Supplemental material

The impact of eplet mismatch load on de novo occurrence of donor-specific anti-HLA antibodies, rejection and graft failure after kidney transplantation: an observational cohort study

Aleksandar Senev[1,2,], Maarten Coemans[1,3*], Evelyne Lerut[4], Vicky Van Sandt[2], Johan Kerkhofs[2], Liesbeth Daniëls[2], Marleen Vanden Driessche[2], Veerle Compernolle[2], Ben Sprangers[1,5], Elisabet Van Loon[1,5], Jasper Callemeyn[1,5], Frans Claas[6], Anat R. Tambur[7], Geert Verbeke[3], Dirk Kuypers[1,5], Marie-Paule Emonds[1,2*] and Maarten Naesens[1,5*]*

[1] Department of Microbiology, Immunology and Transplantation, KU Leuven, University of Leuven, Belgium
[2] Histocompatibility and Immunogenetics Laboratory, Belgian Red Cross-Flanders, Mechelen, Belgium
[3] Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat), Department of Public Health and Primary Care, KU Leuven—University of Leuven, Leuven, Belgium
[4] Department of Imaging & Pathology, University Hospitals Leuven, Leuven, Belgium
[5] Department of Nephrology and Renal Transplantation, University Hospitals Leuven, Leuven, Belgium
[6] Department of Immunohematology and Blood Transfusion, Leiden University Medical Centre, Leiden, the Netherlands
[7] Transplant Immunology Laboratory, Comprehensive Transplant Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

Contents

Both first and last authors contributed equally.
Correspondence to Maarten Naesens, maarten.naesens@uzleuven.be.

***Figure S1*: Flow chart inclusion criteria**

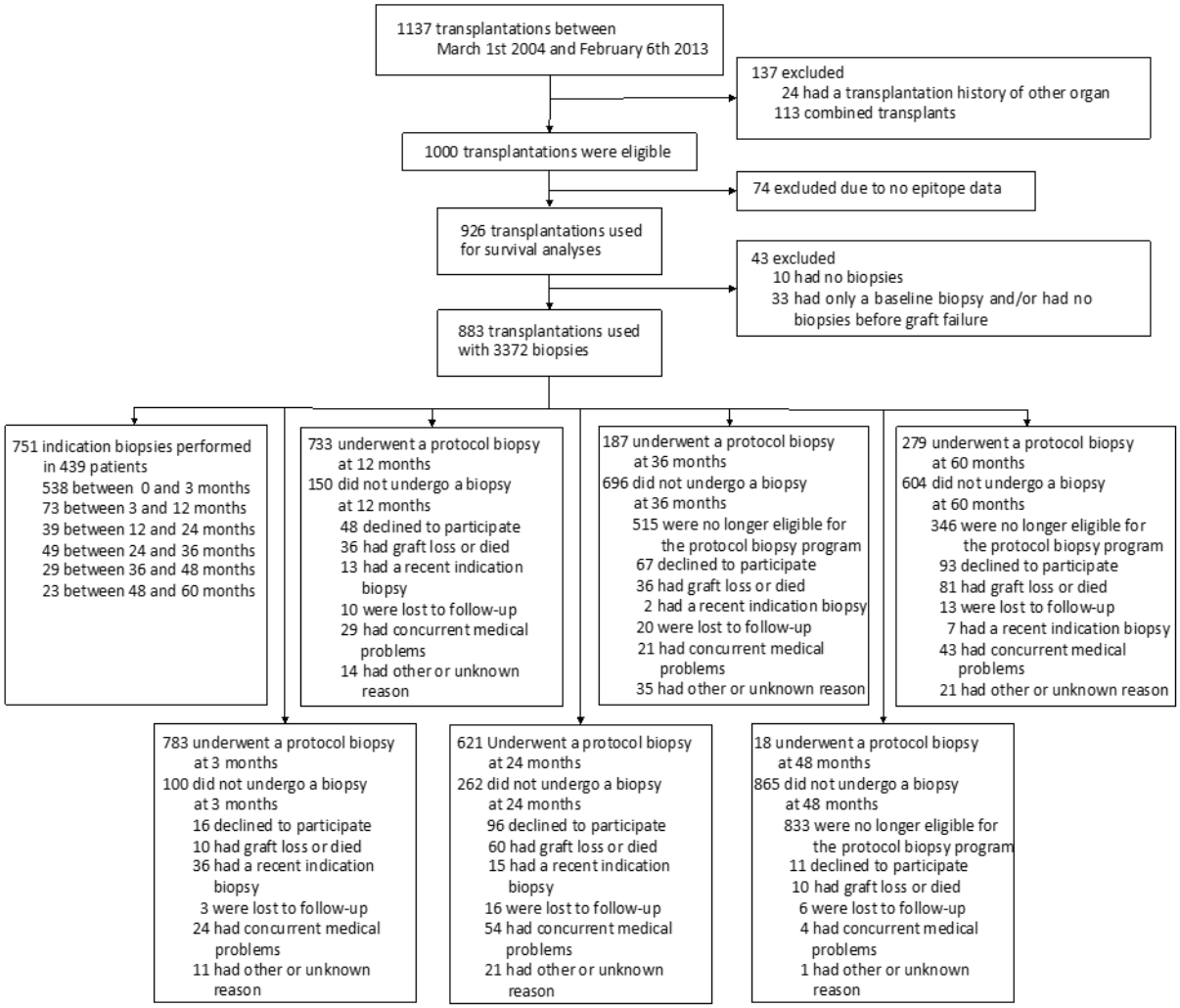


***Figure S2*: Violin plots of total eplet mismatch load per number of HLA antigen mismatches for (A) locus A, B, and DR (0–6) and for (B) locus A, B, DR, and DQ (0–8) (n=926)**

Pearson correlations between the number of total eplet mismatches and the number of HLA-ABDR (0–6) and HLA-ABDRDQ (0–8) antigen mismatches amounted to 0·63 (p<0·001) and 0·72 (p<0·001), respectively. HLA=human leukocyte antigen.

