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Research Article

Outcomes in Pediatric Liver Transplantation: A Single-Center 20-Year Experience

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Abstract

Key objectives: Liver transplantation (LT) in pediatric age is a relatively recent reality with limited information about long-term natural history. This study aimed to describe long-term outcomes in LT children followed-up for more than two decades, with particular interest to late post-transplant complications and patient survival rates. **Methods:** We conducted a single-center retrospective study including all pediatric patients who underwent LT from 1987 to 2013 and followed-up until november 2023 at the "Federico II" University Hospital of Naples. **Results:** A total of 119 patients have been enrolled with a median age at the time of LT of 1.71 years (25^{th}-75^{th} percentile: 0.73-6.14) and a median follow-up time of 23.2 years (25^{th}-75^{th} percentile: 17.9-27.5). Long-term immunosuppression-related complications included metabolic bone disease (12.6%), arterial hypertension (10.1%) and chronic kidney dysfunction (10.1%). De novo malignancies occurred in 20 patients (16.8%), mostly represented by lymphoproliferative disorders (18/20). Twenty-two re-transplantations were performed in 13 patients with a 20-year graft survival rate of 81.6%. Six deaths (5%) have been registered with a 20-year survival rate of 95%. **Conclusions:** The present study shows a good patient and graft survival rate in LT pediatric patients and confirms the less frequent onset of complications compared with the adult setting.

Keywords: Pediatrics; Liver Transplantation; Follow-up Studies; Survival Rate; Graft Rejection; Immunosuppression Therapy; Postoperative Complications.

Introduction

Liver transplantation (LT) provides life-saving therapy for children with end-stage liver disease and liver-inborn errors of metabolism. Over the last decades important advances have been made both from the surgical and clinical point of view making LT an effective and widely available treatment in children, ensuring notable results in terms of patient and graft survival rates [1-3]. Despite favorable long-term survival, patients and their families face major challenges after LT, particularly related to post-transplant complications, life-long immunosuppression and periodic follow-up [4].

Since LT in pediatric age is a now well-established reality, there is still limited knowledge about its long-term impact in terms of quality of life and chronic immunosuppression effects [5-6].

This study aims to retrospectively describe a cohort of consecutive liver transplanted children followed-up for more than two decades at the "Federico II" University Hospital of Naples and analyze the incidence of post-transplant complications (hepato-biliary, immunological, infectious, neoplastic), the adverse effects of chronic immunosuppressive therapy and the survival rates.

Patients and Methods

Study design

A single-center retrospective study was performed to evaluate the outcomes of LT children followed-up for more than 10 years at "Federico II" University Hospital of Naples in Italy.

Patients were enrolled according to the following inclusion criteria:

- Pediatric patients undergoing LT from 1987 to 2013
- Patients followed-up for at least 10 years at the Pediatric Liver Unit and then at the Hepatology Unit of "Federico II" University Hospital of Naples

Patients were included and consecutively enrolled in the study with a data collection time going from January 2022 to November 2023 from the analysis and consultation of each patients' medical record (both paper and electronic records).

Patients' follow-up was performed according to the guidelines and evidence in literature evolving over time and available at the time of patient management [7-9]. All patients were followed-up on an outpatient basis. During the first 3 months post-LT, and often up to the first year, management was shared with the Transplant Center. Data about donors, obtained through a detailed analysis of the reports received from the transplant centers, made it possible to trace the type of grafts.

In the definition of post-LT onset diseases, all events with an established causal relationship with the surgical LT procedure and/or with chronic immunosuppressive therapy were classified as complications. Instead, the diseases arising in the post-LT period that cannot be related to chronic immunosuppression and LT, but for which it is likely that there are different contributing factors were defined as comorbidities.

For each patient demographic data (sex, weight, height, Body Mass Index, date of birth, educational qualification level, employment, marital status, possible maternity/paternity status) and data about LT history (date of LT, transplant center where the surgery was performed, indication to LT, presence of any pre-transplant comorbidities, data on any post-transplant complications and schedule of immunosuppressive therapy) were collected.

