clinic (the "Mayo model") (5). It estimates survival with native liver for up to four years, and is available as an online calculator tool (22). A subsequent risk model from five European centers was created by Boberg et al. to more accurately estimate one-year survival to inform immediate transplant listing decisions (the "Boberg model") (6). The most recent Amsterdam-Oxford model (the "A-O model") included the largest model creation and validation cohorts to date, and had an added strength of originating from population-based data (10). It estimates survival with native liver out to 15 years, and is also available online (23). Characteristics of these models and their creation and validation cohorts are described in **Table 1**. We aimed to test the predictive utility of the Mayo, Boberg and A-O prognostic models for PSC using data from the Pediatric PSC Consortium, a large, multicenter cohort of children with PSC (12).

Table 1: Characteristics of Adult Prognostic Models for Primary Sclerosing Cholangitis

Model	**Mayo** Kim et al. 2000 (5)	**A-O** de Vries et al. 2017 (10)	**Boberg** Boberg et al. 2002 (6)
Creation Cohort			
Location(s)	four United States referral centers	44 Dutch centers (population-based)	five European referral centers
n	405	692	330
age (years)	42	37 [IQR 27-49]	37 (range 13-82)
% female	33%	35%	32%
% with IBD	74%	70%	83%
% with AIH	0%	5%	0%
median survival with native liver	not reported	20 years	11.7 years
Externally Validated?	Yes	Yes	No
Validation Cohort			
location	King's College hospital London, UK	John Radcliffe hospital Oxford, UK	
n	124	264	
age (median)	36 years	45 years	
% with IBD	71%	74%	
% with AIH	0%	2%	
median survival with native liver	12 years	23 years	
Variables	age at diagnosis albumin AST bilirubin variceal bleeding history	age at diagnosis albumin alkaline phosphatase AST bilirubin large duct phenotype platelets	age at diagnosis albumin bilirubin
Survival with native liver estimates:	1-4 years	1-15 years	1 year

Methods:

We previously reviewed medical records on all known PSC patients at 36 different institutions throughout Europe, North America, the Middle East, and Asia (12). The PSC diagnosis was based on a cholestatic laboratory profile and either cholangiography showing multifocal stricturing and segmental dilations of the biliary tree and/or liver biopsy showing periductal, concentric fibrosis, fibro-obliterative cholangitis, or primary ductular involvement (11). Patients with abnormal cholangiograms were labeled as large duct PSC. Patients with normal cholangiograms but abnormal liver biopsy were labeled as small duct PSC. Autoimmune hepatitis (AIH) was diagnosed in patients who met a 'probable' or 'definite' score on the simplified AIH criteria that have been validated in children (24). We collected demographics, laboratory, histopathology, cholangiography and endoscopy data at liver disease diagnosis, as well as the presence of an esophageal variceal bleeding history. The pediatric PSC consortium cohort contained 781 patients, median age 12 years, 39% female, 76% with IBD, 33% with autoimmune hepatitis overlap, with 10-year survival with native liver of 70%.

We calculated survival probabilities for each child using the equations derived from the Mayo (5), Boberg (6) and A-O (10) risk models **(Appendix 1).** We did not validate other models because they necessitated access to original histopathology (1, 4), full images from cholangiography studies (7, 9), or included subjective assessments of organomegaly (2, 3, 8) that were not included in our dataset. To generate observed survival probabilities, we created a retrospective cohort of all patients and followed them from time of PSC diagnosis to endpoints of liver transplantation or death from liver disease. Person-time was censored at the date of the last known clinical encounter. We used the Kaplan-Meier method to calculate rates of survival each year after diagnosis.