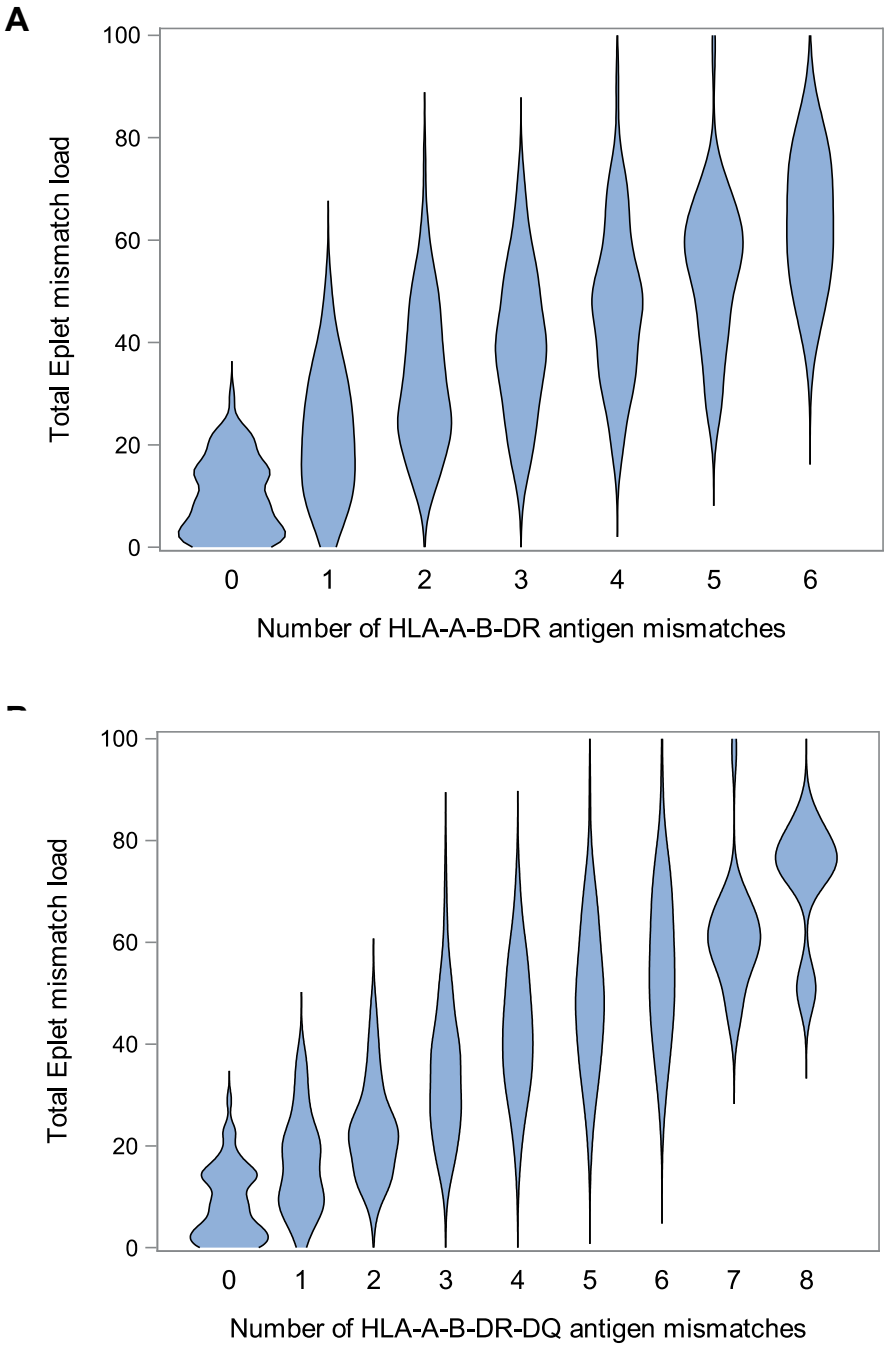


***Figure S3*: Violin plots of total eplet mismatch load per number of HLA antigen mismatches for HLA-A, B, DR, and DQ (n=926)**

Spearman correlations between total eplet mismatches and HLA antigen mismatches were 0·81 (p<0·001) for HLA-A, 0·71 (p<0·001) for HLA-B, 0·79 (p<0·001) for HLA-DR, and 0·79 (p<0·001) for HLA-DQ. HLA=human leukocyte antigen

