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Galactose half-life is a useful tool in assessing prognosis of chronic liver disease in children

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Summary

In children, optimal timing of liver transplantation (LT) is crucial, but reliable prognostic tools for chronic liver diseases are scarce. We assessed the predictive value of galactose half-life (Gal½) for LT or death. A retrospective search of hospital database 2003–2010 revealed 92 consecutive children with chronic liver disease (36 biliary atresia) whose liver function was assessed with Gal½ measurement. Gal½, follow-up data, and liver biochemistry were recorded and pediatric/model for end-stage liver disease (P/MELD) scores calculated. Patients listed for LT or those who died within 1 year of the Gal½ measurement (Group 1) were compared to those surviving without listing (Group 2). Predictive value of Gal½ and P/MELD for listing for LT was assessed with area under the receiver operating characteristic curve (AUROC) analysis. Group 1 had markedly increased median Gal½ [17.0 (interquartile range 12.5–28.5) min] and higher P/MELD [13 (−1–23)] compared with group 2, [10.5 (9.5–12.5) min and −1 (−8–8); $P < 0.001$ for both]. Both Gal½ and P/MELD ($P < 0.001$) predicted listing or death with respective AUROCs of 0.808 (95% CI 0.704–0.913) and 0.780 (0.676–0.890), and 85% sensitivity and 69% specificity for Gal½ ≥12.0 min. Gal½ is a useful tool when evaluating 1-year prognosis in children with chronic liver disease.

Introduction

Optimal timing of liver transplantation (LT) in children is challenging. Established prognostic tools are unsatisfactory especially in chronic liver diseases, and fear of losing the patient may drive the decision toward proceeding to LT [1]. Cirrhotic diseases in children are rare and the range of underlying diagnoses is wide. Also, within a single diagnosis, progression of the disease can vary greatly. Biliary atresia, the most common cause of childhood cirrhosis, usually leads to cholestatic liver failure within a year if the primary treatment portoenterostomy fails; but after a successful portoenterostomy, the fibrotic process progresses slowly [2].

Since 2002, the pediatric end-stage liver disease (PELD) score [3] for <12-year olds and the model for end-stage liver disease (MELD) score [4] for >12-year olds have been used as the allocation criteria for LT by the United Network for Organ Sharing (UNOS) [5]. High MELD scores at listing directly correlate with increased waiting-list mortality [6]. Although a high PELD score also predicts mortality on waiting list [3], a study including 1247 pediatric LT recipients from the UNOS database showed that children with low PELD scores at listing gained no survival benefit of LT within the first year [7]. Accordingly, the PELD score has been criticized for underestimating the mortality risk within 3 months of listing [8,9]. Later studies demonstrated that the PELD score was the primary determinant of liver allocation in only half of pediatric LTs [7,9].

Galactose elimination capacity (GEC) is a quantitative measure of liver function: The hepatocytes metabolize

intravenously administered free galactose monosaccharide into galactose-1-phosphate [10]. The speed of galactose elimination, although somewhat influenced by hepatic blood flow and renal clearance, essentially represents the remaining cytosolic functional capacity of the hepatocytes. In adults, decreased GEC predicts mortality and complications after liver resection for cancer [11] and short- and long-term mortality among cirrhotics [12–14].Two small series on normal values of GEC in children showed that young healthy children have higher GEC than adults [15,16]. In a study of 10 healthy children and 30 children with a chronic liver disease, the children with liver disease had significantly lower GEC than the healthy peers [16]. The usefulness of GEC measurements in pediatric patients with chronic liver disease remains unclear.

At our center, galactose half-life (Gal½) measurement has been routinely performed in assessment of children with liver disorders. This prompted us to evaluate the value of Gal½ in predicting listing for LT or death in children with BA and other chronic liver diseases. The accuracy of Gal½ measurement was compared with PELD or MELD score and liver biochemistry.

Table 1. Diagnoses of all patients (92). Group 1: listed for liver transplantation or died within 1 year, Group 2: survived without listing beyond 1 year.

	All	Group 1	Group 2
Biliary atresia	36	12	24
Metabolic liver disease	15	4	11
Autosomal recessive polycystic kidney disease	10	5	5
Autoimmune hepatitis	6	0	6
Intestinal failure associated liver disease	6	1	5
Alagille syndrome	3	2	1
Budd–Chiari syndrome	2	1	1
Mulibrey nanism	2	0	2
Primary sclerosing cholangitis	2	1	1
Miscellaneous	10	2	8

Patients and methods

The study was performed at the Children's Hospital, Helsinki University Central Hospital, a nation-wide tertiary referral center for pediatric liver diseases. Since 1987, the national pediatric LT program has been running at our center. Finland's healthcare system is tax-funded allowing all permanent residents equal access to health services.