We evaluated ability of each model to yield accurate survival probabilities for a given patient graphically, by comparing overlaid plots of observed and calculated survival probabilities. We plotted the Kaplan-Meier curve of observed outcomes alongside the annual predicted probabilities of survival for each risk group. For the plots of predicted survival, we calculated the median of the annual survival probabilities of each patient within each risk group, and connected these with straight lines (25, 26). The utility of risk score cutoffs specified by the adult models to stratify patients into distinct groups (e.g. "low" and "high" risk) with distinct observed survival probabilities was assessed using the logrank test. The logrank test is used to test the null hypothesis that there is no difference between the risk groups in the probability of an event (transplant or death) at any time point (27). Discriminatory ability of the models was assessed with the concordance statistic (c-statistic). The c-statistic was calculated by comparing observed and expected survival between every possible pairing of two of the 781 patients in the cohort (1 vs. 2, 1 vs. 3, … , 780 vs. 781). The c-statistic is the percentage of all 609,180 of these possible pairings that the model "guessed" correctly (assigned a worse predicted survival to the patient with the worst observed survival) (28). The c-statistic ranges from 0.5 (no discrimination, e.g. random risk stratification using a coin toss) and 1.0 (perfect discrimination), with values of 0.7 or higher generally regarded as "good discrimination" (29).

All calculations were done using Stata version 13.0 (StataCorp, College Station, TX). The protocol of the study was approved by the institutional review and/or research ethics board of each collaborating institution.

Results:

The Revised Mayo Clinic Model:

Overall, the Mayo model offered reasonable discrimination of outcomes with a c-statistic of 0.78. Predicted vs. observed SNL was similar in low, medium and high risk groups at one-year (99 vs. 99, 97 vs. 98, and 80 vs. 79%, respectively), but more disparate at four years (98 vs. 96, 89 vs. 79, and 33 vs. 47%, respectively). The low, medium and high risk cutoffs created three distinct populations of patients with progressively worse outcomes, logrank $p<0.001$ between all groups as shown in **Figure 1**. Most children were correctly stratified to the low risk group.

Serum albumin and aspartate aminotransferase levels made up the majority of the risk score for each patient, whereas total bilirubin, patient age, and variceal hemorrhage history contributed very little to the risk score, as shown in **Figure 2**. Each of the predictor variables varied significantly between groups as shown in **Table 2**. Inflammatory bowel disease was most prevalent in low vs. medium and high risk groups: 80 vs. 73 vs. 52%, while autoimmune hepatitis was least prevalent in low vs. medium and high risk groups: 29 vs. 39 vs. 52%, respectively. Large duct disease was distributed evenly among risk groups.

Table 2: Characteristics of each risk group in the Mayo model

	Overall risk score	Age (yr)	Albumin (g/dL)	AST (U/L)	Bilirubin (mg/dL)	Bleeding History
Low n=507	-1.02 (-1.59 to -0.47)	12.0 (7.6-14.5)	4.1 (3.9-4.4)	82 (46-156)	0.5 (0.3-0.9)	0.6% (3/507)
Med n=236	0.51 (0.14 to 1.06)	13.0 (10.5-15.0)	3.9 (3.4-4.0)	190 (147-261)	1.5 (1.3-2.4)	20% (47/236)
High n=31	2.79 (2.39 to 3.19)	13.0 (7.3-14.3)	3 (2.7-3.4)	336 (206-1216)	7.5 (2.9-11.7)	61% (19/31)
p		0.0001	0.0001	0.0001	0.0001	0.0001

Data presented as median(IQR) or n(%)

Figure 1. Observed vs. Predicted survival with native liver by risk group in the Mayo model

