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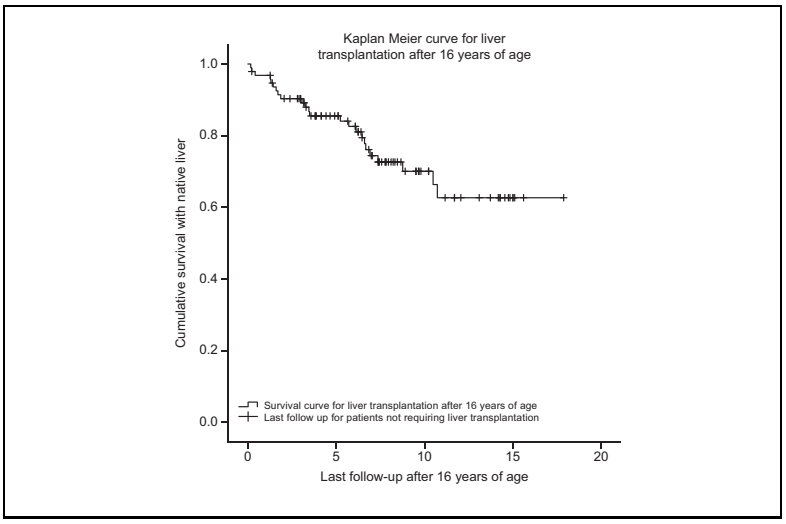
Prognostic markers at adolescence in patients requiring liver transplantation for biliary atresia in adulthood

Graphical abstract



Highlights

- Patients with biliary atresia are at risk of needing a liver transplant when >16 years old.
- Higher bilirubin and lower creatinine at 16 years of age are predictors of the need for liver transplant.
- Cholangitis and varices in adolescence increase the risk of needing a liver transplant when >16 years old.

Authors

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Lay summary

Patients with biliary atresia commonly require liver transplantation before reaching adulthood. Those who reach adulthood with their own liver are still at risk of needing a transplant. This study aimed to identify tests that could help clinicians predict which patients with biliary atresia who reach the age of 16 without a transplant will require one in later life. The study found that the presence of bilirubin $\geq$21 μmol/L, lower creatinine levels, and a history of portal hypertension or gastro-oesophageal varices at 16 years, as well as cholangitis in adolescence, could predict the future likelihood of needing a liver transplant for young people with biliary atresia.

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Prognostic markers at adolescence in patients requiring liver transplantation for biliary atresia in adulthood

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Background & Aims: In patients with biliary atresia (BA), the rate of native liver survival (NLS) to adulthood has been reported as 14–44% worldwide. Complications related to portal hypertension (PHT) and cholangitis are common in adulthood. For those requiring liver transplantation (LT), the timing can be challenging. The aim of this study was to identify variables that could predict whether young people with BA would require LT when they are >16 years of age.

Methods: This study was a single-centre retrospective analysis of 397 patients who underwent Kasai portoenterostomy (KP) between 1980–96 in the UK. After KP, 111/397 (28%) demonstrated NLS until 16 years of age. At final follow-up, 67 showed NLS when >16 years old (Group 1) and 22 required LT when >16 years old (Group 2). Laboratory, clinical and radiological parameters were collected for both groups at a median age of 16.06 years (13.6–17.4 years).

Results: The need for LT when >16 years old was associated with higher total bilirubin (hazard ratio 1.03, $p = 0.019$) and lower creatinine (hazard ratio 0.95, $p = 0.040$), at 16 years, on multivariate analysis. Receiver-operating characteristic curve analysis demonstrated that a total bilirubin level of ≥21 μmol/L at 16 years old (AUROC = 0.848) predicted the need for LT when >16 years old, with 85% sensitivity and 74% specificity. Cholangitis episode(s) during adolescence were associated with a 5-fold increased risk of needing LT when >16 years old. The presence of PHT or gastro-oesophageal varices in patients <16 years old was associated with a 7-fold and 8.6-fold increase in the risk of needing LT, respectively.

Conclusions: BA in adulthood requires specialised management. Adult liver disease scoring models are not appropriate for this cohort. Bilirubin ≥21 μmol/L, PHT or gastro-oesophageal varices at 16 years, and cholangitis in adolescence, can predict the need for future LT in young people with BA. Low creatinine at 16 years also has potential prognostic value.

Lay summary: Patients with biliary atresia commonly require liver transplantation before reaching adulthood. Those who reach adulthood with their own liver are still at risk of needing a transplant. This study aimed to identify tests that could help clinicians predict which patients with biliary atresia who reach the age of 16 without a transplant will require one in later life. The study found that the presence of bilirubin ≥21 μmol/L, lower creatinine levels, and a history of portal hypertension or gastro-oesophageal varices at 16 years, as well as cholangitis in adolescence, could predict the future likelihood of needing a liver transplant for young people with biliary atresia.