Patient identification and data collection

The medical records of all consecutive children with a Gal½ measurement between 2003 and 2010 were reviewed. Inclusion criteria were a diagnosis of chronic liver disease (Table 1) and, in case of uneventful follow-up, a minimum of 1-year follow-up in the study center after the Gal½ measurement. The laboratory database revealed 179 patients with Gal½ measurements. Of these, 87 were excluded: 46 had undergone LT, 18 had other than parenchymal liver diseases (including seven liver tumors, six patients with cardiac defects, three with leukemia, one methylmalonic acidemia, and one near sudden infant death), 13 had acute liver failure, and 10 had less than 1 year of follow-up after the Gal½ measurement. In total, 92 patients were enrolled (Fig. 1).

Of the patients with multiple Gal½ measurements, we chose the latest measurement or the last one prior to LT. The following data were collected from patient records: diagnosis, date of birth; date of listing for LT, date of LT, date and cause of death; date of end of follow-up (last visit or end of study Dec 31st, 2011); date and result (minutes) of the latest Gal½ measurement. Serum bilirubin, alanine transferase (ALT), aspartate transferase

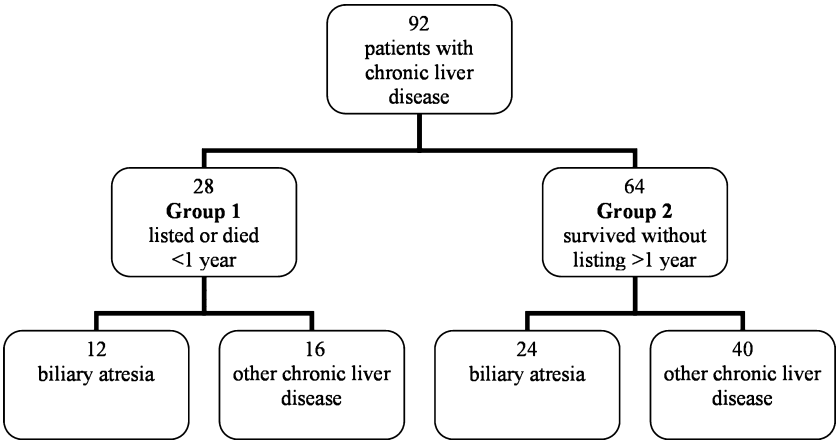

Figure 1 Grouping of patients.

(AST), prealbumin, albumin, hemoglobin, platelets, international normalized ratio (INR), factor V, and creatinine were taken at the same time as the Gal½ measurement were collected.

The 92 patients were divided into two cohorts: Patients listed for LT or died of liver failure within 1 year after the Gal½ measurement (Group 1), and those surviving without listing for LT beyond 1 year after the Gal½ measurement (Group 2). Further subgrouping was performed according to the underlying diagnosis (biliary atresia or other chronic liver disease, Fig. 1).

Measurements and scores

The Gal½ measurement was performed by a previously described method [17]. Briefly, 350 mg/kg of 30% galactose solution (Galaktos APL 300 mg/ml; APL, Stockholm, Sweden) was administered intravenously, after which capillary fingertip blood samples were collected at 20, 30, 40, and 50 min from administration. Blood galactose concentration was measured photometrically (Olympus AU400 analyzer; Olympus, Tokyo, Japan) using galactose dehydrogenase (Cat. 10176303035; Roche, Basel, Switzerland) enzymatic reaction [18]. Blood galactose concentration values were plotted against time on a semi-logarithmic scale, and Gal½ was extrapolated from the graph.

PELD, MELD, and AST to Platelet Ratio Index (APRI) scores were retrospectively calculated for the study purposes using previously described formulae [3,4,19]. PELD consists of bilirubin, albumin, INR, age if <1 year, and growth if less than −2 SDs from age-adjusted mean. MELD consists of bilirubin, INR, and creatinine. The PELD score was used for ≤12 ($n = 65$, 71% of the patients) and MELD for >12-year-old children [5].

A multidisciplinary team (pediatric hepatologists, transplant pediatricians, pediatric gastrointestinal, and transplant surgeons, neurologists) decided on listing for LT based on the following data: (i) original liver disease, quality of life (cholangitis and septic episodes), growth, nutrition, neurology, kidney function, bone health, (ii) portal hypertension (portal flow, spleen size, hypersplenism, varices, ascites), (iii) cholestasis (bilirubin, bile acid levels, itching), (iv) liver biochemistry (ALT, AST, GT, clotting factors, prealbumin, albumin, cholesterol, Gal½), (v) radiological findings (liver and spleen size, parenchymal heterogeneity, biliary lakes, focal lesions), and (vi) liver biopsy findings (fibrosis, cirrhosis, bile ducts).