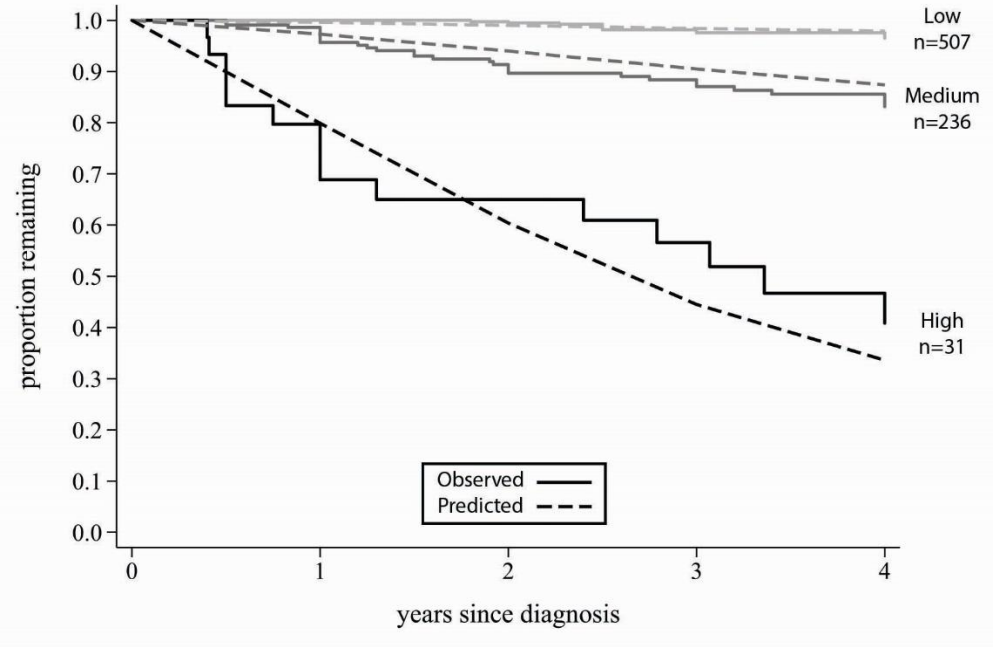
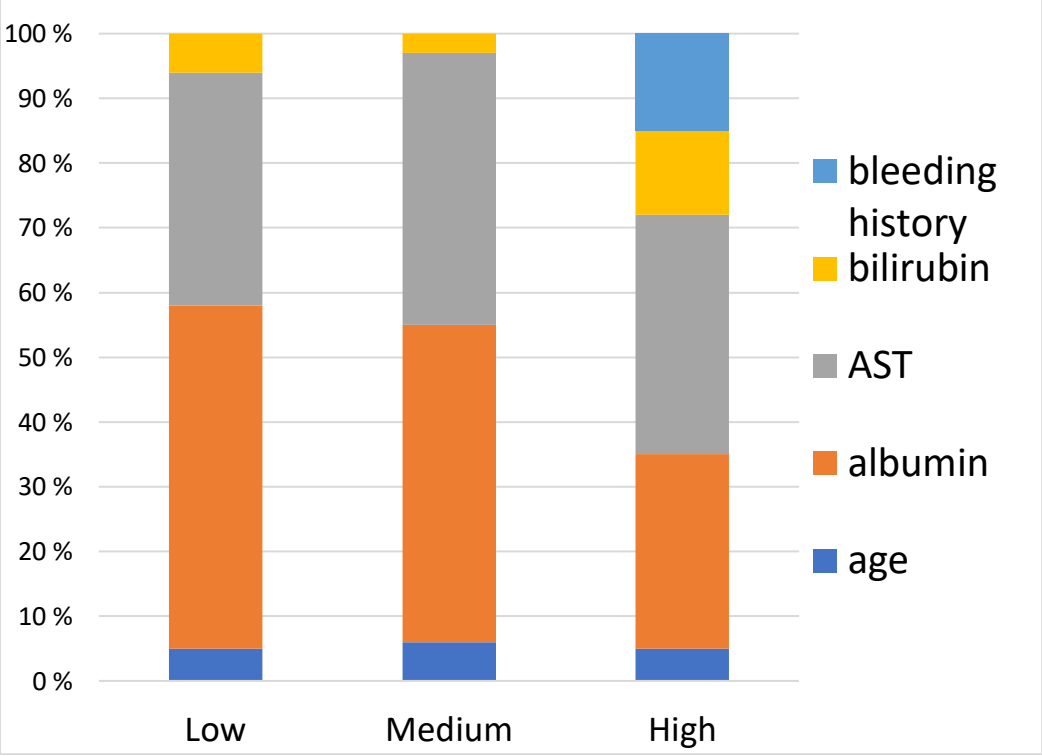