Introduction

Biliary atresia (BA) is an idiopathic neonatal cholangiopathy characterized by progressive inflammatory obliteration of the intrahepatic or extrahepatic bile ducts.[1] The surgical procedure, Kasai portoenterostomy (KP), aims to restore bile flow, and alleviate jaundice. Liver transplantation (LT) is performed in cases where KP is unable to salvage the native liver, with complications including jaundice, cholangitis, portal hypertension (PHT) and/or synthetic failure.[2] Five and 10-year UK native liver survival (NLS) rates in BA have been documented as 46% and 40%, respectively.[3]

Twenty-year NLS rates have been documented as 14–44% worldwide.[4–12] However, most long-term native liver survivors develop complications in adulthood, including cholangitis and PHT,[10,13] with reported LT rates as high as 22%.[10] Hence, it is important to incorporate the management of these young people with BA, into adult training programmes.[14] Timing of LT, and acceptance onto adult waiting lists can be difficult. We know that this unique cohort can progress differently compared to other causes of chronic liver disease, and due to mostly preserved synthetic liver function, these patients often do not fulfil minimal listing criteria. We, as paediatricians, should strive to optimally inform the transition/adult services about the health status of these patients, in order to improve their future management.

Age at KP, and early post-operative resolution of jaundice are well known predictors of short-term BA NLS, and although some studies[4,8,10,12,15,16] have surprisingly shown an association of these parameters with long-term BA NLS, it would seem more appropriate to explore predictive variables that are distant from the KP time-period. Transition services incorporate a multidisciplinary team, ensuring the health of young people is maintained through a holistic approach and supportive environment.[17]

Keywords: Biliary atresia; Prognosis; Prognostic markers; Liver transplant; Kasai.
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Depending on individual readiness, transition is a process that can begin from 12 years of age, through to adult services. By 16 years of age, departure from paediatric services is approaching. Hence, identifying prognostic markers at 16 years of age, which can predict poor outcomes in BA native liver survivors during adulthood, would provide adult hepatologists with greater awareness and knowledge when they come to manage this unique cohort and their disease spectrum. Our aim was to identify laboratory, clinical and radiological parameters at 16 years of age that were associated with an increased risk of needing an LT after 16 years of age.

Materials and methods

Patient population

This retrospective observational study identified a total of 397 patients with BA, who underwent KP procedure at King's College Hospital between 1980 and 1996. The inclusion criterion was NLS until the age of 16 years. Exclusion criteria included (i) absent laboratory and/or clinical data in adolescence, (ii) missing follow-up data after 16 years of age, (iii) death with native liver after 16 years of age. The inclusion criterion was met by 111 patients (28% of total cohort); 15 had missing data after 16 years of age, due to out of hospital transfer, and 1 patient died of a splenic artery aneurysm in pregnancy. Of the remaining 95 patients, 6 had no adolescent data available, leaving a total of 89 eligible patients. Sixty-seven patients survived with their native liver (NLS; Group 1) and 22 had undergone or were awaiting LT (LT; Group 2). Patient selection is illustrated in Fig. 1. In order to compare our survival data with international studies, our 20 year NLS has also been included in this figure (n = 87; 22%). Last follow-up was defined as the last documented clinical visit at the time of data collection (Group 1) and, date of listing for LT (Group 2). Patients were identified and data were collected from electronic and paper patient records. The study was approved and performed under institutional ethical guidelines and informed consent was waived.

