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SEX-SPECIFICS IN PAEDIATRIC KIDNEY TRANSPLANT



Katalin Dittrich - Paediatric Center for Nephrology and Kidney Transplantation

Special Considerations in Paediatric Kidney Transplantation

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- **Our Goals:**
- Earliest possible restoration of adequate kidney function
- Avoidance or minimization of dialysis time
- Ensuring survival

- **Ensuring optimal paediatric development promotes…**
- Growth and pubertal development
- Neurocognitive maturation
- Psychosocial participation
- Long-term quality of life



Special Considerations in Paediatric Kidney Transplantation

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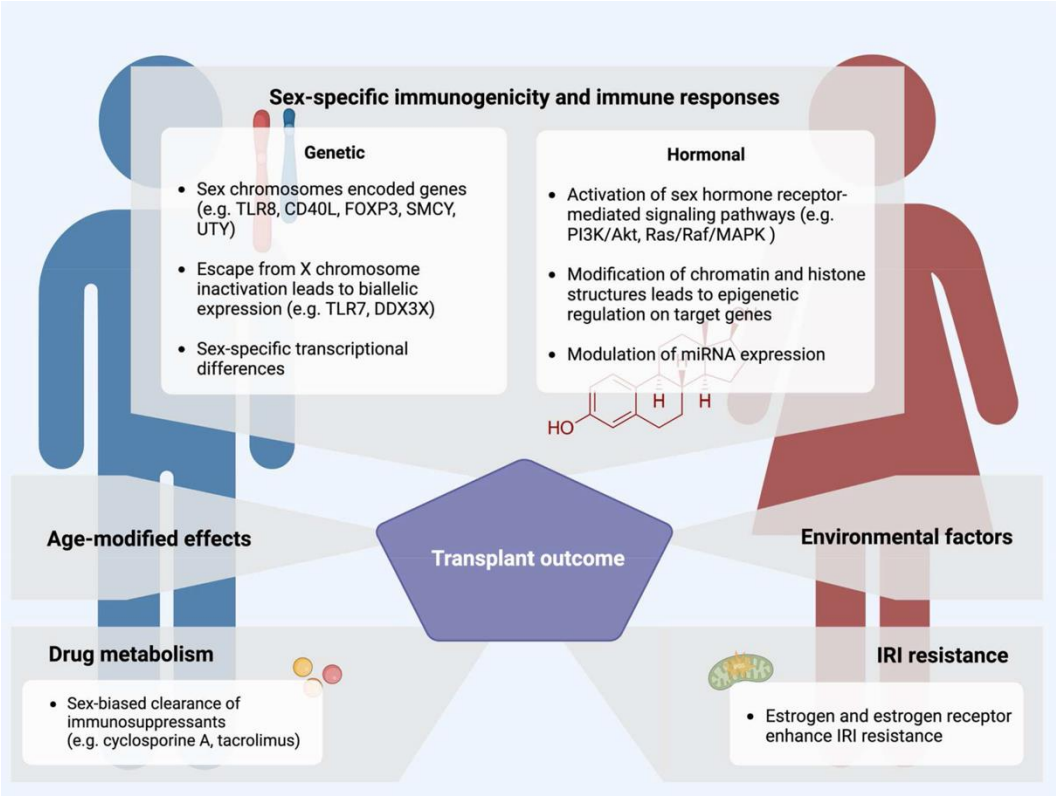
- **The Challenge:**
- Small recipients with distinctive anatomical situations and/or malformations
- Heterogeneous underlying diseases
- Long waiting times (1.7-2.1 years) despite the "paediatric bonus" (*Eurotransplant*) and permitted preemptive listing for deceased-donor kidney transplantation at eGFR < 20 ml/min/1.73 m²
- Dynamic in pubertal development and maturation of the immune system
- EBV- and/or CMV-negative recipients

- **Even with an optimal course, multiple kidney transplantations will be necessary due to graft losses over the lifetime**

What Is Already Known?

- Sex differences in graft outcomes are expected:
- Most graft losses are immune-mediated +
- Immune reactivity is known to differ by sex and change with age



Reproduced from:

Xiao Y et al.: Sex as a biological variable: Mechanistic insights and clinical relevance in solid organ transplantation

American Journal of Transplantation, 2023; 23, 1661-1672

What Is Supported By Clinical Evidence?

