Influence of early biliary complications on survival rates after pediatric liver transplantation—A positive outlook

Valeria Berchtold1 | Franka Messner1 | Annemarie Weissenbacher1 | Rupert Oberhuber1 | Andreas Entenmann3 | Denise Aldrian3 | Georg Vogel3 | Christian Margreiter1 | Hanno Ulmer2 | Johanna Krapf1 | Benno Cardini3 | Georg Vogel3 | Christian Margreiter1 | Hanno Ulmer2 | Judith Schneeberger1

1Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria
2Department for Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria
3Department of Pediatrics I, Medical University of Innsbruck, Innsbruck, Austria
4Department of Surgery, University Hospital Regensburg, Regensburg, Germany

Correspondence
Stefan Schneeberger, Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria.
Email: stefan.schneeberger@i-med.ac.at

Funding information
None.

Abstract
Background: Early biliary complications (EBC) constitute a burden after pediatric liver transplantation frequently requiring immediate therapy. We aimed to assess the impact of EBC on short- and long-term patient and graft survival as well as post-transplant morbidity.

Methods: We analyzed 121 pediatric liver transplantations performed between 1984 and 2019 at the Medical University of Innsbruck for the occurrence of early (<90 days) biliary complications and investigated the influence of EBC on patient and graft survival.

Results: Early biliary complications occurred in 30 (24.8%) out of the 121 pediatric liver transplant recipients. Patient survival at 15 years (89.2% vs. 84.2%, \( p = .65 \)) and all-cause (82.5% vs. 74.0%) and death-censored graft survival (82.5% vs. 75.1%, \( p = .71 \)) at 10 years were similar between the EBC and the non-EBC group. The EBC group had a significantly longer ICU (25 vs. 16 days, \( p < .001 \)) and initial hospital stay (64 vs. 42 days, \( p = .002 \)). Livers of patients with EBC were characterized by multiple bile ducts (33.3% vs. 13.2%, \( p = .027 \)) and patients with EBC had a higher risk to develop late biliary complications (OR 2.821 [95% CI 1.049–7.587], \( p = .044 \)) and bowel obstruction/perforation (OR 4.388 [95% CI 1.503–12.812], \( p = .007 \)).

Conclusion: Early biliary complications after pediatric liver transplantation is frequent. The occurrence of EBC significantly increased post-transplant morbidity without affecting mortality. Multiple bile ducts were the only risk factor for the development of EBC in our cohort.

Abbreviations: ACGS, All-cause graft survival; AN, Anhepatic time; BA, Biliary atresia; BMI, Body mass index; BSA, Body surface area; CI, Confidence interval; CIT, Cold ischemia time; CMV, Cytomegaly virus; DDLT, Deceased-donor liver transplantation; DSGS, Death-censored graft survival; EBC, Early biliary complication; eHAT, Early hepatic artery thrombosis; ESBDL, excluded segmental bile duct leakage; ET, Eurotransplant; HAT, Hepatic artery thrombosis; HJ, Hepaticojejunostomy; ICU, Intensive care unit; LLT, Living-related liver transplantation; MMF, Mycophenolate mofetil; PLT, Pediatric liver transplantation; SD, Standard deviation; SLT, Split-liver transplantation; WLT, Whole liver transplantation.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. Pediatric Transplantation published by Wiley Periodicals LLC

Pediatric Transplantation. 2021;00:e14075.
https://doi.org/10.1111/petr.14075
1 | BACKGROUND/INTRODUCTION

Pediatric liver transplantation (PLT) in the Eurotransplant (ET) region has evolved with the introduction of split-liver and living-donor liver transplantation in 1988 and 1991.\(^1\,^2\) Annually, approximately 200 pediatric liver transplants are performed in the ET region. The 10-year graft survival rate ranges between 63% and 75% and therefore compares favorably to that of the adult population.\(^3\)

Despite the good overall survival, PLT is associated with several graft-related complications.\(^4\,^8\) In 75% of liver transplantations in the ET cohort, technical variant procedures including smaller vessels and surplus bile ducts are recorded.\(^1\) These variations are not only associated with an increased risk of early (<3 months, EBCs), but also of late biliary complications (>3 months, LBCs). The classification of early and late BCs is relevant since different mechanisms are involved and complication management may differ. Early biliary complications are often directly related to the surgical technique; LBCs, in contrast, are most often caused by chronic inflammation.\(^7\,^9\)\(^-\)\(^12\) Reports on the overall incidence of BC range from 10% to 45%.\(^9\,^13\)\(^-\)\(^15\) Untreated BCs lead to a higher risk of graft loss.\(^5\,^6\) These diverging data most likely suggest that different definitions are used to characterize BCs. Previous studies have found that prolonged cold ischemic time (CIT), hepatic artery thrombosis (HAT), donor age, graft quality, ischemic injury of the biliary system, and duct-to-duct reconstructions as risk factors for BCs.\(^10\,^17\)\(^-\)\(^19\)

This study aims to assess the impact of early biliary complications on short- and long-term patient and graft survival as well as post-transplant morbidity following PLT in our cohort.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was approved by the local ethics committee of the Medical University of Innsbruck (AN20 14-0182 338/4.8). We retrospectively analyzed all 146 PLTs at the Medical University of Innsbruck between November 1984 and December 2019. After exclusion of patients with missing follow-up data (n = 21) and patients who received a multivisceral transplantation (n = 3), 121 PLTs in 103 recipients were included in the final analysis.

Donor and recipient characteristics (age, sex, weight, body mass index (BMI), blood work, blood type, cytomegalovirus (CMV) status, surgical data (donor type, CIT, anhepatic time (AN), type of bile duct reconstruction and details of the post-operative course (complications, reoperation, hospital stay, intensive care unit stay, acute rejections)) were collected from medical records. All patients were followed until March 2020, death or until lost to follow-up. Median follow-up time of our cohort was 65.5 months (SD: 23.3–131 months).