Listing for LT or organ allocation was not based on P/MELD score and Gal½ was one of the many measured laboratory parameters. Liver grafts were from deceased donors.

Ethics

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved this study *a priori*.

Statistical analyses

Unless otherwise stated, we report summary statistics using median and interquartile range. The results of all laboratory measurements and P/MELD and APRI scores were tested for normality. Shapiro–Wilkins W-test showed normal distribution only for hemoglobin and factor V, and therefore we chose statistic tests with nonparametric assumptions. To study correlations between laboratory measurements and scores, we used Spearman rank correlation. Continuous variables were compared with Mann–Whitney *U*-test, and dichotomous variables with Chi square or Fisher's exact test. The level of significance was set at 0.003 after the Bonferroni correction. The relationships between sensitivity and the false-positive fractions of Gal½ and P/MELD were illustrated with receiver operating characteristic (ROC) curves. The discriminatory potentials of Gal½, P/MELD, prealbumin, and APRI were analyzed with area under the ROC curve (AUROC) values with 95% confidence interval (CI). Significance of the AUROC was calculated in relation to the area of 0.5. To analyze the accuracy of Gal½ and P/MELD classifying patients for listing for LT, we calculated three cutoff points in ROC analyses for both: (i) the upper normal limit of Gal½ (15 min) and the respective P/MELD value with closest sum of sensitivity and specificity, (ii) Gal½ and P/MELD values with largest possible sums of sensitivity and specificity, and (iii) P/MELD value 15, which according to UNOS classification entitles a higher waiting list status [5], and the respective Gal½ with closest sum of sensitivity and specificity. For statistical tests, we used SPSS Statistics 19 (IBM, Somers, NY, USA). We used the STROBE Statement checklist as a guideline in reporting the results [20].

Results

Of the 92 patients, 26 were listed for LT at median 1.5 (interquartile range 0.3–3.5) months after the Gal½ measurement and two died (one sepsis, one heart defect) without listing at 0.4 and 7.7 months after the Gal½ measurement (Group 1). Three of the listed patients died of liver failure without receiving a transplant at 1.6, 2.3, and 4.1 months after listing, and 23 were transplanted after a median waiting time of 3.0 (1.3 – 5.8) months. Sixty-four patients were not listed and had an uneventful median follow-up of 2.5 (1.6–4.5) years after the Gal½

measurement (Group 2). Twelve (42%) in Group 1 and 24 (38%) in Group 2 had BA (Table 1).

Liver function tests and scores

Gal½ values of the 92 patients ranged from 6.5 to 58.5 min with a mean of 14.5 and a median of 11.0 min. Patients listed for LT or died of liver disease (Group 1) had median Gal½ of 17.0 (12.5–28.5) min as compared with 10.5 (9.5–12.5) min in those who survived without listing for LT (Group 2; $P < 0.001$). Group 1 patients had also higher median P/MELD score (−1 vs. 13, $P < 0.001$), serum bilirubin, AST, and INR, and lower albumin and hemoglobin when compared with Group 2 patients (Table 2 and Fig.ure 2). BA patients in Group 1 had significantly longer median Gal½ (22.0 vs. 10.5 min, $P = 0.001$), higher P/MELD (20 vs. −9, $P < 0.001$), bilirubin, AST, and INR, and lower albumin than BA patients in Group 2 (Table 2 and Fig. 2). Patients with other chronic liver diseases in Group 1 had significantly longer Gal½ than those in Group 2 (Table 2 and Fig. 2).

Relations of Gal½ to other laboratory measurements and P/MELD and APRI scores

In the whole study population, Gal½ correlated positively with P/MELD, bilirubin, and APRI values and inversely with prealbumin, albumin, factor V, and platelets (Table 3 and Figure 3). Among BA patients, Gal½ was positively related to APRI and inversely to prealbumin and albumin (Table 3). Among other chronic liver disease patients, Gal½ correlated positively with P/MELD and inversely with factor V (Table 3). Gal½ showed no significant correlation with ALT, AST, hemoglobin, INR, or creatinine.

