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ORIGINAL ARTICLE

Short- and long-term results of liver transplantation according to age at transplant: a single-center experience of 351 children

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SUMMARY

Pediatric liver transplantation (PLT) has very good results at experienced transplant centers. However, there is still an ongoing discussion about inferior outcomes, especially in young infants. The aim of this retrospective study was to evaluate outcomes of infants compared to older recipients in a single center over 20 years. We conducted a retrospective study of children who received liver transplants at our center between 1991 and 2011. Only patients without other limiting organ involvement were included and compared according to age. The inclusion criteria were fulfilled by 351 patients (173 vs. 178). The most common indication in both groups was biliary atresia (82.1% vs. 49.4%). The 1-, 5-, and 10-year patient survivals were 93.8%/91.8%/91.1% and 93%/90.8%/90.1%, and the graft survivals were 90.4%/83.5%/79.6% and 89.4%/81.8%/77.5%, respectively. Complications such as postoperative bleeding, biliary complications, or perfusion impairment occurred more often in infants. Leading indications for retransplantation (vascular complications/primary nonfunction) and leading causes of death (sepsis/multiorgan failure) were the same in both groups. Significant predictors for patient loss were decade of transplantation, retransplantation, postoperative bleeding, and infections for infants. Predictors for graft loss were bowel perforation, arterial thrombosis, and age >12 months. Children can have excellent results, independent of age at PLT.

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Introduction

Pediatric liver transplantation (PLT) has become the standard treatment for children with end-stage liver disease of various etiologies over the last decades [1–5]. Improvements in surgical techniques, peri- and postoperative care, immunosuppressive medications, and patient selection have led to excellent long-term patient and graft survival rates of up to 90% and 80% ten years after PLT, respectively [4,6–9]. Despite the major advances and the steadily declining average age of PLT recipients [4], there are still relatively few studies focusing on the long-term outcome according to age and particular aspects of timing for PLT [2,10–14]. Patient referral to transplant centers is often delayed because of young age and suspected worse outcome, although historically they have had the highest rates of wait-list mortality among all pediatric candidates [14–17].

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Complications associated with immunosuppression or surgical procedures such as vascular thrombosis, biliary tract complications, and infections are a concern and reported to have a higher incidence in smaller recipients the smaller anatomy makes the operation more difficult, with the potential for subsequent complications and worse outcomes [2,5,14,17]. On the other hand, there may be some immunological advantages for very young liver graft recipients due to the immature immune system, resulting in good outcomes for this age group [18].

Venick *et al.* [2] summarized their single-center experience with more than 200 infant liver transplant recipients and showed that long-term outcomes (especially for infants undergoing PLT) have improved over time. Nevertheless, they found that overall patient survival among infants is not equivalent to that of older children. Byun *et al.* [19] analyzed 152 patients and showed a good, not inferior outcome for infants compared to older graft recipients, although the pre-operative clinical condition of young infants before PLT was often more critical and they had more postoperative complications.

The aim of our retrospective study was to evaluate our large single-center experience of PLT by analyzing short- and long-term results, comparing the outcomes of infants with those of older children, highlighting the differences between these two age groups, and identifying predictors of patient and graft survival.

Patients and methods

We performed a retrospective chart analysis of all children (<18 years) who had received liver transplants at the University Medical Center Hamburg-Eppendorf between 1991 and 2011. Patients were eligible for this current study if they suffered from hepatic failure without other chronic comorbidities that might have influenced the outcome after PLT despite successful PLT. We therefore excluded children with combined organ transplantation, multiorgan diseases, metabolic diseases and acute liver failure of unknown origin. The study population was divided according to age at PLT; group 1 $\leq$ 1 year group 2 $\geq$ 1 year of age.

We analyzed various PLT procedures, for example, living donation, deceased donor whole-liver transplants, and technical variants such as split and reduced-size transplants. The effect of the center´s experience was evaluated by comparing the results of the decades 1991–2001 and 2002–2011.

The following data were collected: patients´ demographic data, donor data, and laboratory data as well as complications during the early postoperative stage and at yearly follow-ups. Growth parameters and side effects of the immunosuppressive therapy were also documented.

Standard medication

Standard immunosuppression after PLT at our center consisted of cyclosporine A (CsA; initial trough levels 150–170 µg/l, maintenance levels after 1 year 100–120 µg/l) and corticosteroids with an initial dose of 60 mg/m^2 vs. 15 mg/m^2 according to transplant era. Steroids were reduced stepwise and usually discontinued after 1 year. From 1998 on, the anti-interleukin-2 receptor antibody basiliximab was administered in two single doses on day 0 and day 4 post-transplant. Acute rejections were treated with a 3-day course of intravenous methylprednisolone bolus therapy (10 mg/kg body weight) followed by 3 days of reduced dose methylprednisolone (5 mg/kg/day). Patients with severe rejection or steroid-resistant rejection were either switched to tacrolimus or mycophenolate mofetil was added. The standard anticoagulation regimen after PLT consisted of intravenous heparin (target partial thrombin time: 45–55 s), which was switched to prophylactic aspirin after abdominal closure (dosage 5 mg/kg, three times weekly). Aspirin was given for up to 1 year.

