AIBT Associazione Italiana di Immunogenetica e Biologia dei Trapianti
XXX Congresso Nazionale
Napoli, 10/12 ottobre 2024
"The programme of this event has been approved by the EFI Education Committee"

Attualità sul Trapianto Pediatrico e Ruolo del Laboratorio di Immunogenetica

Francesco Cirillo

UOC Gastroenterologia ed Epatologia Pediatrica

AORN Santobono Pausilipon

OSPEDALE PEDIATRICO SANTOBONO PAUSILIPON

Il sottoscritto Francesco Cirillo
in qualità di relatore al

XXX CONGRESSO NAZIONALE AIBT
NAPOLI, 10/12 OTTOBRE 2024

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 dell'Accordo Stato-Regione del 19 aprile 2012, per conto di Planning Congressi srl

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- IPSEN SpA

- MIRUM Pharmaceuticals

Napoli, 7/1072024

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Solid Organ Transplant Ages

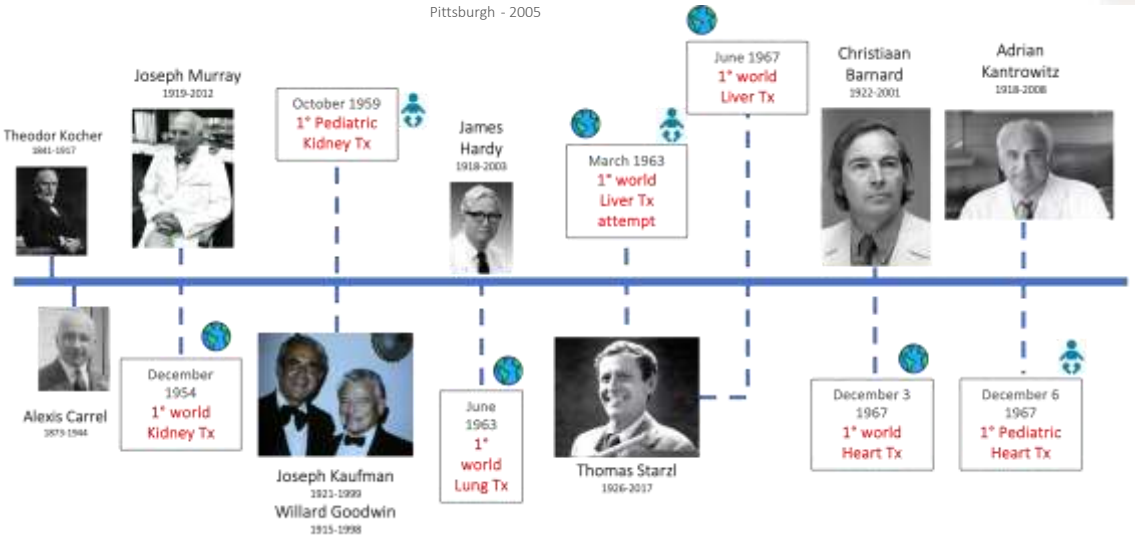
The Myth

Wunder der heiligen Cosmas und Damian - 1515, Anonymous
Landesmuseum Württemberg
Stuttgart, Germany

The Pioneers

Thomas E. Starzl (1926-2017)
Pittsburgh - 2005

The Modern Age



157.494	9.1%	41.792
ORGANS TRANSPLANTED ANNUALLY (2022)	OF INCREASE OVER 2021	ACTUAL DECEASED ORGAN DONORS IN 2022

Data from 91 countries, 75% of the global population.






Kidney	Liver	Heart	Lung	Pancreas	S. bowel
102 090	37 436	8 988	6 784	2 026	170

90%

48676 **(31%)** transplants from living donors

Those 2022 data are based on the Global Observatory on Donation and Transplantation (GODT) data, produced by the WHO-ONT collaboration.

40369 organ transplants in 2022.

25% of global activity in organ transplantation.

58.35 organ transplants per million inhabitants.

Kidney	Liver	Heart	Lung	Pancreas	S. bowel
25 361	9 840	2 444	2 073	611	40

87%

Those 2022 data are based on the Global Observatory on Donation and Transplantation (GODT) data, produced by the WHO-ONT collaboration.

World Health Organization
GODT

Numbers on whole global pediatric solid organ transplantation activity are lacking.

OPTN Organ Procurement & Transplantation Network

789 in 2023

500 to 600/year in Europe

Oomen L, et al. Front Pediatr. 2023

534 in 2023

In Europe 11% of all liver transplant/year

George M, et al Semin Pediatr Surg. 2022

506 in 2023

3192 Primary Transplants between January 1992 and June 2017

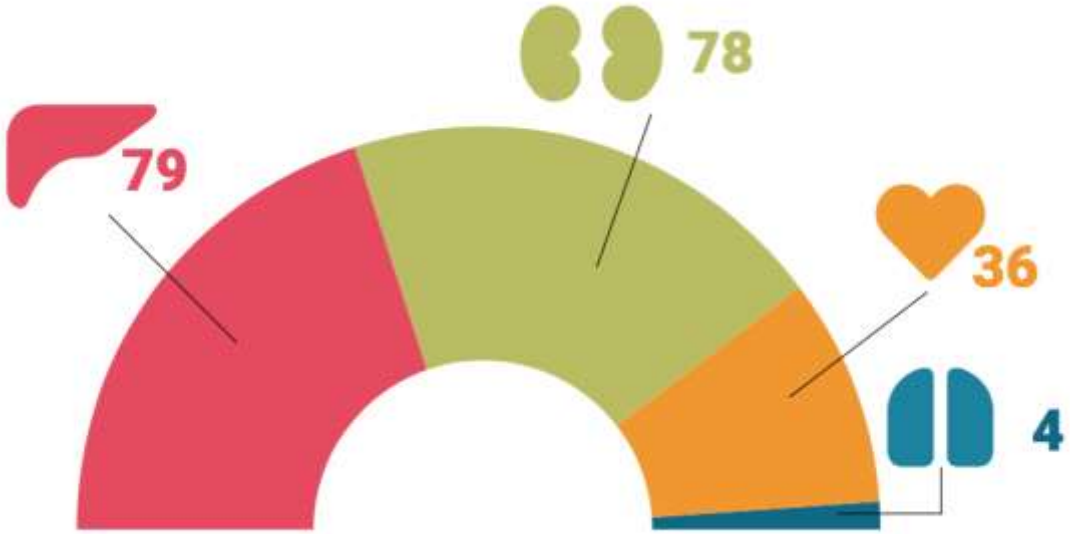
Singh TP, et al. J Heart Lung Transplant. 2023