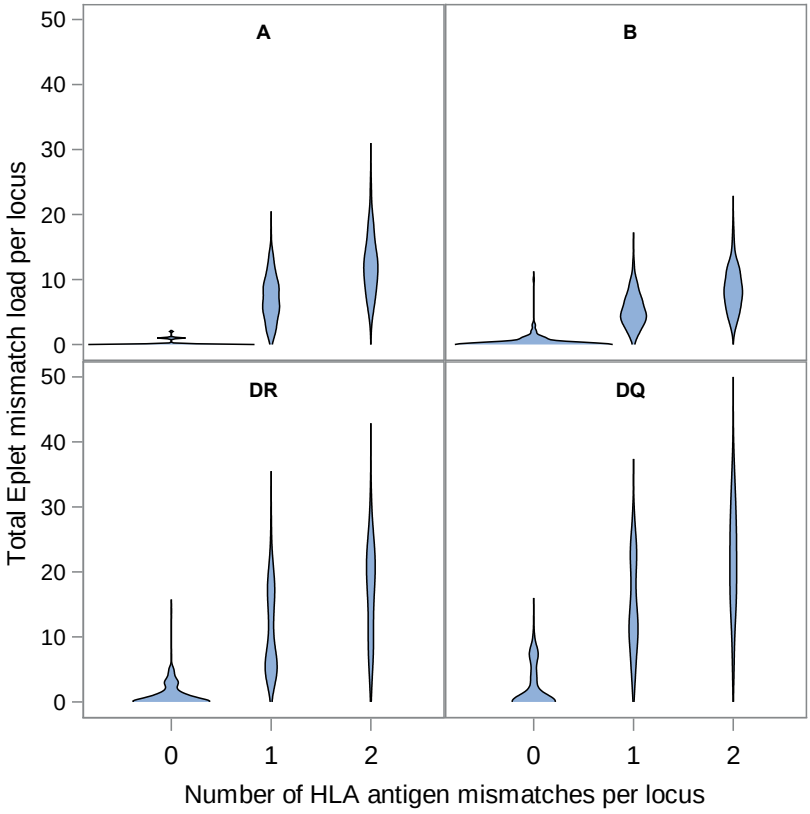


***Figure S4*: Cumulative incidence of overall dnDSA occurrence (n=926)**

(A) Three categories of the number of HLA-ABDR antigen mismatches (0–2, 3–4, 5–6); (B) tertiles of the number of total eplet mismatches (0–27, 28–44, 45–98); (C) three categories of the number of HLA-ABDRDQ antigen mismatches (0–2, 3–4, 5–8); (D) tertiles of the number of antibody-verified eplet mismatches (0–11, 12–20, 21–45); (E) number of HLA-DR antigen mismatches (0, 1, 2); (F) tertiles of the number of DR antibody-verified eplet mismatches (0, 1–4, 5–15); (G) number of HLA-DQ antigen mismatches (0, 1, 2); and (H) tertiles of the number of DQ antibody-verified eplet mismatches (0–1, 2–6, 7–17). All other causes were censored. dnDSA=de novo donor-specific antibodies. HLA=human leukocyte antigen.

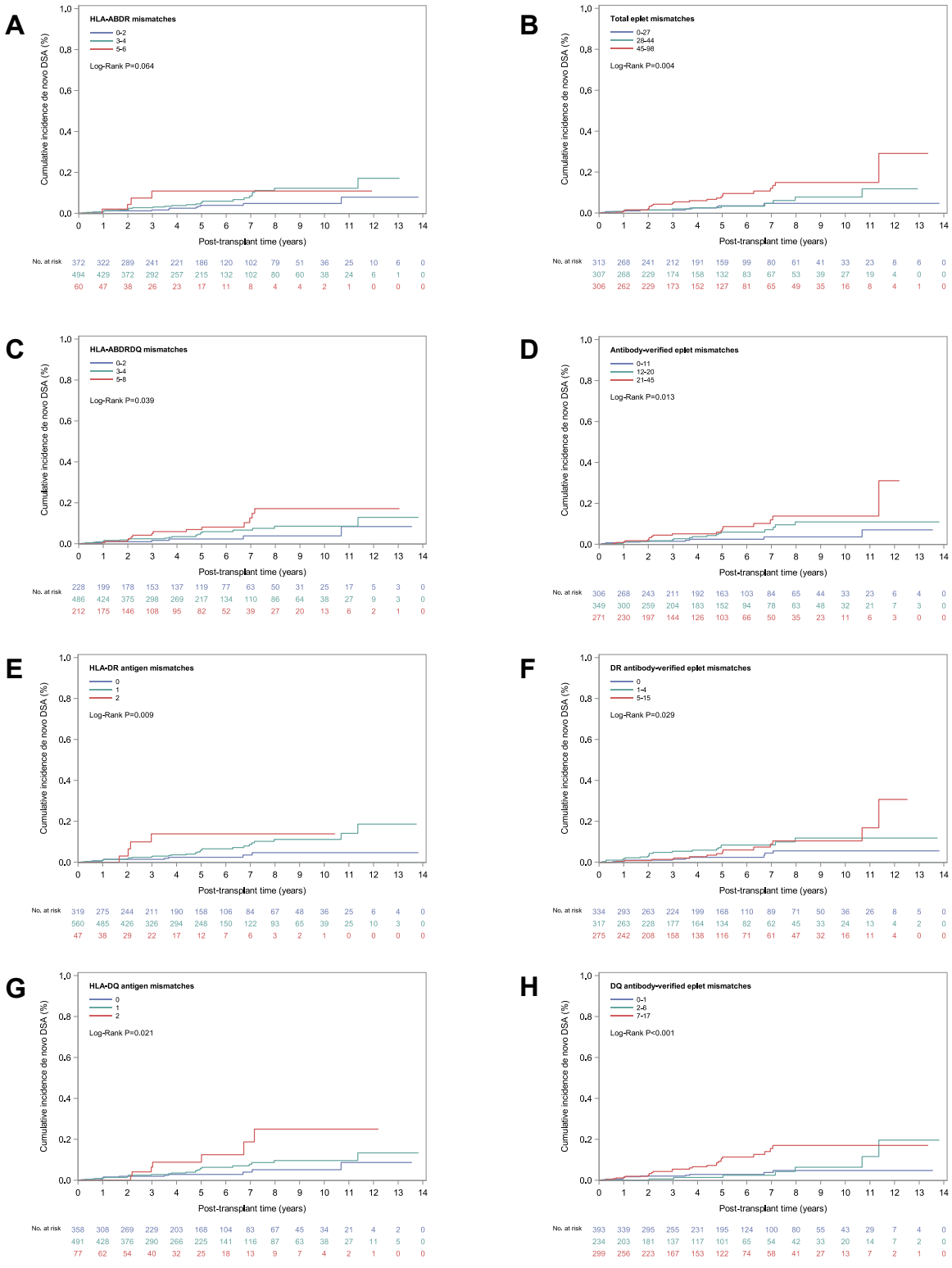
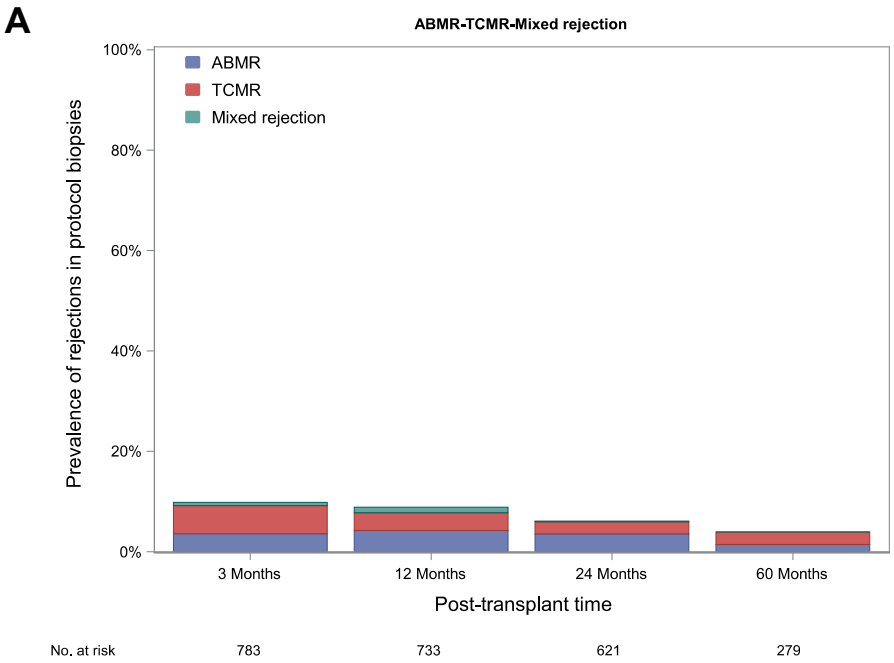