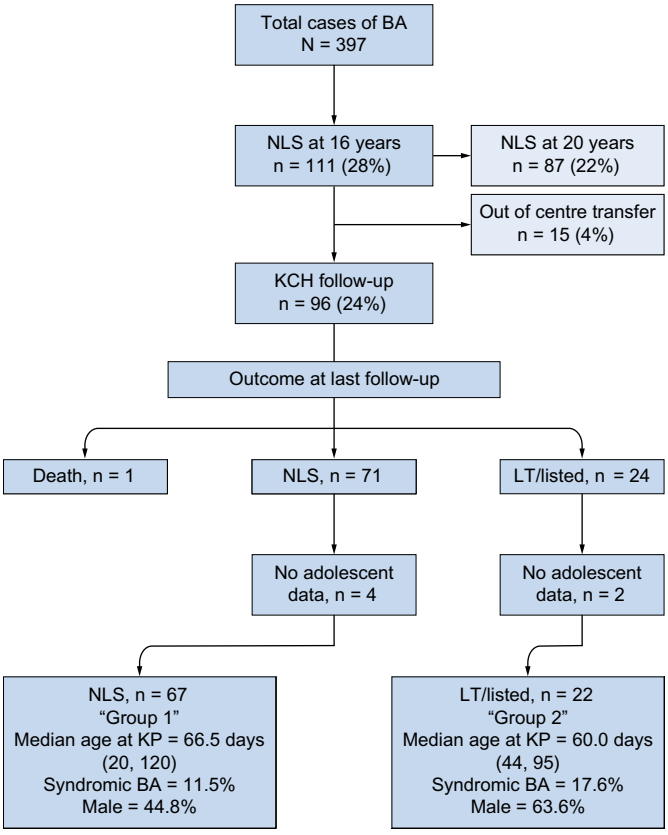

Fig. 1. Flow chart demonstrating the cases selected for inclusion in the study. Group 1 are patients with BA who survived with their native liver until most recent follow-up; Group 2 are patients with BA who were listed for LT before most recent follow-up. Baseline characteristics for Group 1 and Group 2 are shown. There is no significant difference between the groups with regards to age at KP (Mann-Whitney *U*, $p = 0.553$), percentage of syndromic BA (Fisher's exact, $p = 0.679$) or gender (Fisher's exact, $p = 0.146$). BA, biliary atresia; NLS, native liver survival; KCH, King's College Hospital; LT, liver transplant.

Predictor variables

Laboratory, clinical and radiological parameters were extracted from patients at as close to 16 years of age as possible. Laboratory parameters included sodium, creatinine, serum total bilirubin, albumin, international normalized ratio (INR), platelets, aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). Spleen size (cm) was measured radiologically. Clinical parameters included the presence or absence of (i) portal hypertension (PHT; radiologically confirmed splenomegaly and platelet count below 100×10^9/L) at 16 years, (ii) gastro-oesophageal varices (GOV) on endoscopy at 16 years and (iii) cholangitis episode(s) (documented fever associated with jaundice and/or rising aminotransferases) during the transition adolescent period (defined as 12–16 years of age in our cohort).

Statistics

Baseline characteristics and clinical parameters were assessed for normality (Shapiro-Wilk). Six parameters were non-normally distributed, with data presented as median and interquartile range (IQR). Parameters were compared between the 2 groups using the Mann-Whitney *U* test. Categorical variables were analysed using the Chi-square test. Overall NLS was determined using the Kaplan-Meier method. The association of laboratory and clinical variables with LT when >16 years old, was assessed by means of a univariate Cox proportional hazards regression model. Any variable that was identified as significant ($p < 0.05$) in univariate analysis was considered a candidate for multivariate analysis. Area under the receiver-operating characteristic curve (AUROC) analysis was performed for variables identified by multivariate analysis as independent predictors. AUROC analysis was used to calculate the diagnostic accuracy of variables to predict LT when >16 years old, along with 95% CIs. An AUROC ≥0.75 represents reasonable clinical utility for our cohort. Cut-off values from the receiver-operating characteristic analysis, which held sensitivity ≥80% and specificity ≥75%, were deemed as optimal predictive values. All analyses were performed using SPSS (IBM, Armonk, New York, version 24) as confirmed in Supplementary CTAT file. All comparisons were made using 2-sided significance levels of $p < 0.05$.

For further details regarding the materials used, please refer to the CTAT table and supplementary information.

Results

Study population

There were no statistically significant differences in baseline characteristics between the patients with NLS when >16 years

old (Group 1) and those requiring LT when >16 years old (Group 2) (Fig. 1). Median age at KP was lower in Group 2 (60.0 days) *vs.* Group 1 (66.5 days), but not statistically different ($p = 0.55$). Median ages at the time of data collection were 16.0 and 16.1, for Groups 1 and 2, respectively. The median age at last follow-up for Group 1 was 23.4 (16.2–31.6) years, and at time for listing for Group 2 was 19.36 (16.16–26.48) years. In Group 2, seven patients remained listed at the time of publication, with the remainder being transplanted. The median waiting time for LT is 267 (8–1,664) days. Indications for listing were cholangitis (n = 9), gastro-oesophageal variceal bleeding (n = 4), PHT-related synthetic dysfunction (n = 4), PHT-related lethargy (n = 2), jaundice and liver nodule (n = 1), jaundice with intractable pruritus (n = 1) and hepatopulmonary syndrome (n = 1).