Figure 2: Relative contribution of predictors to risk score in each Mayo risk group



The Amsterdam-Oxford Model:

Overall, the A-O model offered fair discrimination of outcomes with a c-statistic of 0.69. Predicted vs. observed SNL was similar in low, low-intermediate, and medium risk groups, but disparate in the high risk group at one-year (100 vs. 99, 100 vs. 98, 100 vs. 97, 96 vs. 90%, respectively), five years (97 vs. 97, 96 vs. 94, 94 vs. 89, 83 vs. 66%, respectively) and ten years (88 vs. , 84 vs. 84, 76 vs. 74, 61 vs. 34%, respectively). The low, low-intermediate, medium and high risk cutoffs created four distinct populations of patients with progressively worse outcomes, log-rank $p<0.001$ between all groups as shown in **Figure 3**. The original model stratified 16, 34, 34 and 16% of adult patients as low, low-intermediate, medium and high risk, respectively. Children were incorrectly stratified with 19, 9, 14 and 57% falling into these respective groups.

Serum aspartate aminotransferase levels and platelet count made up the majority of the risk score for each patient, whereas total bilirubin, alkaline phosphatase, and albumin contributed little to the risk score, as shown in **Figure 4**. Age and large duct phenotype were similar in all risk groups, whereas all of the laboratory-based predictors were significantly different as shown in **Table 3**. Inflammatory bowel disease was slightly more prevalent in lower risk groups: 84 vs. 77 vs. 80 vs. 74%, respectively, while autoimmune hepatitis was more prevalent in higher risk groups: 17 vs. 31 vs. 37% vs. 38%, respectively.

Table 3: Characteristics of each risk group in the Amsterdam-Oxford model

	A-O score	Age (yr)	Albumin (g/dL)	ALP (x ULN)	AST (U/L)	Bilirubin (mg/dL)	Large duct phenotype	Platelets (x1000/L)
Low (n = 145)	0.44 (0-0.75)	13 (10-15)	4.3 (4.0-4.5)	0.6 (0.4-0.8)	41 (29-56)	0.4 (0.3-0.6)	66% (95/145)	296 (255-325)
Low Int (n = 73)	1.35 (1.19-1.46)	12 (9-15)	4.3 (4.0-4.5)	0.8 (0.5-1.1)	71 (47-88)	0.5 (0.4-0.8)	71% (52/73)	325 (244-390)
Medium (n = 112)	1.86 (1.71-2.07)	12 (8-15)	4.0 (3.8-4.3)	0.9 (0.6-1.2)	85 (60-137)	0.6 (0.3-1.0)	71% (80/112)	325 (259-413)
High (n = 444)	3.18 (2.82-4.26)	12 (8-15)	4.0 (3.5-4.0)	1 (0.9-1.9)	190 (135-261)	1.5 (0.7-1.7)	76% (339/444)	325 (242-396)
p		0.165	0.0001	0.0001	0.0001	0.0001	0.08	0.0004

Data presented as median(IQR) or n(%)

Figure 3: Observed vs. Predicted survival with native liver by risk group in the Amsterdam-Oxford model

