The impact of HLA-DQ molecular mismatches on *de novo* occurrence of donor-specific anti-HLA antibodies after kidney transplantation: an observational cohort study

Aleksandar Senev, Maarten Coemans, Vicky Van Sandt, Elisabet Van Loon, Evelyne Lerut, Jasper Callemeyn, Ben Sprangers, Dirk Kuypers, Marie-Paule Emonds, Maarten Naesens

Nephrology and Renal Transplantation Research Group

aleksenev@yahoo.com @Senev

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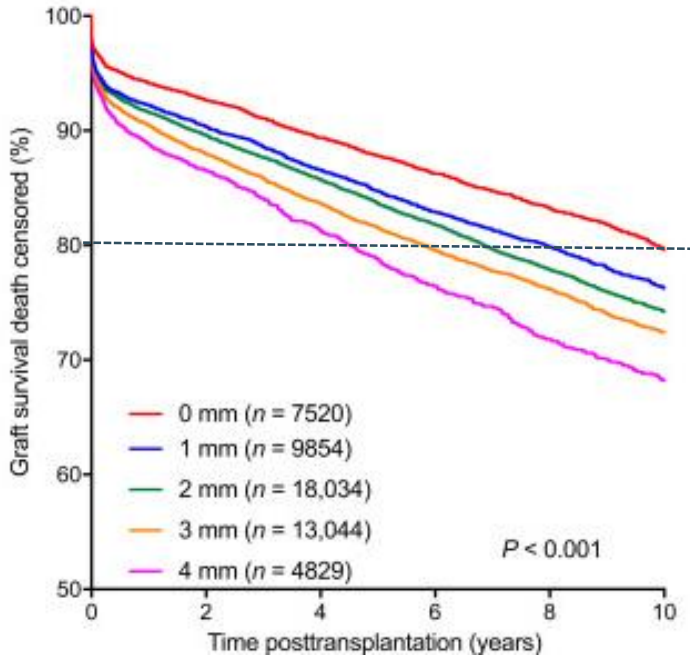
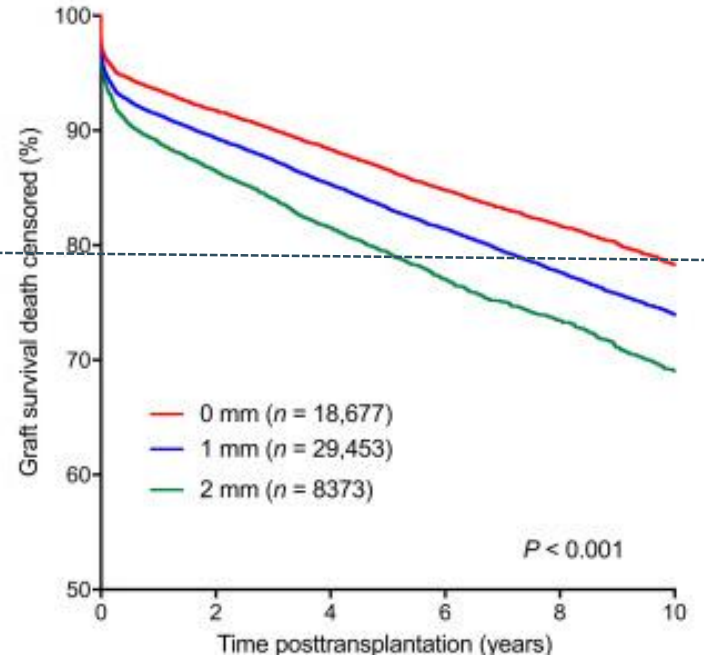
Belgian Red Cross Flanders

After kidney transplantation, graft failure remains a huge problem

- Antigen HLA matching for Class I (A, B)
- Antigen HLA matching for Class II (DR)





~80%

Heidt et al. Kidney Int 2018;93,491-500

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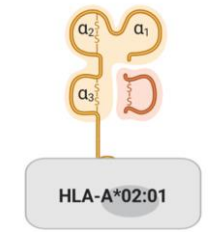
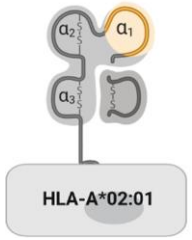
HLA epitope-based matching in transplantation

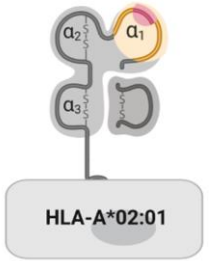
- HLA epitope/eplet analysis gives the possibility for better HLA matching and to improve the long-term graft survival.