***Figure S5*: Prevalence of ABMR, TCMR and mixed rejection in (A) protocol and (B) indication biopsies (n=3372)**



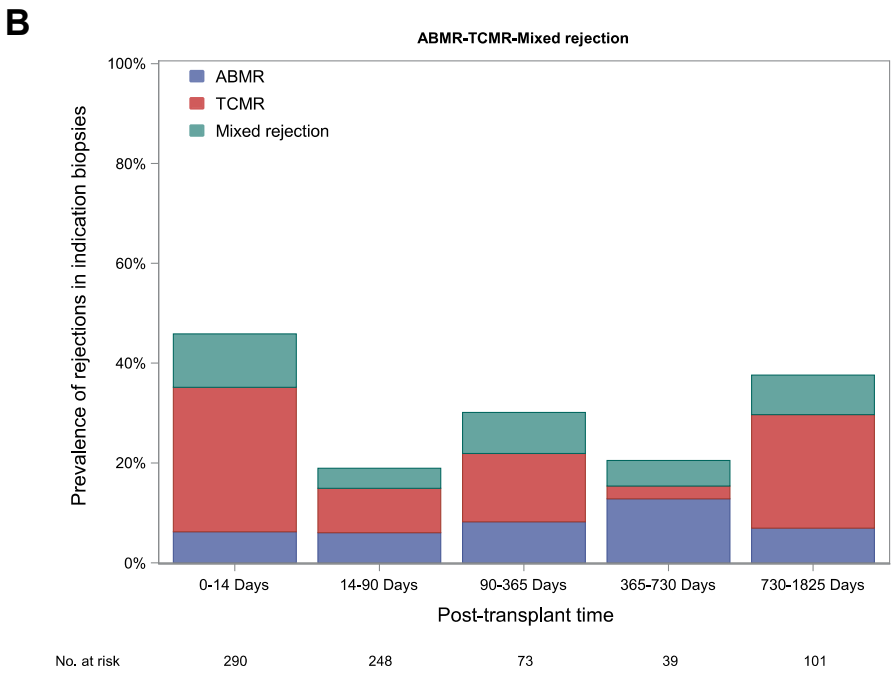


***Figure S6*: Kaplan–Meier survival plots of rejection-free graft survival (n=883)**

(A) Three categories of the number of HLA-ABDR antigen mismatches (0–2, 3–4, 5–6); (B) tertiles of the number of total eplet mismatches (0–27, 28–44, 45–98); (C) three categories of the number of HLA-ABDRDQ antigen mismatches (0–2, 3–4, 5–8); (D) tertiles of the number of antibody-verified eplet mismatches (0–11, 12–20, 21–45); (E) number of HLA-DR antigen mismatches (0, 1, 2); (F) tertiles of the number of DR antibody-verified eplet mismatches (0, 1–4, 5–15); (G) number of HLA-DQ antigen mismatches (0, 1, 2); and (H) tertiles of the number of DQ antibody-verified eplet mismatches (0–1, 2–6, 7–17). HLA=human leukocyte antigen.