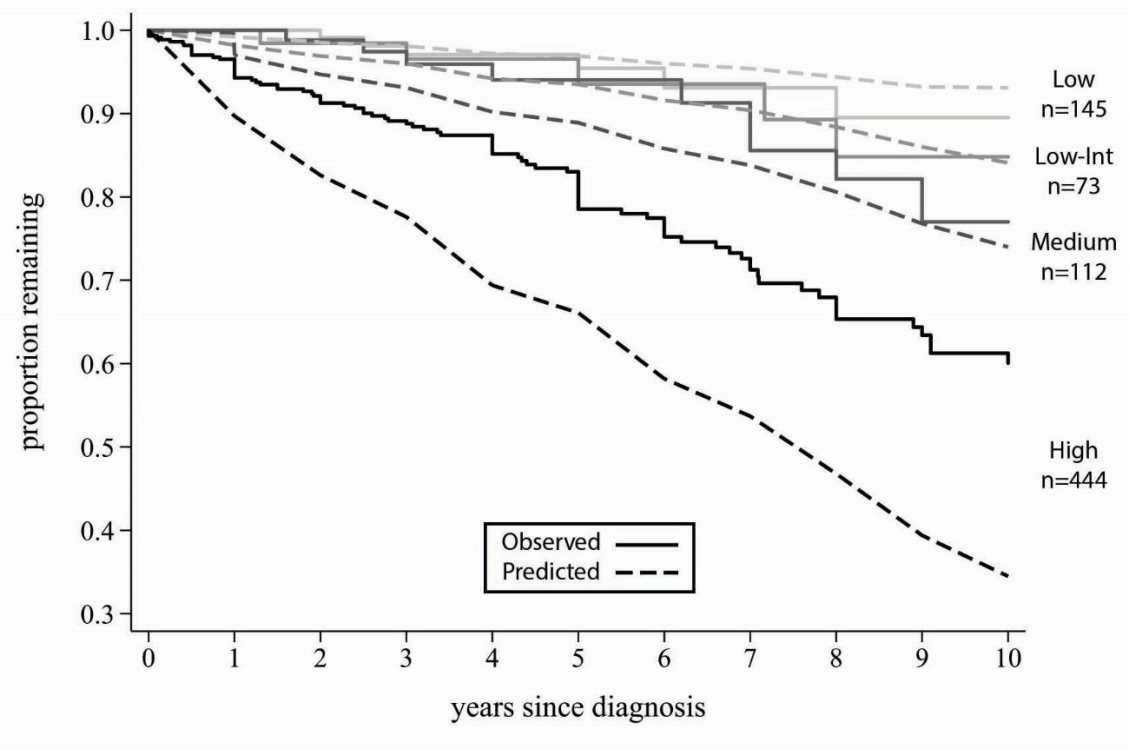
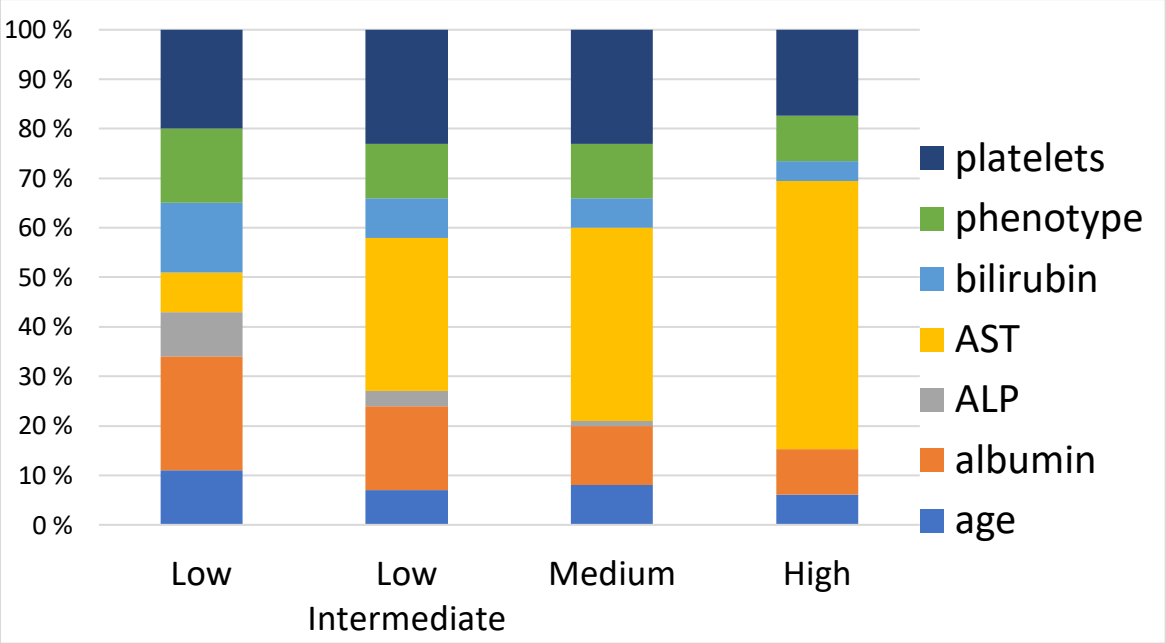


