Prognosis of Children Undergoing Liver Transplantation: A 30-Year European Study

Ulrich Baumann, MD,[a,b,c,d,e,f,*] Vincent Karam, PhD,[d,e,*] René Adam, MD, PhD,[d,e] Constantino Fondevila, MD, PhD,[d,g] Anil Dhawan, MD,[h] Etienne Sokal, MD, PhD,[i] Emmanuel Jacquemin, MD, PhD,[j] Deirdre A. Kelly, MD,[b,c] Enke Grabhorn, MD,[f,k] Joanna Pawlowska, MD, PhD,[f,l] Lorenzo D'Antiga, MD,[f,m] Paloma Jara Vega, MD,[f,n] Dominique Debray, MD, PhD,[f,o] Wojciech G. Polak, MD, PhD,[e,p] Jean de Ville de Goyet, MD, PhD,[q,**] Henkjan J. Verkade, MD, PhD,[e,r,**] for the European Liver and Intestine Transplant Association (ELITA) and all ELTR contributing centers

abstract

OBJECTIVES: The European Liver Transplant Registry has been collecting data on virtually all pediatric liver transplant (PLT) procedures in Europe since 1968. We analyzed patient outcome over time and identified parameters associated with long-term patient outcome.

METHODS: Participating centers and European organ-sharing organizations provided retrospective data to the European Liver Transplant Registry. To identify trends, data were grouped into consecutive time spans: era A: before 2000, era B: 2000 to 2009, and the current era, era C: since 2010.

RESULTS: From June 1968 until December 2017, 16 641 PLT were performed on 14 515 children by 133 centers. The children <7 years of age represented 58% in era A, and 66% in the current era (P <.01). The main indications for PLT were congenital biliary diseases (44%) and metabolic diseases (18%). Patient survival at 5 years is currently 86% overall and 97% in children who survive the first year after PLT. The survival rate has improved from 74% in era A to 83% in era B and 85% in era C (P <.0001). Low-volume centers (<5 PLT/year) represented 75% of centers but performed only 19% of PLT and were associated with a decreased survival rate. In the current era, however, survival rates has become irrespective of volume. Infection is the leading cause of death (4.1%), followed by primary nonfunction of the graft (1.4%).

CONCLUSIONS: PLT has become a highly successful medical treatment that should be considered for all children with end-stage liver disease. The main challenge for further improving the prognosis remains the early postoperative period.

Full article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2022-057424

[a]*Hannover Medical School, Divisions of Paediatric Gastroenterology and Hepatology, Department for Paediatric Kidney, Liver, and Metabolic Diseases, Hannover, Germany;* [b]*Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom;* [c]*Liver Unit, Birmingham Women's and Children's Hospital, Birmingham, United Kingdom;* [d]*European Liver Transplant Registry, AP-HP Hôpital Paul Brousse, Research Unit "Chronotherapy, cancers and transplantation," University Paris-Saclay, Villejuif, France;* [e]*European Liver and Intestine Transplant Association, Padova, Italy;* [f]*European Reference Network TransplantChild, La Paz University Hospital, Madrid, Spain;* [g]*Department of General and Digestive Surgery, Hospital Universitario La Paz, IDIPAZ, CIBERehd, Madrid, Spain;* [h]*King's College Hospital, London, United Kingdom;* [i]*Cliniques Universitaires Saint Luc, Catholic University of Louvain, Brussels, Belgium;* [j]*Pediatric Hepatology and Liver Transplantation Unit, National Reference Centre for Biliary Atresia and Genetic Cholestasis, FILFOIE, ERN RARE LIVER, Bicêtre Hospital, Assistance Publique: Hôpitaux de Paris, University Paris-Saclay, Le Kremlin-Bicêtre; Inserm U1193, Hepatinov, University Paris-Saclay, Orsay, France;* [k]*Childreńs Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [l]*Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland;* [m]*Paediatric Hepatology, Gastroenterology, and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy;* [n]*Paediatric Hepatology Service, Coordinator ERN TransplantChild, Hospital Infantil Universitario La Paz, Madrid, Spain;* [o]*Pediatric Liver Unit and Reference Center for Biliary Atresia and Genetic Cholestasis, APHP-*

WHAT'S KNOWN ON THIS SUBJECT: Liver transplantation in children has developed into the standard effective therapy for children with otherwise untreatable liver disease. The main indications in children are biliary atresia and inherited diseases. Half of these patients are <2 years of age.

WHAT THIS STUDY ADDS: The patient survival improved to 86% at 5 years after PLT and to 97% in children who survived the first year after PLT. Over time, the outcome was better in centers with a volume of >5 PLTs per year.

To cite: Baumann U, Karam V, Adam R&00E9, et al. Prognosis of Children Undergoing Liver Transplantation: A 30-Year European Study. *Pediatrics*. 2022;150(4):e2022057424

Liver transplantation in childhood has undergone a dramatic evolution from its early pioneering days, from the introduction of effective immune suppression in the 1980s and innovative surgery in the 1990s to facing the shortage of size-matched organs to the current challenges in long-term morbidity and mortality.[1,2] Worldwide, >30 000 children and adolescents have undergone liver transplantation over the last 4 decades. Most of these patients have been registered in large continental or national scientific databases, such as the national Organ Procurement and Transplantation Network in the United States[3] and the Registry of the Japanese Liver Transplantation Society.[4]

Indications for liver transplantation (LT) in children differ profoundly from those in adults. Viral hepatitis, hepatocellular carcinoma (<1% of all indications), and alcohol toxicity play a minor or no role in pediatric liver transplantation (PLT) and, instead, early acquired cholestatic and genetic (structural or metabolic) liver disease prevail. Young children require less immunosuppression compared with older patients.[5] In addition, the recurrence of the primary disease is far less common in PLT than in adult LT. Detailed data on liver transplantation in Europe have been systematically recorded from the beginning, coordinated since 1985 by the European Liver Transplant Registry (ELTR). The registry has collected the clinical and laboratory data of virtually all liver transplant procedures in Europe. ELTR is based on the voluntary collaboration of European Liver Transplant Centers in 31 countries and is governed by the European Liver and Intestine Transplant Association. ELTR holds data on >170 000 LT procedures and is, next to the North American Organ Procurement and Transplantation Network, the largest database on liver transplantation. A recent analysis of ELTR data on donor characteristics and graft outcome in PLT has shown that graft survival is excellent, with a current half-life of >31 years.[6] Excellent graft outcome has also been reported by the Japanese Liver Transplantation Society on 3347 children in whom overall graft survival at 30 years was 75.4%.[7] Single-center reports like the one from France with 79% 20-year patient and 64% graft survival in 128 children further confirm the good outcome.[8] One can only speculate as to what extent this long graft survival further improves long-term patient outcome; we, therefore, hypothesized that patient outcome, as documented in ELTR, will have significantly improved beyond long-term graft survival. The objective of this study is to describe the patient characteristics and indications for transplantation in the largest cohort of (European) patients who have undergone PLT. We also identified parameters associated with improved long-term patient outcome.