https://optn.transplant.hrsa.gov

197 pediatric transplant in 2023

4% of total solid organ transplants in Italy

~18% from living donors (LD)



~30% of pediatric liver transpant from LD

~15% of pediatric kidney transpant from LD

Those 2023 data are based on the Report Attività Annuale Rete Nazionale Trapianti, produced by Centro Nazionale Trapianti.

Rete Nazionale Trapianti
Centro Nazionale Trapianti

Outcome

Patient Survive

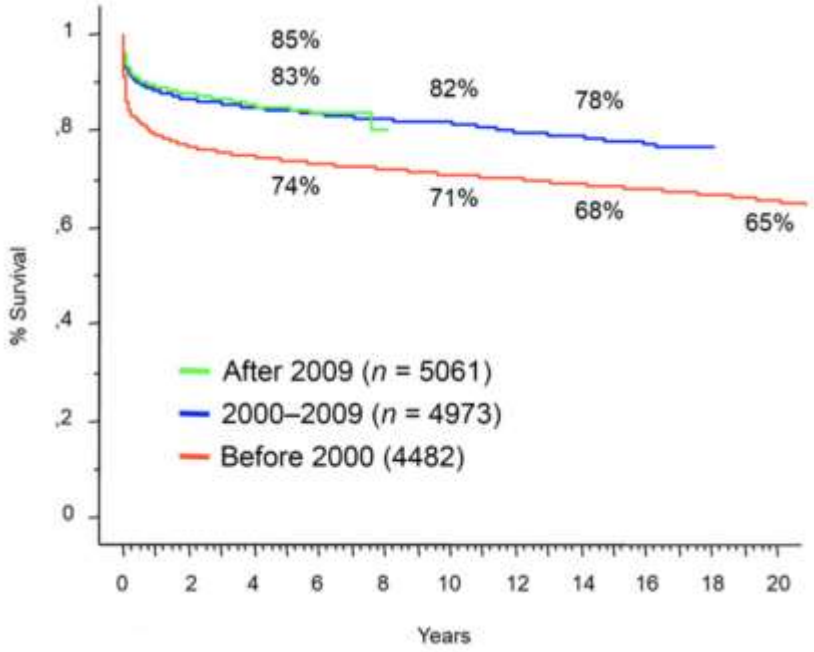


Pediatric Liver Transplant Patient Survival

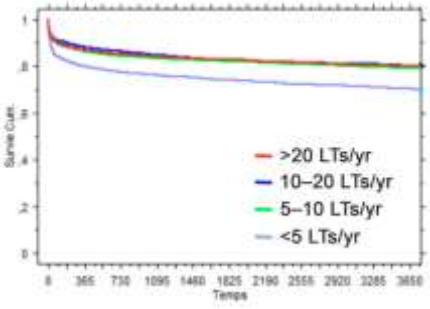
Prognosis of Children Undergoing Liver Transplantation: A 30-Year European Study

16 641 Pediatric Liver Transplant (PLT) performed on 14 515 children by 133 european centers from 1968 until 2017.

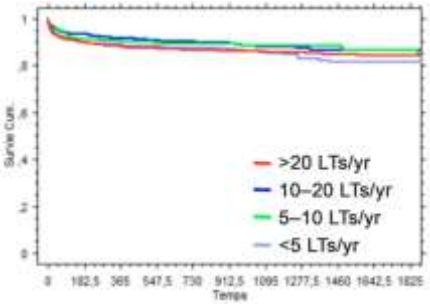
Patient survival at 5 years is currently 97% in children who survive the first year after PLT.



Overall Population



After 2009



Baumann U, et al. Pediatrics. 2022

Pediatric Liver Transplant Patient Survival

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

	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.

2010 - 2017

Infection was the cause of death in 111/576 **(19%)** patients.

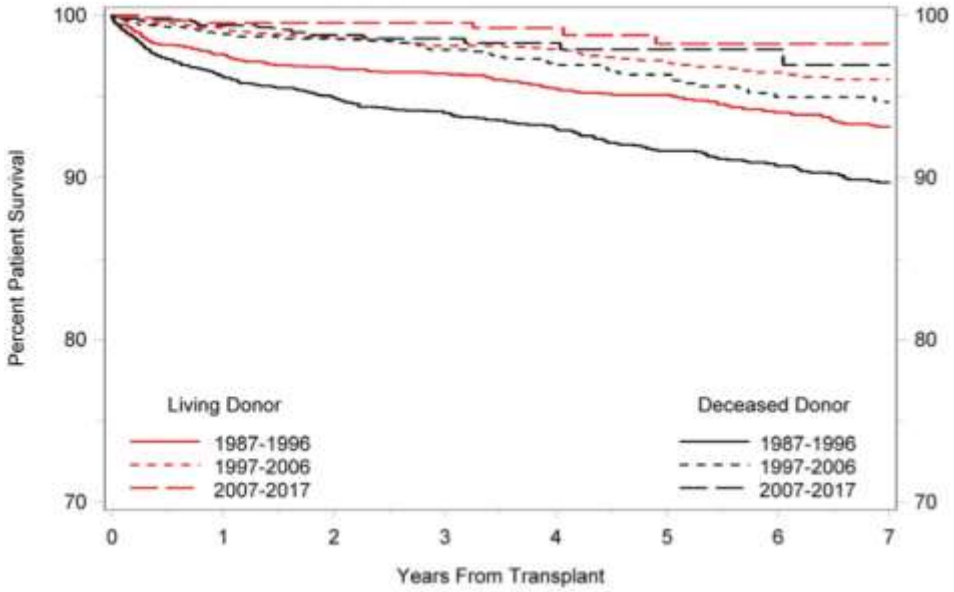
In 127/576 **(22%)** patients cause of death was unknown.