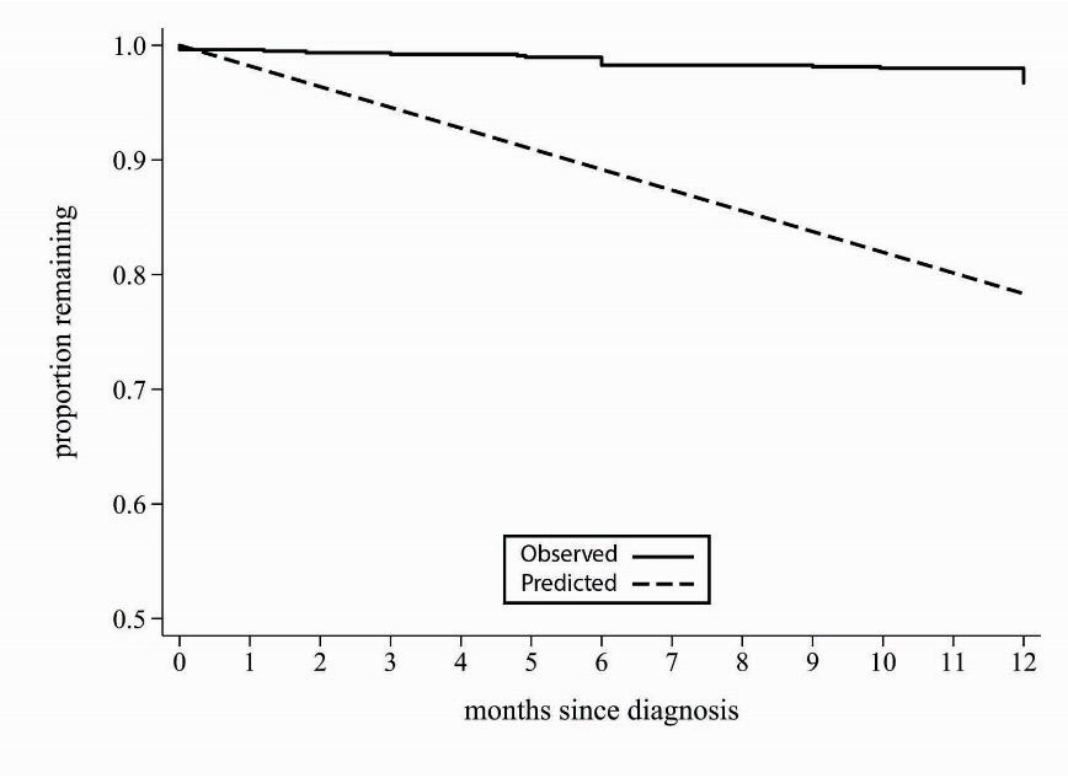
Figure 4: Relative contribution of predictors to risk score in each Amsterdam-Oxford risk group



The Boberg model:

The Boberg model provided excellent discrimination of one-year outcomes, with a c-statistic of 0.87. It was generally good at predicting if an individual patient would require liver transplantation or not. The model was overly pessimistic in predicting SNL for the group however. We observed 24 deaths or liver transplants in the first year after diagnosis, whereas the Boberg model predicted that over 260 would have occurred. The observed vs. predicted SNL at one year was 98% vs. 78%, respectively, as shown in Figure 5.