Amanda J. Vinson et al.: *Age-dependent Sex Differences in Graft Loss After Kidney Transplantation. Transplantation 2022;106: 1473–1484*

- Analysis of > 400 000 individuals from 3 large, international transplant registries.
- Sex differences in the risk of graft loss vary by recipient age and donor sex
- Sex differences are fairly uniform internationally
- Absolute risk difference between young male and female recipients for losing a kidney from a male donor is similar to that between recipients of 1/6 versus 6/6 HLA-mismatched organs!

Graft Loss Rates per 100 Person-Years

by donor-recipient sex combination and recipient's current age

- Highlights particular challenges associated with pubertal development in our patients.
- Higher graft loss rates in older male than female recipients, regardless of donor sex, may reflect better medication adherence in females.

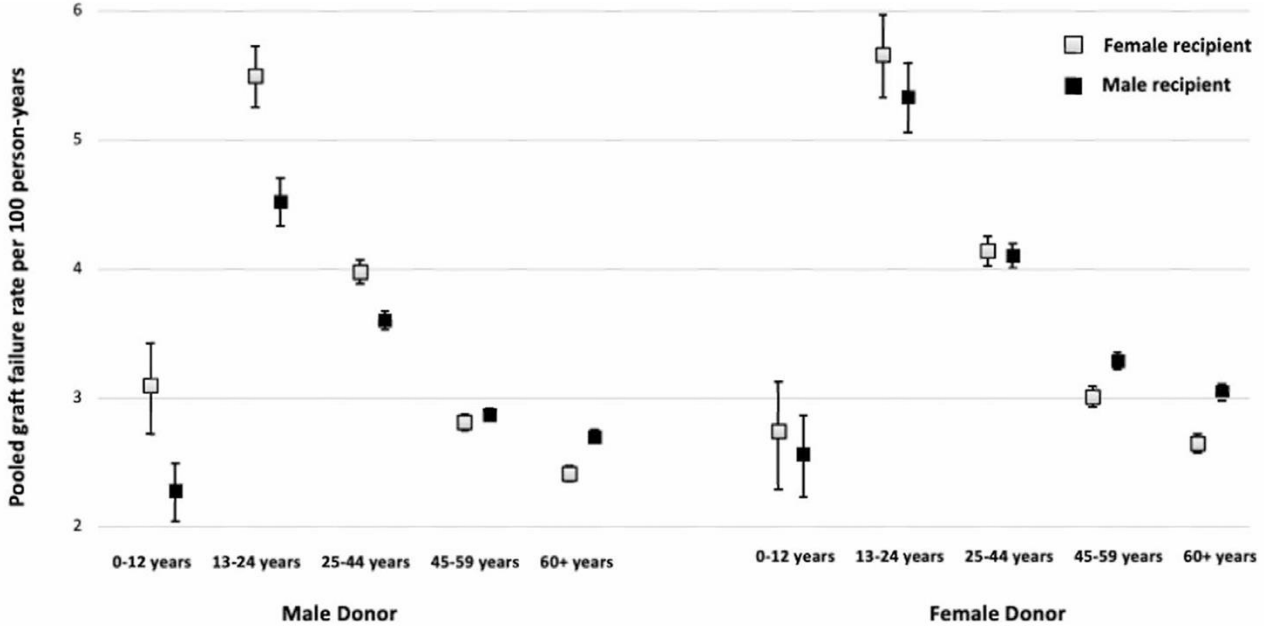


FIGURE 1. Crude death-censored graft loss rates per 100 person-years by donor-recipient sex combination and recipient current age pooled across SRTR, ANZDATA, and CTS. Pooled crude rates were weighted by the number of patient-years of observation in each registry. Because age was treated as a time-varying variable, individuals could contribute person-time to multiple current-age intervals. ANZDATA, Australia and New Zealand Dialysis and Transplant; CTS, Collaborative Transplant Study; SRTR, Scientific Registry of Transplant Recipients.

Relative Hazards of Graft Loss in Female vs. Male Recipients

- Higher risk of male donor graft loss in younger females, even before puberty
- Important role for the **minor histocompatibility H-Y antigen** in this relationship.