“Antigen” – entire HLA molecule



“**Epitope**” is the part of an antigen (polymorphic **amino acid residues** on the molecular surface) that is recognized by the immune system (antibody).



“**Eplet**” is a portion (**key element**) of the epitope that determine the antibody **specificity**.

Objectives

- In a large high-resolution HLA genotyped cohort:
  - To evaluate the impact of the eplet mismatches on de novo DSA formation after transplantation

  - To evaluate the impact of the eplet mismatches on kidney allograft survival;

  - To investigate the effect of the eplet mismatches on ABMR and TCMR rejection;

Patients and allograft histology

- Included 926 single kidney transplantations:
  - all transplantations were performed with CDC-XM negative;
- Transplanted at University Hospitals Leuven (Belgium):
  - between March 2004 and February 2013
  - No patient received preconditioning HLA antibody desensitization
- Indication and protocol kidney allograft biopsies:
  - posttransplant at 3M, 1-, 2-, 3-, 4-, 5-year
  - all rescored to the latest Banff 2017

N=926

UZ Leuven

2004 - 2013

3617 biopsies

HLA profiling of the cohort

Anti-HLA antibodies was systematically monitored in one HLA laboratory (HILA - Red Cross Flanders).

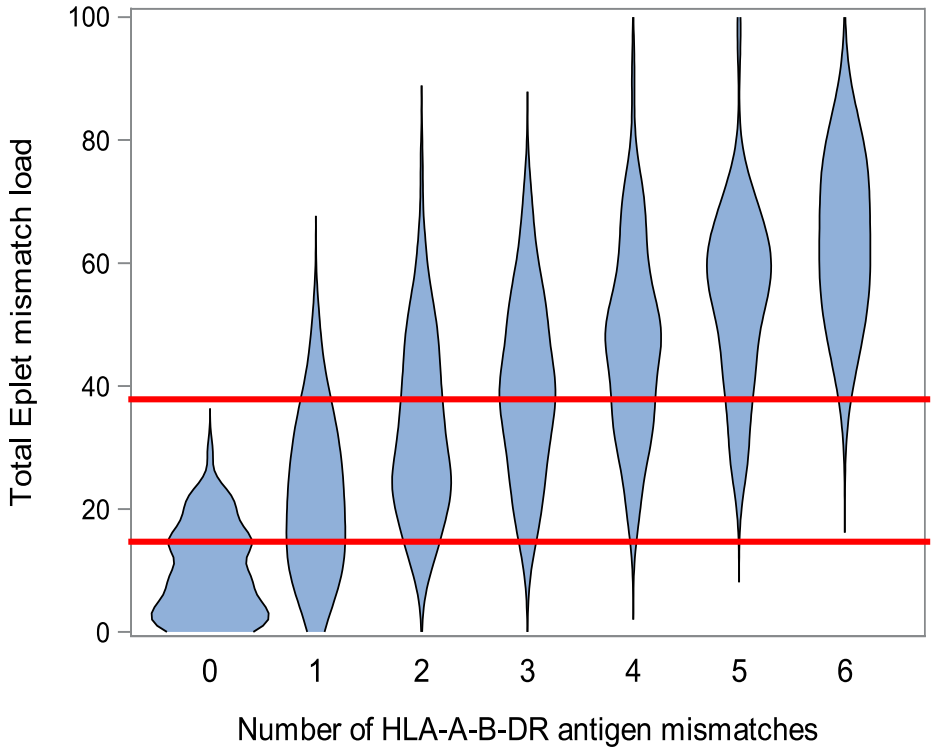
- LIFECODES LifeScreen Deluxe (LMX) kit
- LIFECODES Single Antigen Bead (LSA) kits