2.2 | Surgical procedure of pediatric liver transplantation

The living-donor liver transplant program at the Medical University of Innsbruck has been established in 1997. The choice of technical approach was chosen based on the indication, availability of a living donor, surgical conditions, and urgency. In case of a full-size liver transplant, a bicaval technique with cava replacement was performed, while split-liver transplantations (SLTs) were performed using the piggy back technique. Graft type, underlying disease, and previous surgical interventions decided about the biliary reconstructions. Whenever possible, a duct-to-duct anastomosis was performed. In patients with biliary atresia, pre-existing bile duct conditions, or grafts with short bile ducts, a hepaticojejunostomy with a Roux-en-Y reconstruction was used. In case of multiple bile ducts, the distance between both orifices determined whether they were anastomoses conjointly or separately.

The hepaticojejunostomy or duct-to-duct reconstruction were performed with monofilament absorbable sutures in an interrupted fashion. T-tubes and stents have been used when indicated. The hepatic artery anastomosis was performed with interrupted sutures employing microsurgical principles. Vascular intrahepatic flow monitoring during transplantation was routinely assessed by Doppler ultrasound after portal vein, arterial, and bile duct anastomosis as well as before and after abdominal closure. In case of large liver volume in relation to upper abdominal cavity capacity, the initial abdominal closure was performed using a Gore-Tex patch for abdominoplasty. Subsequently, the patch was gradually reduced and eventually removed in all cases. All patients underwent close postoperative monitoring with repeat laboratory testing and ultrasound every 6–8 h for the first post-transplantation week followed by two daily examinations during the second week and daily examinations until discharge from hospital. PLTs were categorized into living and deceased liver transplants as well as split-liver transplants comprising all living- and deceased-donor split-liver transplantations.

2.3 | Diagnosis of early biliary complications

Diagnostic criteria of EBCs were based on repeated analysis of collected abdominal drain fluid, laboratory values, ultrasound findings, and clinical symptoms. At our center, management of EBCs was preferably performed surgically, especially in case of a leakage or stricture.

KEYWORDS
early biliary complications, pediatric liver transplantation
2.4 | Post-operative immunosuppressive regimes and antimicrobial therapy

Immunosuppression consisted of basiliximab for induction during surgery and on post-operative day 4 (12 mg/m² BSA and max 20 mg; in select cases since 2003 and routinely since 2015). Methylprednisolone (10 mg/kg, max. 200 mg) was applied only perioperatively. For maintenance, a steroid-free regime was introduced at since 2000 and tacrolimus monotherapy was established as a routine. In some exceptions, steroids were maintained (2 mg/kg) until post-operative day 6. Mycophenolate mofetil was introduced only in case of rejection during the first year after transplantation (10–40 mg/kg/d in two single dosages per day). Prior to the introduction of this protocol, immunosuppression consisted of Cyclosporine A, azathioprine, or mycophenolic acid together with a steroid taper. Perioperative antibiotic prophylaxis consisted of piperacillin/tazobactam (150 mg/kg/d), and the antiviral prophylaxis was comprised of intravenous ganciclovir (2 mg/kg/d) followed by oral valganciclovir (15 mg/kg/d) for three months post-transplantation in case of CMV ± mismatch.

2.5 | Primary and secondary end-points

Primary outcome parameters were patient as well as all-cause (ACGS) and death-censored graft survival (DCGS). Patients that died with functioning grafts were censored. Secondary end-points include the median initial length of stay at the intensive care unit (ICU) and at the hospital, the occurrence of early hepatic artery and early and late portal vein complications, bowel obstruction/perforation, late biliary complications, and rejections.

2.6 | Statistical analysis

Results are expressed as median and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. For continuous variables, Student’s t-test was applied for normal distribution, and Mann–Whitney U test and Kruskal–Wallis test for variables with non-normal distribution. For categorical variables, a chi-square test was performed. Patient and graft survival were estimated using the Kaplan–Meier method, and the log-rank test was used.

### Table 1: Donor demographics stratified by early bile duct complications

| Demographics          | All        | EBC        | No EBC     | p-Value |
|-----------------------|------------|------------|------------|---------|
| Number (%)            | 121(100)   | 30(24.8)   | 91(75.2)   |         |
| Donor age, median (IQR)| 29(12.5, 36)| 29(13, 36)| 29(12, 38) | .796    |
| Donor BMI, median (IQR)| 22.1(18.4, 24.5)| 22.3(18.2, 24.7)| 22.1(18.1, 24.5) | .877    |
| Donor male (%)        | 59(48.8)   | 14(46.7)   | 43(47.3)   | .674    |
| Donor CMV+ (%)        | 57(47.1)   | 15(50)     | 42(46.2)   | .829    |
| Donor blood type (%)  |            |            |            | .039    |
| A                     | 40(33.1)   | 7(23.3)    | 33(36.3)   |         |
| AB                    | 8(6.6)     | 4(13.3)    | 4(4.4)     |         |
| B                     | 14(11.6)   | 1(3.3)     | 13(14.3)   |         |
| O                     | 59(48.7)   | 18(60.1)   | 41(45.1)   |         |
| Donor INR, median (IQR)| 1.1(1.0, 1.2)| 1.1(1.0, 1.1)| 1.1(1.0, 1.2) | .793    |
| Donor pTT (s), median (IQR)| 31(27, 34) | 31(27, 32.3) | 32(27, 35) | .458    |
| Donor platelet count (g/L), median (IQR)| 226(151.5, 300)| 228(170.5, 262) | 222(142, 326.5) | .544    |
| Donor type (%)        |            |            |            | .406    |
| Living donor          | 61(50.4)   | 17(56.7)   | 43(47.3)   |         |
| Deceased donor        | 60(49.6)   | 13(43.3)   | 48(52.7)   |         |
| Graft type (%)        |            |            |            | >.9     |
| Whole liver           | 41(33.9)   | 10(33.3)   | 31(34.1)   |         |
| Split Liver           | 80(66.1)   | 20(66.7)   | 60(65.9)   |         |
| CIT (min), median (IQR)| 200(89.3, 510.8)| 134(88.3, 531)| 238(88.5, 492.8) | .813    |
| Anhepatic time (min), median (IQR)| 54(46, 63) | 54(47, 66.5) | 54.5(46, 63.5) | .752    |
| Bile duct management (%)|           |            |            | .576    |
| Hepaticojejunostomy   | 101(83.5)  | 24(80)     | 77(84.6)   |         |
| Duct-to-duct reconstruction | 20(16.5) | 6(20)     | 14(15.4)   |         |