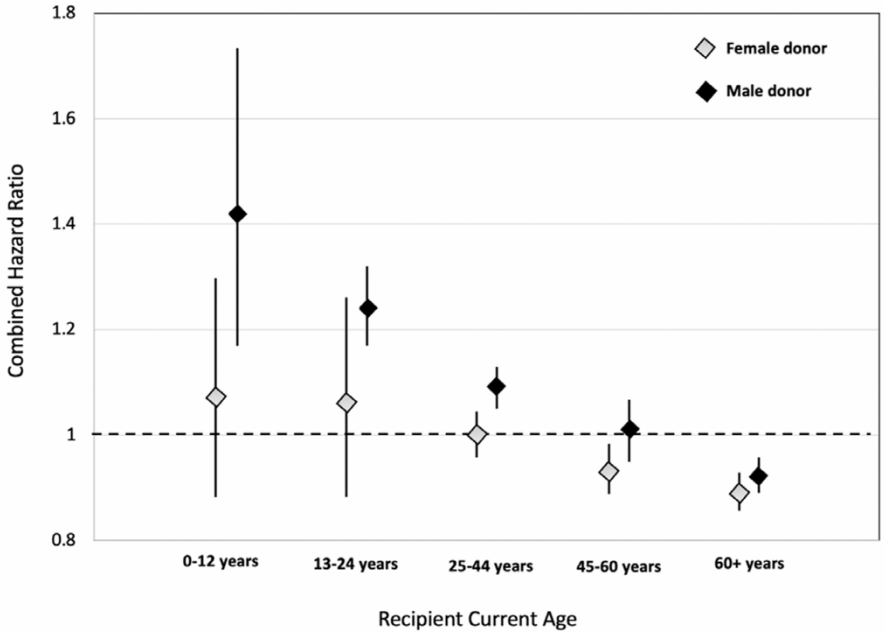


FIGURE 3. Age-specific relative hazards of death-censored graft loss in female compared with male recipients of kidney transplants from female (gray) and male (black) deceased donors using data combined from SRTR, CTS, and ANZDATA. This figure summarizes the combined adjusted HR shown in Figure 2A and B. Final models were adjusted for recipient ancestry, primary cause of ESRD, dialysis pretransplant, donor age, donor:recipient weight ratio (not available for CTS), and panel reactive antibody. ANZDATA, Australia and New Zealand Dialysis and Transplant; CTS, Collaborative Transplant Study; ESRD, end-stage renal disease; SRTR, Scientific Registry of Transplant Recipients.

UK Historical Cohort Study

1316 transplant procedures in 20 years

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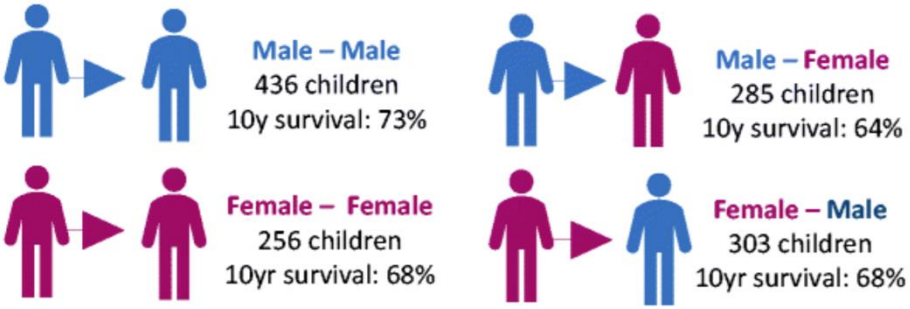
The Impact of Donor and Recipient Sex on Kidney Allograft Survival in Pediatric Transplant Recipients

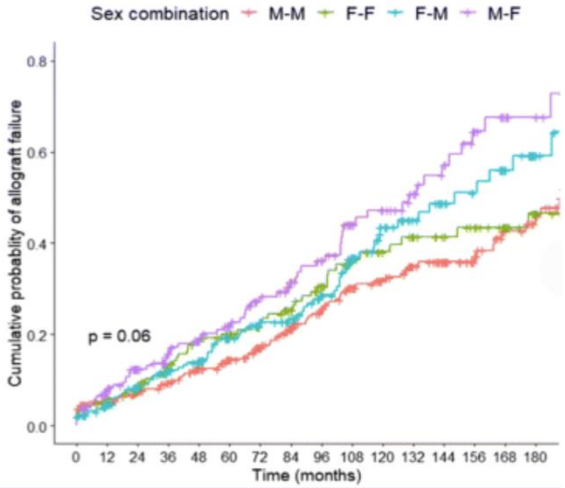
Graphical Abstract

HYPOTHESIS: Matching donor and recipient sex would increase paediatric kidney transplant survival