Baumann U, et al. Pediatrics. 2022

Pediatric Kidney Transplant Patient Survival

Kidney transplant practice patterns and outcome benchmarks over 30 years: The 2018 report of the NAPRTCS

12920 Pediatric (age <21 years) Kidney Transplant (PKT) performed on **11870** children from 1987 until December 2017.



Infections accounting for 27.9% of deaths in the entire cohort, 25% from 2007 to 2017.

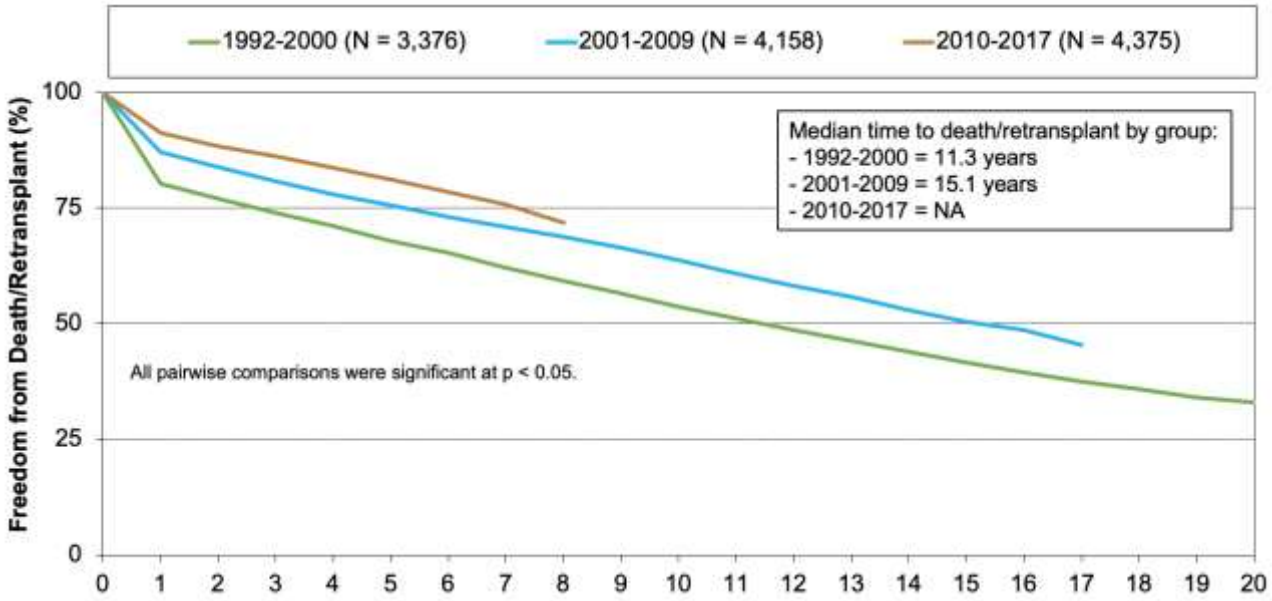
Cardiopulmonary accounting for 14.5% of deaths, malignancy 11.3%.

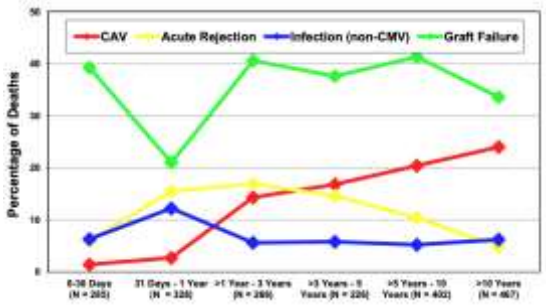
Chua A, et al. Pediatr Transplant. 2019

Pediatric Heart Transplant Patient Survival

11,909 pediatric recipients who underwent primary transplant between 1992 and 2017 with follow-up data in the International Society for Heart and Lung Transplantation (ISHLT) Registry through April 2019

Pediatric Heart Recipients by Transplant Era





ISHLT 2023 ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
JHLT. 2023 Oct; 42(10): 1321-1333

