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ORIGINAL ARTICLE

Retrospective Cohort Study

Primary liver transplantation *vs* transplant after Kasai portoenterostomy in children with biliary atresia: A retrospective Brazilian single-center cohort

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Abstract

BACKGROUND

Biliary atresia (BA) is the most common indication for pediatric liver transplantation, although portoenterostomy is usually performed first. However, due to the high failure rate of portoenterostomy, liver transplantation has been advocated as the primary procedure for patients with BA. It is still unclear if a previous portoenterostomy has a negative impact on liver transplantation outcomes.

AIM

To investigate the effect of prior portoenterostomy in infants un-dergoing liver transplantation for BA.

METHODS

This was a retrospective cohort study of 42 pediatric patients with BA who underwent primary liver transplantation from 2013 to 2023 at a single tertiary center in Brazil. Patients with BA were divided into two groups: Those undergoing primary liver transplantation without portoenterostomy and those undergoing liver transplantation with prior portoenterostomy. Continuous variables were compared using the Student's *t*-test or the Kruskal-Wallis test, and

categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate. Multivariable Cox regression analysis was performed to determine risk factors for portal vein thrombosis. Patient and graft survival analyses were conducted with the Kaplan–Meier product-limit estimator, and patient subgroups were compared using the two-sided log-rank test.

RESULTS

Forty-two patients were included in the study (25 [60%] girls), 23 undergoing liver transplantation without prior portoenterostomy, and 19 undergoing liver transplantation with prior portoenterostomy. Patients with prior portoenterostomy were older (12 *vs* 8 months; $P = 0.02$) at the time of liver transplantation and had lower Pediatric End-Stage Liver Disease scores (13.2 *vs* 21.4; $P = 0.01$). The majority of the patients (35/42, 83%) underwent living-donor liver transplantation. The group of patients without prior portoenterostomy appeared to have a higher incidence of portal vein thrombosis (39 *vs* 11%), but this result did not reach statistical significance. Prior portoenterostomy was not a protective factor against portal vein thrombosis in the multivariable analysis after adjusting for age at liver transplantation, graft-to-recipient weight ratio, and use of vascular grafts. Finally, the groups did not significantly differ in terms of post-transplant survival.

CONCLUSION

In our study, prior portoenterostomy did not significantly affect the outcomes of liver transplantation.

Key Words: Hepatic portoenterostomy; Biliary atresia; Liver transplantation; Patient outcome assessment; Portal vein; Survival

Core Tip: Children with biliary atresia comprise the majority of patients undergoing liver transplantation worldwide. Timely portoenterostomy can postpone or even remove the need for liver transplantation. Current data are not conclusive regarding whether performing a portoenterostomy negatively affects the transplantation procedure. In this study, we compared the outcomes of liver transplantation in patients with biliary atresia with or without prior portoenterostomy in a single center. Our results indicate that it does not affect the outcomes.

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INTRODUCTION

Biliary atresia (BA) is a progressive fibroinflammatory process that leads to obstruction of the biliary tree and cirrhosis if left untreated. It affects people worldwide across ethnicities. BA is the most common cause of pediatric liver-related death and the leading indication for pediatric liver transplantation (LT)[1]. Symptoms are usually present in the 1st weeks of life, with a pattern of obstructive jaundice and abnormal liver function test results. Early diagnosis and portoenterostomy (PE) are essential for adequate bile flow, clearance of jaundice, and normalization of the serum bilirubin concentration.

Kasai PE is the standard initial procedure for BA, followed by LT for patients in whom PE fails or the condition progresses to liver cirrhosis. Less than 50% of patients with BA undergoing the Kasai PE procedure gain 10 years of transplant-free survival[2]. However, successful PE can increase the life of the native liver, thus postponing the need for LT[3].

Advances in pediatric LT have improved outcomes. A subset of patients with BA benefit from primary LT without first undergoing PE, especially those who are diagnosed at a later stage[4]. PE before 60 d of life is associated with a higher native liver survival rate than PE after 60 d[5]. However, whether prior PE negatively affects LT outcomes in patients with BA remains unclear[6-11].

Here, we aim to add further data on this issue by comparing the outcomes of children with BA who underwent LT without previous PE with those who underwent PE before LT at our institution.

