HLA, Eplet Matching & Immunosuppressants in Kidney Transplantation

Sean Kennedy MBBS PhD FRACP

I have nothing to disclose…but my ignorance.

What makes pediatric transplantation special?

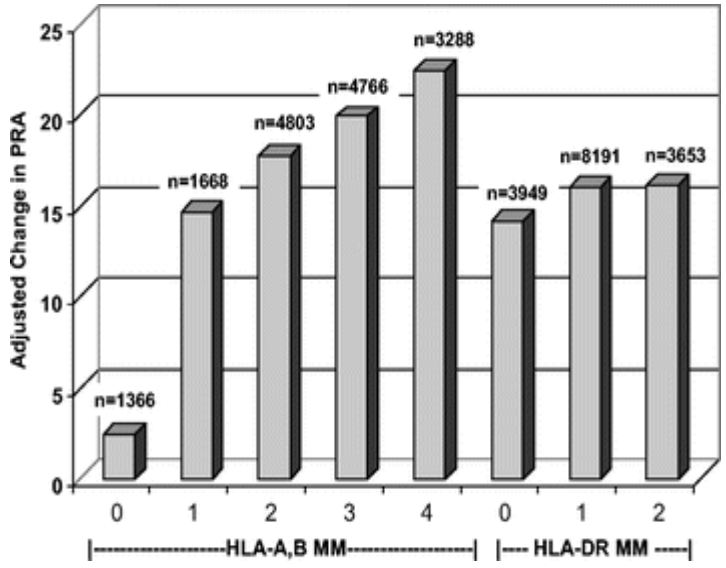
Most of our recipients will need a second transplant.

A lifetime versus a graft life approach redefines the importance of HLA matching in kidney transplant patients.
Meier-Kriesche HU et al Transplantation (2009)

15,980 patients relisted after loss of primary transplant

Factors associated with change in panel reactive antibody (PRA) from initial to subsequent listing

- Number of mismatches (MM) at HLA A, B or DR
- Living donor
- Younger recipient
- Longer duration between listings



What makes pediatric transplantation special 2 ?

Our recipients have to navigate the high risk period of adolescence and young adulthood.

NEPHROLOGY

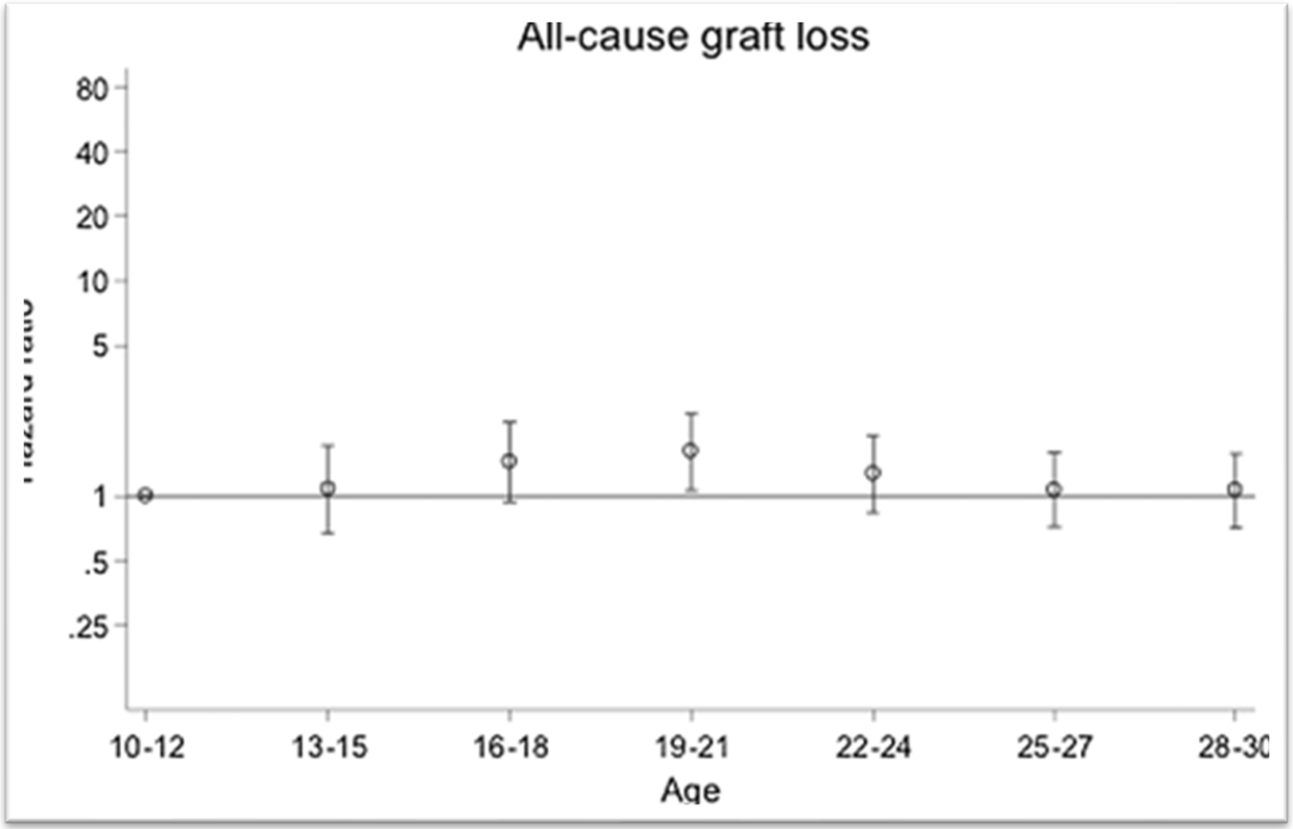
Nephrology **23** (2018) 585–591

Original Article

Age-specific risk of renal graft loss from late acute rejection or non-compliance in the adolescent and young adult period