Overall native liver survival

Kaplan-Meier analysis (Fig. 2A) for NLS >16 years old, in the entire cohort (n = 95), showed 75% of patients survived a mean of 6.9 years with their native liver. Approximately 80% and 60% were alive with their native liver at 5 and 10 years respectively, after their 16th birthday. Fig. 2B shows no statistical difference in NLS >16 years old, depending on the era of KP (1980–1988 *vs.* 1989–1996).

Laboratory and radiological parameters

Median values for laboratory parameters and spleen size were compared between Groups 1 and 2 (Table 1). Sodium was the only parameter that was not significantly different between groups. Univariate analysis; in the univariate Cox proportional hazard model (Table 1), the following parameters were found to be associated with an increased risk for LT when >16 years old; serum total bilirubin, creatinine, albumin, AST, GGT, ALP, INR, platelet count and spleen size. A lower creatinine value was associated with an increased risk for LT when >16 years old.

Cholangitis

The percentage of patients that experienced ≥1 episode of cholangitis during the transition adolescent period, were 3.03% and 31.8% for Group 1 and 2, respectively ($p = 0.001$). Correspondingly, univariate Cox proportional hazard model reveals a more than 4-fold increase in the risk of needing LT when >16 years old with the presence of cholangitis during the transition adolescent period (hazard ratio [HR] 4.897; 95% CI 1.973–12.158; $p = 0.001$). Kaplan-Meier curve analysis (Fig. 3) illustrates the significant difference in NLS ($p < 0.001$) when >16 years of age based on cholangitis status during adolescence.

Portal hypertension, spleen size and varices

The presence of PHT or GOV on endoscopy when ≤16 years old demonstrates a 7-fold (HR 7.054; 95% CI 2.354–21.139, $p < 0.001$) and 8.6-fold (HR 8.597; 95% CI 3.287–22.480; $p < 0.001$) increased risk of needing LT when >16 years old, respectively. Kaplan-Meier curve analysis (Fig. 4) illustrates the significant difference in NLS when >16 years old ($p < 0.001$) based on PHT at 16 years. Median spleen size was significantly different between groups (Group 1, 15.6 (10.1–27.4) *vs.* Group 2, 21.6 (12–28) $p < 0.001$). Univariate analysis revealed an increased risk for LT when >16 years old based on increased spleen size (HR 1.173; 95% CI 1.062–1.295; $p = 0.001$).