MATERIALS AND METHODS

Population

This was a retrospective, single-center cohort study of patients who underwent LT for BA at Santa Casa de Porto Alegre, Brazil, a tertiary center. Data were extracted from a database of children who underwent LT at our center from 2013 to

2023. Only recipients of primary LT with a diagnosis of BA were selected and divided into two groups: BA without prior PE (no-PE) and BA with prior PE (PE). Demographic and perioperative variables such as sex, age at LT, Pediatric End-Stage Liver Disease (PELD) score, Model for End Stage Liver Disease score, and weight were included in the analysis. Post-LT outcomes, such as vascular and biliary complications, hospital and intensive care unit (ICU) stay, and acute and chronic rejection, were also evaluated. The hospital's ethics committee approved this study.

Liver transplant procedure and follow-up

ABO blood group compatibility determined recipient and donor selection, and no incompatible blood type transplantations were performed during the study period. The grafts were orthotopically implanted using a "piggyback technique." The graft's portal vein was anastomosed in an end-to-end fashion, either to the recipient's portal vein trunk or by interposition of the vascular grafts. In all cases, the hepatic artery was reconstructed using microvascular techniques with 9-0 or 10-0 nylon sutures (Ethicon, Edinburgh, United Kingdom). Biliary anastomosis was performed by Roux-en-Y bilioenteric reconstruction.

Tacrolimus (FK 506, Prograf) and steroids were used for immunosuppression in the majority of recipients. Basiliximab (Simulect; Novartis, Basel, Switzerland) was used to induce immunosuppression in the majority of the recipients. Doppler ultrasound was routinely performed on the 1st postoperative day, and thereafter, according to the clinician's discretion upon clinical assessment. Vascular or biliary alterations upon Doppler ultrasound were confirmed by contrast imaging, either computed tomography or magnetic resonance imaging.

Statistical analyses

Means ± standard deviations and medians (interquartile ranges) were calculated to summarize continuous variables, and the results were compared using the Student's *t*-test or the Kruskal-Wallis test as non-parametric test when distributional assumptions were in doubt. Categorical variables are expressed as numbers and percentages. Differences between groups were assessed using the χ^2 or Fisher's exact test, as appropriate. Patient and graft survival analyses were conducted with the Kaplan-Meier product-limit estimator, and patient subgroups were compared using the two-sided log-rank test. Multivariable Cox regression analysis was performed, adjusting for risk factors. Variables with $P < 0.1$ during univariate analysis and those deemed clinically significant were included in the model. The study was reviewed by our expert biostatistician, Gabriele Dell'Era, MD.

RESULTS

In summary, prior PE did not significantly affect post-LT outcomes in our study. The apparent trend for more portal vein thrombosis (PVT) events in the no-PE group was probably due to the smaller size and younger age of patients in this group. The post-LT survival did not differ between the groups. Larger multicenter studies are required to confirm our results.

DISCUSSION

LT is primarily indicated for patients with BA in whom initial PE fails or who present with advanced, progressive liver disease at the time of diagnosis. The reported impact of prior PE on LT outcomes differ between studies. A meta-analysis conducted by Wang *et al*[12] did not reveal statistically significant differences in major outcomes, overall survival, and complications between patients undergoing LT with prior PE and those undergoing LT without prior PE. Subsequent studies have not resolved the question[13-16]. Our study did not reveal in survival between the groups.

Kasai PE is performed in an attempt to salvage the native liver and reestablish biliary flow. It yields 10-year LT-free survival in more than 50% of patients with BA. Although the procedure is effective in most cases, adequate biliary drainage is not achieved in approximately 30% of patients, requiring another surgical procedure or LT. Moreover, many long-term complications, such as recurrent cholangitis, portal hypertension, ascites, infections, gastrointestinal bleeding, and failure to thrive, are observed in those who live with their native liver[17,18].