Predictive value of Gal½ and P/MELD

Gal½ and P/MELD were both significant predictors of LT listing within a year, as analyzed by ROC curves (Table 4 and Fig. 4a). The P/MELD score cutoff value 11 corresponded to the Gal½ value of 15.0 min. The best accuracy was obtained with a cutoff level of 12.0 min in Gal½ measurement [85% sensitivity, 69% specificity, 73% PPV (positive predictive value), and 82% NPV (negative predictive value] and >7 in P/MELD score (67% sensitivity, 75% specificity, 56% PPV, 82% NPV). The Gal½ value of 19.0 min showed the sensitivity and specificity closest to P/MELD 15, which allows for a higher urgency state in the UNOS classification.

Among the BA subgroup, P/MELD had the largest AUC of 0.947 and the score of 3 showed 83% sensitivity and 84% specificity. Gal½ was a less significant predictor of listing with AUC of 0.814; the most accurate cutoff 12.0 min showed 83% sensitivity and 64% specificity (Table 4 and Fig. 4b). Among patients with other disorders, Gal½ >13.0 min gave 80% sensitivity and 82% specificity, whereas P/MELD showed no significant predictive value (Table 4 and Fig. 4c).

Five patients (5%) died of liver failure; their Gal½ values ranged from 9.0 to 30.5 min (four >12.0 min) and P/MELD scores from 16 to 26. Because of the small number of deaths, the risk calculations are uncertain. In AUC analysis, Gal½ showed no significant predictive value for death (AUC 0.606, 95% CI 0.379–0.834, $P = 0.427$) and the best accuracy was at >12.0 min (80% sensitivity, 56% specificity). P/MELD was a significant predictor of death (AUC 0.901, 95% CI 0.834–0.969, $P = 0.003$) with the cutoff level of >14 showing 100% sensitivity and 86% specificity. Of all the biochemistries and scores measured, bilirubin was the most significant predictor of death with an AUC of 0.938 (95% CI 0.882–0.994, $P = 0.001$), cutoff >151 μmol/l showing 100% sensitivity and 89% specificity.

Discussion

This is to our best knowledge, the first study assessing the value of a galactose elimination measurement in listing of children for liver transplantation. According to our results, Gal½ measurement and P/MELD scoring were both useful parameters in this decision making. The median Gal½ was significantly higher in patients who were listed for LT or died of chronic liver disease than in those survived without listing (17.0 vs. 10.5 min, $P < 0.001$), and the difference was present in the BA subgroup (22.0 vs. 10.5 min, $P = 0.001$) as well as among patients with other disorders (17.0 vs. 10.5 min, $P < 0.001$). Gal½ showed significant correlation with the P/MELD score and liver function tests bilirubin, prealbumin, albumin, platelets, and factor V, and APRI score. Among BA patients, Gal½ and P/MELD both associated with listing for LT with considerable overlap in the AUROC CIs. Interestingly, among patients with other chronic liver diseases, only Gal½ correlated with listing. The cutoff with the best possible sum of sensitivity and specificity among BA patients was Gal½ 12.0 and P/MELD 3, and among patients with other chronic liver diseases, the respective figures were Gal½ 13.0 and P/MELD 11.

In general, a diagnostic test with an AUROC below 0.6 is as worthy as tossing a coin, between 0.7 and 0.8 is considered fair, 0.8–0.9 good, and 0.9–1 excellent. Thus, Gal½ among children with BA and other chronic liver diseases can be considered as a good predictor of liver failure (respective AUROCs 0.814 and 0.807), 95% CI ranging from fair to excellent (0.654–0.974 and 0.664–0.950, respectively). Among children with BA,

Table 2. Gal½, P/MELD score, liver biochemistry, and APRI in study groups. Group 1: listed for liver transplantation or died within 1 year, Group 2: survived without listing beyond 1 year.