Statistical analysis

Continuous variables were summarized with mean $\pm$ standard deviation or median and interquartile range. Categorical variables were presented as percentages and frequencies. Patient and graft survival were assessed using Cox proportional hazards regression. First, we performed univariate Cox regressions with all variables, which were as follows: gender, diagnosis, year of transplantation, retransplantation, death, surgical complications, patch, infection, rejection, aspartate-aminotransferase (ASAT), alanin-aminotransferase (ALAT), gamma-glutamyltransferase (GGT), bilirubin, creatinine, creatinine clearance, Quick value, and international normalized ratio (INR). These variables were controlled for age group and decade of PLT. In this step, we checked the interactions between age group and the specific variable, and between decade and the specific variable. In a second step, all significant variables and (if applicable) significant interactions in a multivariate Cox regression were analyzed and a backward selection of the non-significant variables was performed. The final models are presented in forest plots with the hazard ratio, its 95% confidence interval and the

P value. A two-sided *P* value <0.05 was considered statistically significant. All data were analyzed with SPSS, version 24 (IBM Corp., Armonk, NY, USA).

Results

In the study period from 1991 to 2011, 649 PLTs were performed at our center. 351 children fulfilled the inclusion criteria and were divided into two groups according to age at transplant as mentioned above.

Patient characteristics

In group 1, we analyzed 173 infants younger than 12 months (82 female). The most common indication leading to PLT in this group was biliary atresia (82.1%), neonatal hepatitis (5.2%), and neonatal hemochromatosis (2.3%; now called GALD = gestational alloimmune liver disease). At the time of PLT, the median age in group 1 was 7 months (range: 0–12 months) and the median weight was 5.9 kg (range: 2–11 kg). There were only 9 children transplanted in the first 3 months of age (5%). The graft types that were used during primary transplantation were 10 whole (5.8%), 72 segmental (41.6%), and 91 living-related (52.6%) organs. Eleven patients (6.3%) were transplanted under high urgency conditions. The mean donor age was 26.9 years (range: 6 months to 64 years).

In group 2, there were 178 children (89 female) from 1 to 17 years of age. The most frequent indications leading to PLT were biliary atresia (49.4%), cirrhosis of unknown origin (14.1%), and progressive familial intrahepatic cholestasis (PFIC; 9.6%). The median age at the time of PLT was 5 years (range: 1–17 years), and the median weight was 18.5 kg (range: 5–78 kg). Graft types that were used in this group were 40 whole (22.5%), 54 living-related (30.3%), and 84 segmental (47.2%) organs.

In group 2, 7 out of 178 primary LTX (3.9%) were high urgency transplantations. The mean donor age was 25.3 years (range: 5 months to 61 years). Diagnoses are summarized in Table 1 and demographic data in Table 2.

Table 1. Primary diagnosis leading to PLT.

Variable	Group 1 (*n* = 173)	Group 2 (*n* = 178)
Biliary atresia, *n* (%)	142 (82.1%)	88 (49.4%)
Crigler–Najjar syndrome, *n* (%)	2 (1.2%)	10 (5.6%)
Neonatal hemochromatosis*, *n* (%)	4 (2.3%)	–
PFIC, *n* (%)	4 (2.3%)	17 (9.6%)
Neonatal hepatitis, *n* (%)	9 (5.2%)	4 (2.2%)
Cirrhosis of unknown origin, *n* (%)	5 (2.9%)	25 (14.1%)
Secondary biliary cirrhosis, *n* (%)	4 (2.3%)	16 (8.9%)
Alpha-1 antitrypsin deficiency, *n* (%)	–	7 (3.9%)
Caroli syndrome, *n* (%)	–	1 (0.6%)
Wilson disease, *n* (%)	–	5 (2.8%)
Other liver diseases, *n* (%)	2 (1.2%)	4 (2.2%)

PFIC, progressive familial intrahepatic cholestasis.

*Now:GALD = gestational alloimmune liver disease.

Table 2. Patient characteristics (all children, primary LT).