The present study revealed interesting results in the subgroup of patients who underwent LT without prior PE, including a higher incidence of PVT than in the group who had previously undergone PE. In accordance with the literature, patients with BA who underwent LT without prior PE were younger and smaller in this study. This combination, especially in the setting of living donor LT (LDLT), which was the most common in our cohort, usually results in a higher graft-to-recipient weight ratio (GRWR), although this difference was not statistically significant in our study. A higher GRWR can lead to large-for-size syndrome, which, in turn, increases the risk of PVT. Patients with BA who undergo LT usually present with sclerotic portal veins that can be replaced with vascular grafts during LDLT to ensure adequate portal flow. However, these same vascular grafts have been associated with PVT after pediatric LDLT[19]. In our cohort, venous grafts were used in 10 (24%) recipients. Similar to the results reported by Neto *et al*[19], these grafts were used in a seemingly higher proportion of recipients in the group that developed PVT in our study, although this result was not statistically significant. The PVT subgroup analysis was exploratory in this study and requires vali-dation in larger cohorts.

Excellent outcomes have been reported with LDLT for BA[20,21]. LDLT is considered the first-choice graft in various centers for children with BA, particularly in Asian countries. In accordance with other high-volume centers in Brazil[7],

Table 1 Pre and intra-operative variables in biliary atresia recipients who underwent liver transplantation with and without previous portoenterostomy, *n* (%)

Parameter	No-PE, *n* = 23	PE, *n* = 19	*P* value
Sex, female	13 (56.5)	12 (63.2)	0.75
Age at LT, months	8 (6-10)	12 (7-23)	0.02
Weight at LT, kg, median (IQR)	6.5 (5.7-7.4)	7 (6.4-13.5)	0.15
PELD/MELD, mean ± SD	21.4 ± 9.5	13.2 ± 8.9	0.01
Living donor	19 (82.6)	16 (84.2)	1
Deceased donor	4 (17.4)	3 (15.8)	
GRWR, mean ± SD	4.0 ± 1.3	3.7 ± 1.7	0.4
RCBT in mL/kg, mean ± SD	2.4 ± 0.9	1.6 ± 1.3	0.15
CIT in min, median (IQR)	81 (61-140)	105 (73-189)	0.24
WIT in min, mean ± SD	39.4 ± 12.5	33.8 ± 8.4	0.11
Time to extubate in d, median (IQR)	1 (0-2)	0 (0-1)	0.55
ICU stay in d, median (IQR)	12 (6-17)	8 (5-14)	0.4
Hospital stay in d, median (IQR)	21 (16-37)	23 (15-30)	0.25

Data are *n* (%). CIT: Cold ischemia time; GRWR: Graft-to-recipient-weight-ratio; ICU: Intensive care unit; IQR: Interquartile range; LT: Liver transplant; PE: Portoenterostomy; RCBT: Red cell blood transfusion; SD: Standard deviation; WIT: Warm ischemia time.

our cohort was mainly composed of children undergoing LDLT (83%). In contrast to Asian countries, deceased donations are widely accepted in Brazil. However, pediatric and adult donors suitable for graft reduction or splitting are scarce, and LDLT is a safe alternative for enlisted patients[22,23].

The early BA diagnosis and the timing to perform the Kasai procedure also influences the decision to indicate a primary LT for BA. A recent European cohort study in BA patients compared early Kasai, late Kasai and primary LT. As expected, native liver survival in 5-y was under 50% (47% early, 30% late Kasai, and 4% for those without a portoenterostomy). Overall 5-y survival, however, was quite comparable among the same groups (91, 83 and 80%, respectively). This study raises an important question as to whether age alone should limit the indication to perform a Kasai procedure [24].

Lemoine *et al*[25] documented their cohort of 113 patients with BA who underwent LT. Notably, only 14 individuals (12%) in their study underwent primary LT. By contrast, our findings indicate that 54.7% of BA patients in our report underwent primary LT. This observation could suggest the influence of delayed BA diagnosis, preventing the implementation of the Kasai procedure in developing countries, such as Brazil.

Limitations of the study

The retrospective nature of the study and relatively small sample are acknowledged as drawbacks. However, survival and post-transplant complication rates in this study were in accordance with those of large transplant centers[19]. Our study might have been underpowered due to the small size of the cohort. The impact of PE on the outcome of LT remains debatable, and center expertise, especially with LDLT, plays an important role in the outcomes of children with BA. Larger, multicenter studies could help in answering this question.