Statistical analysis

The normality of data was assessed by the Kolmogorov–Smirnov test. Continuous variables were expressed as median and 25^{th}-75^{th} percentiles. Categorical variables were described as absolute frequency and percentage. Cumulative survival of patients and liver grafts was calculated with Kaplan-Meier curves. Patients' survival was computed from the date of liver transplantation until the date of death (from any cause) or last follow-up visit, while patient death and re-transplantation were considered as graft loss. Statistical analyses were performed using SPSS statistical software (Rel SPSS 21.0; IBM Corporation, Armonk, NY, USA, 2012).

Results

Current Status

Between 1987 and 2013, 119 patients underwent LT during childhood and followed-up at the University Hospital Federico II of Naples, Italy, met the inclusion criteria for being enrolled in the study. For these patients the median follow-up time was 23.2 years (25^{th}-75^{th} percentile: 17.9-27.5) with a minimum follow-up of 10 years and a maximum follow-up of 36.5 years.

The general characteristics of our population, including data about immunosuppressive therapy and post-LT comorbidities, are shown in (Table 1) and in Supplemental Digital Content.

Characteristics	Overall (n=119)
Gender, n (%)	
Male	62 (52.1)
Female	57 (47.9)
Age at enrollment, yrs (median; 25^{th}-75^{th} percentile)	26 (20.3-34.3)
< 18 years, n (%)	24 (20)
18-30 years, n (%)	49 (41)
>30 years, n (%)	46 (39)
Body Mass Index at enrollment, kg/m^2 (median; 25^{th}-75^{th} percentile)	21.75 (19.8-24.5)
< 18.5 kg/m^2, n (%)	18 (15.12)
18.5-24.9 kg/m^2, n (%)	76 (63.87)

25-29.9 kg/m^2, n (%)	19 (15.97)
> 30 kg/m^2, n (%)	6 (5.04)
Age at LT, yrs (median; 25th-75th percentile)	1.71 (0.73-6.1)
< 1 year, n (%)	43 (36.1)
1-5 years, n (%)	44 (37)
>5 years, n (%)	32 (26.9)
Indication to LT, n (%)	
Biliary Atresia	75 (63)
Liver-based metabolic defects[†]	12 (10.1)
Autoimmune liver diseases[‡]	9 (7.6)
Progressive Familial Intrahepatic Cholestasis	7 (5.9)
Alagille Syndrome	4 (3.4)
Cryptogenic cirrhosis	3 (2.5)
Acute Liver Failure	3 (2.5)
Hepatoblastoma	3 (2.5)
Other[§]	3 (2.5)
Type of graft	
Whole liver	30 (25.2)
Split liver	89 (74.8)
First line post-LT immunosuppressive drugs[¶], n (%)	
Calcineurin inhibitor	119 (100)
Antimetabolite	13 (10.9)
mTOR inhibitor	2 (1.7)
Steroids	119 (100)
Single drug, n (%)	105 (88.2)
Two or more drugs, n (%)	14 (11.8)
Long-Term Steroids (more than 6 months post-LT), n (%)	17 (4.3)
Immunosuppressive drugs at the time of enrollment[¶], n (%)	
Calcineurin inhibitor	116 (97.5)
Antimetabolite	29 (24.4)
mTOR inhibitor	5 (4.2)
Single drug, n (%)	89 (74.8)
Two or more drugs, n (%)	30 (25.2)
Steroids, n (%)	12 (10.1)
Comorbidities[‖], n (%)	

Allergic	
Urticaria and angioedema	20 (16.8)
Food allergies	19 (16)
Atopic dermatitis	6 (5)
Hematologic	
Autoimmune thrombocytopenic purpura	8 (6.7)
Polycythaemia	7 (5.9)
Neuro-psychiatric	
Intellectual disability	9 (7.6)
Sensorineural hearing loss	3 (2.5)
Generalized anxiety disorder	4 (3.4)
Major depressive disorder	3 (2.5)
Other[α]	9 (7.6)
Gastroenterological	
Crohn's disease	2 (1.7)
Coeliac disease	2 (1.7)
Endocrinological	
Hypothyroidism	3 (2.5)