Variable	Group 1 (*n* = 173)	Group 2 (*n* = 178)
Sex		
Female, *n* (%)	82 (47.4%)	89 (50%)
Male, *n* (%)	91 (52.6%)	89 (50%)
Median age at LT	7 months	5 years
Median weight at LT	5.9 kg	18.5 kg
High urgent, *n* (%)	11 (6.3%)	7 (3.9%)
Median waiting time	33 days	85 days
Median CIT	372 min	572 min
Graft type, *n* (%)		
Whole	10 (5.8%)	40 (22.5%)
Reduced	20 (11.6%)	16 (9.0%)
Split	52 (30%)	68 (38.2%)
Living related	91 (52.6%)	54 (30.3%)
Era of retransplantation		
Transplanted until 2001	88 (50.9%)	97 (54.5%)
Transplanted after 2001	85 (49.1%)	81 (45.4%)

CIT, cold ischemia time.

Graft and patient survival

The 1-, 5-, and 10-year patient and graft survivals in group 1 were 93.8%/91.8%/ 91.1% and 90.4%/83.5%/ 79.6%, respectively.

In group 2, the 1-, 5-, and 10-year patient and graft survivals were 93%/90.8%/90.1% and 89.4%/81.8%/ 77.5%, respectively. There was no statistically significant difference.

Patient and graft survival curves for infants versus older children are shown in Figs 1 and 2.

Complications

Twenty patients in group 1 died (11.6%). The leading causes of death were infections with sepsis and

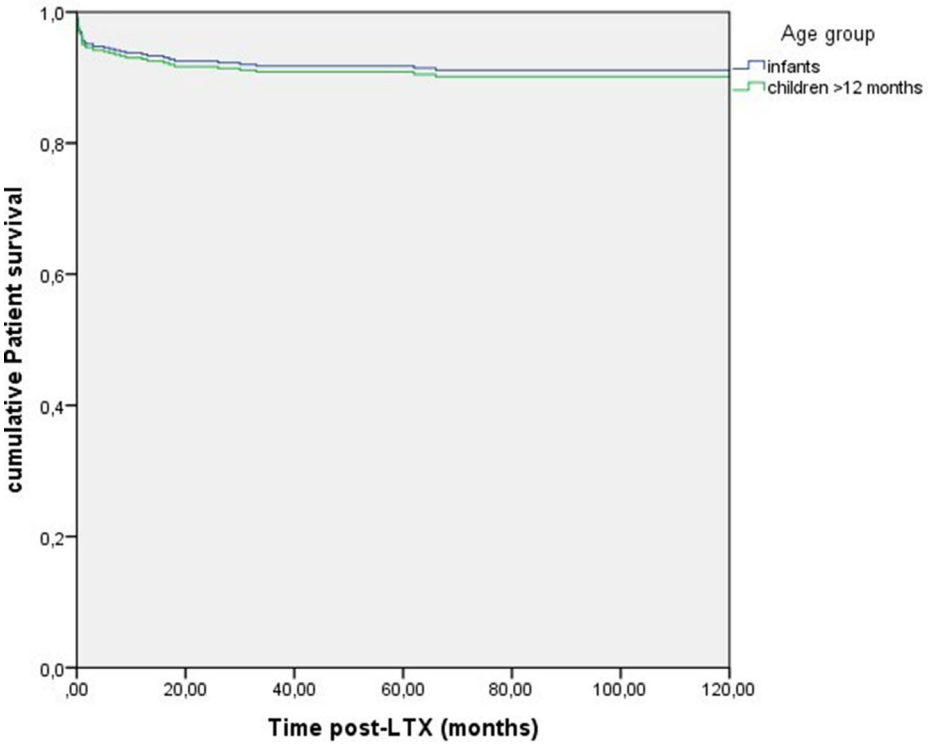

Figure 1 Overall patient survival (censored).

multiorgan failure. Other reasons were bleedings and PTLD ($n = 1$). Twenty-nine infants were retransplanted due to vascular complications, primary nonfunction, or chronic rejection with organ dysfunction. Regarding vascular complications, the most common one was a HAT, which was the reason for retransplantation in 6 cases. Less often a portal vein thrombosis ($n = 2$) or a thrombosis of the Vena hepatica ($n = 1$) was found as a reason for Re-LT. Eleven children were retransplanted within one month, the other 18 children later (range: 4 months to 9 years after the primary PLT).

The most frequent surgical complications in this group were postoperative bleedings (12.1%), biliary complications (11.5%), perfusion impairment (9.8%), and bowel perforation (8.7%). Seventy-one children showed rejection episodes. Acute rejections occurred in 63 infants (36.4%) in 8 children (4.6%) the rejection was defined as chronic rejection. In the early course after PLT, 110 infants suffered from infections (63.6%), mostly bacterial (nearly 50%) but also viral (~ 40%) and fungal. The incidence of PTLD was 3.4% ($n = 6$) during the follow-up time of 10 years. All of these six children had a Kasai procedure prior to LT.