	All patients				Biliary atresia			Other chronic liver disease		
	All	Group 1	Group 2	*P*	Group 1	Group 2	*P*	Group 1	Group 2	*P*
Number of patients	92	28	64		12	24		16	40	
Age at measurements	6.5 (1.5–13.1)	2.0 (0.8–13.0)	7.4 (3.0–13.1)	0.053	0.8 (0.4–1.5)	3.3 (1.2–7.3)	0.024	10.3 (1.9–14.0)	10.1 (5.9–14.3)	0.279
Gal½, min	11.0 (10.0–16.5)	17.0 (12.5–28.5)	10.5 (9.5–12.5)	**<0.001**	22.0 (12.0–29.0)	10.5 (9.5–13.5)	**0.001**	17.0 (13.0–27.0)	10.5 (9.0–11.5)	**<0.001**
P/MELD	5 (−8–11)	13 (−1–23)	−1 (−8–8)	**<0.001**	20 (7–29)	−9 (−9–−2)	**<0.001**	9 (−2–16)	6 (−3–10)	0.205
Bilirubin, μmol/l	16 (8–41)	55 (13–392)	14 (8–25)	**<0.001**	295 (39–530)	11 (6–16)	**<0.001**	27 (8–203)	16 (8–34)	0.196
ALT, U/l	46 (26–117)	63 (27–152)	44 (23–116)	0.561	88 (65–169)	44 (28–94)	0.028	40 (18–126)	44 (19–143)	0.733
AST, U/l	77 (46–134)	135 (63–236)	66 (43–103)	**0.002**	171 (122–235)	70 (54–109)	**<0.001**	63 (39–363)	53 (38–98)	0.219
Prealbumin, mg/l	146 (98–184)	122 (93–165)	147 (108–186)	0.135	98 (88–127)	146 (98–176)	0.015	152 (99–197)	148 (109–200)	0.988
Albumin, g/l	37.3 (30.6–40.4)	30.7 (27.0–38.0)	39.3 (33.3–41.3)	**<0.001**	28.2 (25.4–33.8)	37.4 (33.7–39.8)	**<0.001**	37.1 (28.9–38.6)	40.4 (32.4–42.5)	0.005
Hemoglobin, g/l	121 (107–131)	107 (96–122)	124 (113–132)	**0.001**	109 (89–118)	127 (114–133)	0.004	107 (99–131)	123 (110–129)	0.055
Platelets, E9/l	174 (94–289)	139 (96–250)	198 (93–312)	0.559	176 (138–239)	203 (94–312)	0.601	116 (83–338)	179 (89–318)	0.560
APRI	1.2 (0.5–1.9)	1.6 (0.9–4.0)	0.9 (0.4–1.7)	0.006	1.8 (1.0–5.1)	0.7 (0.4–2.0)	0.012	1.4 (0.6–4.0)	0.9 (0.4–1.5)	0.122
INR	1.0 (1.0–1.2)	1.2 (1.1–1.5)	1.0 (1.0–1.2)	**0.001**	1.5 (1.2–1.9)	1.0 (0.9–1.0)	**<0.001**	1.1 (1.0–1.3)	1.0 (1.0–1.2)	0.566
Factor V, %	92 (70–109)	78 (57–111)	94 (80–109)	0.067	67 (50–104)	95 (91–107)	0.105	81 (64–115)	91 (75–111)	0.292
Creatinine, μmol/l	29 (18–42)	22 (13–50)	31 (20–42)	0.283	13 (11–21)	22 (14–31)	0.031	40 (21–212)	40 (25–48)	0.861
Follow-up, years	1.8 (0.3–3.6)	0.1 (0.0–0.3)	2.5 (1.6–4.5)	**<0.001**	0.1 (0.0–0.3)	1.6 (1.1–2.1)	**<0.001**	0.1 (0.0–0.3)	3.9 (2.6–6.8)	**<0.001**

Data as median (interquartile range); Mann–Whitney *U*-test. Significance set at 0.003 (Bonferroni correction). Significant *P*-values in bold.

Gal½, galactose half-life; P/MELD, pediatric/model for end-stage liver disease; APRI, AST to platelet ratio index; ALT, alanine transferase; AST, aspartate transferase; INR, international normalized ratio.