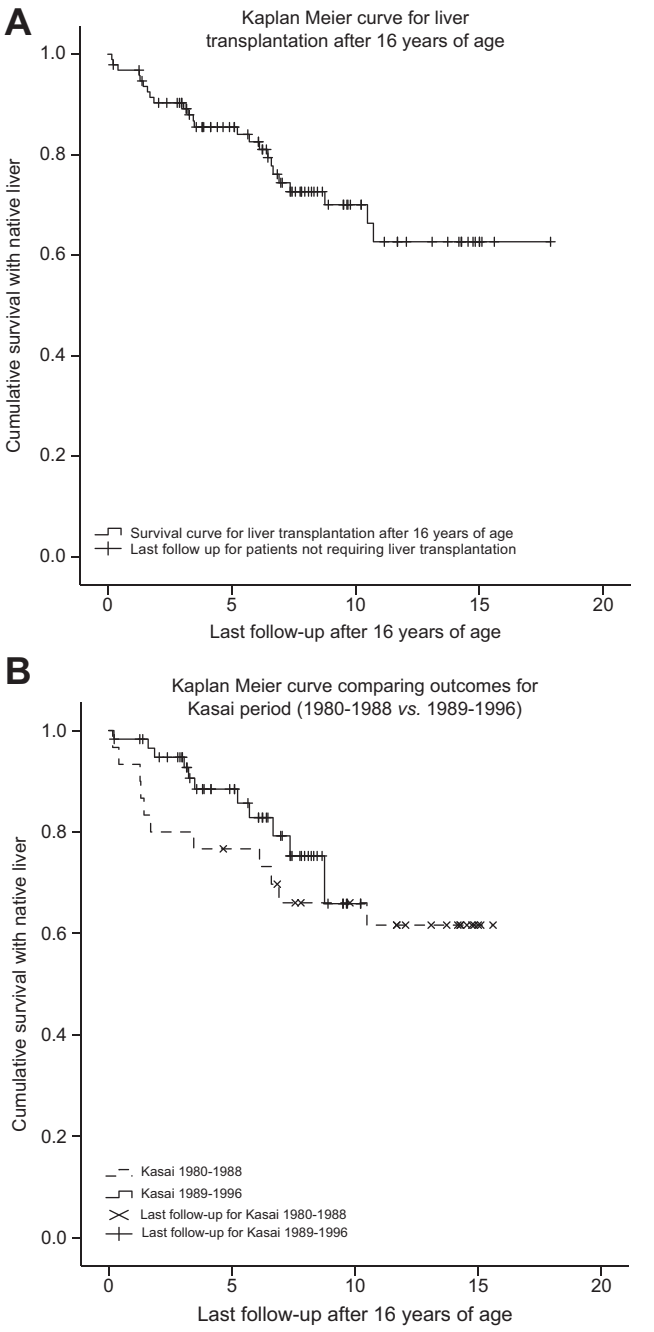

Fig. 2. Kaplan-Meier curves showing NLS time for the 16-year-old NLS cohort. (A) Kaplan-Meier curve showing survival time with native liver for the entire 16-year NLS cohort (n = 95). (B) Kaplan-Meier curve showing survival time with native liver for the entire 16-year NLS cohort (n = 95) depending on era of KP; 1980–1988 *vs.* 1989–1996. No statistical difference, log-rank test, $p = 0.401$. KP, Kasai portoenterostomy; NLS, native liver survival.

Multivariate analysis

A multivariate analysis (Table 2) found serum total bilirubin and creatinine to be independent predictors of needing LT when >16 years old. Receiver operator curve analysis: serum total bilirubin and creatinine predicted the need for LT when >16 years old with AUROCs of 0.8 and 0.3, respectively. A serum total bilirubin of ≥21 μmol/L had 85% sensitivity and 74% specificity for predicting the need for LT when >16 years old (Fig. 5).

Table 1. Comparison of laboratory and radiological parameters between groups.

Laboratory and radiological parameters	Median (range)		
	Group 1 (n = 67)	Group 2 (n = 22)	*p* value
Sodium (mmol/L)	141 (137–154)	140 (135–145)	0.117
Creatinine (μmol/L)	68 (37–107)	57 (32–80)	**0.005**
Bilirubin (μmol/L)	12 (3–44)	38.5 (6–130)	**<0.001**
Albumin (g/L)	45 (27–52)	37.5 (31–50)	**<0.001**
INR	1.05 (0.84–1.34)	1.14 (1.00–1.42)	**<0.001**
AST (IU/L)	40 (13–267)	81 (38–241)	**<0.001**
ALP (IU/L)	164 (53–1,113)	321 (49–740)	**0.002**
GGT (IU/L)	56 (3–1,218)	157 (55–1,198)	**<0.001**
Platelets ($\times 10^9$/L)	143 (40–463)	53 (23–298)	**<0.001**
Spleen size (cm)	15.6 (10.1–27.4)	21.6 (12–28)	**<0.001**

The median values for each parameter are shown. 6 variables were non-normally distributed so Groups 1 and 2 were compared using the Mann-Whitney *U* test. Significant *p* values are indicated in bold font. Group 1: patients that exhibited natural liver survival when >16 years old; Group 2: patients that required a liver transplant when >16 years old.

ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; INR, international normalized ratio.

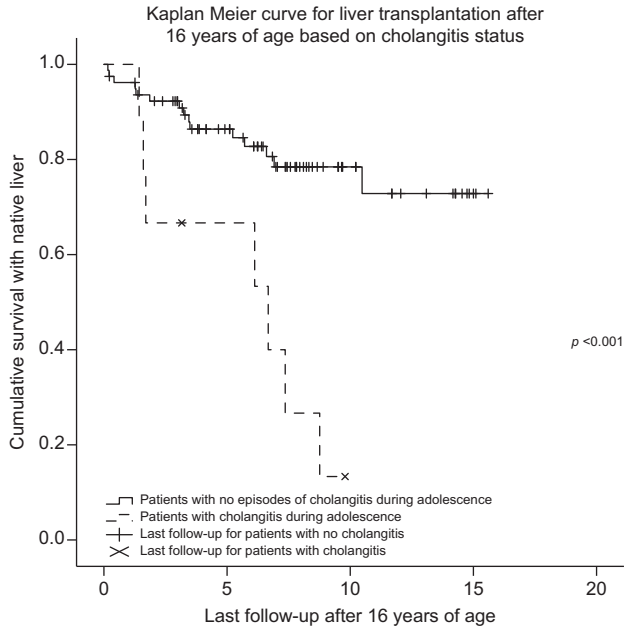

Fig. 3. A Kaplan-Meier curve for NLS in patients >16 years old based on development of cholangitis between 12–16 years old. Log-rank test was used and a significant difference in survival was found, p <0.001. NLS, native liver survival.