Table 1: Characteristics of enrolled patients; **Note**: † Including Hemochromatosis (2 patients), Crigler-Najjar syndrome type 1 (3 patients), Glycogen storage disease type 4 (2 patients), Wilson's disease (2 patients), Lysosomal acid lipase deficiency (1 patient), Ornithine transcarbamylase deficiency (1 patient) and Long-chain fatty acids transport defect (1 patient); ‡ Including Autoimmune hepatitis (5 patients) and Primary sclerosing cholangitis (4 patients); § Including Hepatic epithelioid haemangioendothelioma (1 patient), Cytomegalovirus-associated fulminant hepatitis (1 patient) and Hepatitis C-related liver cirrhosis (1 patient); ¶ One patient can simultaneously receive more than one immunosuppressive drug, so the sum of the drugs used did not necessarily sum to 100%; ‖ One patient can have more than one comorbidity, also within the same group of diseases (e.g. Urticaria and angioedema and food allergies); α Including Epilepsy (2 patients), Language disorders (2 patients), obsessive-compulsive disorder (1 patient), Attention-Deficit/Hyperactivity Disorder (1 patient), Tremor and nystagmus (1 patient), Facial paralysis (1 patient), short-term memory loss (1 patient).

Post-LT complications

(Table 2) shows the post-transplant complications occurred in the 119 patients. Details in Supplemental Digital Content. Of note, skin neoplasms in the entire population were not observed. Post-LT liver disease recurrence was observed in 2 cases (hepatoblastoma and primary sclerosing cholangitis), while 5 patients developed de novo advanced chronic liver disease unrelated to the LT indication (2 Hepatitis C Virus-related, 1 cryptogenic, 1 case of Budd-Chiari syndrome and 1 case secondary to chronic bile duct obstruction).

Vascular complications represented the most frequent cause of graft failure (8/28, 28.6%). Hepatic artery thrombosis (2.5% of the first LT recipients) occurred in the 80% of the cases in the first 30 days, with only 1 case of late hepatic artery thrombosis (after 90 days). Instead, portal vein thrombosis occurred in the 5% of the patients and was mostly a late complication (only 2 cases in the first 30 days after LT).

Post-LT Complications	Overall (n=119)
Hepato-biliary, n (%)	28 (23.6)
Anastomotic biliary strictures	10 (8.4)
Portal vein thrombosis	6 (5)
Portal vein stenosis	4 (3.4)
Hepatic artery thrombosis	3 (2.5)
Biliary Fistulas	3 (2.5)
Bile leaks	1 (0.8)
Hepatic vein stenosis	1 (0.8)
Immunological, n (%)	68 (57.1)
Acute rejection	38 (31.9)
Chronic rejection	23 (19.3)
De novo Autoimmune hepatitis	7 (5.9)
Metabolic, n (%)	43 (36.1)
Metabolic bone diseases	
Osteopenia	10 (8.4)
Osteoporosis	5 (4.2)
Diabetes mellitus	2 (1.7)
Dyslipidemia	2 (1.7)
Arterial hypertension	12 (10.1)
Nephropathy	12 (10.1)
Infectious, n (%)†	81 (68)
Epstein-Barr virus	34 (28.6)
Cytomegalovirus	29 (24.4)
Varicella-zoster virus	15 (12.6)
Herpes-virus simplex	14 (11.8)
Candida species	4 (3.4)
Neoplastic, n (%)	20 (16.8)
PTLDs Non-Hodgkin Lymphoma	14 (11.8)
Hodgkin Lymphoma	4 (3.4)
Non-PTLDs	
Multiple rhabdomyomas	1 (0.8)
Embryonic bladder rhabdomyosarcoma	1 (0.8)
Need of re-transplantation, n (%)	13 (10.9)
Deaths, n (%)	6 (5)

Table 2: Overall complications after liver transplantation; Note: † One patient may have been affected by more than one pathogen.