CONCLUSION

Of the forty-two recipients with BA, twenty-five (60%) were girls. LDLT was the main LT modality (83% of patients). Twenty-three patients were in the no-PE group and nineteen in the PE group. Patients in the no-PE group were significantly younger than those in the PE group (8 *vs* 12 months; $P = 0.02$). Patients in the no-PE group had higher PELD scores than those in the PE group (21.4 ± 9.5 *vs* 13.2 ± 8.9; $P = 0.01$). The groups did not differ in terms of ischemia times, blood transfusion volume, or hospital and ICU stay (Table 1).

The no-PE group had a seemingly higher incidence of PVT (39% *vs* 11%; $P = 0.07$) (Table 2). Although this difference was not statistically significant, we conducted a subgroup analysis on patients with PVT as it might have been clinically significant.

The PVT and no-PVT groups did not reach statistically significant difference in terms of age (8 *vs* 10 months; $P = 0.06$) or mean GRWR (4.38 + -1.20 *vs* 3.75 + -1.56; $P = 0.08$). The use of vascular grafts as substitutes for the portal vein (cryopreserved deceased-donor iliac vein or living-donor inferior mesenteric vein) also did not reach statistically significant difference between these subgroups (45% *vs* 16%; $P = 0.09$) (Table 3).

Table 2 Outcomes in biliary atresia recipients who underwent liver transplantation with and without previous portoenterostomy

Parameter	No-PE, *n* = 23	PE, *n* = 19	*P* value
HAT	2 (8.7)	4 (21.1)	0.38
PVT	9 (39.1)	2 (10.5)	0.07
PVS	4 (17.4)	4 (21.1)	1
Biliary fistula	9 (39.1)	6 (31.6)	0.75
Biliary stricture	5 (21.7)	8 (42.1)	0.19
Reoperation	7 (30.4)	2 (10.5)	0.14
Acute rejection	5 (21.7)	3 (15.8)	0.7
Chronic rejection	2 (8.7)	0	0.49
EBV infection	14 (60.9)	9 (47.4)	0.5
CMV infection	19 (82.6)	13 (68.4)	0.46

Data are *n* (%). CMV: Cytomegalovirus; EBV: Epstein Barr virus; HAT: Hepatic artery thrombosis; LT: Liver transplant; PE: Portoenterostomy; PVS: Portal vein stenosis; PVT: Portal vein thrombosis.

Table 3 Pre and intra-operative variables in biliary atresia recipients who underwent liver transplantation who developed portal vein thrombosis comparing with those who did not develop portal vein thrombosis

Parameter	No-PVT, *n* = 31	PVT, *n* = 11	*P* value
Age at LT, months, median (IQR)	10 (6-15)	8 (5-8)	0.06
Weight at LT, kg, median (IQR)	7 (6.2-10)	6.4 (5.7-7.3)	0.2
PE	17 (54.8)	2 (18.2)	0.07
PELD/MELD, mean ± SD	16.1 ± 10.3	22 ± 8	0.12
Living donor	26 (83.9)	9 (81.8)	1
Deceased donor	5 (16.1)	2 (18.2)	1
Portal vein graft	5 (16.1)	5 (45.5)	0.09
GRWR, mean ± SD	3.75 ± 1.56	4.38 ± 1.2	0.08
RCBT in mL/kg, mean + SD	1.8 ± 1.3	2.5 ± 0.9	0.14
CIT in min, median (IQR)	95 (66-163.5)	88 (68-127)	0.8
WIT in min, mean ± SD	36.1 ± 9.9	39 ± 14.1	0.7

Data are *n* (%). BA: Biliary atresia; CIT: Cold ischemia time; GRWR: Graft-to-recipient-weight-ratio; LT: Liver transplant; PE: Portoenterostomy; PVT: Portal vein thrombosis; RCBT: Red cell blood transfusion; SD: Standard deviation; WIT: Warm ischemia time.

Table 4 Logistic regression analysis for portal vein thrombosis

Parameter	OR	95%CI	*P* value
PE	0.35	0.05-2.27	0.27
GRWR	1.03	0.52-2.02	0.92
Age at LT	0.84	0.63-1.12	0.24
Portal vein graft	2.87	0.54-15.1	0.21

CI: Confidence interval; GRWR: Graft-to-recipient-weight-ratio; LT: Liver transplant; OR: Odds ratio; PE: Portoenterostomy; PVT: Portal vein thrombosis.