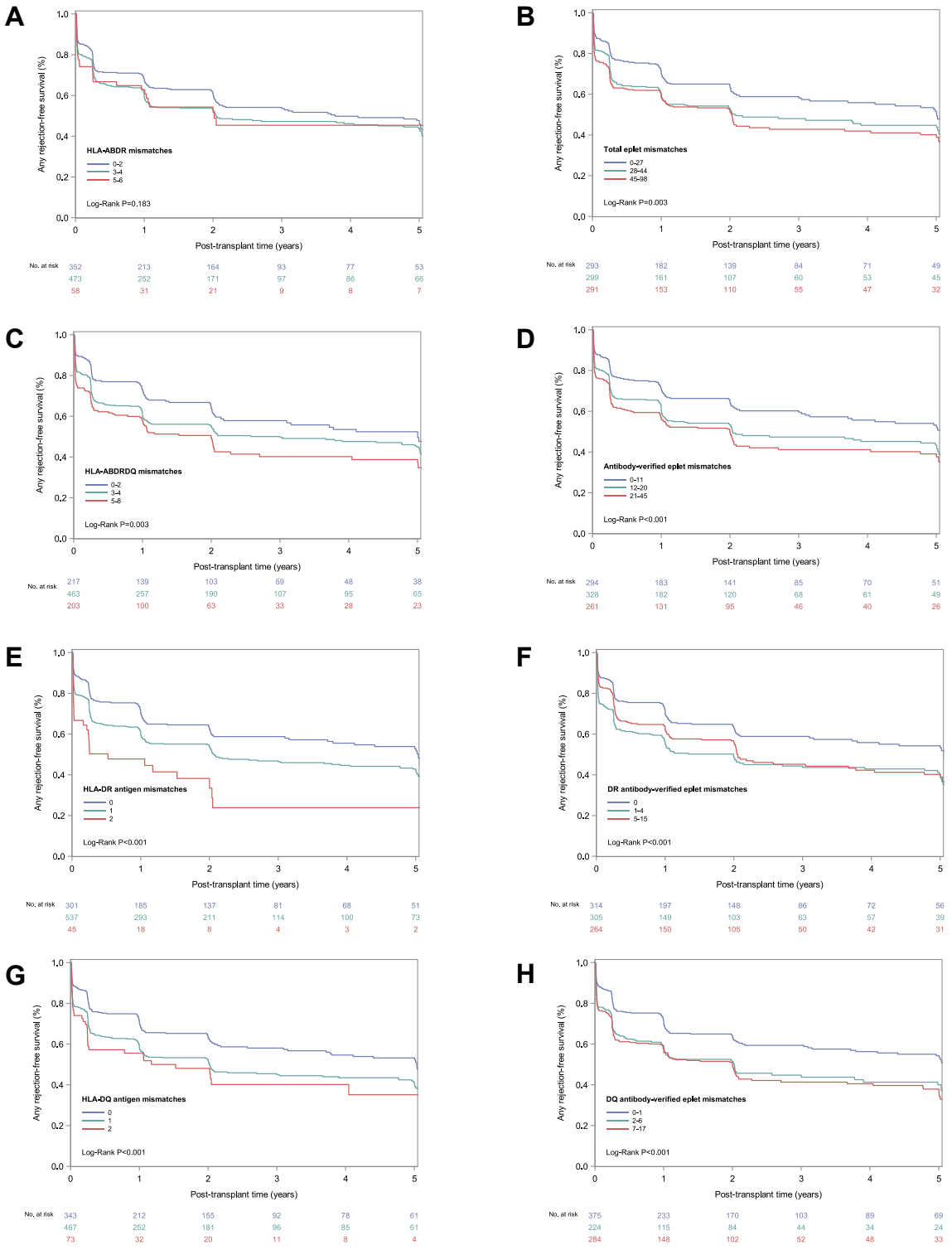


***Figure S7*: Low, intermediate and high eplet mismatch risk groups vs. dnDSA, rejection and graft failure.**

(A) Cumulative incidence of de novo DSA occurrence against DR and/or DQ, (B) any-rejection free survival and (C) death-censored graft survival, according to the low, intermediate and high risk groups (as proposed by Wiebe et al. Am J Transplant 2019). (A) and (C) were based on the cohort of 926 transplantations, (B) was based on the biopsy cohort (n=883).