DESIGN & OUTCOMES:



Population historical cohort study (01/1999 – 01/2020)
From the data collected by the UK renal registry



CONCLUSION: In male donor transplantation, the multivariable risk of allograft failure was 1.47 time greater for female (compared to male) recipients. There was no difference amongst other sex combinations

Mudalige et al. 2021

Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association

Pediatric Kidney Transplantation in Germany

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- Germany: ~ 60% of the Eurotransplant population
- Yet, 78% of children on the kidney waiting list are from Germany. (vs. 65.9% of adults)

Why does organ shortage disproportionately affect children?

- All children with an indication for transplantation are listed, but there is no true “Young for Young” allocation program.
- Living kidney donation is less common in children than in adults.
- DCD donation is not available in Germany.

Should additional allocation criteria be considered in this situation?



Summary

- Sex, waiting time/dialysis exposure, viral serostatus, and donor–recipient size are interdependent determinants of paediatric transplant outcome.
- MD→FR is associated with a measurable graft-failure signal in the paediatric evidence, but sex alone should not determine allocation.
- Pre-emptive transplantation and avoidance of prolonged dialysis exposure are among the most actionable strategies.
- For small, prepubertal children, size matching and adequate nephron mass are central; female donors may offer favourable size compatibility.
- EBV D+/R− and CMV D+/R− require deliberate prevention, surveillance, and individualized immunosuppression.

The optimal strategy is integrated risk stratification rather than single-factor matching.

Take-Home Messages for Paediatric Kidney Transplantation

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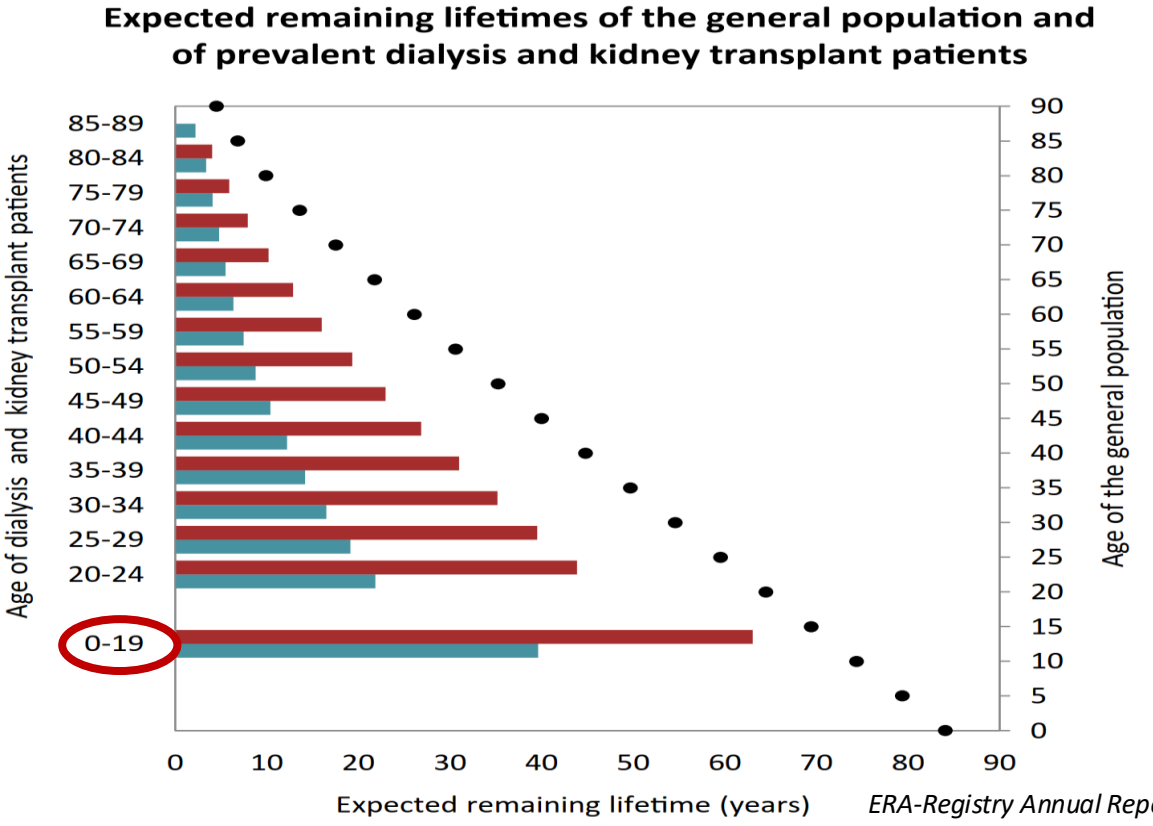
- Currently, the best therapeutic option for children and adolescents with end-stage kidney disease. In the setting of organ shortage, every effort should be made to maximize graft survival.
- Optimal graft survival requires individualized treatment and monitoring strategies, taking into account sex, age, and pubertal development.
- Ideally, future clinical decision-support tools should repeatedly integrate an individual pattern of multiple biomarkers and clinical parameters to enable dynamic, patient-specific treatment decisions.