Abbreviations: +, positive; BMI, body mass index; CIT, cold ischemia time; CMV, cytomegaly virus; EBC, early biliary complications; INR, international normalized ratio; IQR, interquartile range; min, minutes; pTT, partial thromboplastin time; s, seconds; (Y), yes.
used to compare unadjusted survival curves, and confidence intervals were computed using MedCalc® (MedCalc Software Ltd, Belgium). Cox proportional hazards regression adjusted for year of transplantation, type of liver graft, and previous abdominal surgery was used to compare graft survival of the EBC and non-EBC groups. Proportional hazards were visually inspected with complementary log-log plots. Logistic regression was used to calculate the odds of rejection, bleeding/hematoma, early and late portal vein and hepatic artery

**Table 2** Recipient demographics stratified by early bile duct complications

| Demographics | All          | EBC           | No EBC          | p-Value |
|--------------|--------------|---------------|-----------------|---------|
| Recipient age (months), median (IQR) | 34 (8.110) | 33 (8.87) | 34 (8.120) | .692    |
| <1 year (%) | 41 (33.9) | 11 (36.7) | 30 (33) | .824    |
| <5 years (%) | 71 (58.7) | 18 (60) | 53 (58.2) | .9       |
| Recipient male (%) | 66 (54.5) | 17 (56.7) | 49 (53.8) | .835    |
| Liver disease (%) | | | | .697    |
| Mb Wilson | 11 (9.1) | 2 (6.7) | 9 (9.9) |         |
| Biliary atresia | 55 (45.5) | 16 (53.3) | 39 (42.9) |         |
| Alagille syndrome | 8 (6.6) | 2 (6.7) | 6 (6.6) |         |
| CFLD | 9 (7.4) | 2 (6.7) | 7 (7.7) |         |
| Alpha-1 antitrypsin deficiency | 7 (5.8) | 2 (6.7) | 5 (5.5) |         |
| Others | 31 (25.5) | 6 (19.9) | 25 (27.4) |         |
| Recipient weight (kg), median (IQR) | 12 (6.5, 25) | 11.0 (6.7, 27) | 12.7 (6.4, 25.5) | .961    |
| Recipient weight under 6 kg (%) | 21 (17.4) | 5 (16.7) | 16 (17.6) | .9       |
| Kasai procedure (%) | 42 (34.7) | 11 (36.7) | 31 (34.1) | .827    |
| Recipient CMV+ (%) | 37 (30.6) | 7 (23.3) | 30 (33) | .365    |
| CMV mismatch (Y, %) | 25 (20.7) | 10 (33.3) | 15 (16.5) | .180    |
| Recipient blood type (%) | | | | .9       |
| A | 45 (37.2) | 11 (36.7) | 34 (37.4) |         |
| AB | 10 (8.3) | 2 (6.7) | 8 (8.8) |         |
| B | 19 (15.7) | 5 (16.7) | 14 (15.4) |         |
| O | 47 (38.8) | 12 (40) | 35 (38.5) |         |
| Recipient initial hospital stay, median (days, IQR) | 46 (31, 68.5) | 64 (42.87) | 42 (29.59) | .002    |
| Recipient initial hospital stay >46 days (%) | 47 (38.8) | 18 (60) | 29 (31.9) | .019    |
| Recipient initial stay Intensive care unit (IQR) | 18 (12.3, 23.8) | 25 (18, 33) | 16 (11, 21) | .000    |
| Year of Transplantation, median (IQR) | 2009 (2003, 2016) | 2010 (2003, 2017) | 2008 (2002, 2015) | .351    |
| Transplantation before 2010 (Y, %) | 63 (52.1) | 14 (46.7) | 49 (53.8) | .533    |
| Death | 15 (12.4) | 3 (10.0) | 12 (13.2) | .760    |
| Graft loss | 26 (21.5) | 5 (16.7) | 21 (23.1) | .533    |
| Re-transplantation (%) | 18 (14.9) | 3 (10) | 15 (16.5) | .557    |
| Rejection (%) | 30 (24.8) | 9 (30) | 21 (23.1) | .625    |

Pre-transplant laboratory parameter

| Recipient bilirubin (mg/dl), median (IQR) | 5.3 (3.0, 9.2) | 6.3 (3.2, 11.5) | 5.0 (2.9, 8.8) | .359    |
| Recipient platelet counts (g/L), median (IQR) | 92 (59, 144) | 95 (57, 170) | 92 (60, 133) | .524    |
| Recipient GOT (mg/dl), median (IQR) | 441 (237, 938) | 439.5 (308, 867) | 444 (227, 954) | .898    |
| Recipient GPT (mg/dl), median (IQR) | 313 (142, 592) | 324 (182, 479) | 307 (134, 617) | .938    |
| Recipient GGT (mg/dl), median (IQR) | 55 (33, 91) | 66 (33, 101) | 52 (33, 84) | .393    |
| Recipient Creatinine (mg/dl), median (IQR) | 0.44 (0.29, 0.72) | 0.35 (0.22, 0.69) | 0.45 (0.33, 0.77) | .057    |
| Recipient pTT (seconds), median (IQR) | 40 (35, 52) | 42 (38, 54) | 40 (35, 52) | .511    |

Note: Others: Malignancy, Intoxication, Alpha-1 antitrypsin deficiency, cholestatic liver disease of unknown origin, Crigler-Najjar, primary sclerosing cholangitis, poly cystic liver and kidney disease, PFIC (Byler Syndrome), Walcott-Rallison syndrome, biliary cirrhosis.