Figure 5: Observed vs. Predicted survival with native liver in the Boberg model:



Discussion:

We used a large dataset of pediatric-onset PSC cases to assess the validity of prognostic and risk stratification tools created for adult PSC patients. We showed that the Boberg model offered the best discrimination of outcome at one year. The Mayo and A-O models accurately estimated SNL in patients for 4-5 years after diagnosis. The Mayo model provided the best stratified to low, medium and high risk groups. The largest source of inaccuracy of the models appeared to be weighting of AST that did not take into account the high prevalence of autoimmune hepatitis in children.

AST level contributed the largest variance explained in calculating risk scores in the Mayo and A-O model, and in stratifying patients into higher risk groups. AST rises with extensive fibrosis and cirrhosis. Indeed, the AST to Platelet ratio index (APRI) is a useful surrogate marker of hepatic fibrosis in many liver diseases (30-32), including PSC (33, 34). While an important predictor of disease progression, the Mayo and A-O models do not take into account the high prevalence of features of AIH overlap in children. At least one third of children with PSC are affected with AIH (12) compared to 0-5% of the adult cohorts (5, 6, 10) used to create these models. The median AST at diagnosis in children with PSC-AIH overlap was 290 U/L, yet most of these children had an uncomplicated clinical course, with a five-year SNL of 90% (12). The large number of children with marked elevations of AST that are unrelated to fibrosis, and which do not imply a negative prognosis, is the largest source of inaccuracy in prediction and risk stratification in these models.

It may seem remarkable that the models provide reasonable discrimination of outcomes at all, given the derivation and validation cohorts range in median age from 36-45 years old, and the median child in our cohort is only 12. Despite differing prevalence of complications at diagnosis of PSC, disease progression to new adverse liver events is similar between children and adults, occurring in approximately 4% of patients per year. There are no known differences in the pathogenesis of PSC in children as compared to adults. Other than patient age, the laboratory markers and phenotypic features included in the adult models have generally been shown to be useful predictors in children (12, 13). It is likely that an optimized pediatric-specific model will include many of the same predictors, but will apply different weights to each.

The strength of this study was the large size of the validation cohort we utilized. The Pediatric PSC Consortium is the largest cohort of pediatric-onset PSC patients, and includes a diverse mix of secondary and tertiary referral centers. The weakness of the study is the retrospective nature of the Pediatric PSC Consortium data. This prevented a standardized diagnostic and therapeutic algorithm for each patient, and misclassification bias may be present. While we were able to evaluate the most popular and user-friendly risk stratification models, were unable to evaluate all existing prognostic models due to lack of original histopathology and cholangiography data, and lack of subjective assessments of organomegaly in all patients.

In conclusion, we used the Pediatric PSC Consortium dataset to evaluate the validity of adult-derived prognostic models to predict clinical outcomes in children. The best balance of discrimination, prediction and risk-stratification was provided by the Mayo model. None of the models accounted for the high prevalence of features of autoimmune hepatitis overlap in children and the associated elevations of aminotransferase levels that are unrelated to cirrhosis. A pediatric-specific natural history model, with weighting of predictors that accounts for the unique biochemical profile of children, is likely to yield more useful and accurate predictions and risk-stratification for pediatric-onset PSC.