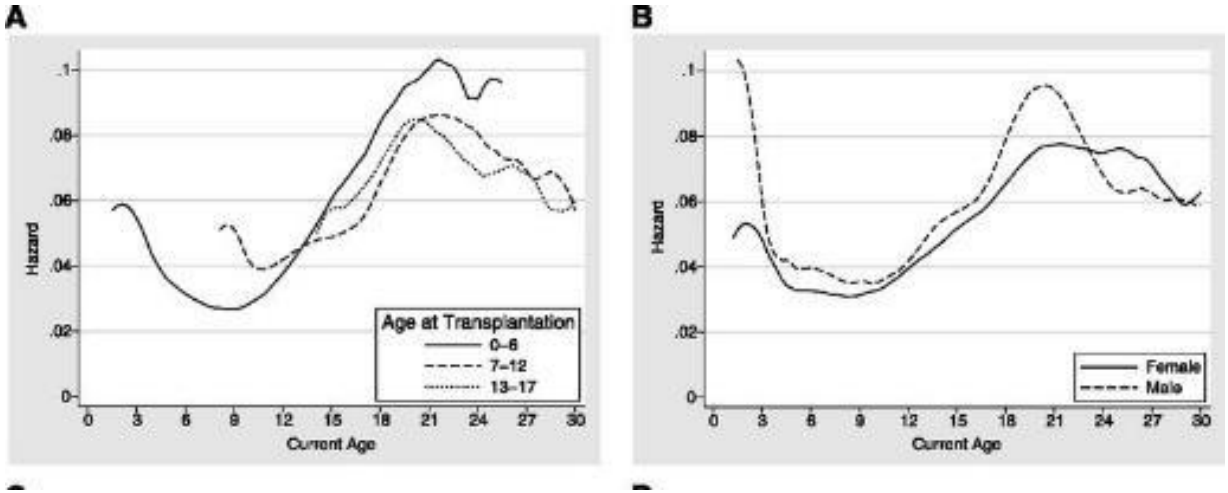
ANGUS G. RITCHIE,[1,2,3] PHILIP A. CLAYTON,[3,4] STEPHEN P. MCDONALD[3,5] and SEAN E. KENNEDY[1,2]

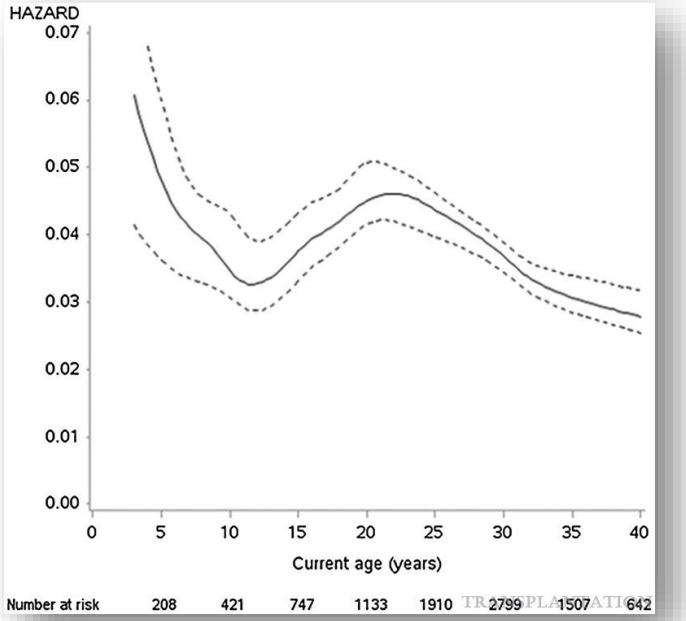
ANZ DATA
AUSTRALIA & NEW ZEALAND
DIALYSIS & TRANSPLANT REGISTRY



UNSW SYDNEY

***Age at Graft Loss after Pediatric Kidney Transplantation*: Exploring the High-Risk Age Window.** *Kyle J. Van Arendonk et al. CJASN 2013;8:1019-1026*





Age-Dependent Risk of Graft Failure in Young Kidney Transplant Recipients
Remi Kaboré et al. Transplantation101(6):1327-1335, June 2017.

Pediatric Transplantation

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Medication Adherence Status and Influencing Factors in Adolescent Kidney Transplant Recipients

Yanhua Li[1] | Yutong Chen[1] | Shijun Pu[1] | Suxia Yang[1] | Li Zeng[1] | Yazhe Duan[2] | Xiaoying Lu[2] | Wenyu Zhao[1]

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60% of 115 adolescent kidney transplant recipients reported poor adherence

UNSW SYDNEY

Nephrology

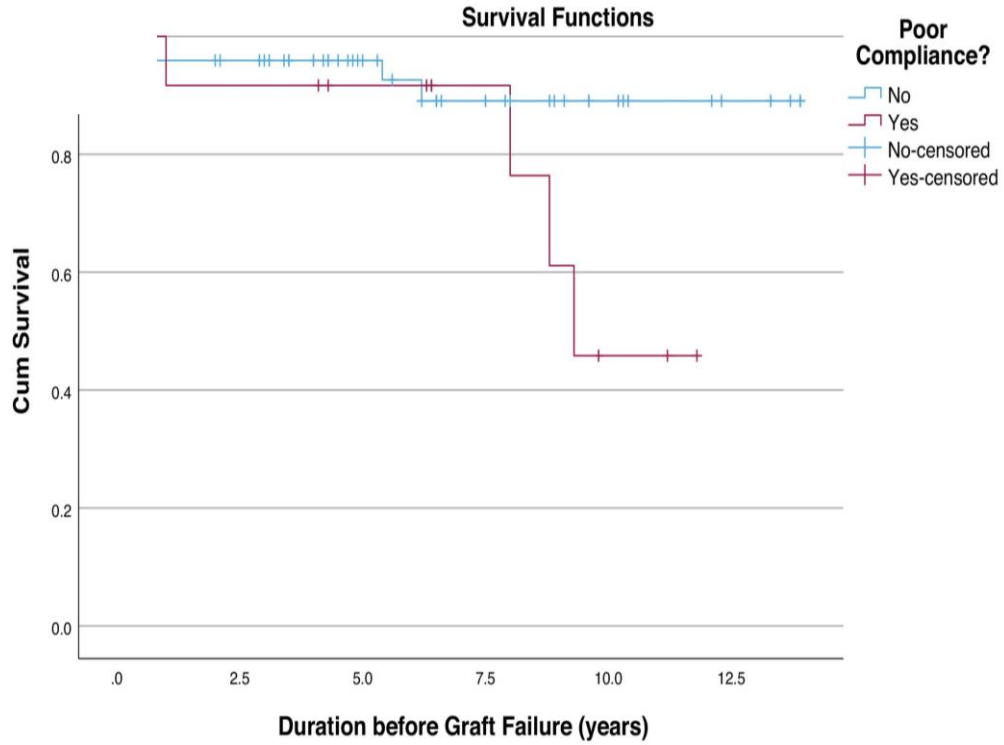
WILEY

NEPHROLOGY

ORIGINAL ARTICLE OPEN ACCESS

Long-Term Clinical Outcomes of Paediatric Kidney Transplantation in Hong Kong—A Territory-Wide Study