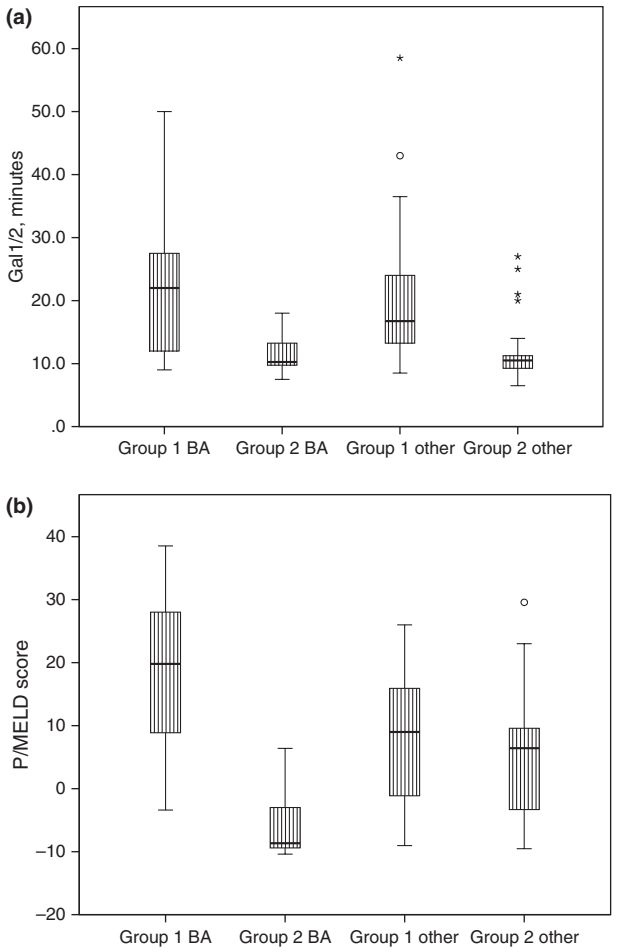

Figure 2 (a) Galactose half-life (Gal½) levels in study groups. (b) Pediatric/model for end-stage liver disease (P/MELD) score levels in study groups. Group 1 listed for liver transplantation within 1 year of measurements, Group 2 no listing required. BA = biliary atresia. The box represents the interquartile range, line across the box median, and whiskers minimum – maximum range. Circles are outliers >1.5 box-lengths and asterisks >3 box-lengths from the box edge.

Table 3. Correlations of Gal½ with P/MELD score, liver biochemistry, and APRI.

	All patients			Biliary atresia		Other chronic	
	n	*r*	*P*	*r*	*P*	*r*	*P*
Age at measurement	92	0.022	0.836	−0.141	0.412	0.202	0.136
P/MELD	82	0.395	**<0.001**	0.437	0.010	0.423	**0.003**
Bilirubin	89	0.328	**0.002**	0.418	0.011	0.256	0.064
Prealbumin	85	−0.331	**0.002**	−0.596	**<0.001**	−0.130	0.369
Albumin	85	−0.337	**0.002**	−0.515	**0.002**	−0.243	0.085
Platelets	91	−0.342	**0.001**	−0.429	0.010	−0.329	0.013
APRI	80	0.400	**<0.001**	0.527	**0.001**	0.316	0.033
Factor V	74	−0.409	**<0.001**	−0.300	0.129	−0.438	**0.002**
Follow-up	92	−0.483	**<0.001**	−0.396	0.017	−0.497	**<0.001**

Spearman rank correlation. Significance set at 0.003 (Bonferroni correction). Significant *P*-values in bold.
Gal½, galactose half-life; P/MELD, pediatric/model for end-stage liver disease; APRI, aspartate transferase to platelet ratio index; LT, liver transplantation.

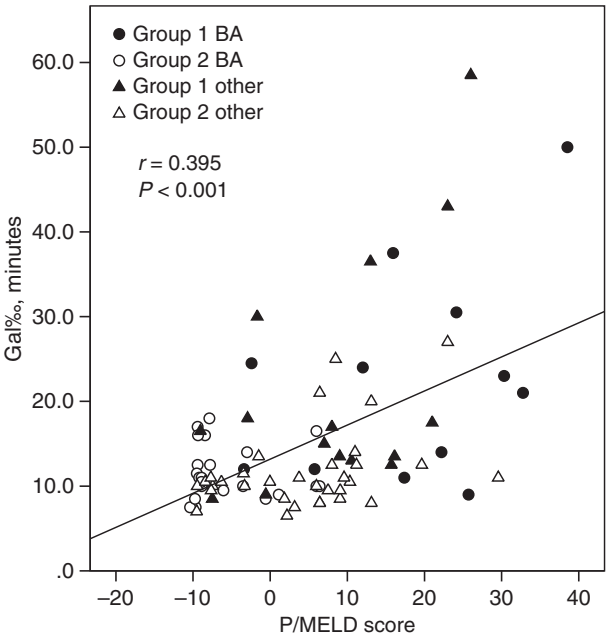

Figure 3 Correlation of galactose half-life (Gal½) to Pediatric/model for end-stage liver disease (P/MELD) score.

P/MELD was an excellent marker for LT listing (AUROC 0.947, 95% CI 0.877–1.000), but among children with other chronic liver diseases, P/MELD's predictive value was poor (AUROC 0.616, 95% CI 0.435–0.797).

Most publications on galactose elimination use the method described by Tygstrup [10] based on series on adults, measuring the maximal galactose elimination capacity (V_{max}) while the serum galactose concentration is high enough to saturate the galactokinase enzyme. During the fetal period, the liver galactokinase activity is high [21]. The level of serum galactose concentration saturating the galactokinase enzyme in children is not known. The half-life method used here [17] does not assume a blood galactose concentration saturating the galactokinase enzyme and accepts that extrahepatic factors like liver blood flow may influence the elimination curve. The functional reserve of the liver is relatively large, and thus a diseased liver appears to function normally while the reserve is constantly in use. The presumed value of the galactose elimination measurement is the sensitivity to detect a reduction in the liver functional capacity while the function is still compensated,

Table 4. Gal½ and P/MELD score as predictors of listing for liver transplantation or death within 1 year of the measurement. Area under the receiver operating characteristic curve analysis with 95% CIs and significance. Cut-off values: (i) Gal½ ≥15.0 min and the respective P/MELD score, (ii) Gal½ and P/MELD score with the best accuracy, and (iii) P/MELD score ≥15 and the respective Gal½.