In group 2, 23 children (12.9%) died of severe bacterial infection with multiorgan failure; 36 children (20.2%) had to undergo retransplantation. In this group, 19 children were retransplanted within the first 30 days after primary PLT, and 17 later after PLT (range: 1.5 months to 14.5 years). Surgical complications seen in this group were mostly biliary (7.8%), perfusion impairment/thrombosis (5.6%), and postoperative bleeding (5.1%).

Acute rejection occurred in 67 children (37.6%), in nine patients (5%) a chronic rejection was diagnosed. Infections, mostly viral (>50%), were seen in 55 patients (30.9%). We recorded two cases of temporary diabetes after LT. In this group, no cases of PTLD occurred. The data are summarized in Table 3.

In both groups, there were no cases with end-stage renal disease requiring dialysis or renal transplantation.

Growth and weight

In group 1, valid data concerning growth/weight were available for 107/115 children after one year, 76/77 after 5 years, and 44/45 after ten years. After one year, 35 children (32.7%) had normal height and 80 children (69.6%) had normal weight according to reference age (between the 10th and 90th percentile). After 5 years, 71 children (93.4%) had normal height and 65 (84.4%) had normal weight, while after 10 years, 36 children (81.8%) had normal height and 33 (73.3%) had normal weight.

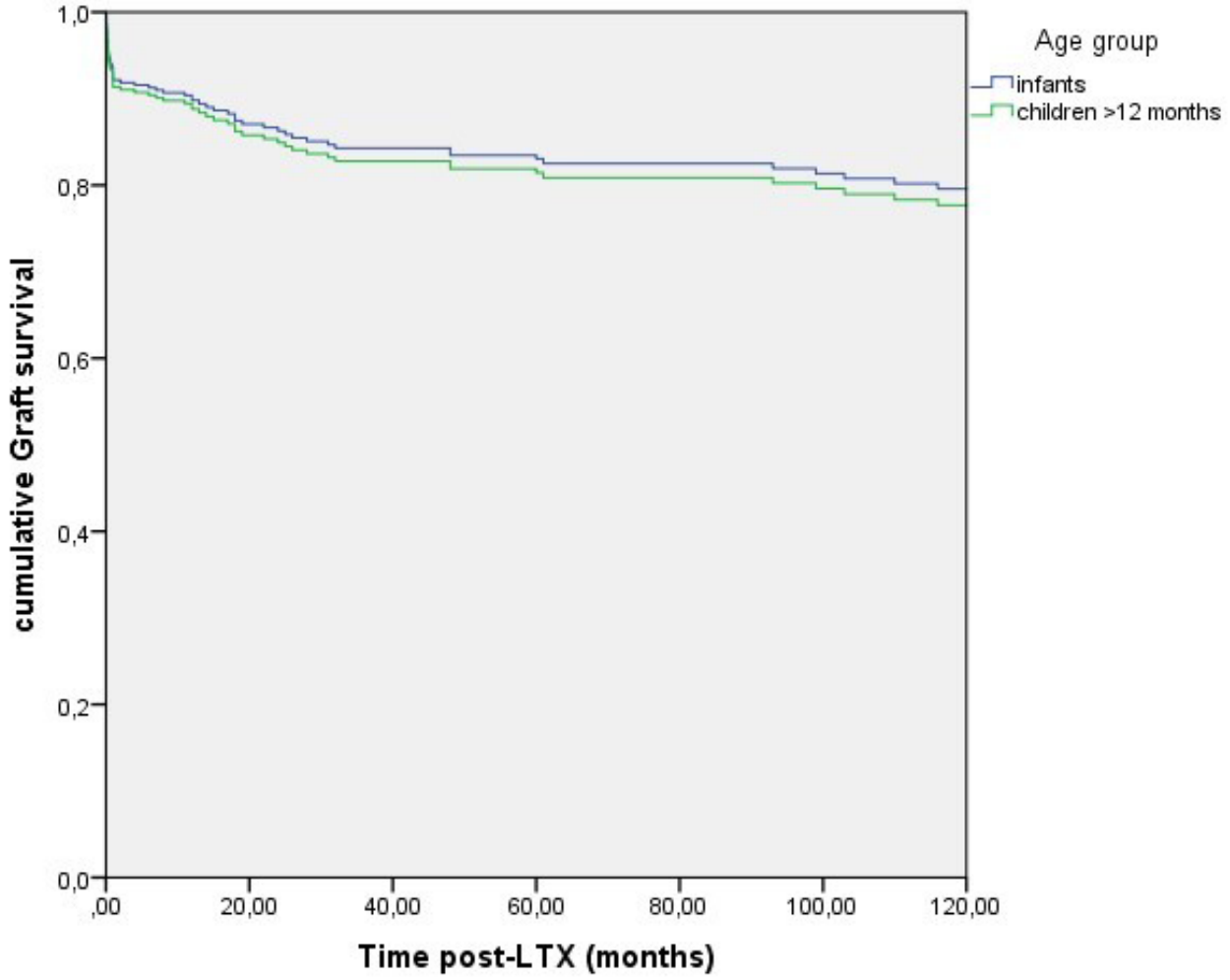

Figure 2 Overall graft survival in infants versus children older than 12 months after PLT between 1991 and 2011 (censored).