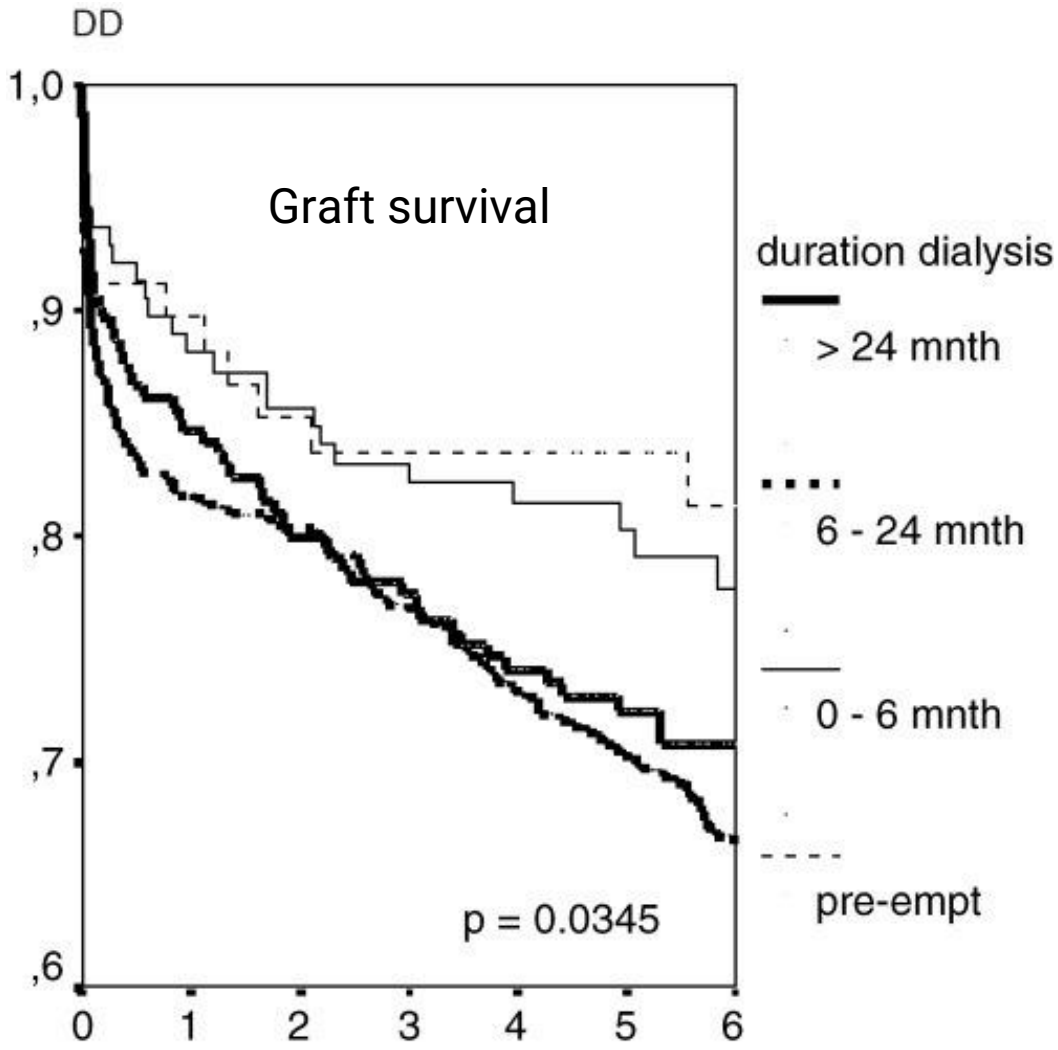
Tsz-wai Ho[1] | Alison Lap-Tak Ma[1] | Lawrence K. Ma[2] | Fiona Fung-Yee Lai[3] | Kyle Ying-kit Lin[1] | Sze-wa Wong[1] | Justin Ming-yin Ma[1] | Pak-chiu Tong[1] | Wai-ming Lai[1] | Desmond Y. H. Yap[4] | Eugene Yu-Hin Chan[1,5]



Duration of Dialysis Before Transplant Impacts Graft Survival

Kidney Transplantation Without Prior Dialysis in Children: The Eurotransplant Experience.
Cransberg, K. et al
American Journal of Transplantation 2006

1113 first kidney transplants in children performed between 1990 and 2000



The Perfect Donor Kidney

- Living donor, short ischemia time
- Young adult donor
- Male donor for male recipients
- Same blood group
- No preformed antibodies
- Well matched