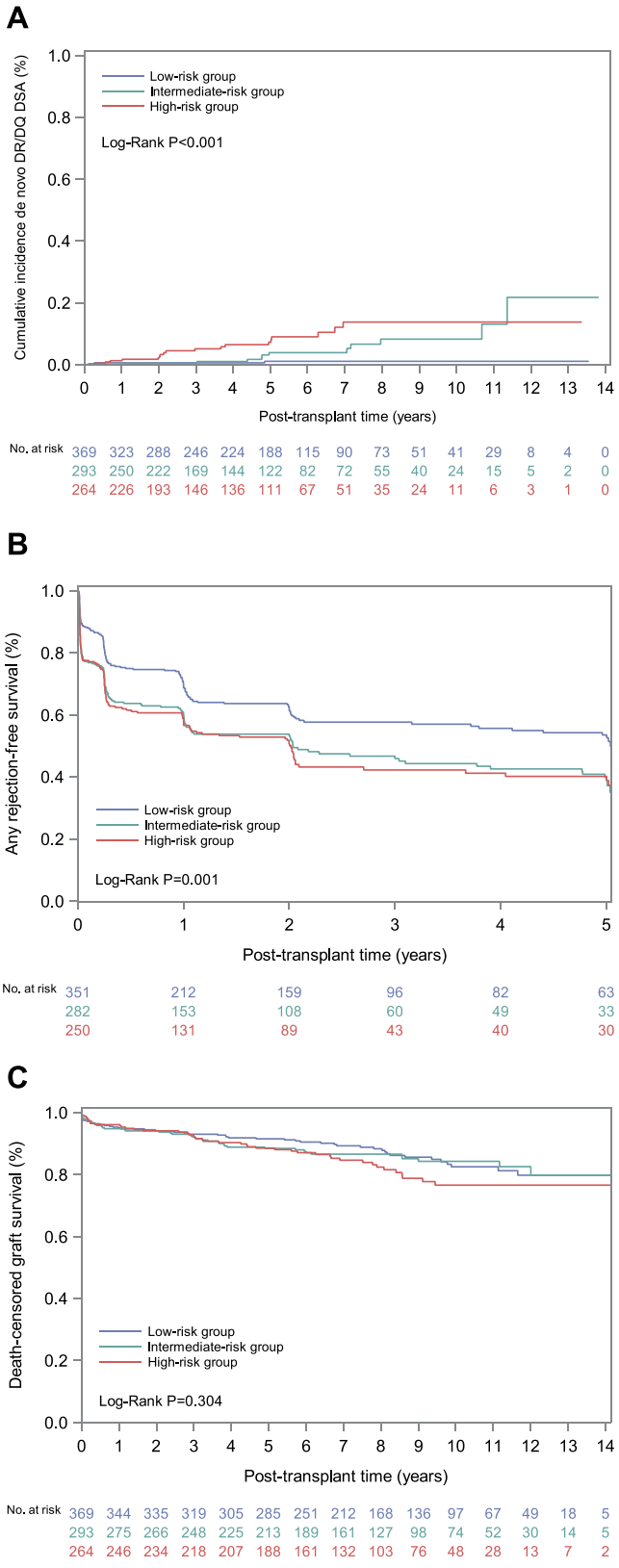


***Figure S8*: Kaplan–Meier survival plots of death-censored graft survival (n=926).**

(A) Three categories of the number of HLA-ABDR antigen mismatches (0–2, 3–4, 5–6); (B) tertiles of the number of total eplet mismatches (0–27, 28–44, 45–98); (C) three categories of the number of HLA-ABDRDQ antigen mismatches (0–2, 3–4, 5–8); (D) tertiles of the number of antibody-verified eplet mismatches (0–11, 12–20, 21–45); (E) number of HLA-DR antigen mismatches (0, 1, 2); (F) tertiles of the number of DR antibody-verified eplet mismatches (0, 1–4, 5–15); (G) number of HLA-DQ antigen mismatches (0, 1, 2); and (H) tertiles of the number of DQ antibody-verified eplet mismatches (0–1, 2–6, 7–17). HLA=human leukocyte antigen.