Abbreviations: +, positive; CFLD, cystic fibrosis liver disease; CMV, cytomegaly virus; GGT, Gamma-Glutamyl-Transaminase; GOT, Glutamat-Oxalacetas-Transamian; GPT, Glutamat-Pyrovat-Transaminase; IQR, interquartile range; pTT, partial thromboplastin time; (Y), yes.
complications, bowel obstruction/perforation, late biliary complications, and prolonged length of hospital stay (>median length) in patients with EBCs compared to patients without EBCs. Significance was classified as \( p \leq .05 \) (two-sided). Confidence intervals (CI) are presented on a 95% level. Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corporation, USA).

3 | RESULTS

3.1 | Study population

We performed 121 PLTs in 103 recipients. Of the 121 PLTs, EBC occurred in 24.8% \( (n = 30) \) while in 75.2% \( (n = 91) \) no EBC was detected. Early BCs consisted of biliary leakage \( (21 \text{ [17.3%]} \) ), anastomotic strictures \( (6 \text{ [5.0%]} \) ), and bile duct necrosis \( (3 \text{ [2.5%]} \) ). Most EBCs required surgical treatment \( (23 \text{ of } 30 \text{ [76.7%]}) \), while only a small proportion of patients could be treated interventionaly \( (5 \text{ of } 30 \text{ [16.7%]} \) or conservatively \( (2 \text{ of } [6.6%]) \).

Compared to the non-EBC group, patients with EBCs did not differ with respect to donor age \( \text{[median 29 [IQR 12–38.5] vs. 29 [IQR 2213–36]; } p = .796 \) ), donor BMI \( \text{[median 22.1 [IQR 18.1–24.5] vs. 22.3 [IQR 18.2–24.7]; } p = .877 \) ), donor type \( \text{[(living donation: 47.3% vs. 56.7%; deceased donation: 52.7% vs. 43.3%; } p = .406 \) ), graft type \( \text{[(SLT: 65.9% vs. 66.7% and WLT: 34.1% vs. 33.3%; } p = 1.000 \) ), cold ischemic time \( \text{[median 238 [IQR 88.5–492.8] vs. 134 [IQR 88.3–531]; } p = .813 \) ), and bile duct reconstruction \( \text{[(hepaticojejunostomy: 84.6% vs. 80.0% and duct-to-duct reconstruction: 15.4% vs. 20.0%; } p = .576 \) ). A detailed overview on donor characteristics can be found in Table 1.

Recipients without and with EBC were of comparable age \( \text{[median 34 months [IQR 8–120] vs. 33 [IQR 8–87]; } p = .692 \) ), sex \( \text{(male: 53.8% vs. 56.7%; } p = .835 \) ), weight \( \text{[median 12.7 kg [IQR 6.4–25.5] vs. 11.0 [IQR 6.7–27]; } p = .961 \) ), and CMV status \( \text{[CMV+: 33.0% vs. 23.3%; } p = .365 \) ). Recipients of both groups had similar underlying diseases \( \text{(Table 2 [recipient demographics]; } p = .697 \) ), numbers of previous abdominal surgery \( \text{[34.1% vs. 36.7%; } p = .827 \) ), and re-transplantation rates \( \text{[16.5% vs. 10.0%; } p = .557 \) ). The year of transplantation did not differ \( \text{[median 2008 [IQR 2002–2015] vs. 2010 [IQR 2003–2017]; } p = 1.000 \) .
3.2 | Impact of early biliary complications on patient and graft survival

Patient, death-censored (DCGS) and all-cause graft survival (ACGS) were similar between both groups. With a patient survival of 96.7%, 89.2%, 89.2%, 89.2% and 89.2% in the EBC group compared to 90.0%, 88.7%, 88.7%, 84.2%, and 84.2% in the non-EBC group at 90 days, 1, 5, 10, and 15 years, similar excellent survival was achieved (Figure 1; log rank \( p = .653 \)). DCGS at 90 days, 1, 5, and 10 years was 90.0%, 86.4%, 82.5%, 82.5% in the EBC group and 84.5%, 81.9%, 80.3%, and 74.0% in the non-EBC group, respectively (Table 3 and Figure 2; log rank \( p = .628 \)). All-cause graft survival at the corresponding timepoints was 90.0%, 86.4% 82.5%, and 82.5% in the EBC group and 84.5%, 84.5%, 80.3%, and 74.0% in the non-EBC group. After adjustments for year of transplantation, type of liver graft and previous abdominal surgery both groups demonstrated comparable graft (Table 4; DCGS: aHR 0.869 [95% CI 0.341–2.248]; \( p = .920 \); ACGS: aHR 0.786 [95% CI 0.326–2.338] \( p = .873 \)) and patient survival aHR 0.874 [95% CI 0.242–3.152]; \( p = .837 \). Causes of early graft loss (>90 days post-transplant) were early hepatic artery thrombosis (EBC group \( n = 1 \), non-EBC group \( n = 9 \)), portal vein complications (EBC group \( n = 5 \); non-EBC group \( n = 7 \)), and primary non-function (EBC group \( n = 1 \); non-EBC group \( n = 1 \)). Fibrosis (non-EBC group \( n = 3 \)) and cirrhosis (non-EBC group \( n = 1 \)) were reasons for late graft loss (>90 days post-transplant). In the non-EBC group, 12 patients died (13.2%) and 21 (23.1%) lost their graft. In the EBC group, 3 patients (10.0%) died and 5 (16.7%) lost their graft. Graft failure and death causes are listed in Table 5.