Singh TP, et al. J Heart Lung Transplant. 2023

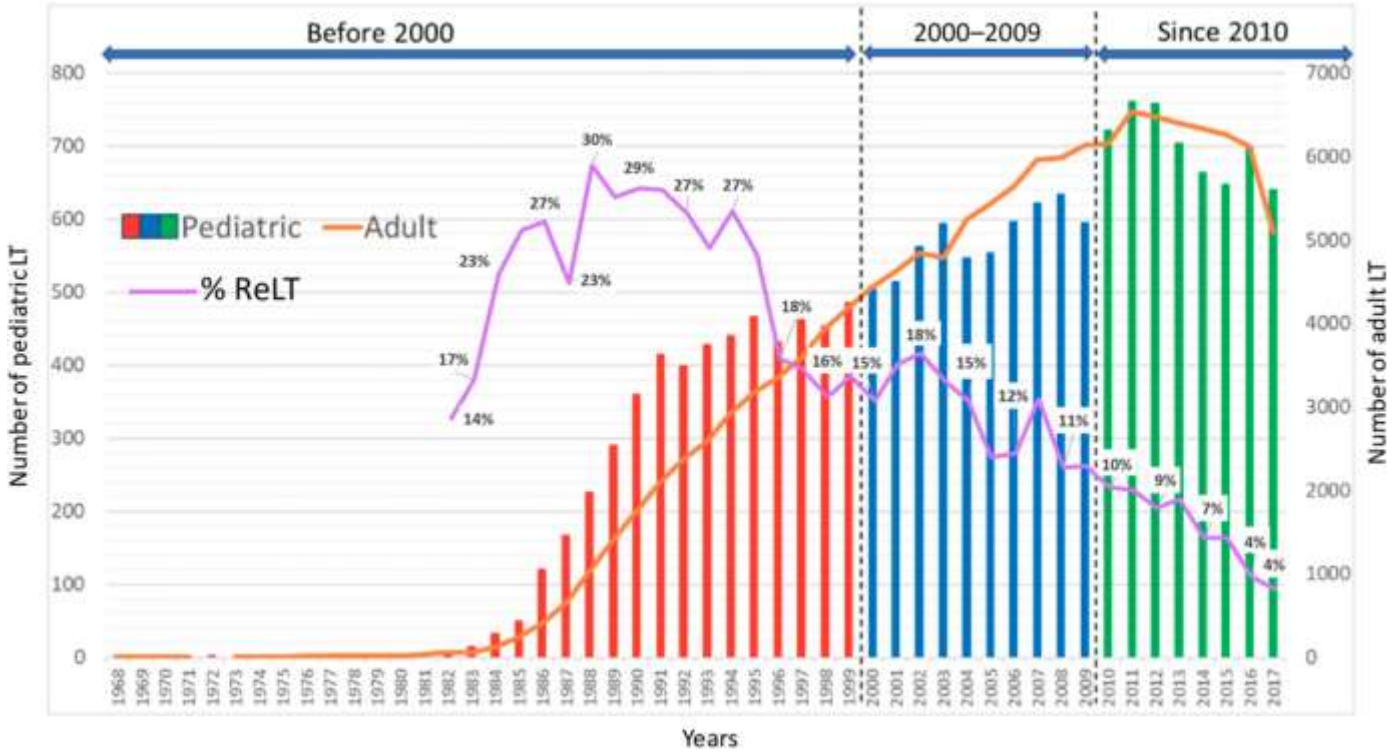
Outcome

Graft Survive

Pediatric Liver Transplant Graft Survival

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

Overall, the need for retransplantation reduced with time from 23.1% before 2000 to 7.5% since 2010 ($p < 0.0001$), in recent years only 4%.



Baumann U, et al. Pediatrics. 2022

Pediatric Liver Transplant Graft Survival

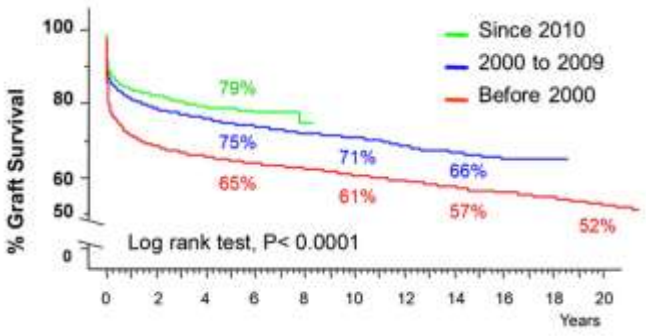
European Liver Transplant Registry: Donor and transplant surgery aspects of 16,641 liver transplantations in children

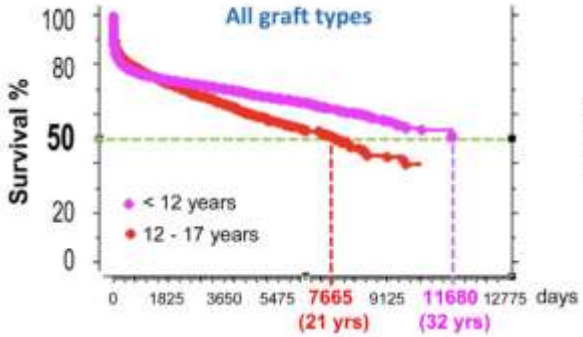
Retransplantation in 2126 cases; 1813 (85%) within the pediatric age.

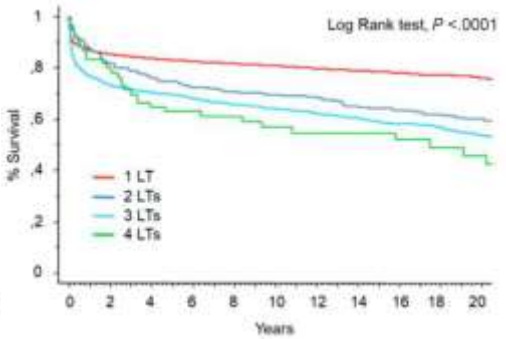
Mean interval between transplants 11.8 ± 7.1 years. Chronic rejection was the leading indication (41%) in > 18 years recipients.

Overall, the calculated graft half-life was 31 years.

Even after 4 transplants, long-term survival of >20 years was observed.