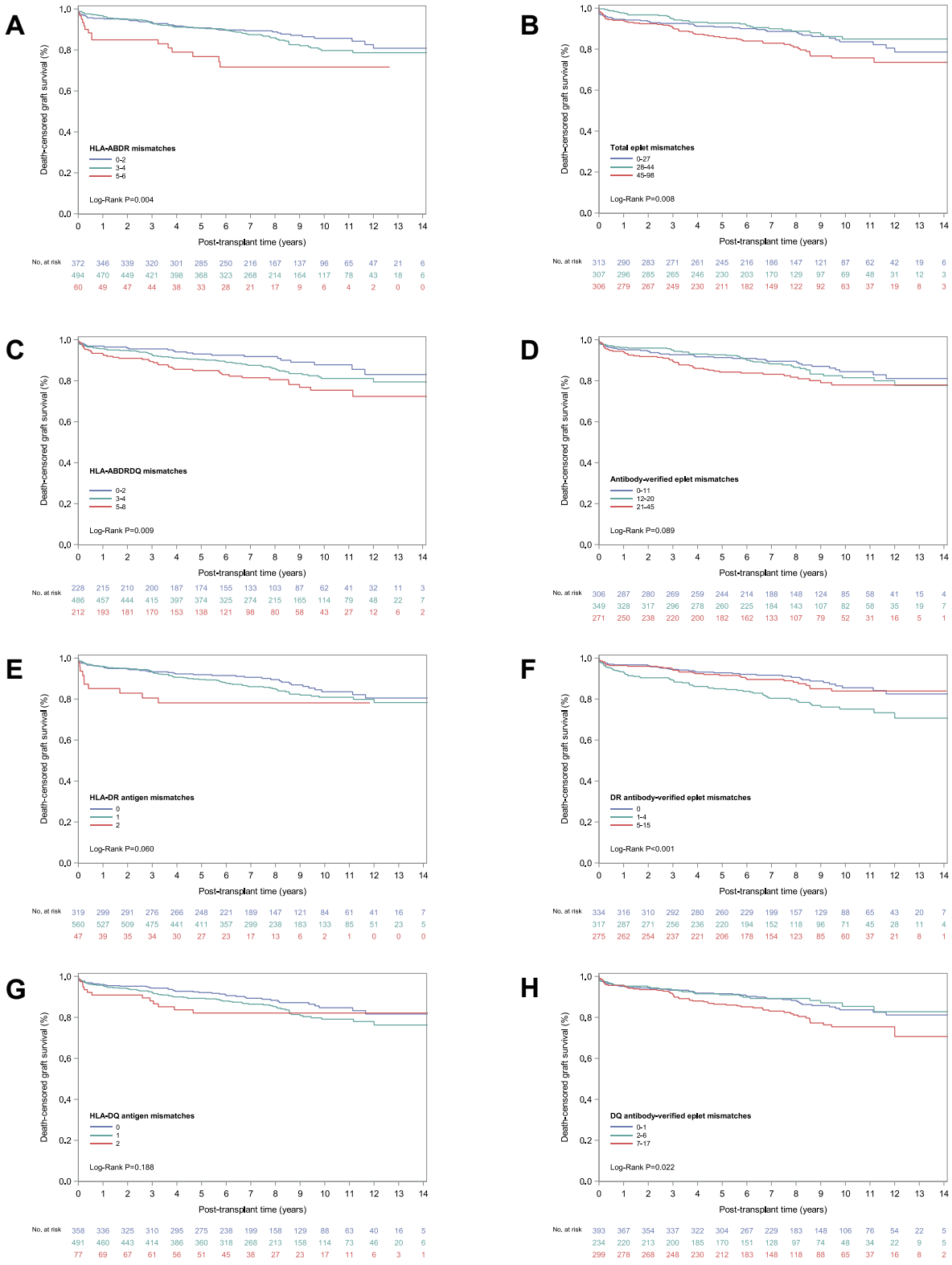


***Table S1*: Number of eplet mismatches in overall cohort, per class and per locus (n=926)**

	Eplet mismatches, n	
	Total eplet	**Antibody-verified eplet**
Total eplet mismatch load, mean ± SD	36·7 ± 18·0	16·0 ± 8·7
Class I eplet mismatch load, mean ± SD	12·3 ± 7·0	6·8 ± 4·2
Class II eplet mismatch load, mean ± SD	24·4 ± 15·5	9·1 ± 7·1
A eplet mismatch load, mean ± SD	6·4 ± 5·5	3·5 ± 3·2
B eplet mismatch load, mean ± SD	5·1 ± 3·7	2·3 ± 2·0
C eplet mismatch load, mean ± SD	5·0 ± 4·0	2·1 ± 2·0
DR eplet mismatch load, mean ± SD	7·9 ± 7·5	3·0 ± 3·5
DQ eplet mismatch load, mean ± SD	10·5 ± 9·3	4·5 ± 4·6
DP eplet mismatch load, mean ± SD	6·0 ± 5·3	1·6 ± 1·6

***Table S2*: HLA class- and molecule-specific dnDSA according to HLA antigen mismatches and eplet mismatch load (n=926)**

HLA mismatches	Patients at risk	Events	Univariable HR (95% CI)	p value	Multivariable† HR (95% CI)	p value
Antigen (split level)						
Class I HLA antigen mismatches (A+B+C)	926	11	1·60 (1·03–2·47)	0·036	1·57 (1·00–2·47)	0·052
A+B antigen mismatches	926	8	1·66 (0·83–3·33)	0·152	-	··
Class II HLA antigen mismatches (DR+DQ+DP)	926	34	1·60 (1·21–2·10)	<0·001	1·67 (1·23–2·26)	0·001
DR+DQ antigen mismatches	926	32	2·02 (1·44–2·83)	<0·001	2·80 (1·80–4·35)	<0·001
A antigen						
0 mismatch	243	0	1	··	1	··
1 mismatch	468	2	-	-	-	-
2 mismatches	215	3	-	-	-	-
B antigen						
0 mismatch	180	0	1	··	1	··
1 mismatch	545	2	-	-	-	-
2 mismatches	201	2	-	-	-	-
DR antigen						
0 mismatch	319	1	1	··	1	··
1 mismatch	560	9	-	-	-	-
2 mismatches	47	0	-	-	-	-
DQ antigen						
0 mismatch	358	1	1	··	1	··
1 mismatch	491	19	-	-	-	-
2 mismatches	77	5	-	-	-	-
Antibody-verified eplets						
A molecule	926	5	1·33 (1·04–1·71)	0·03	-	-
B molecule	926	4	1·12 (0·71–1·76)	0·62	-	-
C molecule	926	5	1·26 (0·83–1·90)	0·28	-	-
DR molecule	926	10	1·20 (1·04–1·39)	0·02	-	-
DQ molecule	926	25	1·25 (1·15–1·37)	<0·001	1·30 (1·18–1·44)	<0·001
DP molecule	926	3	1·31 (0·70–2·45)	0·40	-	-

†Multivariable models were corrected for donor and recipient sex, donor and recipient age, recipient race, recipient body mass index, donor type, cold ischaemia time, repeat transplantation, and pretransplant HLA antibodies (absence; non-DSA HLA antibodies; DSA).

***Table S3*: Eplet mismatch load calculated per HLA locus and single HLA molecule for DRB_{1345}, DQA_1B_1 and DPA_1B_1 dnDSA (n=38)**

Thresholds for de novo DSA development are: per HLA locus, DRB_{1345}<10 and DQA_1B_1<17 and per single HLA molecule: DRB_{1345}<7 or DQA_1B_1<9. The DSA that were developed below the suggested threshold for the given HLA locus or HLA molecule are highlighted in yellow.

		HLA locus		Single HLA molecule			
Patient ID	**HLA locus targeted by dnDSA**	**Total eplet mismatch load in targeted locus**	**Antibody-verified eplet mismatch load in targeted locus**	**Mismatch at antigen level**	**HLA molecule targeted by dnDSA**	**Total eplet mismatch load per single HLA molecule**	**Antibody-verified eplet mismatch load per single HLA molecule**
#1	DRB_{1345}	18	8	Yes	Yes	18	8
				No	No	0	0
#2	DRB_{1345}	15	5	Yes	Yes	15	5
				No	No	0	0
#3	DRB_{1345}	10	5	Yes	Yes	9	5
				Yes	No	1	0
#4	DRB_{1345}	1	1	No	Yes	1	1
				No	No	0	0
#5	DRB_{1345}	16	11	Yes	Yes	16	11
				No	No	0	0
#6	DRB_{1345}	5	4	Yes	Yes	5	4
				No	No	0	0
#7	DRB_{1345}	6	2	Yes	Yes	4	2
				No	No	2	0
#8	DRB_{1345}	19	11	Yes	Yes	15	11
				No	No	4	0
	DQA_1B_1	12	8	Yes	Yes	12	8
				No	No	0	0
#9	DRB_{1345}	18	7	Yes	Yes	18	7
				No	No	0	0
	DQA_1B_1	20	10	Yes	Yes	20	10
				No	No	0	0
#10	DRB_{1345}	8	1	Yes	Yes	7	1
				No	No	2	0