METHODS

European Liver Transplant Registry Database

ELTR encompasses both retrospective and prospective data collection. Data requested include a specified set of variables which is reviewed and redefined at regular intervals by the European Liver and Intestine Transplant Association board. Clinical, laboratory, and outcome data are provided by individual health care providers performing LT in Europe and are supplemented by data interface to the European organ-sharing organizations (OSOs) (ie, National Health Service Blood and Transplant for the United Kingdom, the Spanish Organizacion Nacional de Transplantes, Eurotransplant Foundation, etc).[9] Data are included from Belarus, Georgia, and Azerbaijan. Follow-up data are provided by transplant centers at regular intervals, including such events as retransplantation and death. Registered data are retrospectively monitored by ELTR staff at regular intervals.[10]

ELTR centers are required to regularly update the follow-up of their patients (date of latest news, date of graft loss and its cause, date of death and its cause) whether in their national database, which serves as the source of the ELTR data or for centers that do not have an OSO, by directly reporting the follow-up in our secure platform. If the patient is lost to follow-up, the national mortality registers are requested either by the centers or by the study nurses relocated by certain OSOs.

Within Europe, ELTR documentation of LT patients is estimated to be as high as 95%; data obtained from the ELTR database can thus be described as quality-controlled and representative of past and current practices in Europe.

Study Population

We have included data on all patients registered with ELTR from 1968 to December 31, 2017 who underwent PLT before their 18th birthday. No exclusion criteria were applied. For this retrospective cohort study, data were extracted from the ELTR database by using a limited prespecified set of pseudoanonymized patient characteristics, including patient age, sex, anthropometry, diagnosis of liver disease, indication for PLT, transplant center volume, patient survival, and cause of mortality.

Study Design and Analysis Plan

From May 1, 1968 until December 31, 2017, 16 641 PLT procedures were performed in 14 515 patients <18 years of age. To identify changes over time, we separated the data into 3 consecutive timespans,

each encompassing similarly sized patient cohorts: era A: before 2000 (n = 4482), era B: 2000–2009 (n = 4972), and era C: since 2010 (n = 5061). Each era has specific characteristics and therefore provides a homogenous overview. Era A, the historical period, was the era in which the procedure was novel and experimental. Era B was primarily characterized by surgical innovation and the wider application of the surgical split technique. In Era C, PLT had become a standard treatment modality, with the focus on reduction of long-term morbidity and mortality and improvement of the quality of posttransplant life. For analysis and discussion, the latter era (C) is considered as describing current clinical practice.

Data Management and Statistical Analyses

The plausibility of the dataset extracted for this study was checked by ELTR staff and the authors of this manuscript. Follow-up for each individual patient included the time from first LT to last recorded visit at the transplant center or death. Patient survival time was defined as the time between first LT and death. Censoring due to loss of follow-up in ELTR documentation was assumed to occur at random. Retrospective data monitoring has shown that an average of 5% of data are incomplete, with a discrepancy rate of 2.5%.

For each variable, we only used data that were complete, with no data imputation for statistical analysis. Statistical analysis was performed by using StatView version 5.0 (SAS Institute Inc, Cary). Categorical variables were summarized as frequencies and percentages, and groups were compared by using χ^2 tests, as appropriate, and Fisher's exact tests. Continuous variables are presented as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. The overall survival rate was assessed according to the Kaplan-Meier method with the log-rank test. Significance was accepted with a P value $<.05$ and 95% confidence.

RESULTS

Patients and Transplant Activity

The number of PLT increased rapidly between 1985 and 1991 and slowed thereafter until peaking at a maximum of 762 transplants in 2011. Since 2012, transplantation numbers seem to have reached a plateau (Fig 1).

The average percentage of retransplants per era has dropped considerably from 23% in era A to 14% in era B and 7% in era C (in recent years only 4%).

Age at Transplantation

ELTR data show that 66% of liver transplant procedures in era C were performed in children aged <6 years (Fig 2). Over time, liver