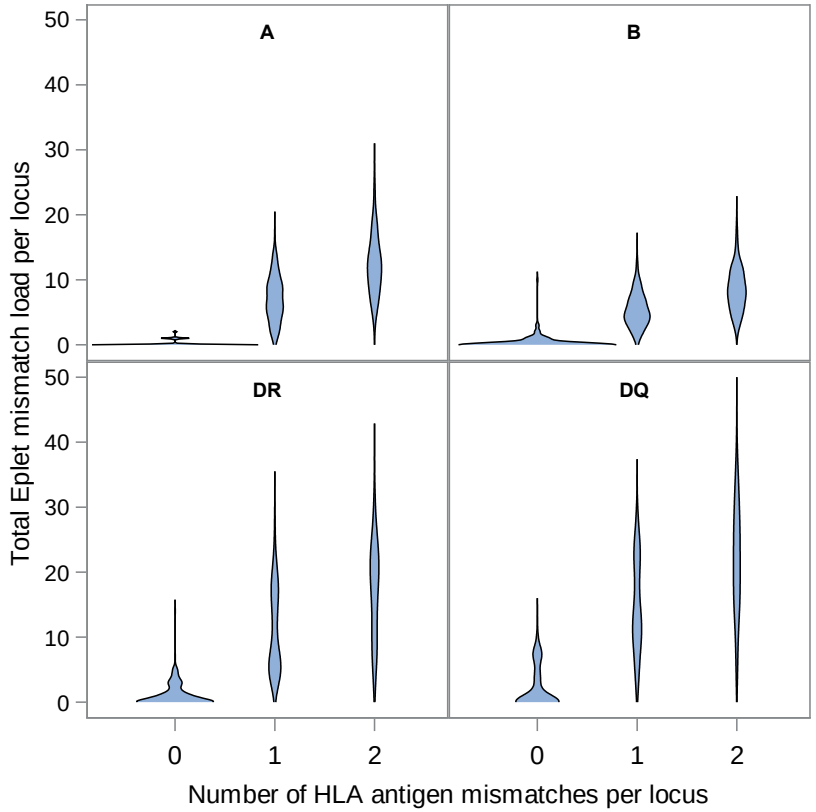
IMMUCOR

- High-resolution HLA typing of the transplant pairs by NGS:
  - MIA FORA NGS FLEX 11 HLA Typing Kit (Immucor)
  - Antigen Recognition Site (exon 2, 3 and 4 for HLA class I and exon 2 and 3 for HLA class II)

HLAMatchmaker (HLA-ABCv02 and HLA-DRDQDPv02.2) to calculate the total number of eplet mismatches (theoretically predicted and antibody-verified eplets);

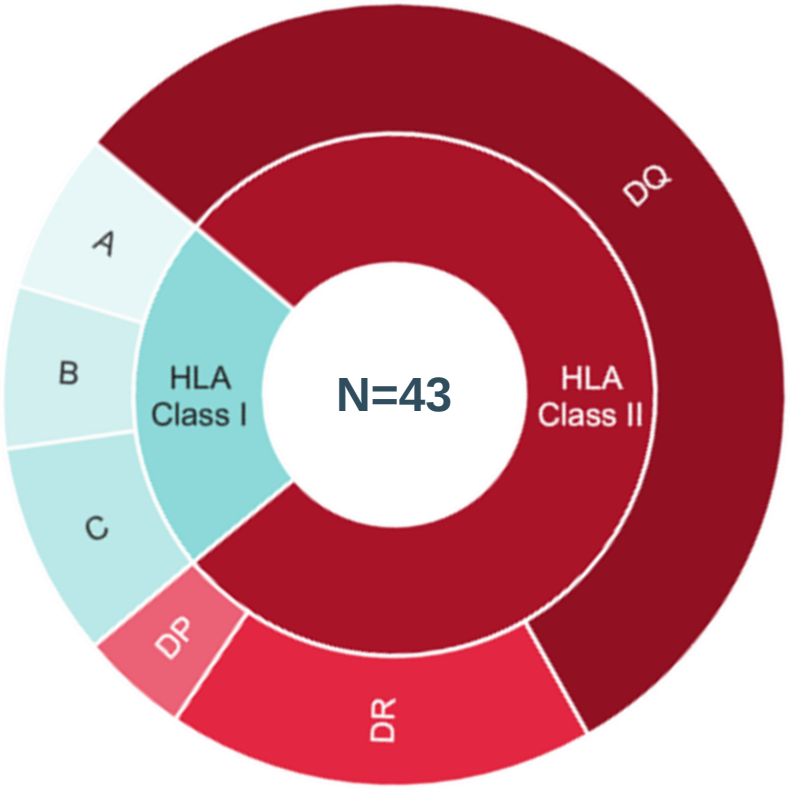
Eplet mismatch load and antigen mismatches