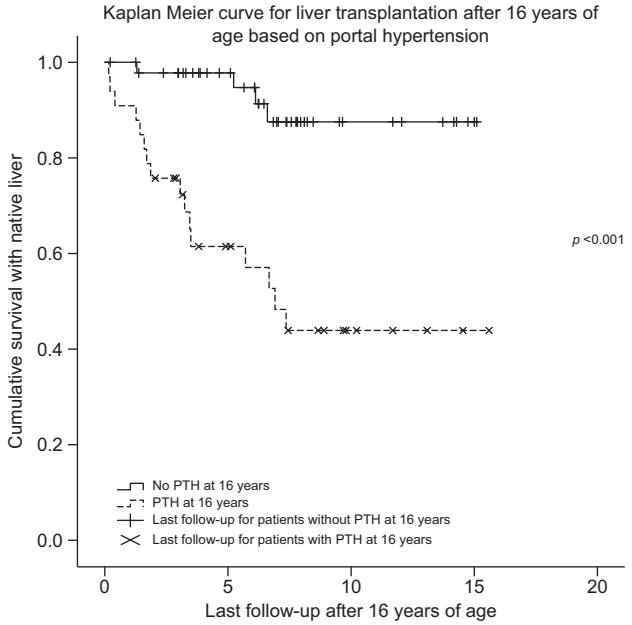

Fig. 4. Kaplan-Meier curve for NLS in patients >16 years old based on portal hypertension by 16 years of age. Log-rank test was used and a significant difference in survival was found, p <0.001. NLS, native liver survival; PTH, portal hypertension.

As the AUROC for creatinine was <0.75, it was not deemed to have optimal accuracy in predicting LT >16 years old.

Discussion

This is the first study exploring adolescent prognostic markers in BA for survival outcomes in adulthood. It is our aim that these findings provide better guidance for health professionals involved in the management of these young people. At our centre, the 16-year BA NLS was 28%, with a quarter of these patients being listed for LT after 16 years of age. Although most studies have reported 20-year NLS,[4–12] we chose 16-year NLS as our threshold, as this is the typical time-point when readiness of transition from paediatric to adult services occurs. Therefore, we considered information at this age,[17] to offer more valuable prognostic information to guide the management of young people leaving the paediatric service.

To facilitate comparisons with worldwide studies, our 20-year NLS was calculated as 22%, which resides within the range of the worldwide spectrum (14–44%); the higher end of the range coming from Japan, where there is a longer experience of KP, and transplantation practice is vastly different.[4–12]

As expected, in our study, age at KP did not predict outcome after 16-years of age. We would consider this baseline characteristic as redundant, when exploring long-term outcomes. We found significant disparities in all laboratory parameters at 16 years, excluding sodium, between those that subsequently require LT in adulthood, and those that do not. Hyponatraemia is a recognised marker of advanced liver disease,[18] with recent incorporation into adult liver disease severity scoring models (model for end-stage liver disease modified for sodium, Na-MELD; United Kingdom model for end-stage liver disease, UKELD).[19–21] In children, hyponatraemia has been associated with an 8-fold increased risk of pre-transplant mortality,[22] and is an independent variable for decreased patient survival

Table 2. Univariate and multivariate Cox regression analysis of laboratory and radiological parameters.

Laboratory and radiological parameters	Cox regression analysis					
	(A) Univariate cox regression			(B) Multivariate cox regression		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sodium (mmol/L)	0.801	0.638–1.004	0.054	–	–	–
Creatinine (μmol/L)	0.937	0.901–0.974	**0.001**	0.947	0.898–0.999	**0.047**
Bilirubin (μmol/L)	1.040	1.026–1.054	**<0.001**	1.030	1.003–1.057	**0.027**
Albumin (g/L)	0.856	0.801–0.913	**<0.001**	0.993	0.814–1.211	0.943
INR	NM	NM	**0.001**	NM	NM	0.197
AST (IU/L)	1.012	1.007–1.017	**<0.001**	1.011	0.991–1.032	0.287
ALP (IU/L)	1.002	1.001–1.003	**0.008**	1.000	0.996–1.004	0.966
GGT (IU/L)	1.001	1.000–1.003	**0.014**	0.999	0.996–1.003	0.687
Platelets ($\times 10^9$/L)	.0988	0.980–0.996	**0.003**	1.004	0.989–1.019	0.613
Spleen size (cm)	1.173	1.062–1.295	**0.002**	1.132	0.898–1.428	0.295
PTH	7.054	2.354–21.139	**<0.001**	1.573	0.152–16.295	0.704
Cholangitis	4.897	1.973–12.158	**0.001**	0.675	0.189–2.405	0.295

(A) A univariate Cox regression analysis was performed (B) Multivariate Cox regression analysis for all parameters significant in the univariate analysis.
NM = not-meaningful (the range of INR values across the cohort is only 0.6). Significant *p* values are indicated in bold font.
ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; HR, hazard ratio; INR, international normalized ratio; PTH, portal hypertension.