GeGe4Nephro
Research for better gender-specific health of kidney transplant patients
gege4nephro.eu

Transplantation Extends Expected Remaining Life Time of Patients



ERA-Registry Annual Report 2019

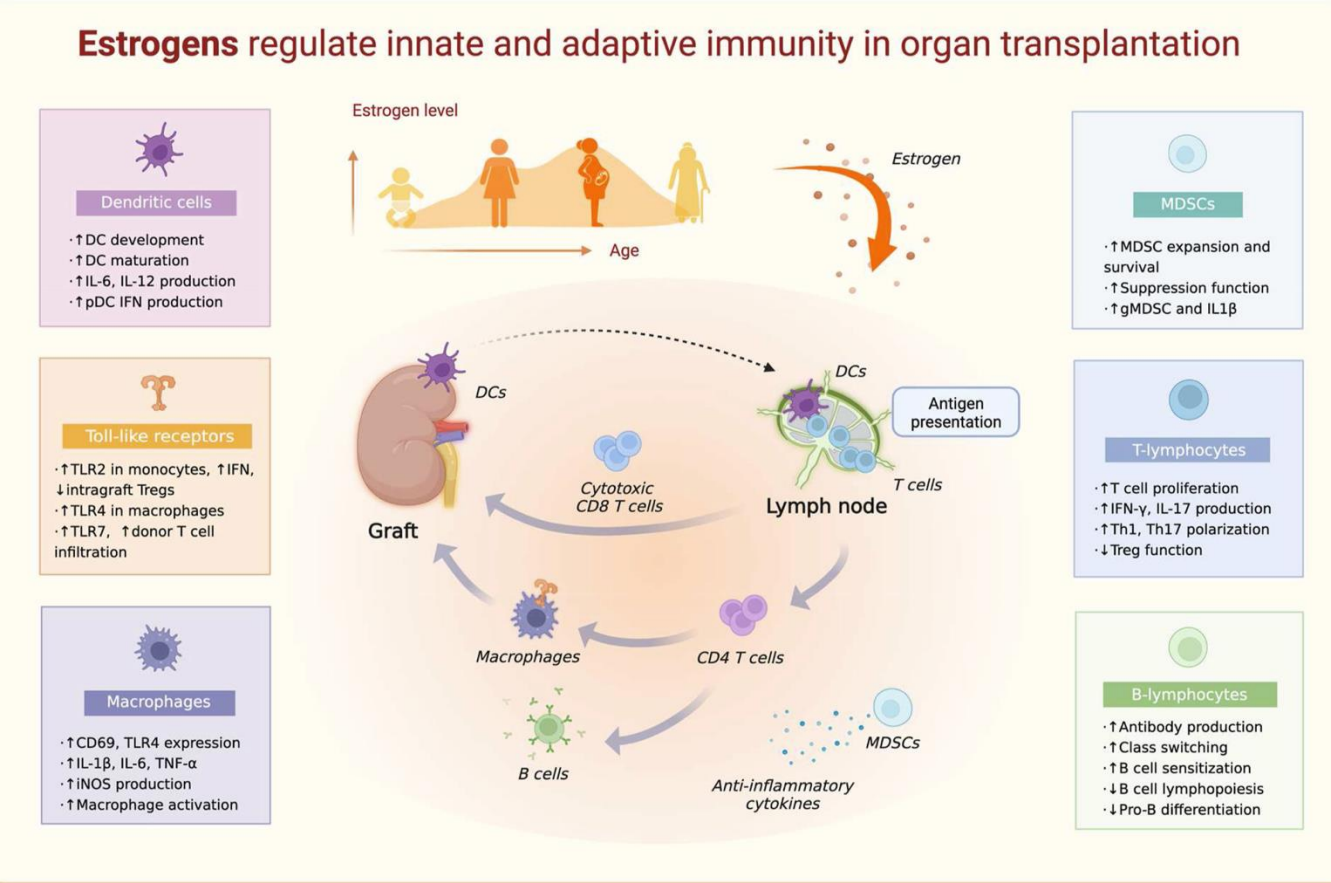
Making the Difference:

- Chronic uraemia and inflammation
- Cardiovascular burden
- Developmental deficits

Sex Hormones Influence Immune Response

	Estrogen (E2)	Progesterone	Testosterone/Androgens
General tendency	Immunostimulatory	Immunosuppressive	Immunosuppressive
T-helper profile	Th2 ↑, Th1 ↓ (dose-dependent)	Th2/Treg ↑, Th1/Th17 ↓	Th1 ↑ (higher Th1:Th2 ratio in men)
Antibody/vaccine response	Higher titers, better seroconversion	Rather suppressive	Weaker antibody response
Susceptibility to infection	Overall lower (especially viral infections)	–	Higher (including parasitic infections and uropathogenic *E. coli*)
Risk of autoimmunity	Increased (especially SLE)	Rather protective	Rather protective
Risk of rejection	**Potentially increased,** particularly through stronger cellular and humoral alloimmune responses	**Potentially reduced,** owing to immunomodulatory and tolerogenic effects	**Potentially reduced,** owing to generally weaker adaptive immune responses

Role of Estrogens in Immune Response



Size Matters

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TABLE 3 Graft survival rates according to BSAi.

Time after transplant	BSAi ≤ 1	1 < BSAi ≤ 2	2 < BSAi ≤ 3	BSAi > 3
Renal transplants from living donors				
1 year	96.7% ±0.9%	97% ±0.3%	97.6% ±0.5%	97% ±0.5%
5 years	78.4% ±2.4%	83.5% ±0.7%	92.7% ±0.9%	93.7% ±0.8%
10 years	58% ±3.3%	62.3% ±1.2%	80% ±1.6%	83.7% ±1.4%
Renal transplants from donors after brain death				
1 year	94.4% ±0.7%	95.9% ±0.3%	95.8% ±0.5%	95.4% ±0.7%
5 years	70% ±1.6%	76.3% ±0.7%	85% ±1.1%	89% ±1.2%
10 years	47.3% ±2.1%	53.5% ±1%	68.9% ±1.8%	73.3% ±2.2%

Abbreviation: BSAi, body surface area index.

Kostakis ID et al. Pediatric renal transplantation-A UNOS database analysis of donor-recipient size mismatch. Pediatr Transplant. 2023 May;27(3):e14470. doi: 10.1111/petr.14470.

Small Paediatric Donor Kidneys Perform Well

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- "Compared with ADKTx, **5-y graft function is superior in SDKTx** and graft survival is similar, even when performed as single KTx. Utilizing small donor organs, preferably as single kidneys in experienced centers, is a viable option to increase the donor pool for pediatric recipients."

ORIGINAL CLINICAL SCIENCE—GENERAL

Favorable Outcome After Single-kidney Transplantation From Small Donors in Children: A Match-controlled CERTAIN Registry Study

Schild, Raphael MD[1]; Carvajal Abreu, Karla MD[2]; Büscher, Anja MD[3]; Kanzelmeyer, Nele MD[4]; Lezius, Susanne MSc[5]; Krupka, Kai Dipl-Inform Med[6]; Weitz, Marcus MD[7]; Prytula, Agnieszka MD, PhD[8]; Printza, Nikoleta MD, MSc, PhD[9]; Berta, László MD[10]; Saygili, Seha Kamil MD[11]; Sellier-Leclerc, Anne-Laure MD[12]; Spartà, Giuseppina MD[13]; Marks, Stephen D. MD[14]; Kemper, Markus J. MD[15]; König, Sabine[16]; Topaloglu, Rezan MD[17]; Müller, Dominik MD[18]; Klaus, Günter MD[19]; Weber, Stefanie MD[19]; Oh, Jun MD[1]; Herden, Uta MD[20]; Carraro, Andrea PhD[21]; Dello Strologo, Luca MD[22]; Ariceta, Gema MD[23]; Hoyer, Peter MD[3]; Tönshoff, Burkhard MD, PhD[6]; Pape, Lars MD, PhD[3]