Patient and graft survival

Overall, 20 years after the first liver transplantation, 113 patients were alive and 13 (10.9%) original grafts were lost. For this latter group, 7 patients underwent a single re-transplantation, and 6 patients underwent multiple re-transplantations, with a total of 22 re-transplants for 13 patients ((**Table 3)** details in Supplemental Digital Content). Numerous re-transplantations occurred during the first year (10/22, 45.4%).

Patient number	Retrasplantation number	Interval since previous transplantations (years)	Indications for retransplantation	Follow-up after last retransplantation (years), outcome
1	2	5 14	Chronic rejection Acute Liver Failure	8, alive
2	4	4 1 month 7 20 days	Portal vein thrombosis Hepatic artery thrombosis Primary Sclerosing Cholangitis recurrence Ischemic cholangiopathy	11, alive
3	1	14 days	Portal vein thrombosis	36, alive
4	1	30	Cryptogenic graft cirrhosis	2, alive
5	2	4 days 14.5	Acute rejection Cryptogenic graft cirrhosis	17, alive
6	1	21	Chronic rejection	2, alive
7	1	3	Chronic rejection	25, alive
8	1	7 days	Portal vein thrombosis	17, death (sepsis)
9	3	9 2 5	Hepato-pulmonary syndrome Degeneration of the extrahepatic biliary tract Ischemic cholangiopathy	6, alive
10	2	3 days 5 months	Hepatic artery thrombosis Hepatic artery thrombosis	20, alive
11	1	2 days	Hepatic artery thrombosis	18, alive
12	2	8 2 days	Cryptogenic graft cirrhosis Primary graft non function	9, alive
13	1	10 days	Hepatic veins stenosis associated to portal vein thrombosis	14, alive

Table 3: Outcome of 13 Children Who Underwent Retransplantation.

Out of a total of 119 patients enrolled in the study, 6 deaths were registered (5%). The death causes were quite varied: 2 patients died because of a sepsis (unrelated to immunosuppressive therapy), 1 developed a fulminant Post-Transplant Lymphoproliferative Disease (PTLD), 1 died for the complications of cirrhosis during wait-list time for liver re-transplantation, 1 died for recurrent hepatoblastoma and the last 1 due to an epilepticus status occurred during a bacterial pneumonia.

The cumulative survival rate of the patients was calculated starting from the age of liver transplant. In **Figure 1a** is reported the Kaplan-Meier survival curve of the patient cohort. Based on a median follow-up of 23.2 years, the 5-year, 15-year and 20-year patient survival rates were 100%, 96.6% and 95%, respectively.

Patient death and re-transplantation were considered as graft loss. The overall graft survival rates at 5, 10, and 20 years were 90.8%, 85.8% and 81.6%, respectively. In **Figure 1b** is reported the Kaplan-Meier survival curve of the liver grafts (Figure 1A, B).