Table 3. Complications after PLT and their effect on survival outcome.

Variable	Total (*n* = 351)	Group 1 (*n* = 173)	Group 2 (*n* = 178)	*P*-value graft loss	*P*-value patient loss
Death, *n* (%)	43 (12.2%)	20 (11.6%)	23 (12.9%)		
Retransplantation, *n* (%)	65 (18.5%)	29 (16.7%)	36 (20.2%)	–	**0.047**
Rejection, *n* (%)	147 (41.9%)	71 (41%)	76 (42.7%)	0.389	0.128
Surgical complications					
Biliary, *n* (%)	34 (9.7%)	20 (11.5%)	14 (7.8%)	0.094	0.724
Bowel perforation, *n* (%)	22 (6.2%)	15 (8.7%)	7 (3.9%)	**0.001**	0.778
HAT, *n* (%)	23 (6.5%)	12 (6.9%)	11 (6.1%)	**0.001**	0.198
PVT, *n* (%)	17 (4.8%)	10 (5.8%)	7 (3.9%)	0.587	0.934
Bleeding, *n* (%)	30 (8.5%)	21 (12.1%)	9 (5.1%)	0.119	**0.002**
Infection, *n* (%)	165 (47%)	110 (63.6%)*	55 (30.9%)	0.326	**0.004***
PTLD, *n* (%)	6 (3.4%)	6 (3.4%)	0 (0%)	0.481	0.773

* Only significant in group 1.

Bold values show significant influence on patient or graft survival in whole population.