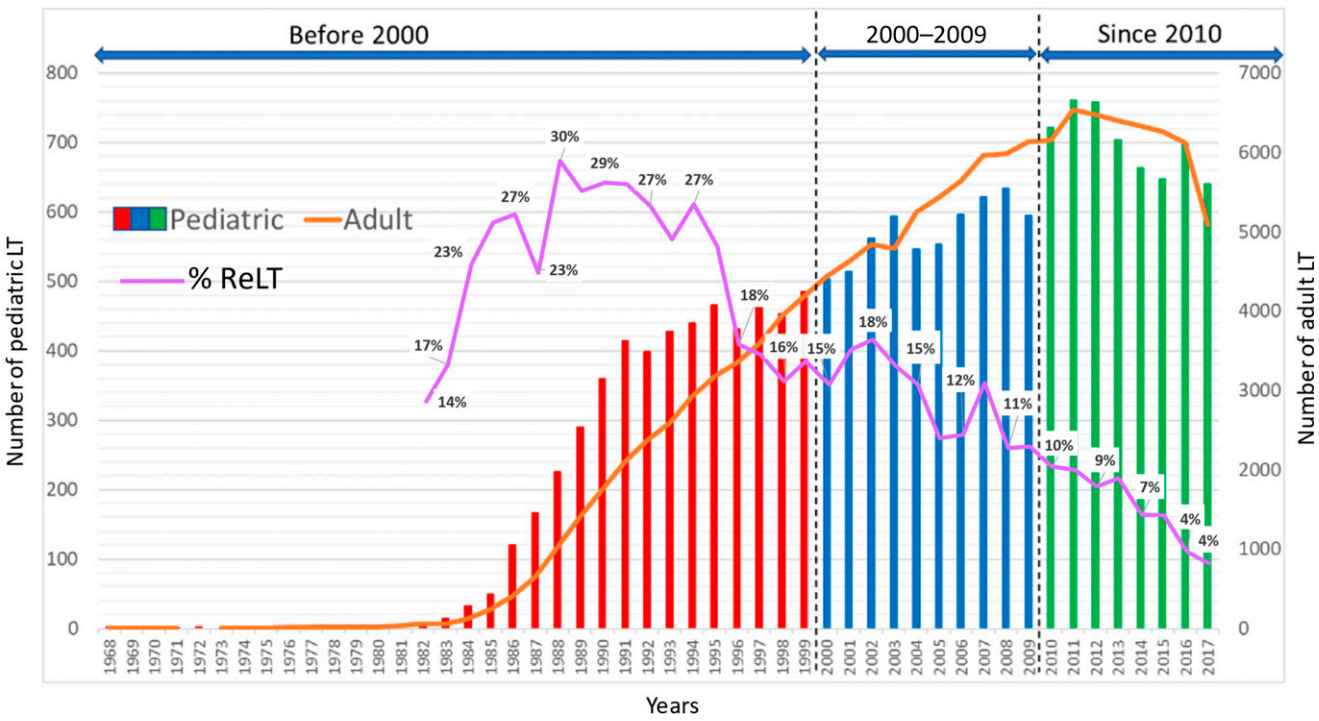


FIGURE 1

Evolution of pediatric liver transplantation in Europe. Displayed are the number of liver transplantations per year for children. Bars are grouped in era A: before 2000, era B: 2000–2009, and era C: since 2010 (see left y axis), adults (yellow line; see right y axis), and pediatric repeat transplantations in % (repeat LT; pink line). Pediatric liver transplant activity from 1968 to 2017 developed similarly to adult liver transplantation, with a peak in 2011.

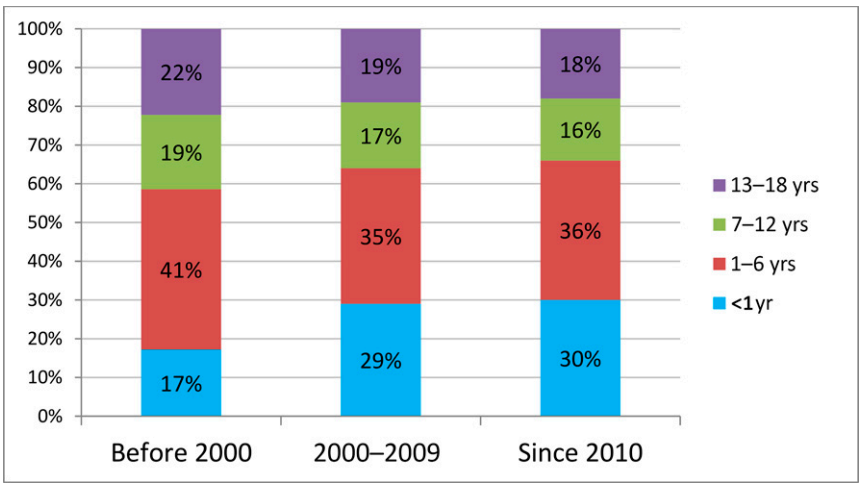


FIGURE 2

Age at transplantation. Patient age at liver transplantation is divided into 4 age groups: <1 year, 2–6 years, 7–12 years, and 13–17 years as a percentage of the total. Over time, more children <1 year of age underwent liver transplantation.

transplantation has been performed in increasingly younger patients, as shown by the decrease in the median age in years (IQR): era A: 3.97 (9.54), era B: 2.63 (9.06), and era C: 2.47 (8.20) (P <.0001). This shift to transplantation at a younger age is most apparent in the absolute and relative numbers of infants (ie, aged <1 year) undergoing PLT: era A: 17% (n = 784), era B: 29% (n = 1429), and era C: 30% (n = 1519; P <.0001). However, the difference between eras B and C is not statistically significant. Supplemental Table 4 provides supplemental information on patient and transplant characteristics.

Indications for Transplantation

The main indications for PLT are congenital biliary diseases (44%) led by biliary atresia (BA) (39%), metabolic diseases (18%), acute (ALF) or subacute liver failures (12%), cirrhosis (8%), cholestatic diseases (7%), and malignancies (6%).

BA remains the predominant indication in the 3 eras, even if the proportion compared with other indications is decreasing: n = 1761% to 41% in era A, n = 1932% to 39%

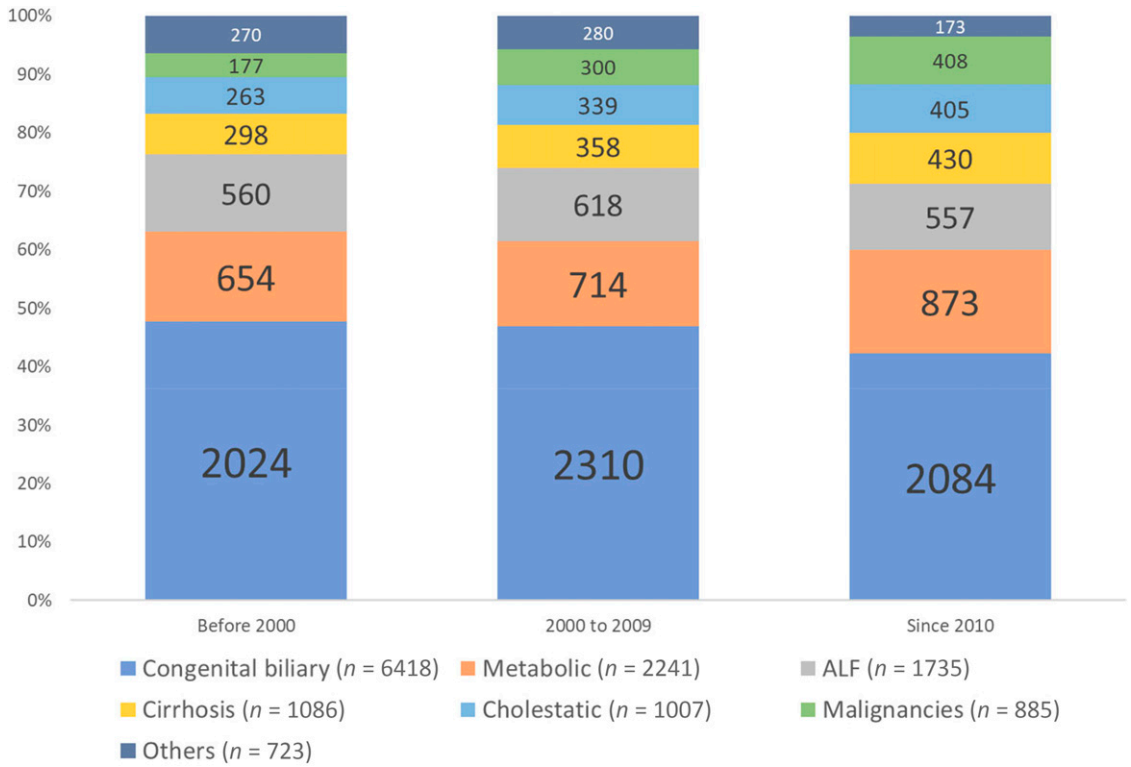


FIGURE 3

Indications for transplantation. Displayed are indications for PLT in % and in absolute numbers (n; in bars). Biliary atresia is the most common indication for liver transplantation in all observation periods. The need for liver transplantation in ALF is consistent in all 3 eras. In Europe, between 60 and 70 children require liver transplantation because of ALF each year.