3.3 | Secondary outcome parameters

Compared to non-EBC patients, patients with EBCs had a significantly longer initial stay at the intensive care unit (16 days [IQR 11–21] vs. 25 days [IQR 18–33]; OR 3.5 [CI 1.382–8.720]; \( p = .007 \)). Initial hospital stay (42 days [IQR 29–59] vs. 64 days [IQR 42–87], OR 3.4 [CI 1.242–9.140]; \( p = .013 \)), and a higher rate of multiple bile ducts for anastomosis (13.2% vs. 33.3%; \( p = .027 \)). Patients with EBCs had a 4.4-fold increased odds of bowel obstruction/perforation (8.8% vs. 30.0%; OR 4.388 [CI 1.503–12.812]; \( p = .007 \)). Similar rates for refection (23.1% vs. 30.0%, OR 1.414 [CI 0.559–3.575]; \( p = .468 \)), bleeding/hematoma (17.6% vs. 26.7%, OR 1.705 [IQR 0.644–4.509]; \( p = .291 \)), as well as early portal vein (7.7% vs. 16.7%, OR 2.351 [CI 0.684–8.068]; \( p = .186 \)) and early hepatic artery complications (11.0% vs. 3.3%, OR 3.45 [CI 0.037–2.522]; \( p = .206 \)) were seen. Results are summarized in Table 6 (secondary outcome parameters) and Table 7 (odds ratio for post-operative complications).

3.4 | Late biliary complications

Late biliary complications occurred in 17.4%\(^2\) of patients. Nine (30%) of the 30 patients with EBCs developed LBCs. Our data demonstrated a 2.8-fold increased odds of late biliary complications (13.2% vs. 30.0%, OR 2.821 [95% CI 1.049–7.587]; \( p = .044 \)) in patients with EBCs compared to those without EBCs. In 57.1% of the patients (\( n = 12 \)), a radiologically proven stenosis of the hepaticojejunostomy was causal for LBC. Three patients (14.3%) presented with late biliary leakage and bilioma, 3 (14.3%) with cholangitis and another 3 (14.3%) with idiopathic cholestasis. In case of consistent size and missing clinical symptoms, bile leakages were managed conservatively; otherwise, a percutaneous drainage was performed. Patients with high-grade stenosis were treated surgically by revision of the hepaticojejunostomy (\( n = 3 \)) or by percutaneous transhepatic drainage (\( n = 4 \)).

4 | DISCUSSION

The present study investigated the impact of early biliary complications in the setting of pediatric liver transplantation. Our data indicate that recipients with EBCs have an excellent patient survival of 89.2% at 15 years and an excellent ACGS of 75.4% 10 years after transplantation. Patients with EBCs have a significantly longer ICU survival compared to non-EBC patients.
FIGURE 2 (A) All-cause and (B) death-censored graft survival in patients with (1) and without (0) early biliary complications (EBC). Similar all-cause (log rank p =) and death-censored (log rank p =) graft survival was seen in both groups. 0, non-EBC group; 1, EBC group; EBC, early biliary complications.
stay and overall hospital stay and face a 4.4-fold increased risk of bowel obstruction/perforation. In the presence of EBCs, a 2.8-fold increased risk toward late biliary complications was observed.

The biliary complication rate has been previously addressed in small and large series.\(^5,8,9,13,16,18,20–22\) The overall incidence of biliary complications after pediatric liver transplantation varies significantly between these reports and ranges from 10% to 45%.\(^5,8,9,13,16,18,20–22\) These variations may partially be explained by the inconsistent use of definitions for early and late biliary complications. In that respect, the detection rate may impact on the BC rate especially in cases with mild clinical symptoms. In our cohort, EBCs occurred in 24.8%—which is higher compared to the single center results from Hsiao et al. (\(n = 9, 6.7\%\)) and Anderson et al. (\(n = 11, 16.8\%\)) but similar to the results from Karakayali et al. (\(n = 21, 28\%\))\(^14\) and Darwish et al. (\(n = 27, 27\%\)).\(^23\) The latter examined diagnostic and treatment options for biliary strictures occurring early after transplantation.\(^9,19,20\) Equivalent to our study, both authors defined EBC as biliary complication that occurs within the first 90 days after transplantation.\(^9,19,20\) Feier et al. reported an overall BC rate of 14.5% (\(n = 71\)). In their study, the authors provided a detailed overview of the different biliary complication types, but also elaborated on diagnostic steps and treatment approaches. In our cohort, the frequent use of Gore-Tex® patches for abdominoplasty (43% of cases), especially in infants of less than 5 years, may factor into the detection rate since subsequent surgeries for patch-size reduction and removal offer the opportunity to inspect the bile duct anastomosis and detect clinically mild or silent fistulas.

Kling et al. who assessed BC in a small cohort of living-related liver transplant recipients (\(n = 48, 5\)-year patient survival, entire cohort: 81%, with BC: 88%) and Feier et al. (\(n = 489, 5\)-year patient survival, with BL: 87.2% vs. without BL: 85%; \(p = .72\); with BS: 87.4% vs. without BS: 85.9%; \(p = .56\)) confirmed that EBCs do not negatively influence patient or graft survival. Both studies, however, did not differentiate between early and late BCs.\(^5,21\)

An analysis by Hsiao et al. demonstrated that EBCs but not LBCs lead to impaired patient survival in their single center study with 55.6% in the EBC group dying (\(p = .079\)). This finding supports early and aggressive surgical treatment of BC to prevent increased mortality.\(^9,20\) In our cohort, EBCs were treated surgically in most instances (80%). Solely in cases of biliary leakages without clinical

### TABLE 4
**Adjusted hazard ratio for patient death, death-censored, and all-cause liver graft failure and patient survival comparing recipients with and without early biliary complications**

|                        | aHR  | 95% CI       | \(p\)-Value |
|------------------------|------|--------------|-------------|
| Liver graft            |      |              |             |
| DCGS                   | 0.869| 0.341–2.248  | .920        |
| ACGS                   | 0.786| 0.326–2.338  | .873        |
| Patient death          | 0.874| 0.242–3.152  | .837        |

Abbreviations: ACGS, all-cause graft survival; aHR, adjusted hazard ratio; CI, confidence interval; DCGS, death-censored graft survival.

*Model adjusted for year of transplantation, type of liver graft and previous abdominal surgery.