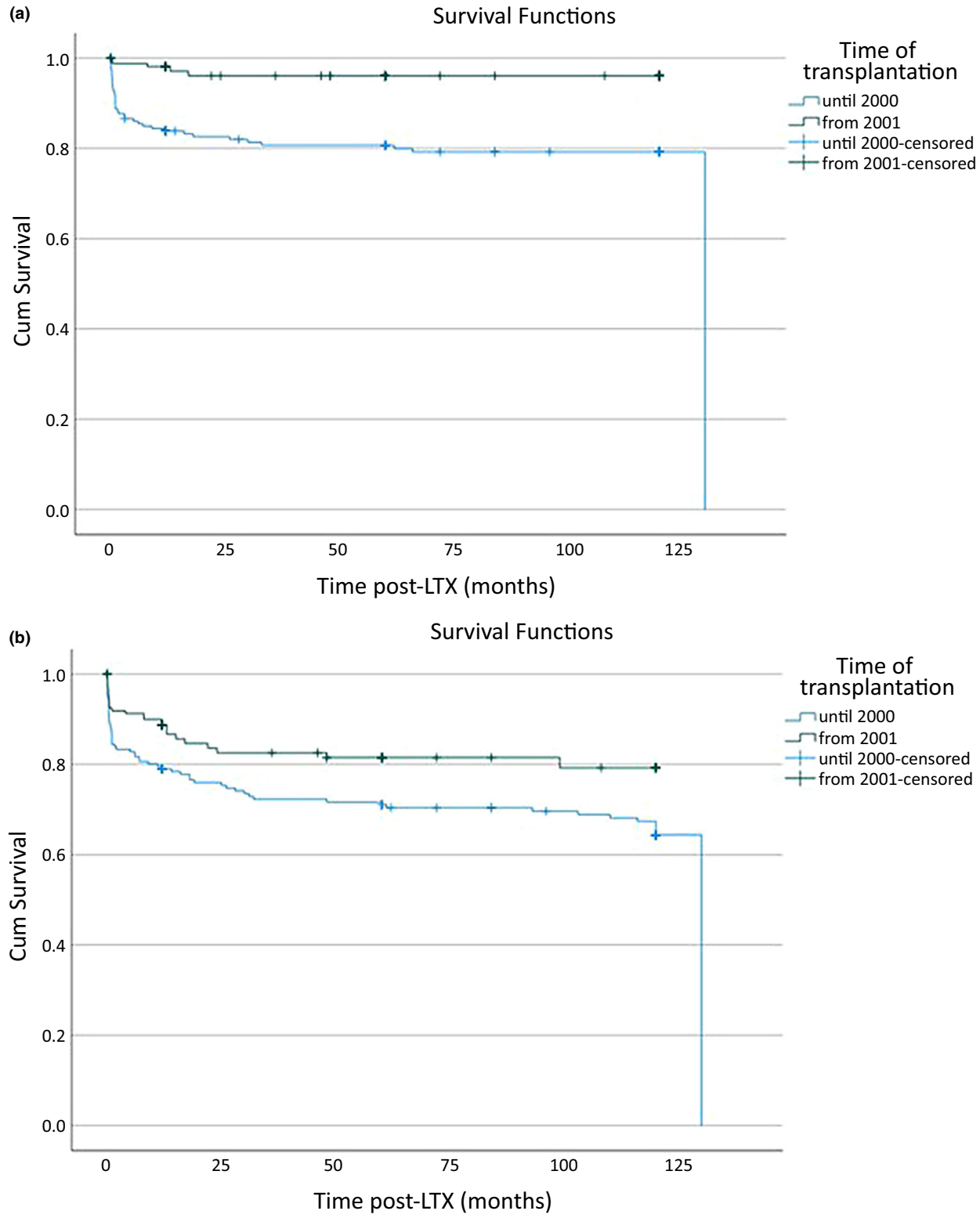

Figure 3 (a) Patient survival according to time of PLT (censored). (b) Graft survival according to time of PLT, (risk strata und censoring).

In group 2, there were valid data from 83/87 children after one year, from 60/61 children after 5 years and from 42/42 children after 10 years. After one year, 51 children (61.4%) showed normal growth and 61 children (70.1%) normal weight. After 5 years, 52 children (86.6%) had normal height and 45 (73.7%) had normal

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weight, while after 10 years, 33 children (78%) had normal height and 30 (71.4%) had normal weight.

Era of PLT

The era of PLT had a significant influence on the global outcomes of both age groups. The 1-, 5- and 10-year patient survival rates increased significantly from 84.9%, 81.8%, and 79% between 1991 and 2001 to 97.5%, 96.7%, and 96.4% between 2001 and 2011 (Fig. 3a). The survival benefit was statistically significant ($P < 0.05$). Graft survival rates also increased from 81%, 72.1% and 67.7% between 1991 and 2001 to 88.1%, 82.8%, and 80.8% between 2001 and 2011 (Fig. 3b).

Predictors of patient and graft survival

There were distinct differences between groups 1 and 2, but only a few were statistically significant. Infants had a significantly higher risk of dying ($P = 0.004$) if they suffered from an infection (Fig. 4), whereas this did not apply to children older than 12 months ($P = 0.841$). However, the age factor was significant with children older than 12 months with regard to the risk of losing their graft ($P = 0.027$) independently of having an infection (Fig. 5).

There were other significant predictors of patient loss that were the same in both age groups. Children who were transplanted in the earlier decade of transplantation had a significantly higher risk of dying

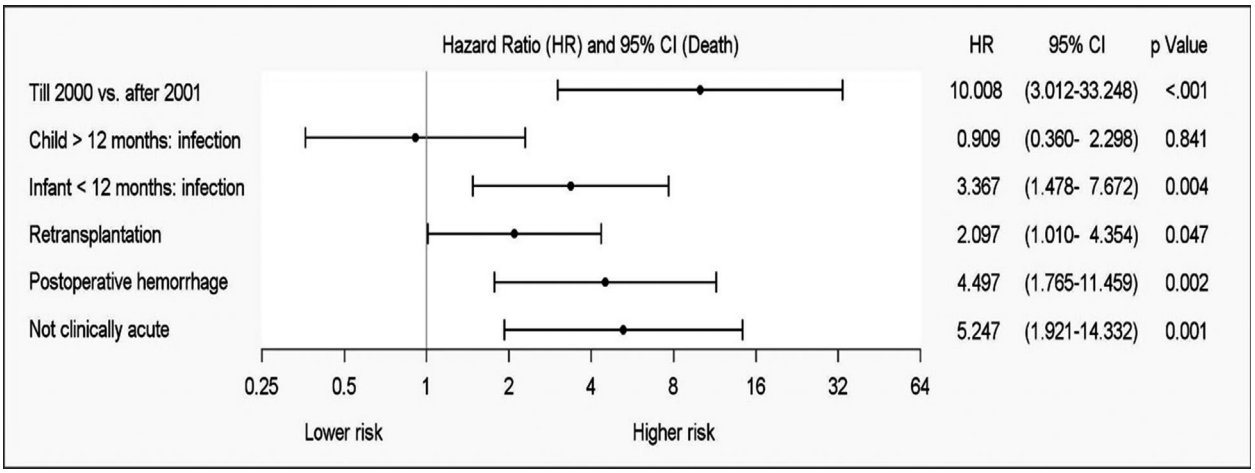

Figure 4 Significant predictors of patient loss. *Note*: "Not clinically acute" means rejections episodes later than 12 months post-liver transplantation.