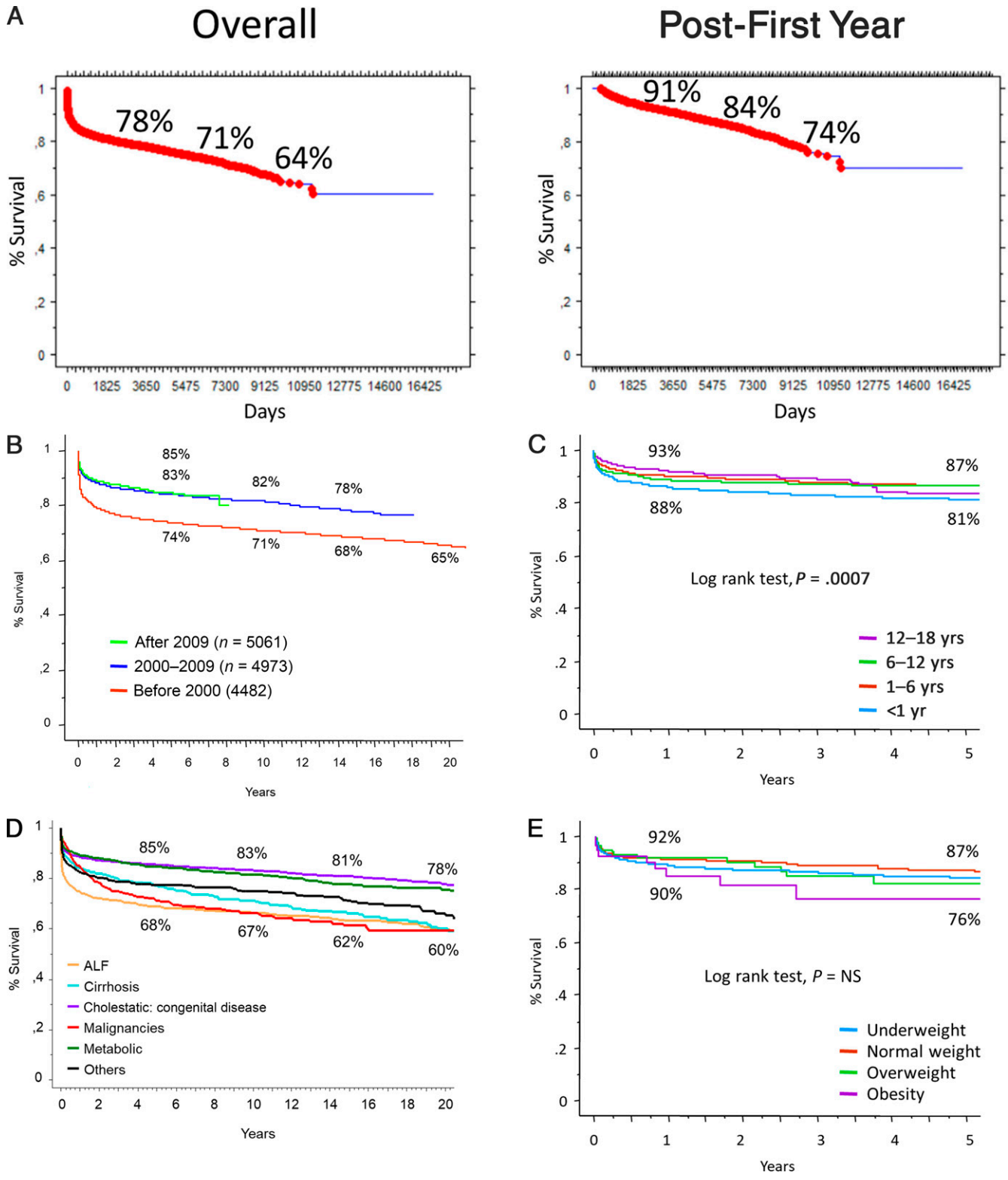


FIGURE 4

Patient risk factors for outcome. Long-term patient survival in primary LT is displayed as overall survival and (A) after exclusion of early mortality during the first postoperative year, (B) transplantation era, (C) recipient age, (D) indication for transplantation, and (E) recipient weight.

TABLE 1 Distribution of Patients and Centers According to The Number of PLT and The Age of Patients.

Center Volume, LTs/yr	Total No of PLT, *n* (%)	Total No of Centers, *n* (%)	Age of All Patients, Median (IQR)
<5	2818 (19.4)	109 (75)	7.9 (12.8)
5–10	1756 (12.1)	13 (9)	3.4 (9.4)
10–20	2521 (17.4)	9 (6)	2.3 (7.9)
>20	7420 (51.1)	14 (10)	2.4 (6.8)

in era B, and $n = 1743\%$ to 35% in era C (Fig 3, Supplemental Table 3). Other congenital biliary diseases include Alagille syndrome ($n = 334$), congenital hepatic fibrosis ($n = 134$), and Caroli disease ($n = 62$). The heterogeneous group of progressive familial intrahepatic cholestasis (in ELTR often labeled as Byler's disease) was the underlying condition for PLT in 262 cases.

Metabolic liver diseases, accounting for 18% of cases overall, is led by Wilson disease ($n = 382$), α-1-antitrypsin deficiency ($n = 320$), primary hyperoxaluria ($n = 188$), cystic fibrosis ($n = 154$), and tyrosinemia Type I ($n = 131$).