HLA matching

HLA class I: A, B & C are

- expressed on nearly all nucleated cells
- signal to CD8 T cells for killing

HLA class II: DR, DQ & DP

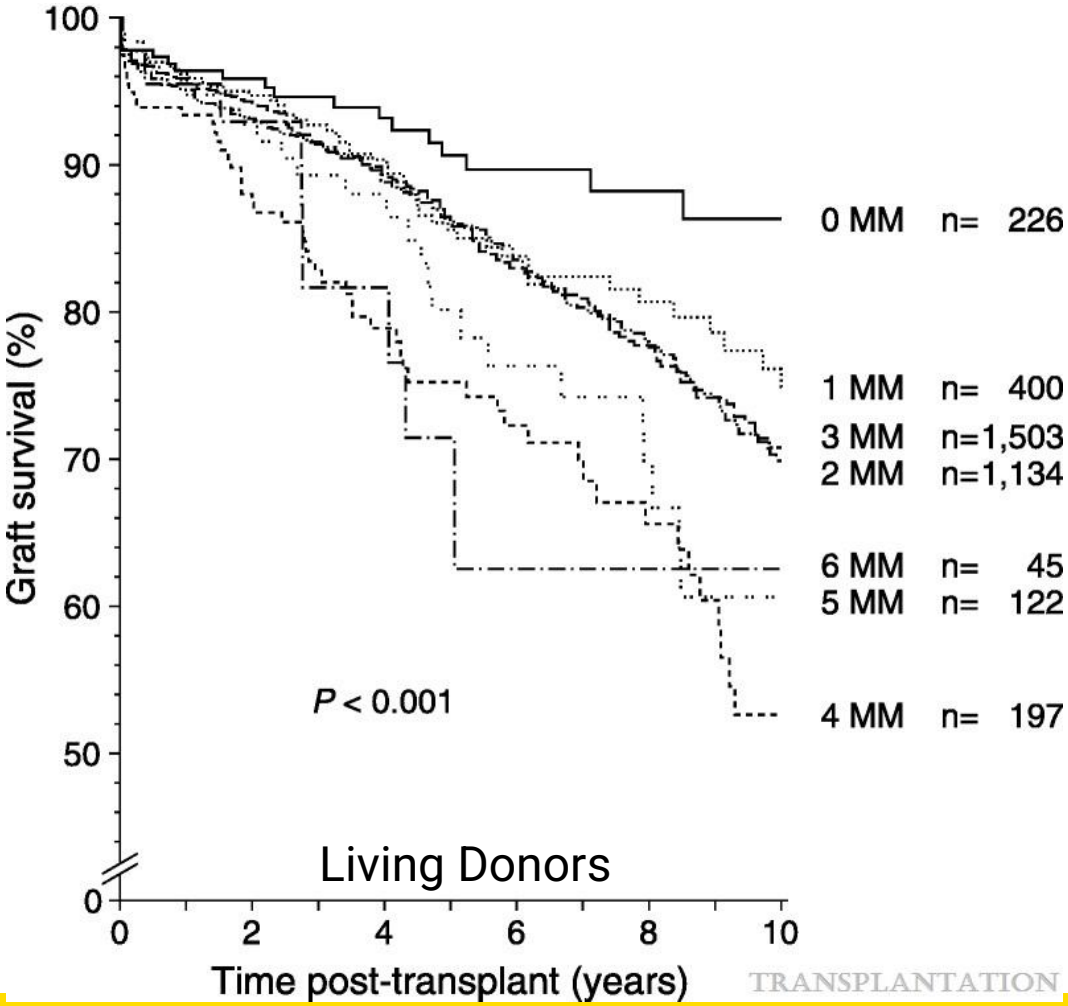
- antigen-presenting cells (APC)
- activate CD4 T cells

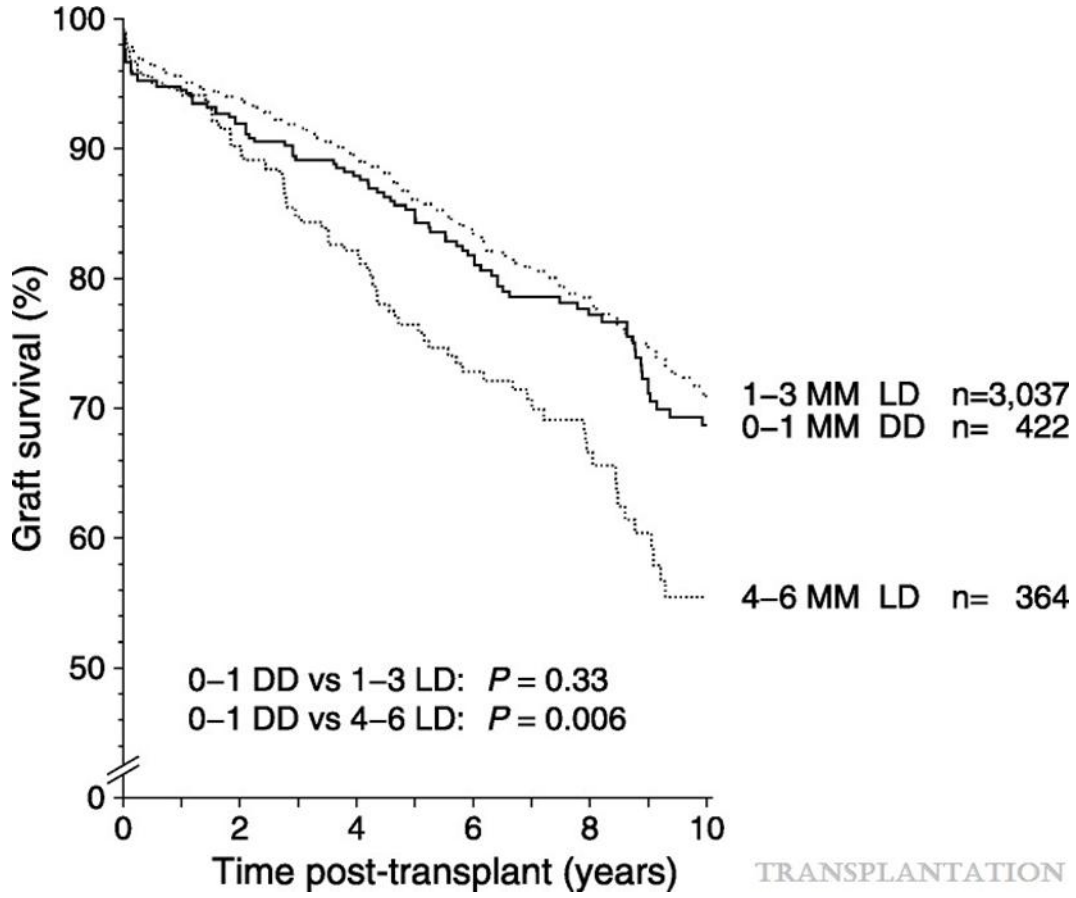
- Traditional matching has used A, B & DR

HLA Matching in Pediatric Kidney Transplantation: HLA Poorly Matched Living Donor Transplants Versus HLA Well-Matched Deceased Donor Transplants

Opelz, Gerhard; Döhler, Bernd; Middleton, Derek; Süsal, Caner; A Collaborative Transplant Study Report