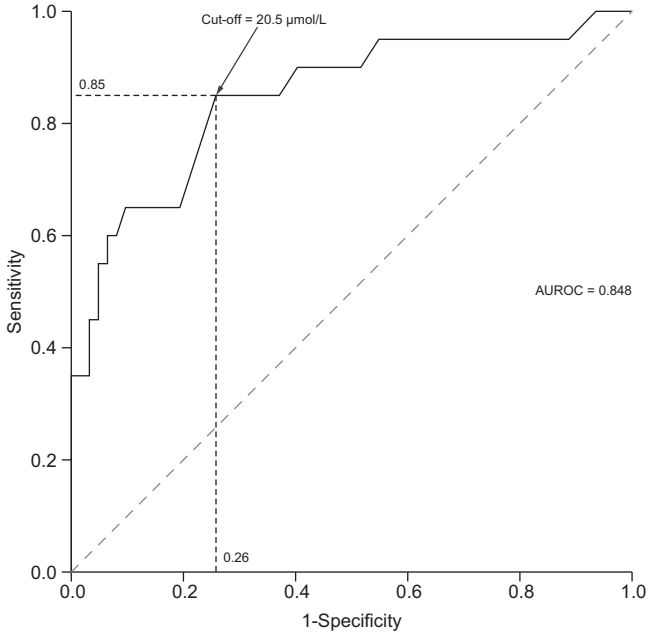

Fig. 5. Receiver-operating characteristic curves for bilirubin as a predictor of the need for LT in patients >16 years old. The AUROC was 0.848 with a sensitivity of 85% and a specificity of 74%. AUROC, area under the receiver-operating characteristic curve; LT, liver transplant.

whilst on the LT waiting list.[23] The non-significance of sodium as a predictor of outcome, perhaps highlights that young people with BA do not decompensate like adult patients with non-BA chronic liver disease and need to be managed differently. Based on our results, sodium-based adult liver disease severity scoring models would not seem an appropriate monitoring tool for this cohort of patients. However, we appreciate that this observation needs to be further validated in a larger cohort of patients, before clinical application.

On multivariate analysis, serum total bilirubin at age 16 years was identified as an independent predictor of LT when >16 years old. Serum total bilirubin is often used as a marker to define the success of KP. We have highlighted the continued prognostic effect of adolescent serum total bilirubin on long-term NLS. A serum total bilirubin ≥21 μmol/L at 16 years (AUROC = 0.848), predicted, with 85% sensitivity and 74% specificity, which patients were likely to have LT when >16 years old. This was an interesting finding, as this discriminatory cut-off level is only just outside the normal range for a healthy population (3–17 μmol/L). In terms of clinical application of this data, we would suggest that adult hepatologists be aware that young people with BA entering the adult services with near-normal bilirubin levels at 16 years, are at risk of future complications and LT, and should therefore, continue to be monitored carefully.

A novel finding from our data was that creatinine, at 16 years of age, is an independent predictor of LT when >16 years old. Creatinine levels are known to be reduced by nutritional state. A poor nutritional state has been robustly shown to be associated with LT or death by 24 months,[24,25] as well as post-LT mortality and graft failure.[26] The incorporation of 'growth failure' into the paediatric end-stage liver disease (PELD) scoring system,[27] further highlights its importance. A recent study by Malenicka *et al.*[28] reported body mass index as the only prognostic marker for death after LT listing in adolescent patients with BA. In our study, lower levels of creatinine at transition may reflect a poorer nutritional state. Chronic liver disease is also associated with a reduction in the serum creatinine pool, due to reduced hepatic production of creatinine.[29] The explanation for the association of low creatinine with poor outcome needs to be further understood (*e.g.* anthropometry in adolescence) in prospective long-term survival studies. Current adult liver disease severity scoring models associate higher creatinine values with increasing severity, yet another pertinent reason for why these adult-centric predictive tools are not appropriate for young people with BA.