The need for PLT in ALF, accounting for 12% of cases overall, has been stable over eras A and B (13%) and decreased to 11% in era C. Only a small proportion of patients was transplanted for acute viral hepatitis ($n = 128$), the majority of those being

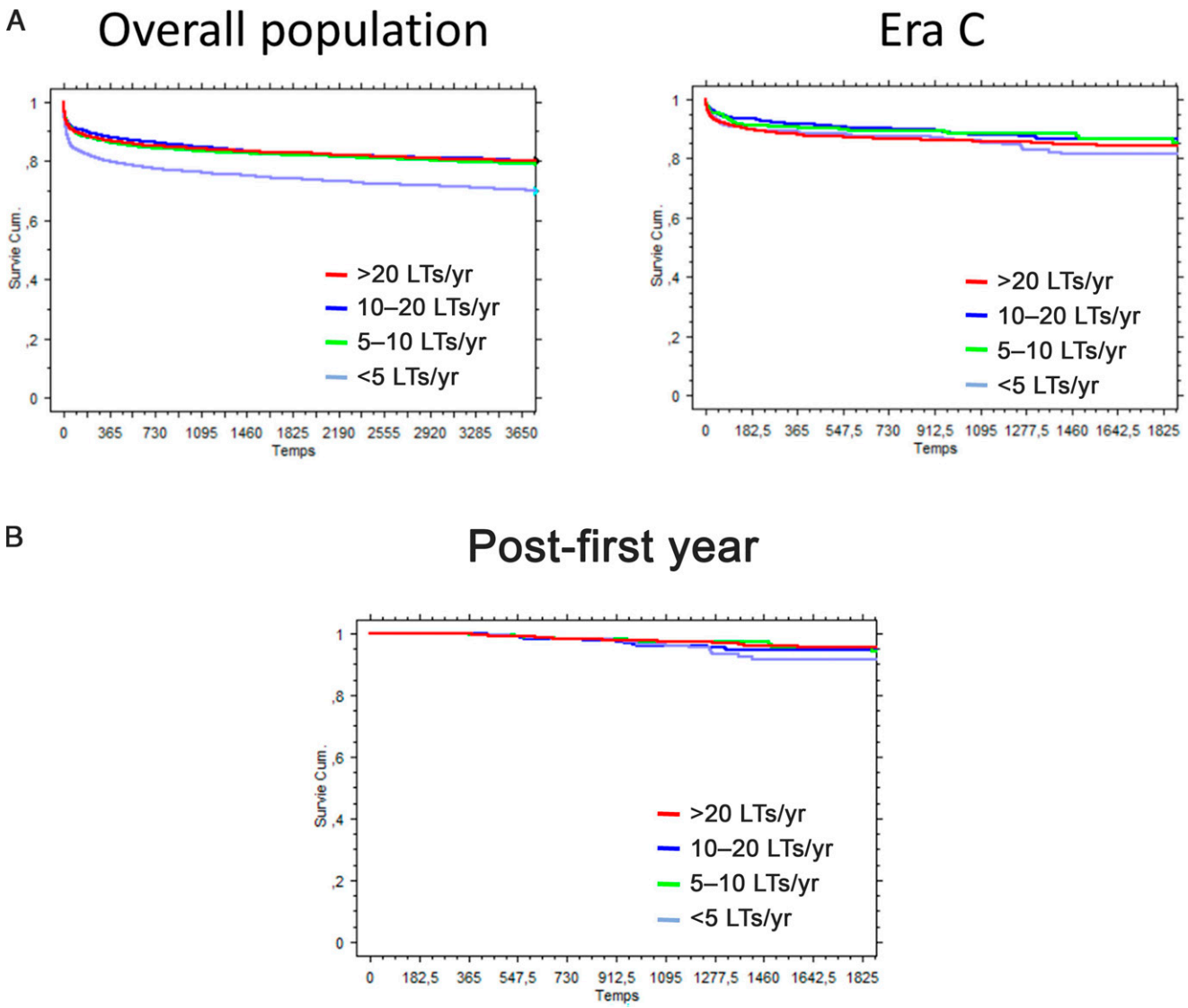
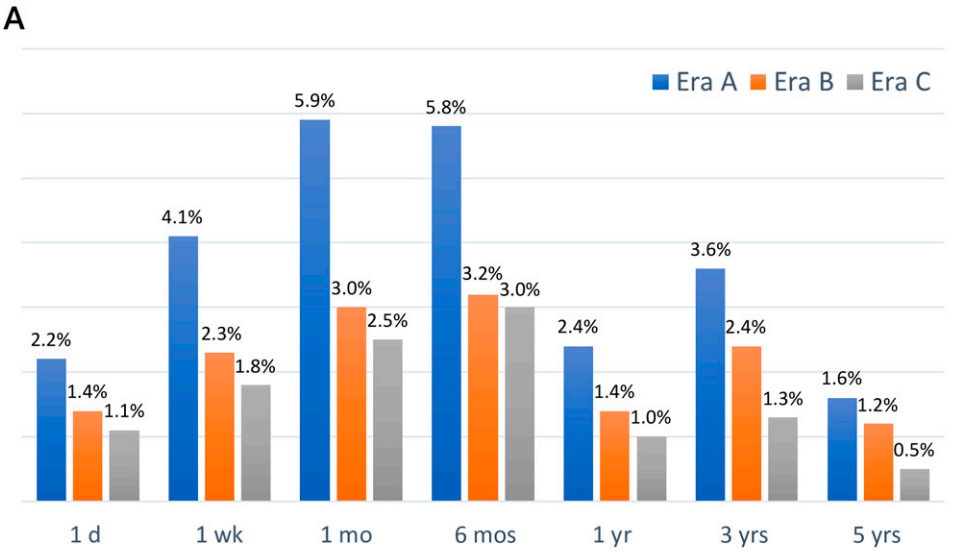


FIGURE 5

Patient survival depending on transplant center volume. Patient survival is displayed over the entire observation period from 1968 to 2017 and (A) compared with patient outcome in era C. Overall patient outcome is better in centers with >5 PLT/year. This difference is no longer detectable in the most recent data. There is also no difference after (B) excluding early perioperative mortality in the first year after transplantation.



Cumulative incidence

	1 d	1 wk	1 mo	6 mos	1 yr	3 yrs	5 yrs
Era A	2%	6%	12%	18%	20%	24%	26%
Era B	1%	4%	7%	10%	11%	14%	15%
Era C	1%	3%	5%	8%	9%	11%	11%

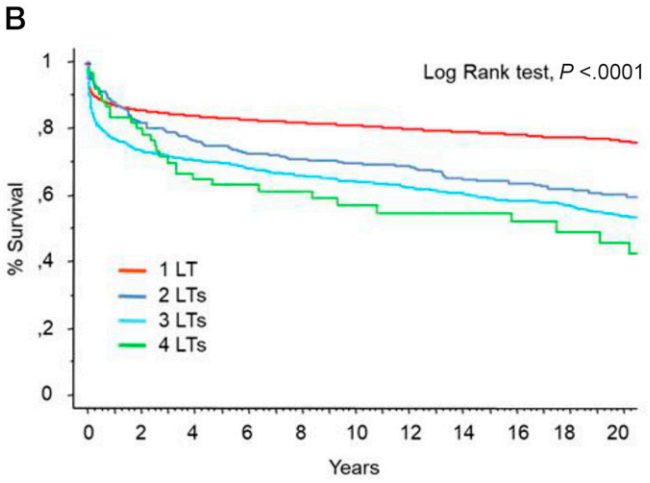


FIGURE 6
Cause of death. Mortality after PLT decreased in all eras but was still high in the first 6 months after PLT. (A) Repeat PLT decreases long-term survival and is poorer with each further transplant procedure. However, even after 4 transplants, (B) long-term survival of >20 years was observed.

for hepatitis A (n = 87, data not shown). The underlying cause of ALF in children requiring PLT was unidentified in approximately half of the cases.