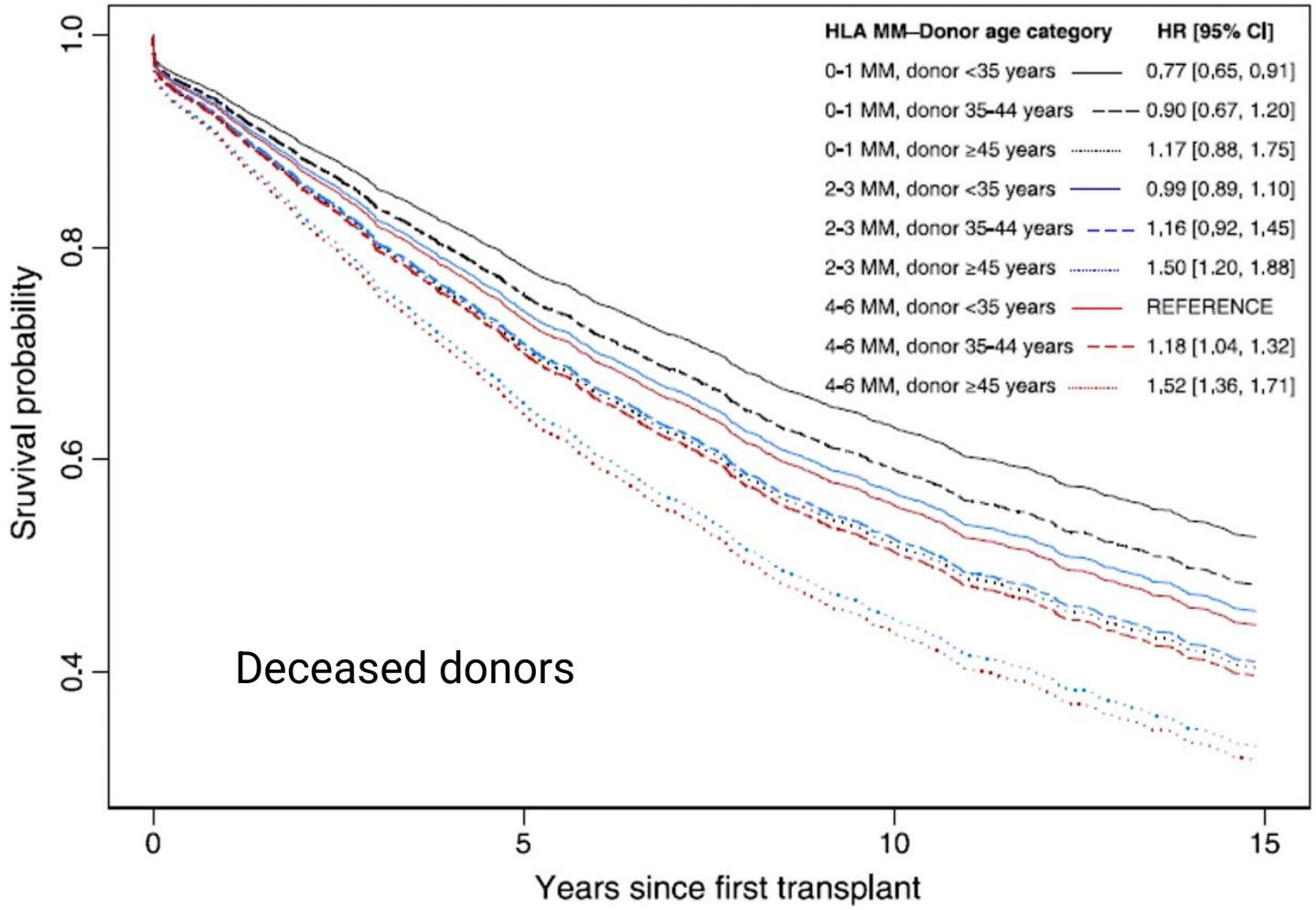
Transplantation 2017





Relative importance of HLA mismatch and donor age to graft survival in young kidney transplant recipients.
Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA Transplantation 2013.

The most poorly matched grafts from the oldest LD had survival similar to or better than any DD.

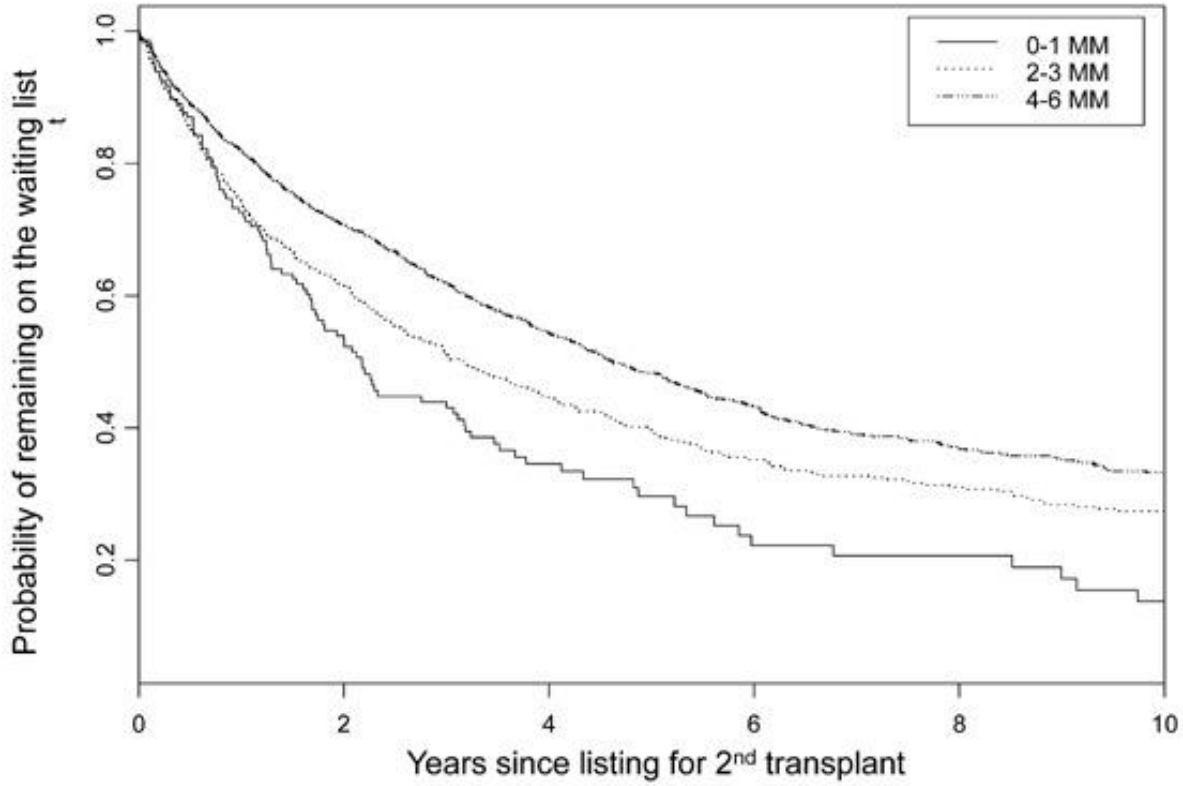


HLA MM & impact on subsequent transplantation

Impact of HLA Mismatch at First Kidney Transplant on Lifetime With Graft Function in Young Recipients

Foster, B.J. et al.