Although cholangitis is considered an important factor in accelerating the process of cirrhosis, the association between early cholangitis and short-term NLS has not been well demonstrated.[30–33] However, the frequency of cholangitis episodes, has been shown to influence NLS.[32,34] Although Nio *et al.* 2012[4] suggested that early cholangitis was associated with an increased risk of persistent jaundice in adulthood, an earlier study by the same group[5] found no association between early cholangitis and cholangitis in adulthood. We would speculate that early cholangitis is too distant an event when exploring long-term outcomes. Cholangitis in late childhood and

adolescence,[35,36] although less common, is well described and can be associated with Roux loop obstruction or anatomically defined intrahepatic bile lakes. In our study, we have found that the incidence of cholangitis between 12–16 years of age is associated with a 4-fold increase in the risk of LT when >16 years old. Although our selected adolescent time-period is somewhat arbitrary, it does highlight, to adult hepatologists, the importance of late-onset cholangitis in predicting future outcomes.

Our study revealed that the presence of PHT was associated with a 7-fold increased risk of LT when >16 years old, respectively. This high risk ratio is consistent with the increasing severity of pathology underlying the development of PHT and GOV. PHT-related complications accounted for nearly half (10/22) of the indications for LT in our cohort. We know that progression of PHT and its complications are underrepresented in adult listing criteria. Our data provide objective measures for the importance of PHT in predicting outcomes in young people with BA and call for separate listing criteria for this cohort. Early GOV bleeding has been associated with short-term NLS,[37] and Sasaki *et al.* have shown that that GOV requiring sclerotherapy in 10-year jaundice free native liver survivors was a poor prognostic factor for 20-year NLS.[38] Our study revealed that the presence of varices was associated with an 8.5-fold increased risk of LT when >16 years old. Only patients who had a gastro-intestinal bleed were examined endoscopically, compared to the current era (2012-present) where patients at high risk for varices (hypersplenism) undergo endoscopy, in addition to those who bleed. This considerable change in practice makes it challenging to apply 'variceal presence' as a reliable prognostic marker for the current era and was hence omitted from the multivariate analysis. Spleen size and platelet count at 16 years old were significantly associated with LT when >16 years old in the univariate analysis, but did not demonstrate independent associations in the multivariate analysis.

We have provided objective data to support the notion that adult liver disease severity scoring models are not applicable to young people with BA. Ideally, the predictive laboratory (serum total bilirubin and creatinine) and clinical (PHT/GOV, late-onset cholangitis) parameters from our study would be validated in a larger cohort of patients with BA, and subsequently incorporated into an adult 'BA liver disease severity scoring model'. The revised Mayo primary sclerosing cholangitis (PSC) risk score (MPSCrs), is an adult prognostic model, incorporating age, bilirubin, AST, variceal bleeding and albumin, for predicting 1- to 4-year mortality rates in PSC.[39] There are distinct similarities between BA and PSC, and preliminary work from our institution[40] found an association between MPSCrs in young people with BA and LT risk. We would propose that this model may be more applicable to young people with BA and suggest further exploration.

A major strength of our study is the incorporation of a large cohort of patients, and the novel exploration of prognostic markers, distant from the KP time-period. We accept that we do not have an extensive follow-up period, due to the limited number of long-term survivors post KP. The univariate and multivariate analyses undertaken have adjusted for the variable follow-up time-periods, after 16 years of age, to account for this. Second, we acknowledge that data from the additional 15 patients excluded from the analysis after 16 years of age, would have been valuable for our analysis; however, this was not possible due to out-of-centre transfer. Third, we realise that for young people with BA, indications for LT can vary in severity and objectivity, *e.g.* PHT-related lethargy compared to GOV bleeding, however, we felt that LT captures a clinically relevant and important objective assessment of outcome in adulthood. Fourth, the time-point of 16 years was chosen as this is a common point of transition to adult services at our centre, but earlier time-points could have been considered for valuable prognostic information. Lastly, as we have mentioned, due to the change in practice in variceal endoscopic surveillance, historic variceal data is challenging to apply in prognostication within the current era.

In conclusion**,** paediatric patients with BA who survive with their native livers into adulthood are at high risk of complications and need specialised management. Laboratory and clinical parameters at 16 years of age could help transition/adult services identify patients with poorer long-term outcomes. Serum total bilirubin ≥21 μmol/l, PHT/GOV by 16 years of age, and cholangitis in adolescence are associated with LT risk in transition/adult services. A lower creatinine at 16 years is independently associated with LT risk, which may reflect the need for more robust nutritional management in adolescence. Current adult liver disease severity scoring models are not appropriate for young people with BA. The derivation of a more appropriate 'BA liver disease severity scoring model' for young people is vital, and the role for MPSCrs in BA should be further explored.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

VJ and MS conceived of the study and its design; CB completed the data analysis; all authors contributed substantially to the interpretation of data. VJ wrote the first draft and all other authors were substantially involved in revisions; all authors gave final approval of the version to the published.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.005.

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Author names in bold designate shared co-first authorship

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