Autoimmune liver disease accounts for 559 elective PLT (excluding ALF) in the 3 eras, equally split between primary sclerosing cholangitis (n = 269) and cirrhosis in autoimmune hepatitis (n = 290). The incidence rate was similar in eras A (4.2%) and B (4.1%) but dropped in era C (3.7%).

Increasing numbers of PLT have been recorded for hepatic malignancy. In eras A and C, the relative figures have doubled (from 4.2% to 8.2%; P <.001). Overall, hepatoblastoma was the main indication for oncological PLT (n = 399), followed by hepatocellular carcinoma (HCC) (n = 189).

Indications for transplantation that have relatively decreased in the 3 eras are α-1-antitrypsin deficiency

TABLE 2 Proportion of Deaths and of Different Causes of Mortality in The 3 Time Periods.

	All Population *n* (%)	Before 1999 *n* (%)	2000–2009 *n* (%)	Since 2010 *n* (%)
Patients	14 515	4482	4972	5061
Deaths	2944 (20)	1498 (33)	870 (17)	576 (11)
Cause of death				
Infection	589 (4.1)	298 (6.6)	180 (3.6)	111 (2.2)
PNF	205 (1.4)	93 (2.1)	66 (1.3)	46 (0.9)
Cardiovascular	115 (0.8)	38 (0.8)	37 (0.7)	40 (0.8)
Pulmonary	150 (1.0)	67 (1.5)	47 (0.9)	36 (0.7)
Vascular	138 (1.0)	57 (1.3)	47 (0.9)	34 (0.7)
GI	125 (0.9)	70 (1.6)	24 (0.5)	31 (0.6)
Rejection	147 (1.0)	100 (2.2)	25 (0.5)	22 (0.4)
Tumor	169 (1.2)	80 (1.8)	68 (1.4)	21 (0.4)
Cerebrovascular	122 (0.8)	66 (1.5)	35 (0.7)	21 (0.4)
Others hep	190 (1.3)	97 (2.2)	57 (1.1)	36 (0.7)
Intraoperative	73 (0.5)	35 (0.8)	29 (0.6)	9 (0.2)
Renal	33 (0.2)	14 (0.3)	14 (0.3)	5 (0.1)
Recurrence	49 (0.3)	27 (0.6)	19 (0.4)	3 (0.1)
Biliary	23 (0.2)	8 (0.2)	12 (0.2)	3 (0.1)
Social	19 (0.1)	12 (0.3)	6 (0.1)	1 (0.02)
Other	279 (1.9)	204 (4.6)	45 (0.9)	30 (0.6)
Missing	518 (3.6)	232 (5.2)	159 (3.2)	127 (2.5)

GI, gastrointestinal.

(n = 129% to 3%, n = 114% to 2.3%, and n = 77% to 1.6%, respectively; P <.001) and progressive familial intrahepatic cholestasis (n = 101% to 2.4%, n = 93% to 1.9%, and n = 68% to 1.4%, respectively; P = .002).

Outcome

Considering the entire study period, crude survival at 10, 20, and 30 years was 78%, 71%, and 64%, respectively. These survival rates reached 91%, 84%, and 74% in children who survived the first year after PLT (Fig 4A). Current 5 year patient survival (era C) for primary PLT is 86% and 97% for those children surviving the first year after transplantation and is better than after repeat LT (68% and 86%; P <.0001; data not shown).

Patient survival after PLT is sensitive to complex confounding factors, such as the era of transplantation (Fig 4B). Patient survival improved up to 2009 but has only marginally increased in the last decade.

Overall, children <1 year of age had a less favorable 5 year survival rate (81%) compared with the older age groups (Fig 4C). Patients aged 1 to 12 years had the best long-term outcome.

Overall, the group of congenital and acquired cholestatic diseases, including BA, had the best long-term results. Despite important progress in survival over time, long-term transplantation outcome has remained the lowest in ALF (5 year survival: 68%) and hepatic malignancy patients (5 year survival: 72%) (Fig 4D).

Regardless of age, long-term patient outcome was also associated with patient body mass index (BMI) at PLT. Underweight patients (BMI ≤18.5) represented 74%, and overweight patients (BMI >25) represented only 4%, of which 1% were obese (BMI >30). Obesity had a significant negative impact on long-term survival (P = .03) in contrast to being underweight (Fig 4E).

We also analyzed the possible relationship between transplant activity and outcome by center. Over the entire observation period, more than half of all PLT (51.1%) were performed in 14 (10%) centers, which had the highest volume (>20 PLT/year) (Table 1). Low-volume centers (<5 PLT/year) represented 75% of all centers but collectively had performed only 19% of PLT with a decreased survival when compared with medium- and high-volume centers (74% vs 83% at 5 years; P <.0001) (Fig 5A). This difference also appears when assessing the long-term outcome of children who survived the first year after transplantation (93% vs 96% at 5 years; P <.0001) (Fig 5B). In the current era, however, survival rates for all patients equalized in all centers irrespective of volume (P = not significantly different). Only 5 year-outcomes of children aged <2 years were worse in low-volume centers performing <5 PLT per year compared with larger-volume centers (Supplemental Fig 7).

Incidence of Mortality and Cause of Death

The numbers in Fig 6A represent the mortality over time after PLT in the percentage of patients transplanted (time zero). Mortality was highest in the early post-LT period (<6 months) in all eras. However, compared with era A, the incidence of mortality has almost halved in the most recent eras, over the whole timespan up to 5 years after transplantation.

Overall, the main causes of death up to 5 years after transplantation were infection (4.1%), primary nonfunction of the graft (PNF) (1.4%), and cardiovascular complications (0.8%). This ranking of causes of death has not changed over time (Table 2). Infection has remained the predominant cause of death after PLT in all 3 eras since 1968. However, the rate of infection (6.6%, 3.6%, and 2.2%) and PNF (2.1%, 1.3%, and 0.9%) have decreased, as have tumor-related (1.8%, 1.4%, and 0.4%) and

intraoperative (0.8%, 0.6%, and 0.2%) causes.