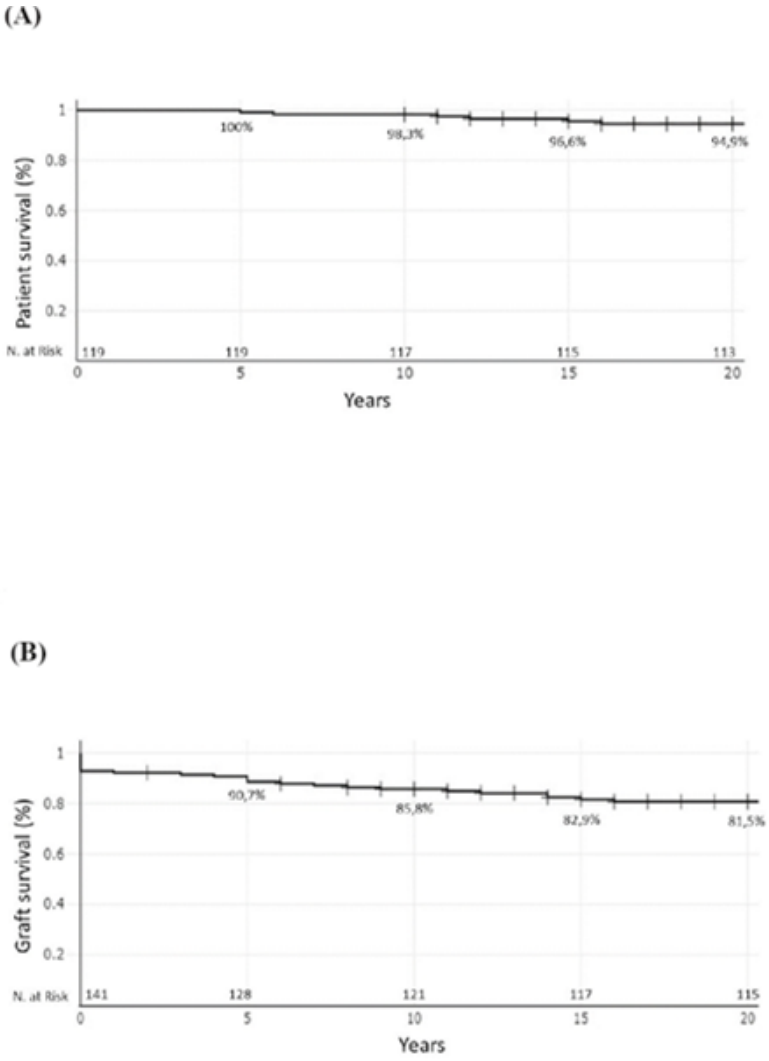

Figure (1A, B): Kaplan-Meier estimate of graft survival rate over time (A) and patient survival rate over time (B).

Discussion

Pediatric liver transplantation has a recent history and for this reason there is a lack of solid data on long-term outcomes in this special setting of patients. Currently very few studies examined such a long follow-up after pediatric LT, up to 30 years with a median time of 23.2 years, including the transition period from pediatric age to adulthood [3,6,10]. To the best of our knowledge, the present study is the largest to date analyzing long-term outcomes of pediatric liver transplantation.

As for age at LT and etiology, our population is comparable to the ones reported in literature, with biliary atresia which is confirmed to be the main cause of transplantation in pediatric age, especially for the age group up to 5 years [6,11-13]. An interesting data concerns the high prevalence of LT performed abroad in the 1980s (6/7, 85.7%) and the 1990s (27/43, 62.8%), especially when compared to the 2000s (2/69, 2.9%), showing the progressive increase of pediatric LTs performed in our country in the last 30 years.

One of the main aims of this study was to define long-term morbidity in pediatric LT recipients. Fourteen patients (11.8%) experienced complications related to bile duct reconstruction in line with Yazigi who described an average incidence of these complications in 5-25% of pediatric liver graft recipients [2]. Instead, a 2017 systematic review of literature by Karjoo et al. assessed the incidence of biliary complications between 22% to 47.3% of the patients [14].

In the studies by Elisofon et al. (2019) and Arnon et al. (2010), both reviewing data from the Society of Pediatric Liver Transplantation Registry in two different periods, the rates of acute hepatocellular rejection were in line with our study: 37.4% (within the first 6 months) and 34.7% (within the first year), respectively [12-13]. Conversely, chronic rejection rate (19.3%) in our study appears to be relatively high if compared with previous reports with an incidence rate of 5-13% [15-16]. However, the length of follow-up and the number of patients undergoing liver biopsy substantially influence this data. In fact, Fouquet et al. who performed liver biopsies 10 years post-LT in 280 children reported a chronic rejection rate of 64% [17]. Chronic graft injury represents one of the major concerns in pediatric LT as confirmed by Feng et al. highlighting that consistently normal results of liver tests may hide a spectrum of histopathology that can only be accurately exposed by tissue examination, supporting the necessity of liver biopsy to guide personalized immunosuppression decision-making [18].