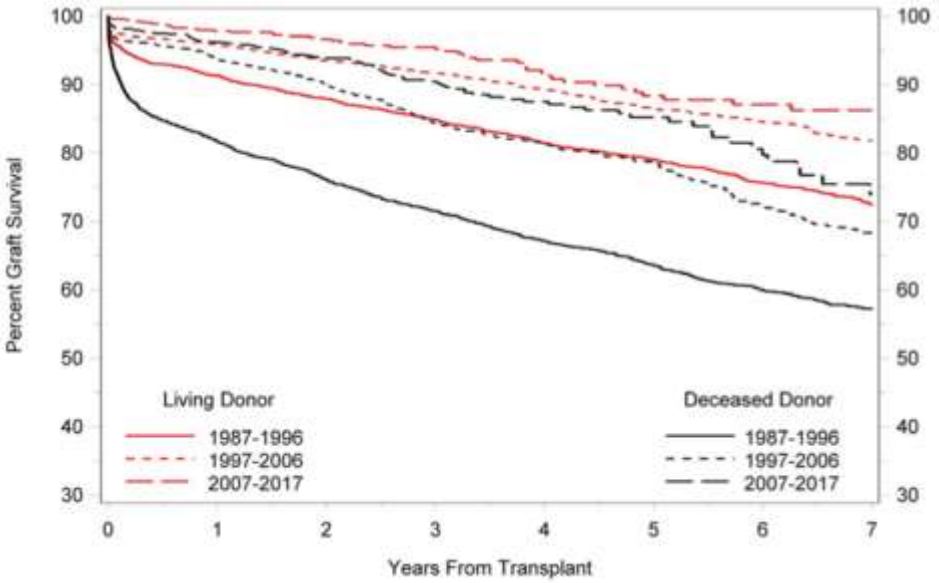


De Ville J, et al. Hepatology. 2022

Pediatric Kidney Transplant Graft Survival

Kidney transplant practice patterns and outcome benchmarks over 30 years: The 2018 report of the NAPRTCS

12920 Pediatric (age <21 years) Kidney Transplant (PKT) performed on 11870 children from 1987 until December 2017.

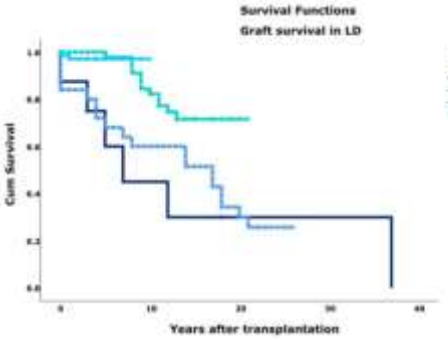


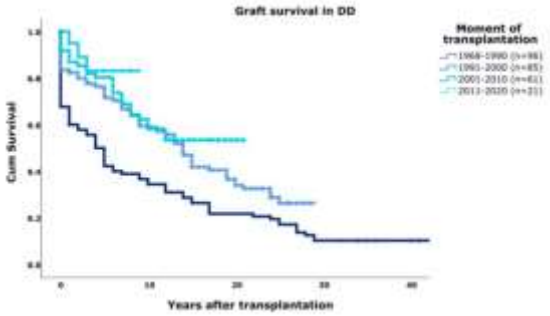
In the 2012-2017 cohort, 1-year graft survival is >99% and >97% for LD or DD recipients; 5-year graft survival now exceeds 90% for both LD and DD recipients.

Chronic rejection (35.6%) and Acute rejection (13.0%) remain the most important cause of allograft failure.

NAPRTCS

Chua A, et al. Pediatr Transplant. 2019





Median graft survival:
20 years (95% CI 16–24) after LD
12 years (95% CI 9–15) after DD
(p = 0.01) even when stratified for decade of transplantation.

Majority of graft loss was caused by both forms of rejection (75%), other causes were recurrence of primary disease (5%) and thrombosis (6%).

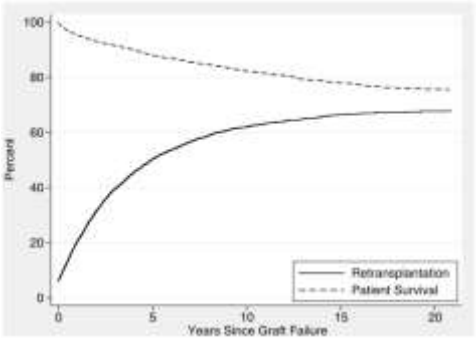
Oomen L, et al. Front Pediatr. 2022

48/287 (16,7%) of children underwent to kidney transplant at Virgen del Rocío University Hospitals (1979-2019) had received a second graft before reaching the age of 18 years; 8/48 (16%) had been transplanted for the third time and 2/8 had already received a fourth transplant before reaching adulthood.

Fijo J, et al. Nefrologia (Engl Ed). 2023

In an analysis of almost 15000 grafts in recipients aged <18 years reported to the Scientific Registry of Transplant Recipients (SRTR) for the period from 1987 to 2010 long- term graft survival rates differed markedly with increasing number of retransplants.

Van Arendonk KJ, et al. Transplantation. 2013

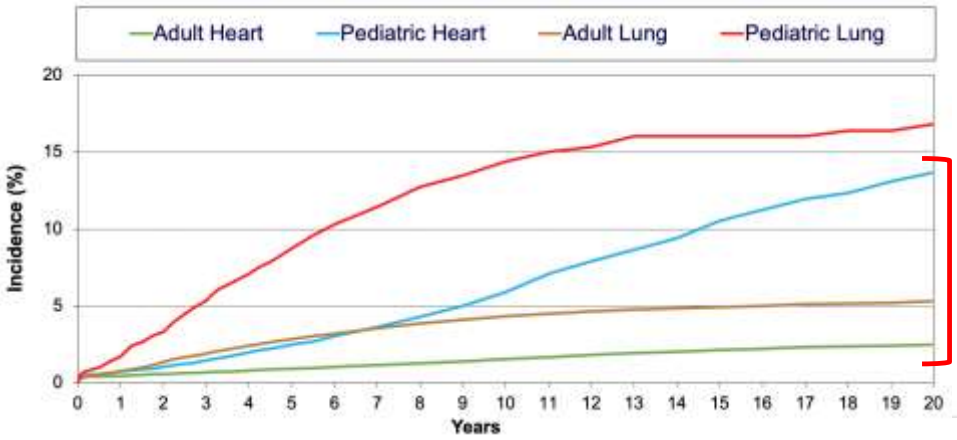


Graft No.	Graft Survival Rate, %		
	1 year	5 years	10 years
1[a]	91.9%	74.8%	56.1%
2	89.3%	65.3%	43.9%
3	89.6%	62.0%	39.1%
4	84.9%	46.8%	19.5%