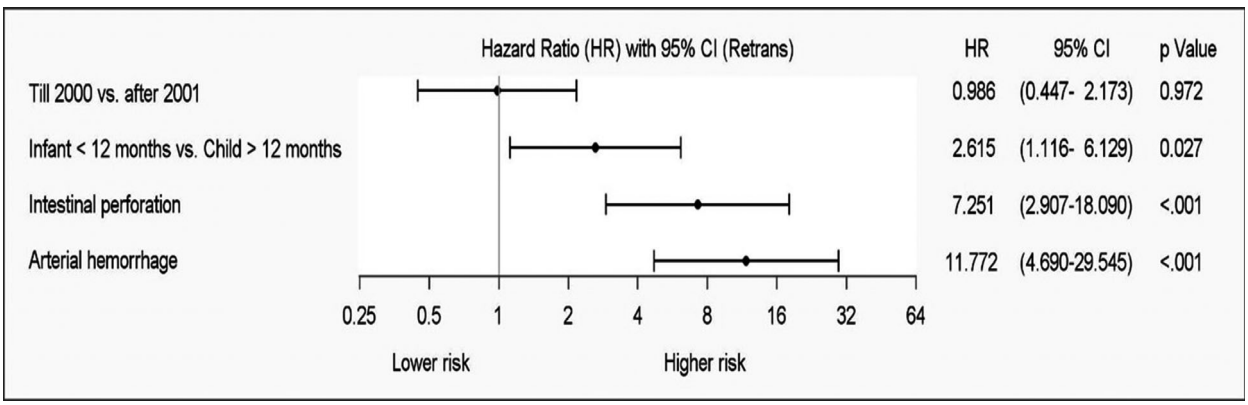

Figure 5 Significant predictors of graft loss.

($P = <0.001$) than children with PLT after 2001. Retransplantation ($P = 0.047$) and postoperative bleeding ($P = 0.002$) were also associated with a significantly higher risk of worse outcomes (Fig. 5).

Other significant predictors of graft loss were bowel perforation ($P = <0.001$) and arterial thrombosis ($P = <0.001$). Children who had these complications were at significantly higher risk of losing their grafts, independently of age (Fig. 5).

Discussion

Liver transplantation in infants is challenging in respect to transplantation procedure and perioperative care. It is still associated with an inferior outcome compared to older children in many studies [2,13,19–22]. The current study reports on our single-center analysis of PLT results in a large cohort, including infants and older children.

We demonstrated excellent 1-, 5-, and 10-year patient and graft survival rates for children undergoing PLT. The outcome for infants was comparable. There was no significant difference between infants and older children in this large cohort of pediatric patients, as seen before in preliminary studies from our center [7,23].

There are only a few studies of larger cohorts that compare outcomes in infants and older pediatric graft recipients [2,19]. Vernick *et al.* [2] also divided recipients into patients under 1 year of age and older recipients. They included all underlying diseases and compared 1-, 5-, and 10-year organ and patient survival rates of infants (75/72/68% and 79/77/75%) with those of older children. Infants had a significantly inferior survival rate than older children. The differences in patient selection can partly explain the less promising patient and graft survival rates in the Venick cohort. In both studies, the leading causes of infant patient loss were sepsis and multisystem organ failure. The most common causes of graft loss were vascular thromboses, primary nonfunction, and immunological complications. In conclusion, a significant predictor of infant graft survival in their study was age less than six months.

The group of Byun *et al.* [19] analyzed 152 pediatric recipients and recently reported 1-, 5-, and 10-year patient survival rates for infants of 93%, 92%, 90%, and 92%, 90%, 88% in older children. They concluded that survival outcome was not inferior in infants, although in infants, there were age-specific complications, for example, portal vein and hepatic artery thrombosis or PTLD that need to considered. The most significant predictor for infant graft survival was hepatic artery perfusion impairment. For older children, significant predictors for patient survival were retransplantation and fulminant hepatic failure as underlying disease, which were also significant predictors for graft survival. These results are partly similar to ours.

As in other studies [24–26], the most common indication for PLT in our study group was biliary atresia in both age groups. Some reports suggest a superior outcome of PLT in patients with cholestatic liver diseases compared to patients with fulminant hepatic failure [2]. As the inclusion criteria were the same in both groups in our study biliary atresia was the main reason for PLT in all age groups, the pre-LT diagnosis was not a significant predictor of patient or graft survival in our study cohort. This is consistent with the findings of other groups [16].