We observed that the use of cyclosporine was associated with a higher incidence of rejection when compared to tacrolimus, with a significantly more pronounced gap in chronic one: 35.7% *vs* 14.7% in chronic rejection and 38.1% *vs* 31.6% in acute one. Previous studies already reported a lower incidence of rejection with the use of tacrolimus when compared to cyclosporin [19].

Another significant post-LT immunological complication is the occurrence of de novo autoimmune hepatitis. According to current literature, de novo autoimmune hepatitis occurs in the 5-10% of pediatric LT recipients and is more frequent than in adult LT setting (1-2%) [20]. Although described in pediatric recipients as a quite aggressive disease [21], none of the 7 patients (2 males and 5 females) of our cohort experienced graft loss or progression to advanced fibrosis and all of them achieved remission of the disease after corticosteroid or azathioprine-based treatment.

Considering that all patients underwent to a Calcineurin Inhibitor as first line post-LT immunosuppressive therapy and more than 97% continued this class of drugs, this study allows important considerations on long-term effects of Calcineurin Inhibitor on pediatric LT recipients. Metabolic bone diseases occurred in the 12.6% of the patients representing the most frequent post-LT metabolic complication recorded. Although the role of chronic liver disease and chronic immunosuppression in determining the reduction of bone mineral density has been widely demonstrated [7,22-23], to date few data have been collected in pediatric recipients. In the adult population a recent meta-analysis and systematic review of literature reported an incidence of osteopenia and osteoporosis after LT of 34.5% and 11.7%, respectively [24]. In children, instead, the evaluation of post-LT bone mineral density led to conflicting results. In fact, if some studies showed low bone mineral density values in pediatric LT recipients with incidence rates ranging from 6% to 15% [25-27], other ones did not demonstrate a significant decrease of this parameter over time[28]. However, none of these studies exceeded a mean post-LT follow-up time of 10 years.

Likewise, in our experience the other metabolic complications showed lower incidence and prevalence rates compared to what has been previously reported in literature. In fact, in pediatric LT patients the incidence of new-onset diabetes type II is estimated around 10% with a range of 8.0–14.1% [29]. and dyslipidemia between 7 to 57% [30], while in our cohort both diseases occurred only in less than 2% of the patients.

Arterial hypertension prevalence rate ranges from 20-28% in pediatric LT recipients [31-33]. In Italian healthy young adults (aged 18-35) and in healthy children (aged less than 18), instead, the prevalence rates are around 11% and 4-6% [34-35], respectively. Our finding of 10.2% is therefore in line with what reported in the healthy population. McLin et al. suggested the following three risk factors for the development of late-onset post-LT arterial hypertension: age at LT between 5 and 8 years, ongoing steroid exposure at the time of the last blood pressure measurement and the presence of a glomerular filtration rate below 90 ml/min/1.73m2 at the time of the last blood pressure measurement [31]. In our cohort none of the 12 patients was transplanted in that age group nor was on steroid treatment when the diagnosis

was established, while 3 of them had a reduction in glomerular filtration rate (25%). However, it should be emphasized that we considered only the defined diagnoses of arterial hypertension (with blood pressure values above the reference ranges for age, sex, and height on at least 3 occasions) while in the study cited above patients were classified as affected by arterial hypertension with a single elevated blood pressure measurement using standard automated techniques at an outpatient visit performed at 5 or up to 10 years post-LT [31].

Twelve patients (10.2%) developed chronic kidney disease (CKD) during the follow-up (glomerular filtration rate primary below 90 ml/min/1.73m^2 on at least 2 occasions 90 days apart). In the study by Martinelli et al. with a 20-years follow-up the overall incidence of CKD, stage 2 and above, was 35% [3]. Similarly, a review by Lacquaniti et al. reported a prevalence of CKD between 25 and 38% and showed that renal issues more frequently appear 5 years after LT [36]. A recent study by Lund et al. (median follow-up: 19 years) further confirms this data (prevalence of CKD at the end of follow-up: 38%) [33]. Harambat et al. in their long-term follow-up study (median follow-up: 9.3 years) identified 3 independent variables as risk factors for CKD after pediatric LT: primary liver diseases with potential renal involvement (a group including among the others Alagille syndrome, inborn error of metabolism such as Wilson's disease and cystic fibrosis, and congenital hepatic fibrosis), use of cyclosporin as first immunosuppressive regimen and development of arterial hypertension during follow-up [37]. Regarding our patients, only two, who later developed CKD, used cyclosporine as first immunosuppressive therapy (16.6%); three, as already mentioned, were affected by both CKD and arterial hypertension but with later onset of the renal damage and two were transplanted for liver diseases with potential renal involvement (1 Alagille syndrome and 1 Wilson's disease). In this case as well, possible bias is represented by the diagnostic criteria adopted in the different studies.