Author Information

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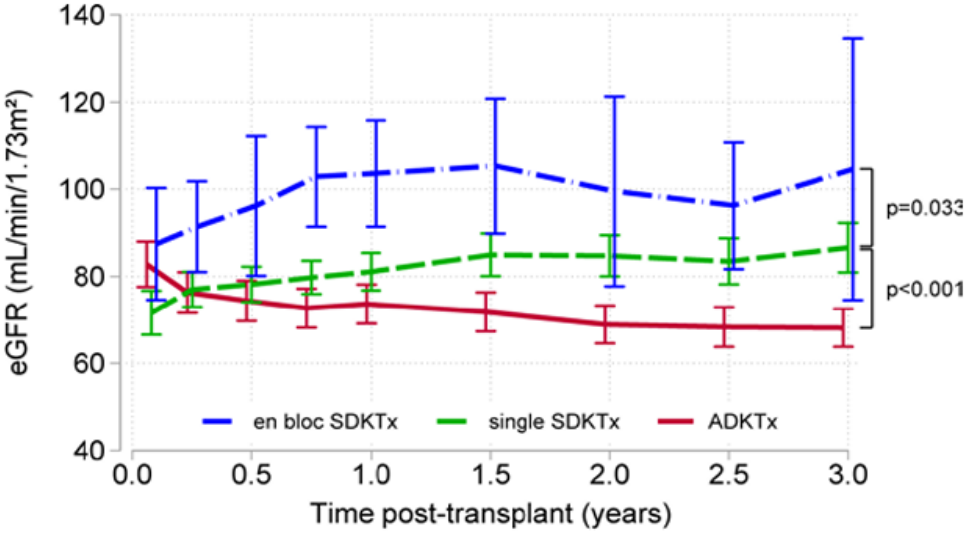


No. of observations							
en bloc SDKTx	23	22	21	19	14	10	8
single SDKTx	152	134	130	88	83	61	52
ADKTx	169	159	156	137	131	123	117

Encouraging outcomes of using a small-donor single graft in pediatric kidney transplantation.

Graphical Abstract

HYPOTHESIS: The use of small pediatric kidneys as single for transplantation is controversial

375 children (< 18y) Single graft KT

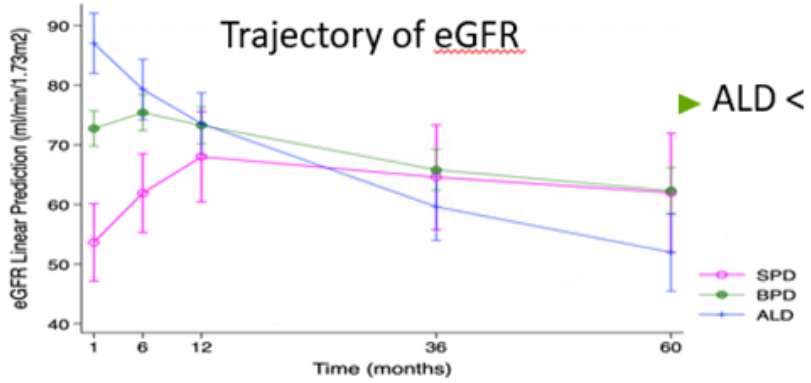
49 (13.1%)
SPD group, ≤ 15 kg
(small pediatric donor)

244 (65.1%)
BPD group, > 15 kg
(bigger pediatric donor)

82 (21.9%)
ALD group
(adult living donors)

Groups had similar baseline main characteristics

At 5 years of follow-up groups were similar in:



- ALD < BPD
- patient survival (94, 96, and 98%)
- graft survival (89, 88, and 93%)
- vascular thrombosis
- proteinuria
- acute rejection
- PTLD
- post-KT surgical intervention
- use of anti-hypertensive drugs

CONCLUSION: In a specialized transplant center, the use of a single small pediatric donor kidney for transplantation is as successful as bigger pediatric or adult living donors, after 5 years of follow-up.

Feltran LS et al. 2021

Pediatric Nephrology
Journal of the
IPNA International Pediatric Nephrology Association