Because of the high death rate in infants on the waiting list in the past, various modalities have been developed to expand the donor pool, especially for smaller recipients. The different graft types; for example, reduced-size, living-related-, or split-liver allografts and their effect on the outcome of PLT have been described by different authors [2,7,16,27–29]. Infants tend to have a better survival rate with living-related donor grafts than older children because of the shorter waiting time and shorter ischemic time than with deceased donor graft transplantation [11,19]. Kim *et al.* [28] reported higher survival rates with living-related donor grafts than with reduced-size organs, but no significant difference between these and split-liver organs. In our study cohort, most of the infants received living-related organs, whereas children older than 12 months mainly received organs from deceased donors. Looking at all types of grafts in both groups, there was no significant difference in patient survival between the types of organs. (This might be a result of a learning effect over the years with the use of different types of graft.)

Surgical complications are reported to occur with a higher incidence in infants due to the small size of organs and blood vessels [18–20]. In our study, complications such as postoperative bleeding, biliary complications, perfusion disorders, or bowel perforation were indeed seen more often in infants. About 12.1% of our infants suffered from postoperative bleeding, whereas this complication was only seen in 5.1% of the older children. However, postoperative bleeding appeared to be a significant predictor ($P = <0.002$) of patient survival in both groups of children. Biliary complications were also seen more often in infants, but were also the most frequent surgical complications in older children

(7.8%). Interestingly, biliary complications had no effect on the outcome of either group. This is different from the situation with vascular complications. As described before, hepatic artery thrombosis (HAT) still remains one of the main reasons for graft loss among pediatric recipients [2,12,21,23,29,30], especially in small recipients [24]. However, the incidence of HAT has steadily declined with technological advances, reducing the rate to 5–10% in large pediatric liver transplant programs [17,19,25,30–32]. In our study population, vascular complications appeared in 9.8% of the infants versus 5.6% in older children. The incidence of HAT was 6.9% in group 1 compared with 6.1% in group 2, which is very similar. In some cases, it led to retransplantation shortly after LT. In group 1, nine of 12 children with HAT had Kasai procedure before LT, whereas in group 2, Kasai was performed in seven out of 11 children with HAT. In summary, the incidence of HAT was not significantly higher in infants, but it is still a significant predictor of overall graft loss.

Immunosuppressive therapy can lead to specific complications, for example, opportunistic infections, PTLD, and CMV infection. The main risks for development of PTLD are EBV naïve recipients, repetitive rejection episodes and therefore intensified immunosuppression. It has already been reported that the incidence of PTLD is higher in younger recipients [19]. One reason is that most young children are EBV seronegative at the time of PLT and during primary exposure to EBV. We had a low rate of PTLD overall, probably due to rather low immunosuppression with a CsA-based regimen, but no cases at all in children older than 1 year at transplant. However, PTLD was no significant prognostic factor for survival outcome. As reported by other centers [30,33,34], early detection of EBV infection and decreasing the dosage of immunosuppressant medication is the most effective approach.

In the current study, retransplantation was necessary in 18.5% of patients after primary LT; the rate was comparable in both groups, with no significant difference. As shown by other groups, retransplantation seems to carry a high risk of death [2,19]. Whereas Byun and Venick *et al.* only reported a significantly higher risk of death after retransplantation for older children, we found no difference between the age groups in our cohort. The main reasons for re-LT were vascular complications, primary nonfunction, and chronic graft rejection. This was the same in both groups and the causes of re-LT were comparable in other centers [2,7,19,35,36].

Patient survival, especially in infant recipients, has improved significantly over the years with increasing experience in most studies [2,37]. Goss *et al.* [16] reported significantly better patient survival of infants younger than one year when transplanted after 1993 in contrast to those receiving an OLT between 1984 and 1993 (84% vs. 64%). We have already noted that the year of PLT proved to be one of the most significant predictors of patient survival [7]. Our current results confirm these data. Children transplanted before 2001 had significantly worse outcomes (1/5/10 year patient survivals of 84.9%, 81.8%, and 79%), compared to children transplanted after 2001 (1/5/10 year patient survivals of 97.5%, 96.7%, and 96.4%). The era of PLT is a significant predictor of patient survival ($P = <0.001$). We attribute this to a learning effect of a stable interdisciplinary team over many years consisting of experienced pediatric transplant surgeons, pediatric hepatologists, pediatric radiologists, and skilled intensive care staff. Standardized procedures were implemented around 2000, which might contribute to the good results.

Although graft survival rates have also improved over the years, the era of PLT is not a significant predictor for graft survival.

Conclusion

The long-term results indicate excellent outcomes of PLT for children of any age. The outcomes have improved substantially over the years. Young age and low body weight should not be regarded as a contraindication for LT.

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Conflict of interest

The authors declare no conflict of interest.

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