American Journal of Transplantation 2014



	0	1	2	5	10
0-1 MM	146	104	66	21	8
2-3 MM	698	504	393	191	70
4-6 MM	1654	1293	1002	470	172

HLA Class II mismatches

DR mismatches associated with

- higher risk of donor specific antibody development and
- antibody mediated rejection (ABMR)
- sensitisation at subsequent transplant

DQ mismatches associated with

- higher risk of donor specific antibody development and
- Acute rejection
- inferior graft survival

Is HLA-DQ mismatching associated with graft loss and acute rejection?

CJASN
Clinical Journal of American Society of Nephrology

Cohort

Primary kidney transplants

UNOS/OPTN data
2005-2014

N=93,782

4.1 years median follow-up

Predictor

HLA-DQ mismatches

Zero mismatch
N=22,730

1 or 2 mismatch
N=71,052

Adjusted for HLA-ABDR, recipient, donor and transplant factors

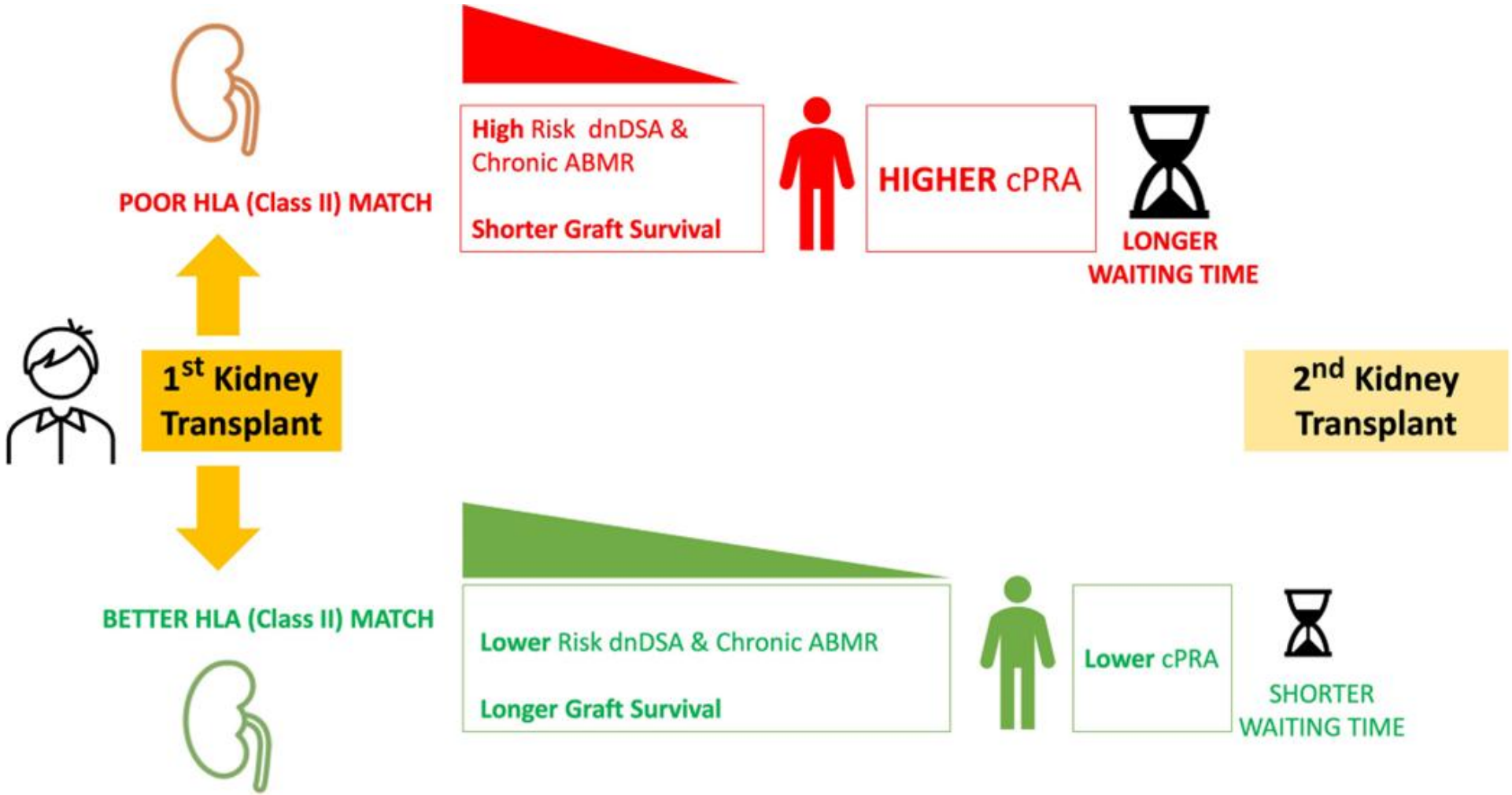
Findings

1 or 2 mismatch compared to zero mismatch
aHR and aOR (95% CI)

	Death-censored graft loss	Acute rejection at 1 year
Living donor	1.18 (1.07-1.30)	1.14 (1.03-1.27)
Deceased donor	1.05 (0.98-1.12)	1.13 (1.02-1.23)
Cold ischemic time ≤17h	1.12 (1.02-1.27)	
Cold ischemic time >17h	0.97 (0.88-1.06)	

Conclusions HLA-DQ mismatching is associated with graft loss and acute rejection independent of HLA-ABDR. Cold ischemic time >17 hours appears to obviate the benefit of zero HLA-DQ mismatches.

Napat Leeaphorn, Jeremy Pena, Natanong Thamcharoen, Eliyahu Khankin, Martha Pavlakis, and Francesca Cardarelli. HLA-DQ Mismatching and Kidney Transplant Outcomes. CJASN doi: 10.2215/10860917.