De novo DSA occurrence in the study cohort

- 43 (4,6%) patients developed de novo DSA after transplantation

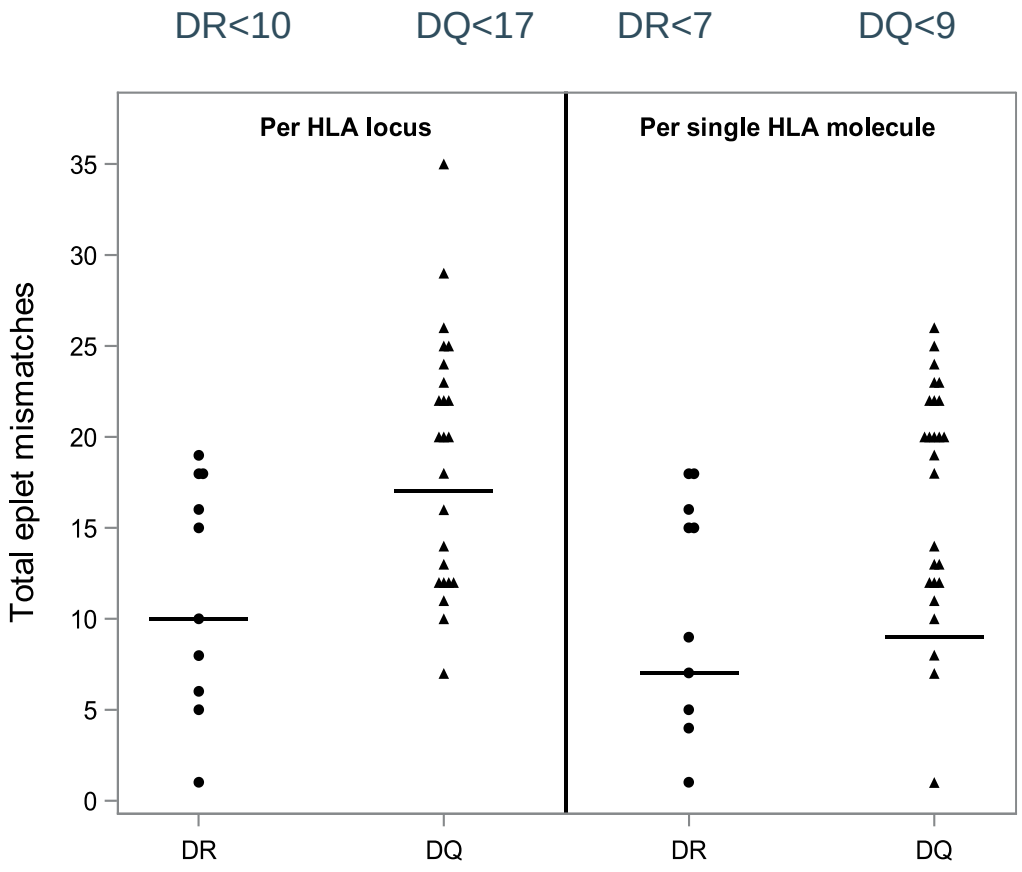


Eplets and de novo DSA occurrence

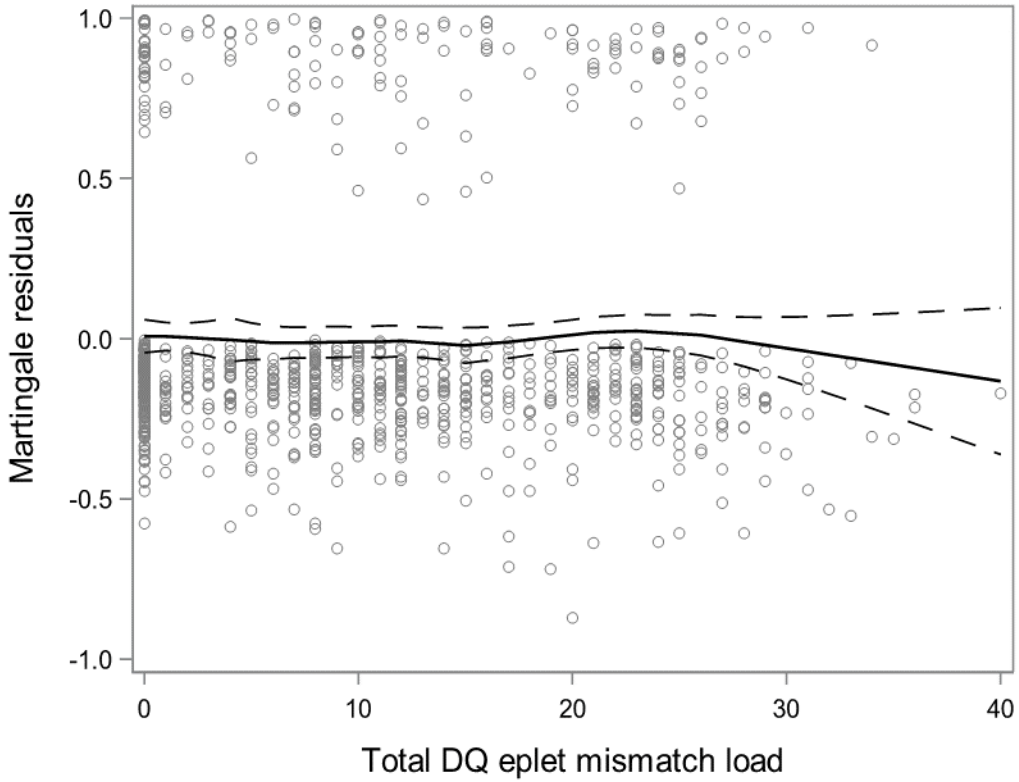
HLA eplet mismatches	Patients at risk	Events	Multivariate Hazard ratio (95%CI)	P value
Total eplets	926	43	1.02 (1.00 - 1.04)	**0.02**
Antibody-verified eplets	926	43	1.06 (1.02 - 1.10)	**0.002**
A molecule	926	43	1.08 (0.99 - 1.19)	0.09
B molecule	926	43	0.94 (0.80 - 1.10)	0.41
C molecule	926	43	0.98 (0.83 - 1.16)	0.82
DR molecule	926	43	1.05 (0.96 - 1.14)	0.27
DQ molecule	926	43	**1.14** (1.07 - 1.22)	**<0.001**
DP molecule	926	43	1.00 (0.82 - 1.21)	0.98

- per single mismatched eplet

There is no specific threshold for DQ eplet mismatches for de novo DSA occurrence