As already reported, allergic diseases were the most frequent comorbidities, especially food allergies, observed in 16.8% of our patients. This finding is consistent with the most recent literature, according to which *de novo* food allergies occur in the 15% of pediatric LT recipients, with younger age at transplant and tacrolimus-based immunosuppressive regimens as risk factors [38].

Last but not the least, of great importance is the impact of pediatric LT on neuropsychological functioning. Vimalesvaran S. et al. described in their long-term follow-up experience a significant incidence of anxiety and depression (19.1%) and of learning difficulties (13.1%), the first ones with an occurrence not far from the corresponding national data, while the second ones with an increased incidence [6]. In our population, 5.9% received a diagnosis of anxiety or depressive disorder and 9.3% showed learning difficulties. This evidence probably testifies lower neuropsychological impact in our transplant cohort but also confirms that great attention should be paid to the psychosocial and mental health status of these patients.

Among the neoplastic complications, PTLDs (16.8% of the patients) were the most diagnosed, especially Epstein-Barr Virus-related non-Hodgkin's lymphomas (44.4% of all PTLDs). A recent retrospective single-center cohort study including 1954 LT patients showed a pediatric PTLDs' incidence rate of 5.1% (*vs* an adults' rate of 2.3%), a pediatric mortality rate of 44.7%, an early post-LT occurrence (median time between LT and PTLDs of 14 months) and a better outcome in children than adults [39]. Furthermore, a 2019 systematic review of literature reported these lymphoproliferative disorders as the most common de novo malignancies after a pediatric LT with an incidence rate between 5 and 20% with the predominance of Epstein-Barr Virus-related non-Hodgkin's lymphomas [40]. Therefore, in addition to the relatively high incidence rate recorded in our population, noticeable data concern the limited number of early-onset PTLDs occurred (5/18 in the first year post-LT, 9/18 in the first 5 years post-LT) as well as the low mortality rate registered (only 1 patient, 5.5%). No significant differences were found in the incidence rate of PTLDs between tacrolimus and cyclosporin (14.7% *vs* 19%). Considering the incidence rate of these neoplasms in healthy children in Southern Europe (2008-2012 regional incidence ranging from 2.9 to 37.3 cases/million with histotype-related variations [41]), PTLDs remain one of the most important causes of morbidity and mortality after pediatric LT.

The absence of skin neoplastic lesions as well as of gastrointestinal malignancies represents another relevant finding. In fact, although non-PTLD neoplasms are rare in pediatric LT recipients, pre-existing literature reported non-melanoma skin cancer as the most common non-PTLD neoplastic disease affecting LT children [42]. Considering all vascular complications, the incidence rate of was 11.76%. In the Society of Pediatric Liver Transplantation Registry 2011-2018, hepatic artery thrombosis was detected in 6.3% of grafts in the first 30 days and in the 0.7% after more than 90 days [12]. Orlandini et al. analyzed 99 patients who underwent deceased donor LT between 1995 and 2009 mainly focusing on vascular complications that occurred in 19.2% of patients with early hepatic artery thrombosis, the most common vascular complication [43]. In the study by Basturk et al., hepatic artery thrombosis and portal vein thrombosis occurred in 4.8% and caused a significant number of graft failures representing also important causes of death (25% and 8.3% of death, respectively) [44]. Therefore, our data are in line with literature further demonstrating an important impact of vascular diseases, especially arterial and early onset ones, on graft survival rates.