Finally, we studied the results of retransplantation. The data indicate that the number of retransplantations per patient is associated with decreasing patient survival ($P < .0001$) (Fig 6B). The 5-year patient survival rate is 83% after the first PLT, 75% after the second PLT, 70% after the third PLT, and 65% after the fourth PLT. Mortality is high during the first 5 years after the fourth PLT but after this period, long-term outcome of 20 years stabilized at 46% survival. (Supplemental Tables 3 and 4)

DISCUSSION

In Europe, between 1968 and 2017, 14 515 children underwent liver transplantation as a long-term treatment of end-stage liver disease, acute liver failure, unresectable liver tumors, or life-threatening metabolic diseases. During this time, PLT continuously developed further from era A to C and into the future, and permanent changes in the field positively impact improved patient outcome. Examples of this are improved graft survival or the systematic decrease in early (perioperative) and late (medical) mortality (Fig 6A). In the majority of children, PLT was performed below school age, and the most common indication for liver transplantation in childhood continues to be BA. Currently, in the era since 2010, 5 year survival (including all reporting European countries, recipient age groups, and indications) is 86% and 97% when immediate transplant-related complications are filtered out and only children surviving the first year are analyzed. Moreover, in the entire group of children from 1968, 74% of children survived >30 years. This figure closely matches data from the United States (projected 30-year patient survival: 80.1%)[11] and provides a reassuring prognosis to children undergoing transplantation today. This excellent outcome also reveals that PLT should be considered the standard therapy for all children with end-stage liver disease or otherwise untreatable liver conditions.

Of note, there is a shift to PLT at an earlier age from era A to era B, which was maintained in era C, and which was illustrated in particular by the increasing absolute numbers of infants undergoing LT over the eras. This may be explained by earlier diagnosis and referral and better surgical utilization of suitable grafts, including those obtained from living donors. Catch-up growth, improvements in bone density, and quality of life, with excellent long-term survival favor early transplantation.[12] The advantages of earlier PLT in chronic cholestasis are further backed by reports on increasing neurocognitive dysfunction in children with persistent hyperbilirubinemia awaiting liver transplantation.[13] A recent analysis also favors PLT at a younger age because graft survival in these children was better compared with children aged >12 years.[6] Our own analysis of present data in children <1 year of age show slightly worse outcomes as compared with children aged 1 to 12 years. A recent study from Norway[14] reveals young age at PLT as a risk factor for poor neurocognitive function in later life. Altogether, the optimal timing of transplantation in its complexity remains controversial. Individual patient needs and center experience will likely determine practice in the foreseeable future.

As expected, the single most common indication for PLT was BA. The relative decrease in the last decade may be explained by expanding the transplant indication for some metabolic or malignant liver diseases. Improving oncological care led to a better selection of patients with hepatoblastoma.[15] Rescue transplantation for hepatoblastoma is still generally being avoided, but recent evidence suggests further improvement from advances in chemotherapy[16] and transplant surgery.[17] Similarly, a recent ELTR analysis of childhood HCC has revealed the superior outcome of PLT compared with LT for HCC in adults.[18]

The overall survival in metabolic liver disease is not as good as in BA or other cholestatic liver diseases. Metabolic conditions are a heterogenous entity and outcome will depend particularly on the persistence of disease-specific extrahepatic manifestations after PLT (ie, in tyrosinemia type I,[19] Niemann Pick disease type C,[20] maple syrup urine disease,[21] or cystic fibrosis).[22]

OVERALL PATIENT SURVIVAL

Although patient survival after PLT has improved significantly after 2000 compared with previous decades, it appears that there has been no further improvement since. This observation is different from a recent report from the United Network for Organ Sharing database.[23] In our analysis there was, however, an important change in case mix during the last decade, with a larger proportion of young children. The well-known high mortality rate in young children on the waiting list with a Pediatric End-Stage Liver Disease score of >20[24] may be the reason for the stable survival rate over the last decade. In this case, the survival plateau over the last 2 decades is a "mirage effect" and may be explained by a higher proportion of younger and/or sicker patients receiving PLT, although better surgical and medical care is provided, leading to overall similar survival figures as in the recent eras, 2000 to 2009 and 2010 to 2017. Of note is the poorer long-term outcome of high-BMI children

in whom vascular and immune mediated morbidity may be increased (Fig 4E). However, we are conscious that high BMI in these children may not necessarily correspond with obesity because gross ascites or organomegaly can contribute to body weight.

The present analysis indicates that, overall, a relatively small PLT center size (<5 PLT/year) is associated with decreased survival after PLT compared with higher-volume centers (Fig 4B). In the most recent era, this difference did not reach statistical significance. These data do not draw conclusions on the optimum size of a transplant center. Centralization and a minimum center size have a number of advantages in the provision of a comprehensive medical service, with specific expertise in the associated specialties of interventional radiology, histopathology, and intensive care. A further detailed analysis, including patient-related factors, would be needed to test whether a minimum-sized center could be reasonably supported by these data.

In conclusion, this analysis suggests that PLT today is likely to lead to long-term survival over decades. The permanent improvement of surgical and medical management in reducing transplant-associated comorbidity has led to the transplantation of younger children with evermore complex illnesses but nevertheless in sustaining or even further improving high survival rates. This has several consequences:

(1) Children (and their families) today can expect to survive to independent adult life, including postgraduate education, work, and family life and need to develop sufficient self-management skills for adulthood.
(2) Equally, medical professionals need to identify emerging new risk factors in such long-term survivors. We are still learning about the impact, for example, of cardiovascular comorbidity in these patients.[25]
(3) Medical professionals should consider this treatment modality as a standard treatment for all children whose life-threatening liver disease cannot be treated otherwise.

ACKNOWLEDGMENTS

The organ-sharing organizations, the French ABM (Sami Djabbour), the Dutch NTS (Maaike de Wolf), the Eurotransplant Foundation (Marieke Van Meel), the Spanish RETH (Gloria de la Rosa), the UK-Ireland NHSBT (Daynes Michael), and the Scandiatransplant (Ilse Duus Weinreich), are acknowledged for the data cross-check and sharing with the ELTR.