### TABLE 5
**Cause of late and early graft loss and death**

| Cause of graft loss (%) | All (\(n = 121\)) | EBC (\(n = 30\)) | No EBC (\(n = 91\)) |
|------------------------|-------------------|------------------|---------------------|
| Early hepatic artery thrombosis | 2 (1.7) | None | 2 (2.2) |
| Small-for-size syndrome | 1 (0.8) | None | 1 (1.1) |
| Primary non-function | 3 (2.5) | 1 (3.3) | 2 (2.2) |
| Cirrhosis | 1 (0.8) | None | 1 (1.1) |
| Fibrosis | 2 (1.7) | None | 2 (2.2) |
| Portal vein thrombosis | 3 (2.5) | 1 (3.3) | 2 (2.2) |
| Ischemic liver failure | 2 (1.7) | None | 2 (2.2) |
| Rejection | 2 (1.7) | 1 (3.3) | 1 (1.1) |
| Infection | 1 (0.8) | None | 1 (1.1) |
| Patient death | 5 (4.1) | None | 5 (5.5) |
| Unknown | 4 (3.3) | 2 (6.7) | 2 (2.2) |

| Cause of death (%) | All (\(n = 103\)) | EBC (\(n = 27\)) | No EBC (\(n = 76\)) |
|-------------------|-------------------|------------------|---------------------|
| Cerebral hypoxia | 2 (1.9) | None | 2 (2.6) |
| MOF | 4 (3.9) | 1 (3.7) | 3 (3.9) |
| Respiratory insufficiency | 2 (1.9) | None | 2 (2.6) |
| Heart failure | 2 (1.9) | None | 2 (2.6) |
| Graft failure | 1 (1.0) | None | 1 (1.3) |
| Progressive malignancy | 1 (1.0) | None | 1 (1.3) |
| Unknown | 3 (2.9) | 2 (7.4) | 1 (1.3) |

Abbreviations: ACGS, all-cause graft survival; EBC, early biliary complications; MOF, multi-organ failure.
signs of infection, the management was conservatively. Our data further suggest that long-term graft loss was rare not directly associated with EBC (7.4% vs. 16.4% in non-EBC).

The incidence of biliary complications following living-related liver transplantation (LLT) is reported to be around 33%.21,24–26 Some studies describe an even higher incidence of BC in reduced size deceased-donor liver grafts, deceased-donor split grafts, and living-donor liver grafts.20,24,27 While a trend toward a higher incidence of EBC in living-related liver transplantation was observed in our cohort (non-EBC: LLT = 47.3%, DDLT = 52.7% vs. EBC: LLT = 56.7%, DDLT = 43.3%; p = .406), our data did not reveal higher rates of EBC in partial grafts compared to whole grafts (non-EBC: WLT = 34.1%, SPL = 95.9% vs. EBC WLT = 33.3%, SLT = 66.7%; p = 1.000). This is in line with data from Laurence et al. who found a similar BC rate between LLT and deceased-donor liver transplantation (DDLT).13 Yet again, the results from the SPLIT database suggest an association between graft type and BC rate (30 day: 7.5% whole, 18.8% split, 16% reduced, 17.5% live-donor).24

A number of risk factors for biliary complications have been described; however, we feel that the interpretation of statistical findings and comparison of single factors should be handled with care due to varying and often low caseloads, different surgical techniques, surgeons experience, and different demographics. In a number of studies, no differentiation between EBC and LBC was made. As the genesis of both differ widely,9,10,19 a discrimination between both entities seems important. According to the literature, early hepatic

### TABLE 6  Secondary outcome parameters stratified by early biliary duct complications

| Outcome parameters                                                                 | All (n = 121) | EBC (n = 30) | No EBC (n = 91) | p-Value |
|------------------------------------------------------------------------------------|---------------|--------------|----------------|---------|
| Number of biliary ducts (%)                                                       |               |              |                | .555    |
| 1 bile duct                                                                        | 99 (81.8)     | 20 (66.7)    | 79 (86.8)      |         |
| 2 bile duct                                                                        | 19 (15.7)     | 9 (30.0)     | 10 (11.0)      |         |
| 3 bile duct                                                                        | 3 (2.5)       | 1 (3.3)      | 2 (2.2)        |         |
| Multiple vs. single bile ducts (%)                                                | 22 (18.2)     | 10 (33.3)    | 12 (13.2)      | .027    |
| Stent/T-tube (%)                                                                  | 13 (10.7)     | 2 (6.7)      | 11 (12.1)      | .513    |
| Late biliary complications (%)                                                    | 21 (17.4)     | 9 (30.0)     | 12 (13.2)      | .050    |
| CMV mismatch (Y, %)                                                               | 25 (20.7)     | 10 (33.3)    | 15 (16.5)      | .180    |
| Early hepatic artery complication (%)                                             | 10 (8.3)      | 1 (3.3)      | 9 (9.9)        | .632    |
| Late hepatic artery complications (%)                                             | 11 (9.1)      | 1 (3.3)      | 10 (11.0)      | .400    |
| Early portal vein complications (%)                                               | 12 (9.9)      | 5 (16.7)     | 7 (7.7)        | .361    |
| Late portal vein complications (%)                                                | 19 (15.7)     | 3 (10.0)     | 16 (17.6)      | .521    |
| Bowel obstruction/bowel perforation post Tx                                       | 17 (14.0)     | 9 (30.0)     | 8 (8.8)        | .020    |
| Post-operative bleeding/hematoma (%)                                              | 24 (19.8)     | 8 (26.7)     | 16 (17.6)      | .574    |
| Type of early biliary complication (% of all transplantations)                    |               |              |                |         |
| Leakage                                                                           | 21 (17.3)     |              |                |         |
| Stricture                                                                         | 6 (5.0)       |              |                |         |
| Bile duct necrosis                                                                | 3 (2.5)       |              |                |         |

Abbreviations: CMV, cytomegaly virus; EBC, early biliary complication; Tx, transplantation; Y, year.