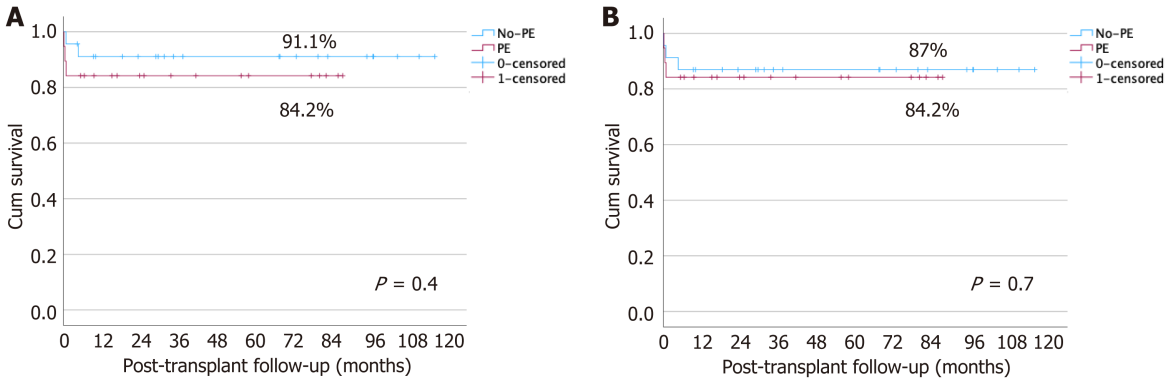

Figure 1 Comparison of patients with and without a portoenterostomy before liver transplantation. A: Post-transplant patient survival; B: Post-transplant graft survival.

Multivariable Cox regression analysis was performed to evaluate factors associated with PVT. After adjusting for age at LT, GRWR, and vascular grafting, the protective effect of PE was attenuated (Table 4). The 1-year patient and graft survival did not differ between the no-PE and PE groups (91% *vs* 84%; $P = 0.4$ and 87% *vs* 84%; $P = 0.7$, respectively) (Figure 1).

ARTICLE HIGHLIGHTS

Research background

Biliary atresia (BA) is the most common indication for pediatric liver transplantation, although portoenterostomy is usually performed first. However, due to the high failure rate of portoenterostomy, liver transplantation has been advocated as the primary procedure for patients with BA. It is still unclear if a previous portoenterostomy has a negative impact on liver transplantation outcomes.

Research motivation

Is there a negative impact of a prior portoenterostomy on liver transplantation outcomes?

Research objectives

To analyze the post-transplant complications and survival in children with BA with or without a previous portoenterostomy.

Research methods

This was a retrospective cohort study of 42 pediatric patients with BA who underwent primary liver transplantation from 2013 to 2023 at a single tertiary center in Brazil. Patients with BA were divided into two groups: Those undergoing primary liver transplantation without portoenterostomy and those undergoing liver transplantation with prior portoenterostomy.

Research results

In our study, prior portoenterostomy did not significantly affect the outcomes of liver transplantation.

Research conclusion

There are no survival differences in patients transplanted with or without a prior portoenterostomy. There is a trend for more portal vein complications in the group of patients transplanted without a portoenterostomy.

Research perspectives

Larger studies, also multicenter studies would be important to better address this issue.

FOOTNOTES

Author contributions: Sanha V, Melere M, and Feier FH designed the research study; Sanha V, Melere M, Farina M, and Feier FH wrote the manuscript; Nader L, Trein C, and Soares C collected and evaluated the data and wrote the manuscript; Ferreira C, Kalil NA, and Lucchese A wrote the manuscript and critically evaluated the final version; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Hospital Santa Casa de Porto Alegre Institutional

Review Board.

Informed consent statement: All patients signed a general informed consent agreeing to the treatment and use of their anonymized clinical data. According to national and institutional regulations, special written consent is not needed for every particular study where anonymized clinical data are used.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at flavia.feier@gmail.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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