ABBREVIATIONS

ALF: acute liver failure
BA: biliary atresia
BMI: body mass index
ELTR: European Liver Transplant Registry
HCC: hepatocellular carcinoma
IQR: interquartile range
LT: liver transplantation
OSO: organ-sharing organizations
PLT: pediatric liver transplantation
PNF: primary nonfunction of the graft

Hôpital Necker, Université de Paris, Paris, France; [p]Department of Surgery, Division of Hepatopancreatobiliary and Transplant Surgery, Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands; [q]Department for the Treatment and Study of Pediatric Abdominal Diseases and Abdominal Transplantation, ISMETT, Palermo, Italy; and [r]Dept. of Pediatrics, Beatrix Children's Hospital/University Medical Center Groningen, University of Groningen, ERN RareLiver, Groningen, The Netherlands

** Contributed equally as co-first authors.*

*** Contributed equally as co-senior authors.*

Drs Baumann, de Ville de Goyet, Karam, and Verkade conceptualized the research idea, defined the research design, analyzed the data from the registry, and drafted the manuscript; Drs Adam, Fondevila, Dhawan, Sokal, Jacquemin, Kelly, Grabhorn, Pawlowska, D'Antiga, Jara Vega, Debray, and Polak critically revised the manuscript and commented on the analysis; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

A complete list of participating centers appears in the Supplemental Information.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2022-057753.

DOI: https://doi.org/10.1542/peds.2022-057424

Accepted for publication Jun 14, 2022

Address correspondence to Ulrich Baumann, Hannover Medical School, Div of Pediatric Gastroenterology and Hepatology, Dep of Paediatric Kidney, Liver, and Metabolic Diseases, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. E-mail: baumann.u@mh-hannover.de

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FUNDING: No external funding.

CONFLICT OF INTEREST DISCLOSURES: The authors have indicated there are no potential conflicts of interest relevant to this article to disclose.

REFERENCES

1. Vimalesvaran S, Souza LN, Deheragoda M, et al. Outcomes of adults who received liver transplant as young children. *EClinicalMedicine*. 2021;38:100987
2. Perito ER, Persyn E, Bucuvalas J, et al. Graft fibrosis over 10 to 15 years in pediatric liver transplant recipients: multicenter study of paired, longitudinal surveillance biopsies. *Liver Transpl*. 2022;28(6):1051–1062
3. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2017 annual data report: liver. *Am J Transplant*. 2019;19(Suppl 2):184–283
4. Umeshita K, Eguchi S, Egawa H, et al. Liver transplantation in Japan: registry by the Japanese Liver Transplantation Society. *Hepatol Res*. 2019;49(9):964–980
5. Ganschow R, Broering DC, Nolkemper D, et al. Th2 cytokine profile in infants predisposes to improved graft acceptance after liver transplantation. *Transplantation*. 2001;72(5):929–934
6. de Ville de Goyet J, Baumann U, Karam V, et al; European Liver, Intestine Transplant Association. European Liver Transplant Registry: donor and transplant surgery aspects of 16,641 liver transplantations in children. *Hepatology*. 2022;75(3):634–645
7. Kasahara M, Umeshita K, Eguchi S, et al. Outcomes of pediatric liver transplantation in Japan: a report from the registry of the Japanese Liver Transplantation Society. *Transplantation*. 2021;105(12):2587–2595
8. Martinelli J, Habes D, Majed L, et al. Long-term outcome of liver transplantation in childhood: a study of 20-year survivors. *Am J Transplant*. 2018;18(7):1680–1689
9. Adam R, Karam V, Cailliez V, et al; European Liver and Intestine Transplant Association (ELITA). 2018 annual report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation. *Transpl Int*. 2018;31(12):1293–1317
10. Karam V, Gunson B, Roggen F, et al; European Liver Transplant Association. Quality control of the European Liver Transplant Registry: results of audit visits to the contributing centers. *Transplantation*. 2003;75(12):2167–2173
11. Bowring MG, Massie AB, Chu NM, et al. Projected 20- and 30-year outcomes for pediatric liver transplant recipients in the United States. *J Pediatr Gastroenterol Nutr*. 2020;70(3):356–363
12. Högler W, Baumann U, Kelly D. Growth and bone health in chronic liver disease and following liver transplantation in children. *Pediatr Endocrinol Rev*. 2010;7(3):266–274
13. Caudle SE, Katzenstein JM, Karpen SJ, McLin VA. Language and motor skills are impaired in infants with biliary atresia before transplantation. *J Pediatr*. 2010;156(6):936–940.e1
14. Ostensen AB, Skarbo AB, Sanengen T, Line PD, Almaas R. Impaired neurocognitive performance in children after liver transplantation. *J Pediatr*. 2022;243:135–141.e2
15. Otte JB, de Ville de Goyet J, Reding R. Liver transplantation for hepatoblastoma: indications and contraindications in the modern era. *Pediatr Transplant*. 2005;9(5):557–565
16. Uchida H, Sakamoto S, Kasahara M, et al; Japanese Liver Transplantation Society. An analysis of the outcomes in living donor liver transplantation for pediatric malignant hepatic tumors using nationwide survey data in Japan. *Transpl Int*. 2021;34(8):1408–1421
17. Uchida H, Fukuda A, Sasaki K, et al. Benefit of early inflow exclusion during living donor liver transplantation for unresectable hepatoblastoma. *J Pediatr Surg*. 2016;51(11):1807–1811
18. Baumann U, Adam R, Duvoux C, et al; European Liver and Intestine Transplant Association. Survival of children after liver transplantation for hepatocellular carcinoma. *Liver Transpl*. 2018;24(2):246–255
19. Santra S, Baumann U. Experience of nitisinone for the pharmacological treatment of hereditary tyrosinaemia type 1. *Expert Opin Pharmacother*. 2008;9(7):1229–1236
20. Yamada N, Inui A, Sanada Y, et al. Pediatric liver transplantation for neonatal-onset Niemann-Pick disease type C: Japanese multicenter experience. *Pediatr Transplant*. 2019;23(5):e13462
21. Mazariegos GV, Morton DH, Sindhi R, et al. Liver transplantation for classical maple syrup urine disease: long-term follow-up in 37 patients and comparative United Network for Organ Sharing experience. *J Pediatr*. 2012;160(1):116–21.e1
22. Flemming G, Baumann U, Richter N, et al. Survival benefits following liver transplantation: a matched-pair analysis in pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr*. 2021;73(3):385–390
23. Hickner B, Anand A, Godfrey EL, et al. Trends in survival for pediatric transplantation. *Pediatrics*. 2022;149(2):e2020049632
24. van der Doef HPJ, van Rheenen PF, van Rosmalen M, Rogiers X, Verkade HJ; Eurotransplant. Wait-list mortality of young patients with biliary atresia: competing risk analysis of a eurotransplant registry-based cohort. *Liver Transpl*. 2018;24(6):810–819
25. Memaran N, Borchert-Mörlins B, Schmidt BMW, et al. High burden of subclinical cardiovascular target organ damage after pediatric liver transplantation. *Liver Transpl*. 2019;25(5):752–762