HLA (emphasis on DQ) compatibility for longer allograft survival in pediatric transplantation: Modern evidence and challenges. *Maria Meneghini, Anat Roitberg Tambur. Pediatric Transplantation 2023*

Molecular Matching

Matching at the amino acid sequence level

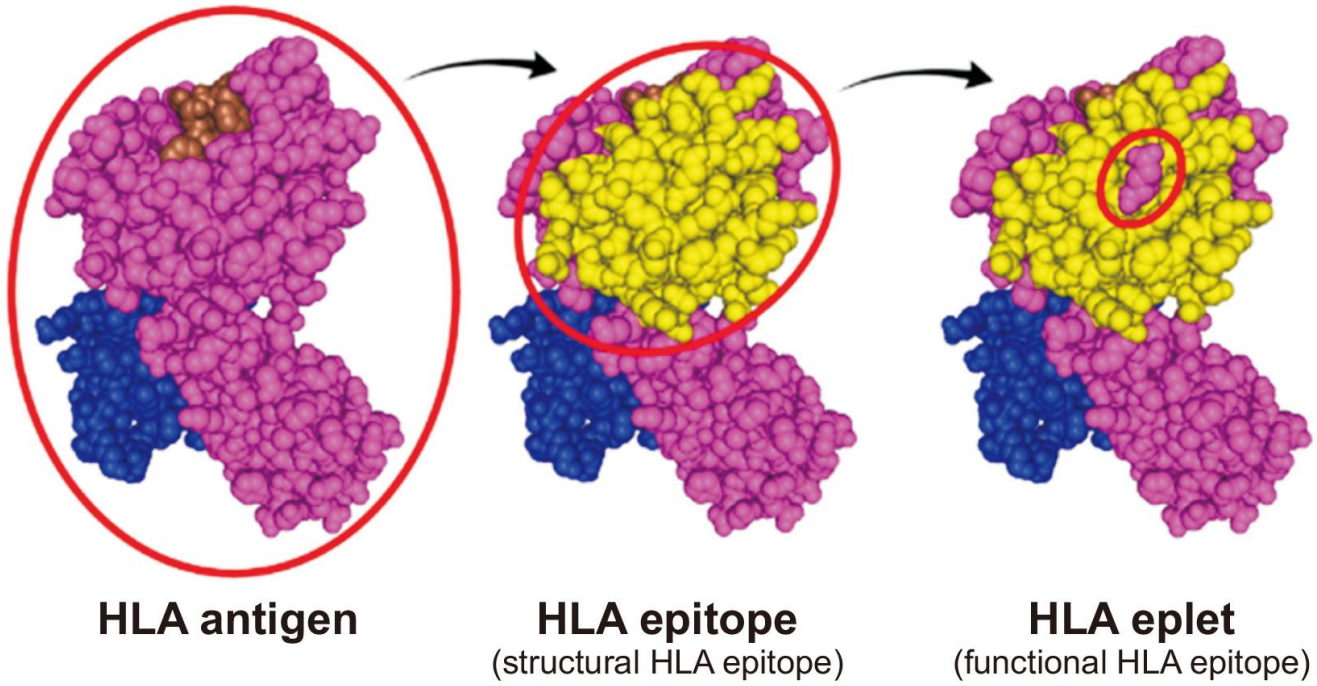
- Eplets
- Amino acid mismatches
- Indirectly presented peptides (netMHCIIpan)
- Electrostatic mismatches
- PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes Presented by HLA Class II Molecule

Eplets

Polymorphic residues on HLA recognized by B cell receptors.

HLA Matchmaker

- Requires high resolution HLA typing of recipient and donor/pool
- Converts HLA alleles to eplets
- Identifies mismatched eplets



Lee H, Oh EJ. Eplet mismatch analysis in kidney transplantation: from concept to clinical practice. Clin Transplant Res. 2025

Higher Molecular Mismatch

Associated with

- De novo DSA
- Antibody mediated rejection (possibly TCMR)
- Graft failure
- Most marked for class II, particularly DQ mismatch
- Linear relationship between eplet load and risk
- May be modified by tacrolimus exposure
  - Lower trough levels or higher co-efficient of variability increase risk

Molecular HLA mismatching for prediction of primary humoral alloimmunity and graft function deterioration in paediatric kidney transplantation *JJ Kim et al. Frontiers in Immunology 2023*

Using eplet mismatching

Retrospectively:

- Risk stratify and guide monitoring (DSA) and management (tacrolimus dosing)

Prospectively: Questions remain

- What is an acceptable eplet mismatch load?
  - HLA I <10 and HLA II <30 (Kausman 2016)
- Is timely eplet matching available for DD?
- Can you access paired kidney exchange?
- What is the impact on waiting time and donor quality?