- Martingale residual plot



Wiebe et al. Am J Transplant 2013
Wiebe et al. Am J Transplant 2019

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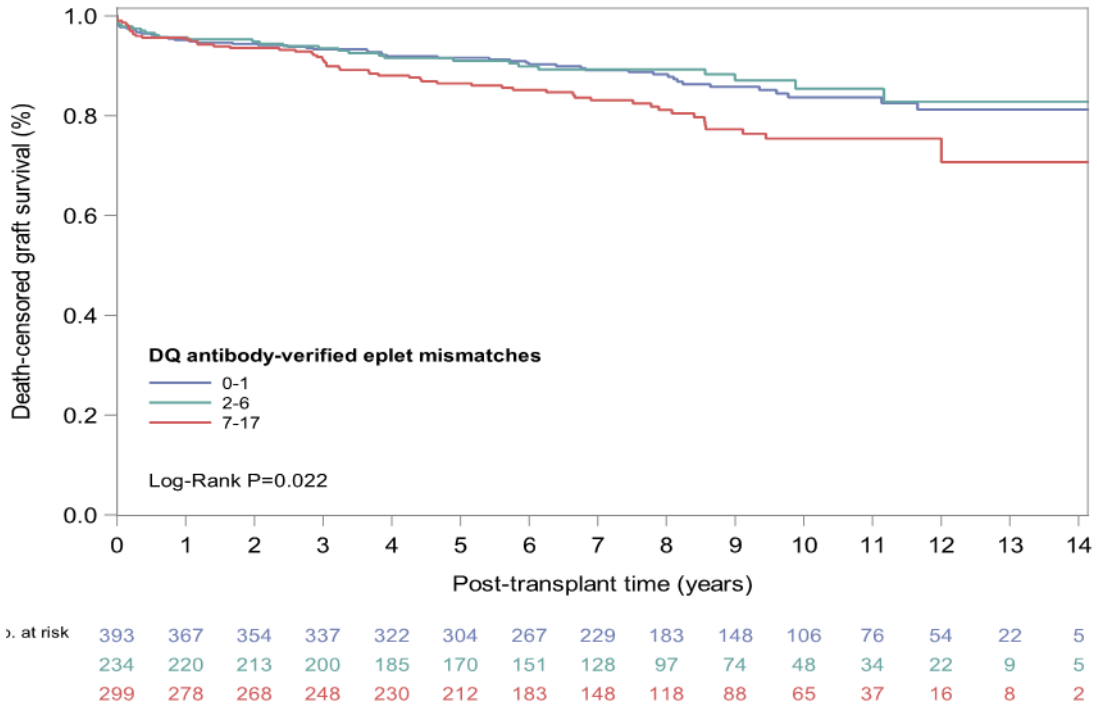
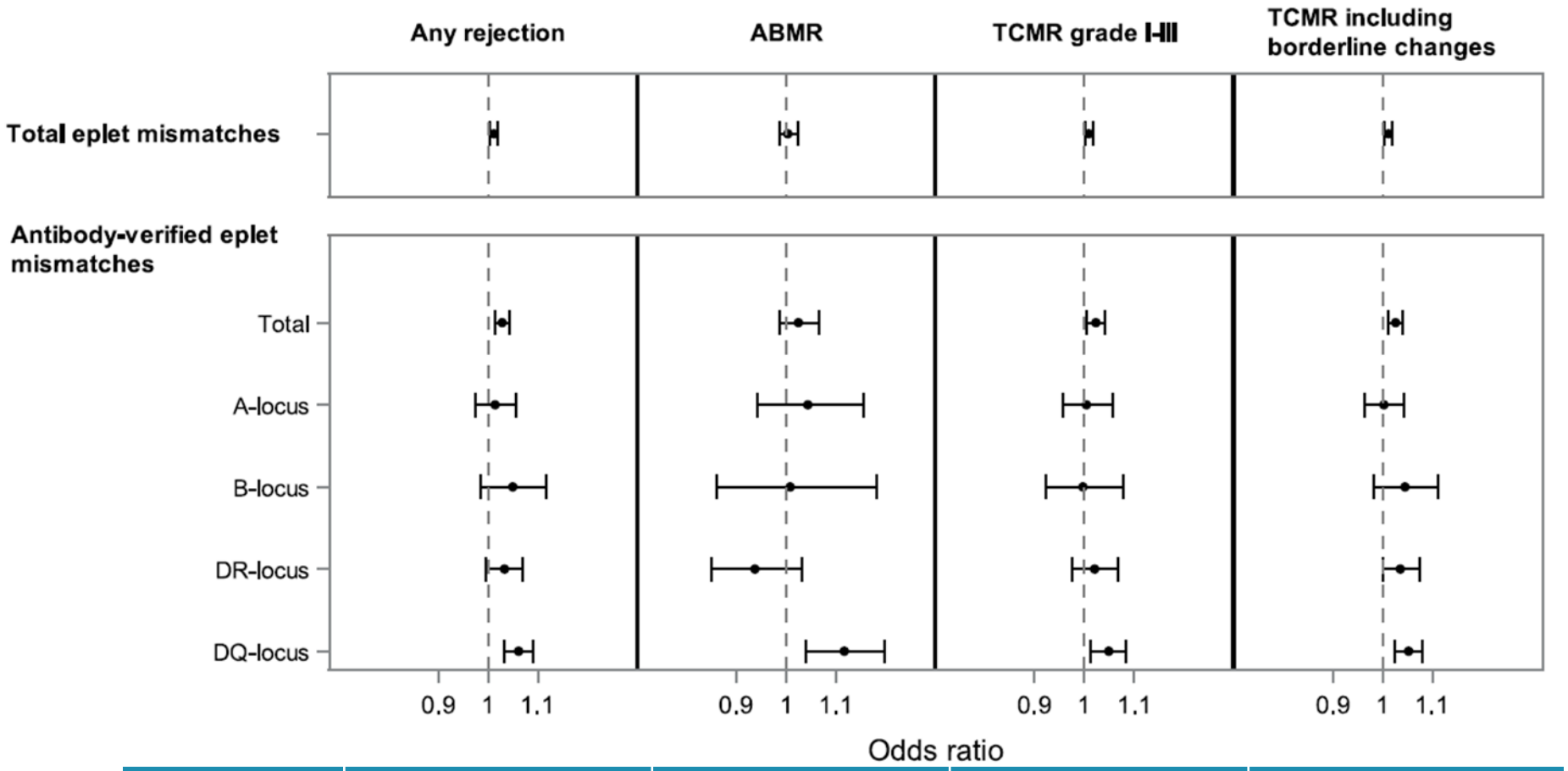
Multivariate hazard ratios for death-censored graft survival and KM curves