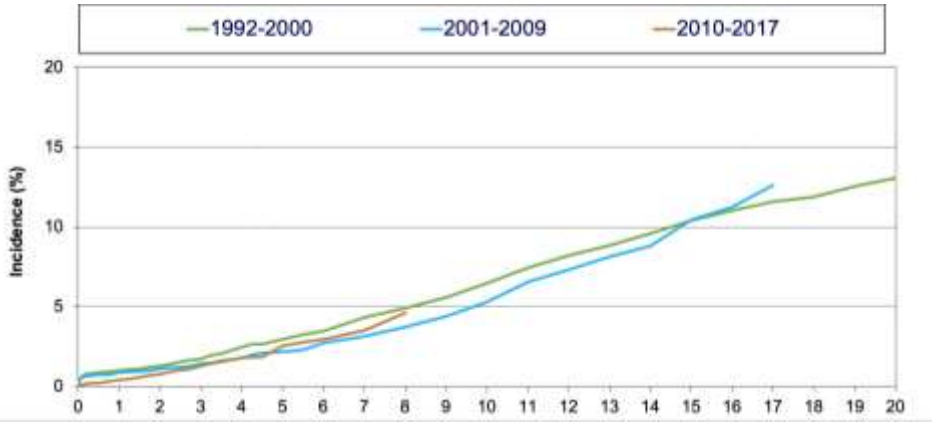
Pediatric Heart Transplant Graft Survival

97,140 adult and **11,909 pediatric HT** recipients who underwent primary transplant between 1992 and 2017 with follow-up data in the International Society for Heart and Lung Transplantation (ISHLT) Registry through April 2019

Cumulative Incidence of Retransplant By Age Group and Organ



Incidence of Retransplant for Pediatric Heart Recipients by Transplant Era



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2023
JHLT. 2023 Oct; 42(10): 1321-1333

Singh TP, et al. J Heart Lung Transplant. 2023

Mean lifetime survival estimates following solid organ transplantation in the US and UK

Survival analyses conducted in 621 447 transplant recipients from US (1990-2018) .

Mean lifetime survival was:

22.79 years after kidney transplant, 20.90 years after liver transplant , 14.82 years after heart transplant.

Graham CN, et al. J Med Econ.. 2022

US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States

The United States Renal Data System (USRDS) registry estimated the expected remaining lifetime of pediatric and young adult end-stage renal disease patients:

57.7 years in the 0–4 age group.

42.3 years for the 18–21 age group.

Saran R, et al. Am J Kidney Dis. 2019

OPTN Organ Procurement & Transplantation Network

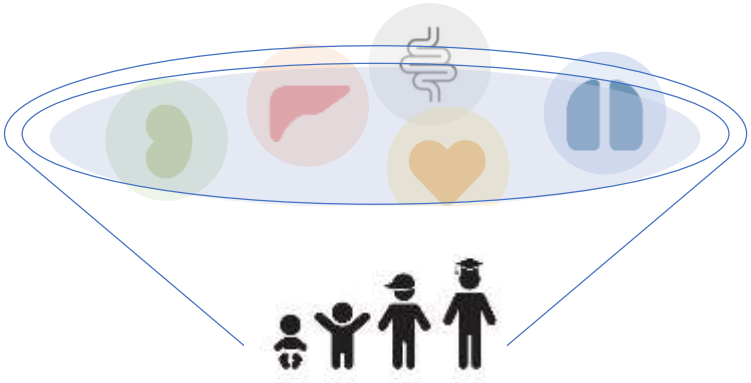
Organ by age U.S. National Waiting List

[*based on OPTN data as of September 25, 2024; (For Count=Candidates)*]

		All Organs	Kidney	Liver	Pancreas	Kidney / Pancreas	Heart	Lung	Heart / Lung	Intestine
All Ages	All Transplant	104,321	90,030	9,457	852	2,191	3,479	927	39	188
	Primary Transplant	93,884	79,980	9,139	764	2,155	3,359	892	38	161
	Repeat Transplant	10,669	10,095	323	89	36	120	35	1	27
< 1 Year	All Transplant	103	1	35	0	0	67	0	0	0
	Primary Transplant	103	1	35	0	0	67	0	0	0
1-5 Years	All Transplant	541	236	114	19	0	182	2	0	30
	Primary Transplant	526	231	107	19	0	179	2	0	30
	Repeat Transplant	15	5	7	0	0	3	0	0	0
6-10 Years	All Transplant	471	266	59	8	1	137	7	1	18
	Primary Transplant	423	229	54	8	1	129	7	1	17
	Repeat Transplant	50	37	5	0	0	8	0	0	1
11-17 Years	All Transplant	967	728	115	21	4	120	7	2	32
	Primary Transplant	813	597	99	21	4	111	7	2	27
	Repeat Transplant	161	131	16	0	0	9	0	0	5

Overall, 10% of patients on waiting list already undergone a previous transplant.