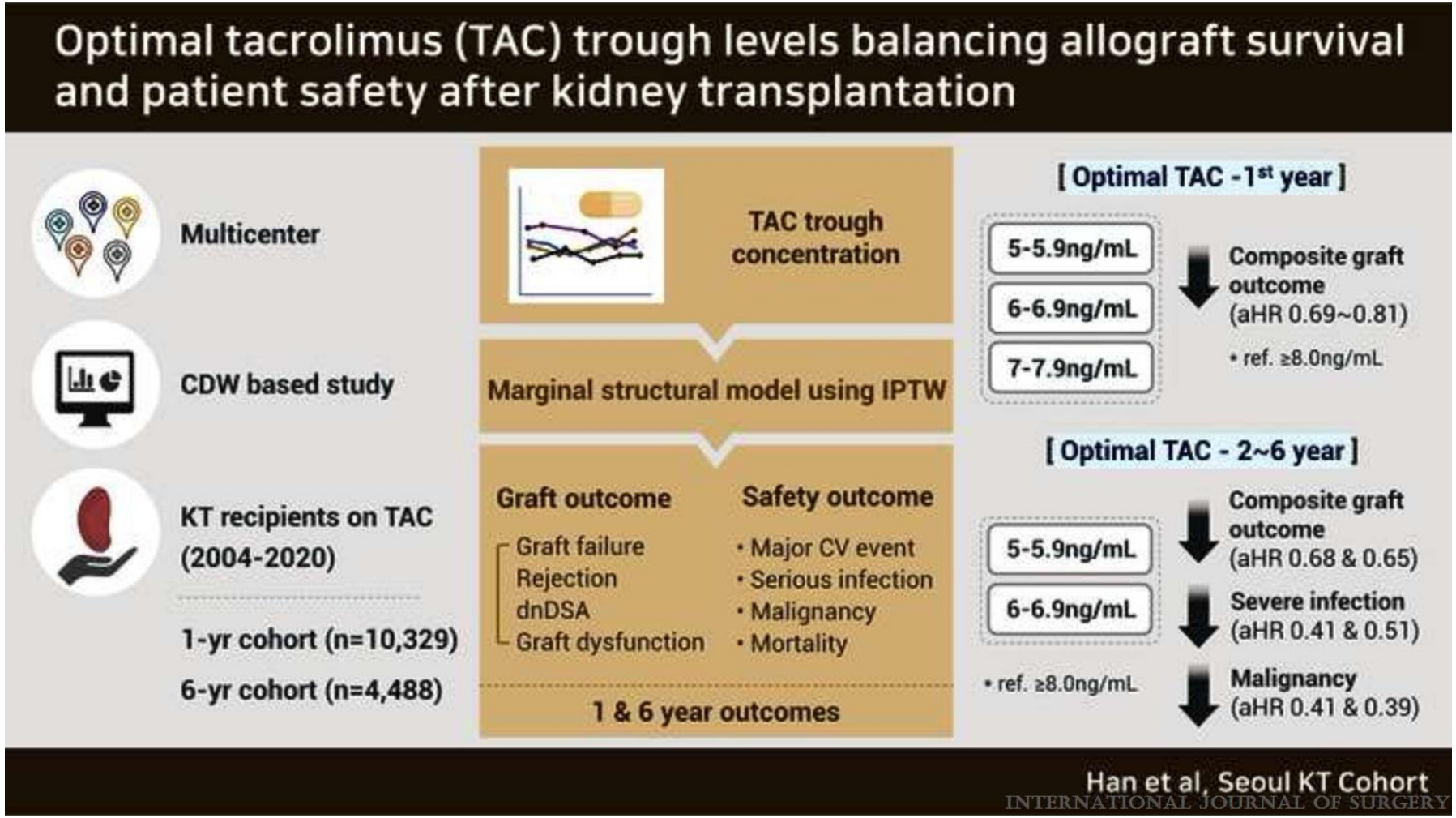
Tacrolimus dosing

Avoid <5 ng/mL

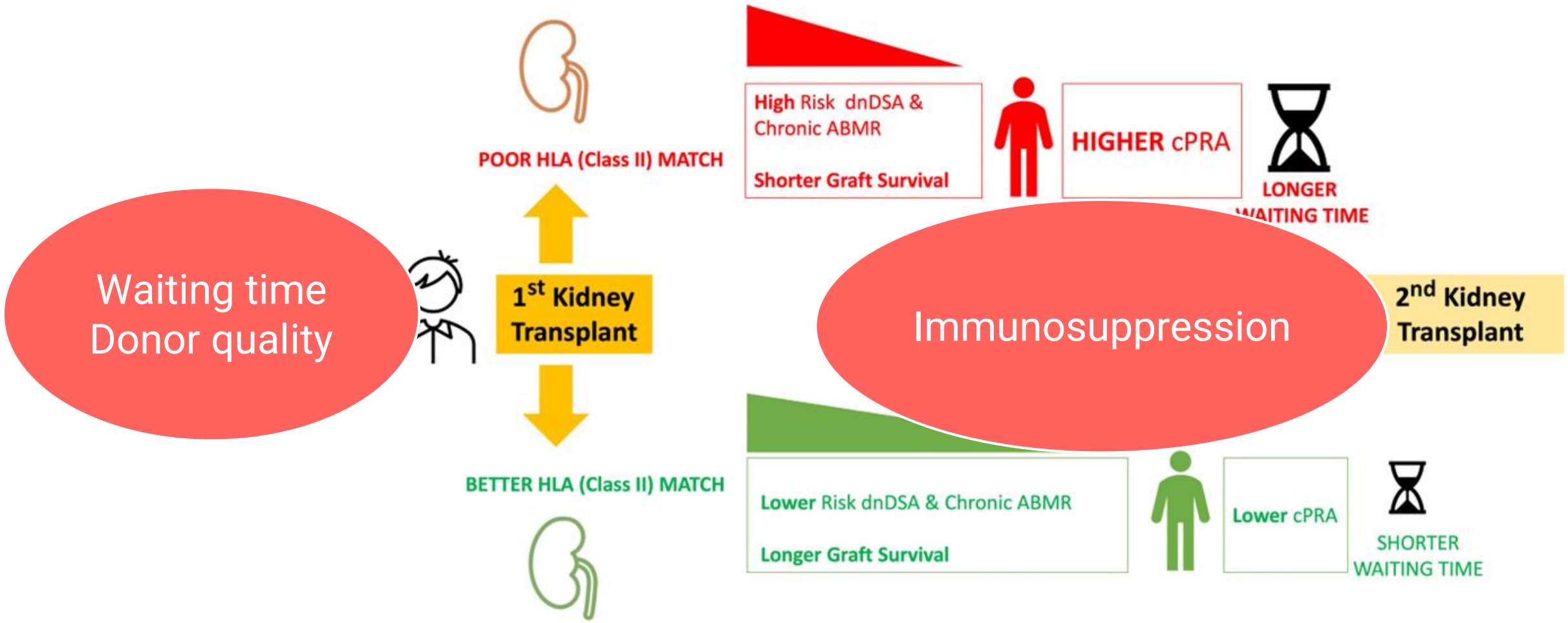
Most guidelines target 5-8 ng/mL after 1 year

Higher target if high risk

What level is associated with tac toxicity?



Han, Ahram; Jo, Ae Jeong; Kwon, Hyunwook; Kim, Young Hoon; et al
International Journal of Surgery110(10):6711-6722, October 2024.


Waiting time
Donor quality
POOR HLA (Class II) MATCH
1st Kidney Transplant
BETTER HLA (Class II) MATCH
High Risk dnDSA & Chronic ABMR
Shorter Graft Survival
HIGHER cPRA
LONGER WAITING TIME
Immunosuppression
2nd Kidney Transplant
Lower Risk dnDSA & Chronic ABMR
Longer Graft Survival
Lower cPRA
SHORTER WAITING TIME