	All patients				Biliary atresia				Other chronic liver disease			
	AUC	95% CI		*P*	AUC	95% CI		*P*	AUC	95% CI		*P*
Gal½	0.808	0.704–0.914		**<0.001**	0.814	0.654–0.974		**0.003**	0.807	0.664–0.950		**0.001**
P/MELD	0.783	0.676–0.890		**<0.001**	0.947	0.877–1.000		**<0.001**	0.616	0.435–0.797		0.201
Cut-off	1	2	3		1	2	3		1	2	3	
Gal½, min	15.0	12.0	19.0		15.0	12.0	19.5		15.0	13.0	20.5	
P/MELD score	11	7	15		6	3	15		11	11	15	

Gal½, galactose half-life; P/MELD, pediatric/model for end-stage liver disease; AUC, area under curve; CI, confidence interval. Significant *P*-values in bold.

both clinically and in the light of conventional liver biochemistry [16].

A wide range of diagnoses is present among pediatric liver disease patients, associated with divergent treatment options and prognoses. For example in BA, the liver disease progresses fast after a failed portoenterostomy, whereas after a successful operation, cirrhosis can develop slowly over several years, even decades. For the fibrotizing liver disease of BA, no other effective treatment besides LT is available, whereas autoimmune hepatitis and certain metabolic diseases may be successfully treated without LT. In ARPKD and cystic fibrosis, liver is not the only affected organ, and often progression of the disease in other organs predominates in decision making on LT. Among our ten ARPKD patients, (five with uneventful follow-up, five listed, six under 12-year olds) the Gal½ cutoff of 13.0 min produced only one false negative and P/MELD cutoff 11 three false negatives and two false positives. It is of interest that ARPKD patients with their native kidneys and a renal disease take a substantial leap up in a P/MELD-based allocation system on their 12th birthday as creatinine is a part of MELD, but PELD includes no measure of renal function. We calculated both PELD and MELD scores for our ten ARPKD patients: median PELD was −6 (range, −10 to −1), whereas median MELD was 16 (7–23), $P < 0.001$.

Searching for prognostic markers and severity-of-disease indicators for children with chronic liver disease is important. Transplantation too early in the course of the disease predisposes the patient to the many risks of transplantation [7], whereas children with an advanced liver disease are at higher risk of dying on the waiting list as well as soon after LT [3,9]. The small number of deaths in our material (5) allows no conclusions concerning Gal½ measurement as a predictor of death. Regarding listing for LT or death, the results of the present study are in line with previous publications in adults. In a study with 781 adult patients with median age of 52 years and newly diagnosed liver cirrhosis, reduced GEC was a strong predictor of 1-month, 1-year, and 5-year mortality [14]. Similarly, a prospective study with 194 adult cirrhotics showed that reduced GEC was an independent predictor of mortality within 2 years [13]. On the contrary, in a recent study assessing 290 adult patients with a GEC measurement at listing, reduced GEC had no predictive value for waiting-list mortality nor correlation with MELD score [22]. In children, we found no previous studies on the predictive value of galactose measurements. One recent study showed that children with chronic liver disease had reduced GEC when compared with healthy peers [16].

Chronic liver disease may progress slowly over the years, like in BA patients after a successful portoenterostomy. When a relatively stable patient comes to follow-up visits for several years, prognostic markers of a looming worsening of the liver function are of importance for the clinician who may want to adjust the frequency of visits and counsel the family of what lies ahead. In our material, two (7%) patients in Group 1 (listed or died) and 31 (48%) in Group 2 had both short Gal½ (<12.0 min) and normal bilirubin (<20 μmol/l), whereas ten (36%) in Group 1 and 23 (36%) in Group 2 had either prolonged Gal½ or elevated serum bilirubin level ($P = 0.023$). Thus, if both Gal½ and bilirubin were at normal levels, one could, with relative confidence, continue with the regular follow-up schedule. In clinical practice, we have found Gal½ measurement as a useful adjunctive test of liver function also in cases of acute liver failure. From the current analysis, we excluded patients (13) with acute liver failure because of the small number and the different clinical setting. We have, however, used repeated Gal½ measurements to indicate possible worsening or improvement of liver function in acute liver failure. The final decision of listing, however, is always based on multiple parameters.