HLA mismatches	Patients at risk	Events	Multivariate[a] Hazard ratio (95% CI)	P value
Total eplets	926	134	1.01 (1.00 - 1.02)	0.072
Antibody-verified eplets	926	134	1.02 (1.003 - 1.04)	**0.02**
A molecule	926	134	1.05 (0.99 - 1.10)	0.11
B molecule	926	134	1.09 (1.00 - 1.18)	**0.04**
C molecule	926	134	0.98 (0.89 - 1.07)	0.60
DR molecule	926	134	1.01 (0.96 - 1.06)	0.85
DQ molecule	926	134	**1.05** (1.01 - 1.09)	**0.01**
DP molecule	926	134	1.00 (0.90 - 1.12)	0.97



- per single mismatched eplet

Effects of eplet mismatches on kidney allograft histology



DQ molecule	1.06 (1.03 - 1.09) p=≤0.001	1.12 (1.04 - 1.20) p=0.002	1.05 (1.01 - 1.08) p=0.006	1.05 (1.02 - 1.08) p<0.001

Logistic mixed models

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Evaluate the discriminative ability of different models

De novo occurrence DSA	
HLA-mismatch models	**Multivariate c-statistic (95% CI)**
Antigen	
HLA-ABDR	0.71 (0.67—0.83)
HLA-ABDRDQ	0.71 (0.66—0.84)
Eplets	
Total antibody-verified eplets	0.72 (0.68—0.84)
DQ antibody-verified eplets	**0.74 (0.69—0.85)**
Combination	
HLA-ABDR antigens + DQ antibody-verified eplets	0.74 (0.70—0.86)
HLA-ABDRDQ antigens + DQ antibody-verified eplets	0.74 (0.70—0.86)

Harrell's C-index

Summary

- We found that antibody-verified eplet mismatches in DQ but not in the other HLA loci confer a significant risk for development of de novo DSA;
- We found no clear threshold for risk of de novo DSA occurrence;
- We demonstrated that DQ antibody-verified eplet mismatches confer a significant risk for graft rejection and graft failure after kidney transplantation;
- This suggests that molecular DQ matching may improve long-term graft survival.

Thank you!

Questions?

aleksenev@yahoo.com @Senev @NephroLeuven

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