In terms of survival, long-term follow-up studies conducted in the last two decades have shown encouraging results with a progressive increase in the survival of both patients and grafts, especially considering pediatric LTs performed since the late 1990s. Our results are perfectly in line with this positive trend showing a higher survival. Twenty years after LT patient and graft survival rate were 95% and 81.6%, further confirming that nowadays late mortality and late graft loss are uncommon events. The explanation for this data may lie in the large number of patients in our cohort transplanted after 2000 (67/119, 58%) and who have therefore benefited from the optimization of management of the last 20 years (Table 4).

First Author	Year	Country	No. of patients	Median follow-up (years)	LT time interval	Graft survival rates (%)				Patient survival rates (%)			
						5 yrs	10 yrs	15 yrs	20 yrs	5 yrs	10 yrs	15 yrs	20 yrs
Wallot MA [45]	2002	Belgium	467	7.36	1984-1998	67	65.8	-	-	80.5	78.6	-	-
Jain A [46]	2002	USA	808	12.6	1981-1998	60	57	52.3	37.9	72.6	69.4	65.8	64.4
Fouquet V [17]	2005	France	280	7.8	1986-2000	73.1	71.4	-	-	82	82	-	-
Oh SH [47]	2010	South Korea	113	6.87± 4†	1994-2006	83	81.5	-	-	86.3	84.8	-	-
Kasahara M [48]	2018	Japan	2085	10.6	1989-2015	90.4	84.6	82	79.9	91.5	87.1	85.4	84.2
Martinelli J [3]	2018	France	128	24	1988-1993	74	73	69	64	84	83	80	79
Elisofon SA[12]	2020	USA/Canada	1911	N/A	2011-2018	87.7	-	-	-	94.2	-	-	-
Pu S [49]	2020	China	260	5.5	2000-2019	76.6	76.6	-	-	80	80	-	-
Moosburner S [50]	2022	Germany	187	7.3	1991-2021	74	69	-	55%‡	82	78	-	78%‡
Guarino M.	2023	Italy	119	23.2	1987-2013	90.8	85.8	82.9	81.6	100	98.3	96.6	95

Table 4: Patient and graft survival rates in our study compared with recent literature; Note: † Mean ± Standard Deviation; ‡30 years survival rates.

The strengths of this study include its study design. It is the first published report about long term outcomes of pediatric liver transplanted patients followed-up in a single center. Secondly, to our knowledge, our data shows for the first time the outcomes of liver transplanted children in adulthood after a median follow-up of 23 years, reaching in several cases more than 30 years. Nonetheless, our study has some limitations. First, the relatively small sample size, even if not so small for a single center experience. Secondly, its retrospective nature makes it vulnerable to several unintended biases.

Conclusions

To date, a considerable improvement in long-term outcomes of liver transplanted pediatric patients has been achieved, allowing these patients to live a normal and full life. In fact, the long-term complications related to the transplant procedure and chronic immunosuppressive therapy are less frequent than previously and better manageable with adequate compliance and periodic clinical-laboratory-instrumental check-ups. Still some critical points remain, like vascular complications, chronic rejection and PTLDs, which continue to have a considerable impact on morbidity and mortality of these patients. So future efforts should be directed toward prevention of these events through early identification and mitigation of risk factors. Furthermore, more studies on long-term follow-up should be realized to confirm these positive findings and even extend the length of the observation period. In conclusion, pediatric LT is an established and highly successful treatment for several liver diseases, but it is increasingly evident that long-term survival depends on several factors including unforeseen surgical complications, infections, immunosuppression-related side effects, as well as neurocognitive difficulties.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Ethics Approval Statement

The study was conducted in accordance with both the Declarations of Helsinki and Istanbul and the protocol was approved by the local ethic board “Federico II” University of Naples (project identification code 81/2023, report n. 13/2023, 25.05.2023).

Patient Consent Statement

Individual informed consent was obtained from patients and parents.

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