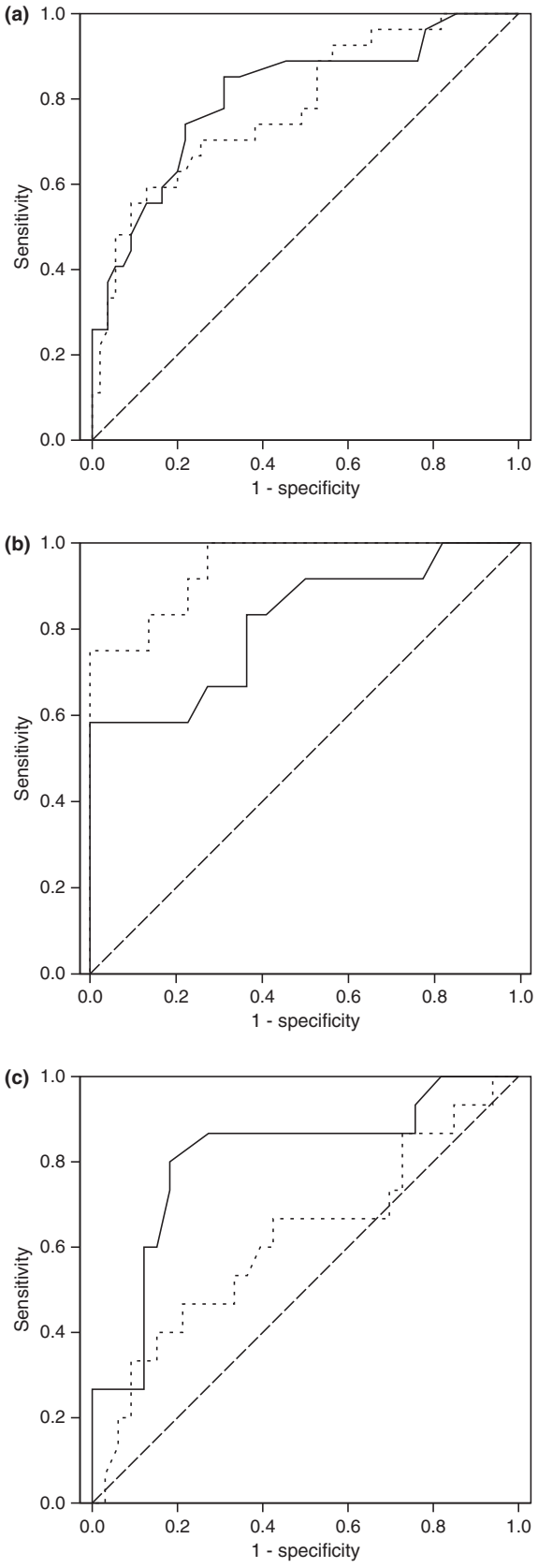

Figure 4 Galactose half-life (Gal½) and pediatric/model for end-stage liver disease (P/MELD) score as predictors of listing for liver transplantation within 1 year of the measurement. Receiver operating characteristic curve. Gal½ continuous line, P/MELD broken line, diagonal reference line. (a) All patients. (b) Biliary atresia patients. (c) Patients with other chronic liver disease.

Our study includes obvious limitations. During the study period, Gal½ was used in Children's Hospital as one of the liver function tests in the follow-up of children with chronic liver disease. A retrospective analysis of a parameter, which was used in the decision making, brings up a bias: here in favor of an association between Gal½ and listing for LT. However, it must be emphasized that the listing for LT took place in a multidisciplinary team and was based on detailed clinical, laboratory, radiological, and biopsy data, Gal½ being only one of the many parameters evaluated. PELD and MELD scores were retrospectively calculated for this study and were not used in the LT listing process. All the components of the scores were, however, available for clinical use. The second limitation in this work is that listing for LT as an endpoint is by no means unambiguous, and it is impossible to determine retrospectively the correctness of the listing decision for those who were transplanted [1]. The third limitation, common to many pediatric single-center evaluations, is the relatively small size of the study population with 92 patients and 28 outcome events, of which two were deaths and 26 listings for LT.

In conclusion, all the discussed limitations considered, Gal½ appears a useful additive tool when evaluating the 1-year prognosis of a child followed-up for a chronic liver disease. However, further preferably prospective studies with larger numbers of children with chronic liver disease are needed in development of reliable prognostic tools.

Authorship

HL: collected and analyzed data, wrote the paper. SK: analyzed data, wrote the paper. HJ: contributed important intellectual content, wrote the paper. MPP: designed research, wrote the paper.

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