### TABLE 7  Odds ratio of long-term complications, length of initial hospital stay and post-operative complications comparing patients with and without EBCs

| Variable                           | OR       | 95% CI          | p-Value |
|------------------------------------|----------|-----------------|---------|
| Bowel obstruction/perforation      | 4.388    | 1.503-12.812    | .007    |
| Rejection                          | 1.414    | 0.559-3.575     | .468    |
| Early hepatic artery complications | 1.345    | 0.037-2.522     | .206    |
| Early portal vein complications    | 2.351    | 0.684-8.086     | .186    |
| Late biliary complications         | 2.821    | 1.049-7.587     | .044    |
| Bleeding/hematoma                  | 1.705    | 0.644-4.509     | .291    |
| Initial hospital stay length > median| 3.369    | 1.242-9.140    | .013    |

Abbreviations: CI, confidence interval; OR, odds ratio.
artery thrombosis and technical errors, especially in segmental grafts with multiple bile ducts, are key drivers of EBC. Interestingly, eHAT was not responsible for EBC in our study. Risk factor assessment in this study reveals only the incidence of multiple bile ducts to be associated with an increased rate of EBCs. In contrast to our findings, Salvalaggio et al. demonstrated a significantly inferior graft survival in case of multiple bile ducts. Another risk factor for BC was revisions after Kasai procedures as shown by Hsiao et al. In their study, the primary Kasai procedure did not correlate with the occurrence of BCs. Lüthold et al. assessed risk factors for different BC in a cohort of 116 patients. They propose that excessively long operating times and HAT are responsible for biliary leakages and that the type of bile duct anastomosis correlates with the occurrence of biliary strictures. In contrast to other reports, neither duct-to-duct nor hepaticojejunostomy were associated with EBCs in our patients. In addition to the aforementioned factors, donor age, blood type mismatch, CMV infections, recipient age, HLA mismatch, and EBV infections have been associated with an increased number of biliary complications.

A rare complication is the orphan duct syndrome or excluded segmental bile duct leakage that has been described after major liver resections and is classified as type D leakage after the classification of Nagano et al. The leakage results from a bile duct which is separate from the main biliary tree but drains bile fluids of functioning liver parenchyma segment. The crux of this complication is the diagnosis as patients often present with refractory biliary leakage or cholestasis if the excluded bile duct was accidentally ligated during donor operation. In our cohort, we detected 4 orphan bile ducts. In all cases, this finding coincided with a bile leakage requiring reoperation. The orphan ducts were only diagnosed during reoperation and an additional HJ was performed in all four cases. Intraoperative cholangiography during the donor operation in LLT has been described to prevent overseeing excluded bile ducts.

In our experience, EBCs result in prolonged intensive care as well as prolonged total hospital stay and increased number of postoperative bowel obstructions/perforations. In patients with EBCs, a significantly higher incidence of LBCs was seen. EBCs therefore represent an increased burden for the patient and family as well as prolonged hospital stay with higher overall costs. The association between EBCs and increased costs has previously been reported by Feier et al., Kling et al., and Englesbe MJ. In our cohort, bowel obstruction/perforations were significantly more frequent in patients with previous abdominal surgeries and/or with reoperations as necessary for most EBCs. Multiple abdominal surgeries are a known risk factor for the development of adhesions and subsequent obstruction.

This study has several limitations. First, we analyzed results over a period of thirty-five years. Over time, surgical techniques, immunosuppressive protocols, organ acceptance and utilization criteria, and recipient selection have changed profoundly and outcomes were not similar across the study period. Different surgical procedures and our rather small annual case load complicate statistical evaluation and accuracy.

In summary, this study demonstrates that EBCs lead to a prolonged ICU and initial hospital stay without compromising patient or graft survival. While no association between EBCs and vascular complications was seen, significantly more bowel obstructions/perforations were recorded in recipients with EBCs. The presence of multiple bile ducts was the only factor significantly associated with the occurrence of EBCs.

5 | CONCLUSION

The relatively high biliary complication rate illustrates the complexity and vulnerability of bile duct anastomoses in pediatric liver transplantation. Whereas a prolonged intensive care unit and hospital stay in patients with early biliary complications was recorded, this had no negative influence on patient and graft survival. EBCs correlated with a higher incidence of LBCs, and thus, these patients should be monitored closely in order to anticipate their occurrence.

ACKNOWLEDGMENTS

The authors would like to thank Heinz Zoller from the Department of Gastroenterology and the Transplant Coordination at the Medical University of Innsbruck for their contribution in pretransplant evaluation.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

VB and FM performed statistical analysis, conceptualized the study, and wrote the manuscript. AW and SS conceived the presented idea and developed the theory. HU supervised the statistical analysis and helped to write the methods section in the manuscript. JK, VB, and AW acquired data for the SPSS file. RM and HS encouraged VB to investigate and helped to acquire the data for the SPSS file. SS, DÔ, TM, BC, RO, and AE supervised the findings of this work. BC and RO provided critical feedback. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author SS on reasonable request.

ORCID

Valeria Berchtold https://orcid.org/0000-0002-6997-3244
Franka Messner https://orcid.org/0000-0003-2100-6914
Annemarie Weissenbacher https://orcid.org/0000-0002-0582-1815
Benno Cardini https://orcid.org/0000-0003-0103-1717
Stefan Schneeberger https://orcid.org/0000-0002-2619-8639