- Kidney (11-17 years) = 18%
- Liver (11-17 years) = 14%
- Liver (All Ages) = 3%
- Heart (11-17 years) = 7.5%
- Heart (All Ages) = 3%



Pediatric Transplantation

New Second Chronic Disease

- ✓ Long life expectancy
- ✓ High risk of graft loss and retrasplantation
- ✓ High risk of long term immunesoppressants side effects

- Malignancy (PTLD, skin cancer, etc)
- Allergic Disorders & Autoimmunity
- Chronic renal disease
- Hypertension
- Metabolic disease (obesity, diabetes, hyperlipidemia)
- Viral Infection (CMV, EBV, BKV etc)
- Growth & developmental delay
- Acute & chronic Rejection due to non-adherence

Improve donor-recipient matching

Optimize immunosuppressive therapy

Improve donor-recipient matching

Organ Allocation Criteria

- Immunological Risk (PRA, retransplantation)
- Time on waiting list
- ABO matching
- HLA D/R matching
- Weight D/R matching

- Severity status (1-1B-2A-2B)
- Time on waiting list
- ABO matching
- Weight D/R matching
- PELD/MELD

- Severity status (Classe 0-1-2*-3)
- Time on waiting list
- ABO matching
- Weight D/R matching
- Geographic criteria

TESTO UNICO DEL DOCUMENTO "PROGRAMMA NAZIONALE DI TRAPIANTO PEDIATRICO"

Protocollo operativo dal 17 maggio 2021

HLA Matching and Pediatric Liver Transplant

Leader

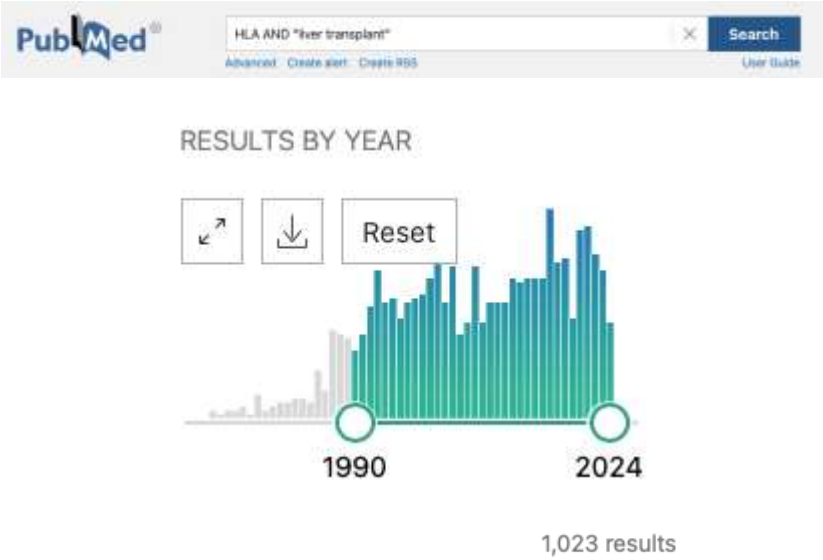
Is HLA matching important for liver transplantation?

James M. Neuberger and David H. Adams
The Liver Unit, The Queen Elizabeth Hospital, Edgbaston, Birmingham, United Kingdom

and renal cardiac allografts appears established, but the data are far less clear for liver grafts. At present, there is insufficient evidence to suggest that HLA matching would be associated with improved graft survival following liver transplantation and, indeed, there are indications that under some circumstances selected mismatches may actually be advantageous. In view of the considerable logistic difficulties involved in HLA matching (or mismatching), it would seem that the way forward at present is to collect more information on the effect of HLA matching and graft outcome so that with larger numbers proper statistical evaluation can be undertaken and future recommendations can be made.

Journal of Hepatology, 1990; 11: 1–4
Elsevier

HLA Matching and Pediatric Liver Transplant



HLA matching between donors and recipients improves clinical liver transplant graft survival

Observational Study > Liver Int. 2024 Feb;44(2):411-421. doi: 10.1111/liv.15774.

22702 liver transplant recipients from the UNOS/OPTN database. Patients were divided into two groups based on number of HLA mismatches (0-3 mismatches vs. 4-6 mismatches).

Allograft survival and risk of acute rejection were associated with degree of HLA mismatch.

This association between HLA mismatch and graft survival persisted in individuals who underwent transplant for hepatitis, metabolic, drug toxicity, and congenital indications.

Nabulsi S, et al. Liver Int. 2024

HLA Matching and Pediatric Liver Transplant

HLA, Non-HLA Antibodies, and Eplet Mismatches in Pediatric Liver Transplantation: Observations From a Small, Single-Center Cohort

Retrospective review of 42 pediatric patients who underwent liver transplant between 1998 and 2016 and had donor-specific antibodies measured.

Presence of anti-HLA class II DSAs was significantly associated with ACR (66.7% vs 26.6%; P = .034), and the median time to development of DQ DSA posttransplant was significantly shorter for patients with ACR at 43.17 months (range, 15.83-93.37 mo) versus 146.27 months (range, 96.87-165.03 mo; P = .02).

Mean portal fibrosis score was significantly lower in patients without anti-HLA class II DSA or antibody against DQ (2.0 vs 1.6; P = .018).

Moreover, patients with antibody against HLA-DQB1*02 antigen were significantly more likely to develop ACR (66.6% vs 36%; P = .024). We found that 13 recipients had a mismatch for HLA-DQB1*02; however, only 9 developed antibody to DQ2.

DQ epitope mismatch load was significantly greater in those who developed class II DSAs (9.7 vs 3.6; P = .001)

An epitope-based mismatching approach can predict DQ de novo DSA development in pediatric liver transplant recipients.