Appendix 1 - Risk stratification formulae:

Revised Natural History Model for PSC (the "Mayo model") (5):

The risk score (R) was calculated using the formula:

$R = 0.03 * [\text{age (years)}] + 0.54 * \log_e [\text{bilirubin (mg/dL)}] + 0.54 * \log_e [\text{AST (U/L)}] - 0.84 * [\text{albumin (g/dL)}] + 1.24$ if history of variceal bleeding was present.

Patients were classified as low risk if $R < 0$, medium risk if $0 \leq R < 2$, and high risk if $R \geq 2$ (35).

We calculated the predicted survival for each patient at years 1-4 using the formula: $S(t)=S_0(t)^{\exp(R-1)}$, where baseline survival probabilities $S_0(t)$ each year were: year 0 = 1, year 1 = 0.963, year 2 = 0.919, year 3 = 0.873, and year 4 = 0.833.

The Amsterdam-Oxford model (the "A-O model") (10):

The prognostic index (PI) was calculated using the formula (where LLN and ULN represent the lower and upper limits of normal, respectively):

$PI = 0.018 * [\text{age at diagnosis (years)}] - 2.485 * \log_{10} [\text{albumin(x LLN)}] + 2.451 * \text{abs} (\log_{10} [\text{platelets(x LLN)}] - 0.5) + 0.347 * \log_{10} [\text{AST(x ULN)}] + 0.393 * \log_{10} [\text{ALP (x ULN)}] + 0.337 * \log_{10} [\text{bilirubin(x ULN)}] + 0.323$ if a large duct phenotype was present

Patients were classified as low risk if $PI < 1.032$, low-intermediate risk if $1.578 > PI \geq 1.032$, moderate risk if $PI\ 2.266 > PI \geq 1.578$, and high risk if $PI \geq 2.266$.

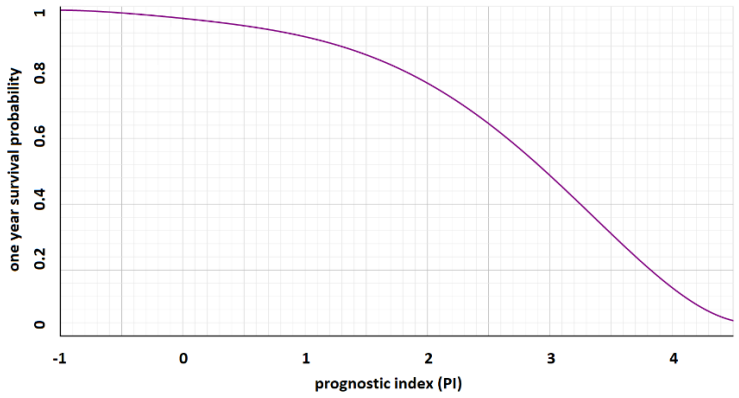
We calculated the predicted survival for each patient at years 1-10 using the formula: $S(t)=S_0(t)^{\exp(PI-1.646)}$, where baseline survival probabilities $S_0(t)$ each year were: year 0 = 1, year 1 = 0.976003276, year 2 = 0.958190391, year 3 = 0.944872387, year 4 = 0.921801174, year 5 = 0.911738594, year 6 = 0.886368701, year 7 = 0.870414839, year 8 = 0.844120125, year 9 = 0.812447482, and year 10 = 0.788752707.

Boberg et al time-dependent Cox regression model (the "Boberg model") (6):

The prognostic index (PI) was calculated using the formula:

$PI = 1.04 * [\log_e (\text{bilirubin[umol/L]}) - 3.31] - 0.12 * (\text{albumin (g/L)} - 37.27) + 0.013 (\text{age at diagnosis (years)} - 36.04)$

The one year survival estimate was obtained by plotting the PI on Figure #, which we obtained by overlaying a best-fit graph on Figure 3 of the original manuscript (6) and generating the following best-fit polynomial equation: survival = 0.0011*PI^5 - 0.0055*PI^4 - 0.0035*PI^3 - 0.01*PI^2 - 0.0379*PI + 0.9641.



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