REFERENCES

1. Adam R, Karam V, Cailliez V, et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation. Transpl Int. 2018;31:1293-1317.
2. Nadalin S, Capobianco I, Panaro F, et al. Living donor liver transplantation in Europe. *Hepatobiliary Surg Nutr*. 2016;5:159-175.
3. Eurotransplant Statistical Reports. https://www.eurotransplant.org/statistics/statistics-library. Accessed July 7, 2020.
4. Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant*. 2009;9:746-757.
5. Feier FH, Chapchap P, Pugliese R, et al. Diagnosis and management of biliary complications in pediatric living donor liver transplant recipients. *Liver Transpl*. 2014;20:882-892.
6. Alvarez F. Portal vein complications after pediatric liver transplantation. *Curr Gastroenterol Rep*. 2012;14:270-274.
7. Evans HM, Kelly DA, McKiernan PJ, Hübscher S. Progressive histological damage in liver allografts following pediatric liver transplantation. *Hepatology*. 2006;43:1109-1117.
8. D’Alessandro AM, Knechtle SJ, Chin LT, et al. Liver transplantation in pediatric patients: twenty years of experience at the University of Wisconsin. *Pediatr Transplant*. 2007;11:661-670.
9. Tsao HY, Ho C-M, Wu Y-M, Ho M-C, Hu R-H, Lee P-H. Biliary complication in pediatric liver transplantation: a single-center 15-year experience. *J Gastrointest Surg*. 2019;23:751-759.
10. Tanaka K, Yol S. Incidence and management of biliary strictures in living-related donor graft. *Pediatr Transplant*. 2002;6:452-455.
11. Liu C, Loong C-C, Hsia C-Y, et al. Duct-to-duct biliary reconstruction in selected cases in pediatric living-donor left-lobe liver transplantation. *Pediatr Transplant*. 2009;13:693-696.
12. Oliveira P. Biliary complications after paediatric liver transplantation. *Pediatr Transplant*. 2010;14:437-438.
13. Laurence JM, Sapisochin G, DeAngelis M, et al. Biliary complications in pediatric liver transplantation: incidence and management over a decade. *Liver Transpl*. 2015;21:1082-1090.
14. Karakayali F, Kirnap M, Akdur A, et al. Biliary complications after pediatric liver transplantation. *Transplant Proc*. 2013;45:3524-3527.
15. Heffron TG, Pillen T, Smallwood GA, et al. Incidence, impact, and treatment of portal and hepatic venous complications following pediatric liver transplantation: a single-center 12 year experience. *Pediatr Transplant*. 2010;14:722-729.
16. Haberal M, Sevms S, Emiroglu R, Karakayali H, Arslan G. Duct-to-duct biliary reconstruction in pediatric liver transplantation: one center’s results. *Transplant Proc*. 2007;39:1161-1163.
17. Lüthold SC, Kasej N, Jannot A-S, et al. Risk factors for early and late biliary complications in pediatric liver transplantation. *Pediatr Transplant*. 2014;18:822-830.
18. Salvalaggio PR, Whittington PF, Alonso EM, Superina RA. Presence of multiple bile ducts in the liver graft increases the incidence of biliary complications in pediatric liver transplantation. *Liver Transpl*. 2005;11:161-166.
19. Chok KS, Chan SC, Chan KL, et al. Bile duct anastomotic stricture after pediatric living donor liver transplantation. *J Pediatr Surg*. 2012;47:1399-1403.
20. Anderson CD, Turmelle YP, Darcy M, et al. Biliary strictures in pediatric liver transplant recipients - early diagnosis and treatment results in excellent graft outcomes. *Pediatr Transplant*. 2010;14:358-363.
21. Kling K, Lau H, Colombani P. Biliary complications of living related pediatric liver transplant patients. *Pediatr Transplant*. 2004;8:178-184.
22. Shirouzu Y, Okajima H, Ogata S, et al. Biliary reconstruction for infantile living donor liver transplantation: Roux-en-Y hepatico-jejunostomy or duct-to-duct choledochocholedochostomy? *Liver Transpl*. 2008;14:1761-1765.
23. Darwish AA, Bourdeaux C, Kader HA, et al. Pediatric liver transplantation using left hepatic segments from living related donors: surgical experience in 100 recipients at Saint-Luc University Clinics. *Pediatr Transplant*. 2006;10:345-353.
24. Diamond IR, Fecteau A, Millis JM, et al. Impact of graft type on outcome in pediatric liver transplantation: a report from Studies of Pediatric Liver Transplantation (SPLIT). *Ann Surg*. 2007;246:301-310.
25. Heffron TG, Pillen T, Welch D, Smallwood GA, Redd D, Romero R. Biliary complications after pediatric liver transplantation revisited. *Transplant Proc*. 2003;35:1461-1462.
26. Osowari H, Lynch SV, Fawcett J, Strong RW, Ee LC. Outcomes of split versus reduced-size grafts in pediatric liver transplantation. *J Gastroenterol Hepatol*. 2005;20:1850-1854.
27. Conzen KD, Lowell JA, Chapman WC, et al. Management of excluded bile ducts in paediatric orthotopic liver transplant recipients of technical variant allografts. *HPB (Oxford)*. 2011;13:893-898.
28. Haberal M, Karakayali H, Atiq A, et al. Duct-to-duct biliary reconstruction without a stent in pediatric living-donor liver transplantation. *Transplant Proc*. 2011;43:595-597.
29. Nagano Y, Togo S, Tanaka K, et al. Risk factors and management of bile leakage after hepatic resection. *World J Surg*. 2003;27:695-698.
30. Honoré C, Vibert E, Hoti E, Azoulay D, Adam R, Castaing D. Management of excluded segmental bile duct leakage following liver resection. *HPB (Oxford)*. 2009;11:364-369.
31. Huang TL, Cheng YF, Chen CL, Chen TY, Lee TY. Variants of the bile ducts: clinical application in the potential donor of living-related hepatic transplantation. *Transplant Proc*. 1996;28:1669-1670.
32. Patrono D, Tandoi F, Romagnoli R, Salizzoni M. Excluded segmental duct bile leakage: the case for bilio-enteric anastomosis. *Updates Surg*. 2014;66:115-119.
33. Englesbe MJ, Dimick J, Mathur A, et al. Who pays for biliary complications following liver transplantation? A business case for quality improvement. *Am J Transplant*. 2006;6:2978-2982.
34. ten Broek RP, Issa Y, van Santbrink EJP, et al. Burden of adhesions in abdominal and pelvic surgery: systematic review and met-analysis. *BMJ*. 2013;347:f5588.

**How to cite this article:** Berchtold V, Messner F, Weissenbacher A, et al. Influence of early biliary complications on survival rates after pediatric liver transplantation—A positive outlook. *Pediatr Transplant*. 2021;00:e14075. [https://doi.org/10.1111/petr.14075](https://doi.org/10.1111/petr.14075)