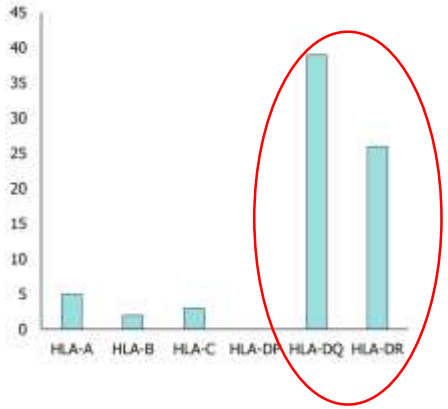
Ekong UD, et al. Exp Clin Transplant. 2019

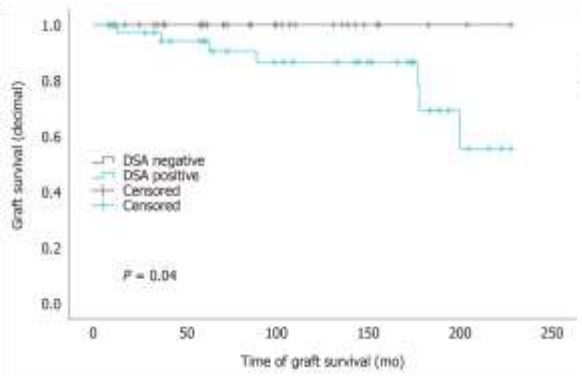
HLA Matching and Pediatric Liver Transplant

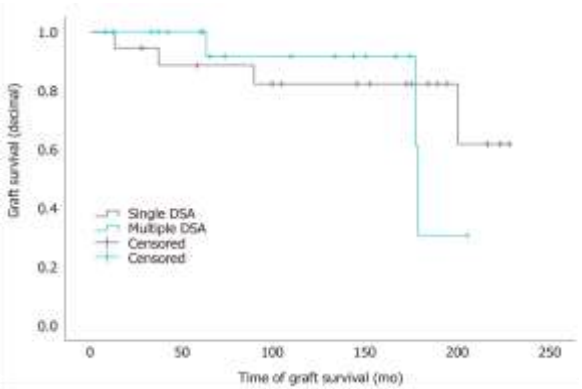
Impact of donor-specific antibodies on long-term graft survival with pediatric liver transplantation

123 pediatric liver transplant from 1993 to 2015 at Universitätsklinikum Hamburg, Germany.

HLA antibodies were found in 74.1% of all patients (*n* = 106), and 43.9% (*n* = 54) presented with DSAs.







DSA prevalence significantly affected long-term liver allograft survival.

Screening for class II DSAs improved early identification of patients at risk of graft loss.

Schotters FL, et al. World J Hepatol. 2021

HLA Eplet Matching and Pediatric Heart Transplant

Eplet matching in pediatric heart transplantation: The SickKids experience

J Heart Lung Transplant. 2022 Oct;41(10):1470-1477.

Retrospective, single centre cohort study (2013-2020); 77 patients, median age at HTx 4.3 years [range 0.05-18].

Median HLA class I and II eplet mismatches were 10 (1-22) and 11 (1-23); median class I and II antigen mismatches were 5 (1-6) and 4 (0-6).

In univariate analysis, patients with HLA Class II DPB eplet mismatches above the median for this cohort had an increased risk of graft loss (OR 5.3 [95%CI: 1.03-27.5], p = 0.039). HLA eplet mismatching was not associated with rejection; antigen mismatching was not associated with either graft loss or rejection.

The number of HLA Class II DPB eplet mismatches was associated with graft loss.

Cardoso B, et al. J Heart Lung Transplant. 2022

DQB1 antigen matching improves rejection-free survival in pediatric heart transplant recipients

J Heart Lung Transplant. 2024 May;43(5):816-825.

4,135 pediatric heart transplant recipients (2010-2021) with complete HLA typing at the DQB1 locus for recipient and donor.

Of those, 503 (12%) had 0 DQB1 donor-recipient mismatches, 2,203 (53%) had 1, and 1,429 (35%) had 2. Rejection-free survival through 5 years trended higher for children with 0 DQB1 mismatches (68%), compared to those with 1 (62%) or 2 (63%) mismatches (pairwise p = 0.08 for both). Subgroup analysis showed the strongest effect in non-Hispanic Black children and those undergoing retransplant.

Matching at the DQB1 locus is associated with improved rejection-free survival after pediatric heart transplant, particularly in Black children, and those undergoing retransplant.

Wright LK, et al. J Heart Lung Transplant. 2024

Optimize immunosuppressive therapy

Tacrolimus-Personalized Therapy

Pharmacodinamics Biomarkers for Tacrolimus Monitoring

- Calcineurin Phosphatase Activity in PBMC
- NFAT Gene Expression

Drug Specific

- Intracellular Cytokines (IL-2, IFNγ)
- DSAs
- Donor Derived Cell-free DNA (dd-cfDNA)
- T-Cell Proliferation and Surface Activaction Markers

Not Drug Specific

Pharmacogenetic Approach

- Analysis of gastrointestinal and hepatic cytochrome P450 (CYP) 3A isoenzymes (CYP3A4, CYP3A5)
- Efflux transporter ABCB1 genotype

New TDM Approaches

- Microsample-Based Tacrolimus Concentration Monitoring (DBS and Others)
- Intracellular and Tissue Tacrolimus Concentration Monitoring (PBMC)

Key Takeaways

Pediatric recipients of solid organ transplants have unique and specific medical, surgical, and programmatic needs that must be met to elevate the quality of their post-transplant lives.

A child currently has a high likelihood of re-transplant, possibly even before reaching adulthood. We should strive to reach «one transplant for life» result.

A child will have a longer exposure to immunosuppressive agents and clear differences in absorption and metabolism of key immunosuppressive agents, starting as early as infancy. Thus, the potential adverse consequences of longstanding immunosuppression will increase morbidity and generate a lasting impact on immune function and development.

The use of customized and innovative immune monitoring and immunosuppressive regimens must be vigilantly pursued and implemented in pediatric transplant recipients.