Patient ID	HLA locus targeted by dnDSA	HLA locus		Mismatch at antigen level	Single HLA molecule		
		Total eplet mismatch load in targeted locus	Antibody-verified eplet mismatch load in targeted locus		HLA molecule targeted by dnDSA	Total eplet mismatch load per single HLA molecule	Antibody-verified eplet mismatch load per single HLA molecule
	DQA_1B_1	7	1	No	Yes	7	1
				No	No	0	0
#11	DQA_1B_1	11	5	Yes	Yes	11	5
				Yes	Yes	1	0
#12	DQA_1B_1	26	10	No	No	0	0
				Yes	Yes	26	10
#13	DQA_1B_1	12	5	No	No	0	0
				Yes	Yes	12	5
#14	DQA_1B_1	20	7	No	No	0	0
				Yes	Yes	20	7
#15	DQA_1B_1	22	11	No	No	0	0
				Yes	Yes	22	11
#16	DQA_1B_1	29	14	Yes	No	21	9
				Yes	Yes	23	10
#17	DQA_1B_1	16	3	Yes	No	14	1
				Yes	Yes	8	2
#18	DQA_1B_1	14	9	No	No	0	0
				Yes	Yes	14	9
#19	DQA_1B_1	20	6	No	No	0	0
				Yes	Yes	20	6
#20	DQA_1B_1	12	7	No	No	0	0
				Yes	Yes	12	7
#21	DQA_1B_1	10	5	No	No	0	0
				Yes	Yes	10	5
#22	DQA_1B_1	18	12	No	No	2	0
				Yes	Yes	18	12
#23	DQA_1B_1	22	11	No	No	0	0
				Yes	Yes	22	11
#24	DQA_1B_1	13	9	No	No	0	0

Patient ID	HLA locus targeted by dnDSA	HLA locus		Single HLA molecule			
		Total eplet mismatch load in targeted locus	Antibody-verified eplet mismatch load in targeted locus	Mismatch at antigen level	HLA molecule targeted by dnDSA	Total eplet mismatch load per single HLA molecule	Antibody-verified eplet mismatch load per single HLA molecule
				Yes	Yes	13	9
#25	DQA_1B_1	24	13	No	No	0	0
				Yes	Yes	24	13
#26	DQA_1B_1	24	13	No	No	0	0
				Yes	Yes	24	13
#27	DQA_1B_1	22	11	No	No	0	0
				Yes	Yes	22	11
#28	DQA_1B_1	23	13	No	No	0	0
				Yes	Yes	23	13
#29	DQA_1B_1	25	11	No	No	0	0
				Yes	Yes	25	11
#30	DQA_1B_1	35	15	Yes	Yes	19	9
				Yes	Yes	20	7
#31	DQA_1B_1	12	7	No	No	1	0
				Yes	Yes	13	7
#32	DQA_1B_1	25	15	Yes	Yes	20	14
				Yes	No	15	9
	DPA_1B_1	9	3	/	Yes	9	3
				/	No	0	0
#33	DPA_1B_1	13	2	/	Yes	13	2
				/	No	0	0
#34	DPA_1B_1	5	2	/	Yes	5	2
				/	No	0	0

dnDSA=de novo donor-specific antibodies. HLA=human leukocyte antigen.

***Table S4*: Univariable and multivariable HRs for dnDSA occurrence**

Patients grouped according to different level of molecular mismatches in HLA DQB_1 and DQA_1 loci (n=926). Statistically significant associations were highlighted in yellow.

DQB_1 MM (4-digit)	DQA_1 MM (2-digit)	Patients at risk	Event	Univariable HR (95% CI)	p value	Multivariable* HR (95% CI)	p value
dnDSA							
0	0	224	7	1	..	1	..
0	1	11	0	..	..	..	..
1	0	252	6	0·72 (0·24–2·13)	0·55	0·63 (0·21–1·90)	0·41
1	1	307	21	2·46 (1·05–5·80)	0·04	2·41 (1·01–5·76)	0·05
2	0	43	3	2·44 (0·63–9·45)	0·20	2·30 (0·57–9·20)	0·24
2	1	77	4	2·21 (0·65–7·58)	0·21	2·39 (0·69–8·36)	0·17
2	2	12	2	6·53 (1·35–31·51)	0·02	9·01 (1·73–46·99)	0·01
Class II dnDSA							
0	0	224	2	1	..	1	..
0	1	11	0	..	..	..	..
1	0	252	5	2·08 (0·40–10·75)	0·38	1·72 (0·33–9·01)	0·52
1	1	307	20	8·41 (1·96–36·00)	0·004	8·22 (1·89–35·71)	0·005
2	0	43	2	5·42 (0·76–38·55)	0·09	5·15 (0·70–38·13)	0·11
2	1	77	4	8·12 (1·48–44·48)	0·02	9·11 (1·62–51·16)	0·01
2	2	12	1	10·95 (0·99–121·21)	0·05	16·88 (1·42–201·12)	0·03

dnDSA=de novo donor-specific antibodies. HLA=human leukocyte antigen. HR=hazard ratio. MM=mismatch.

*Multivariable models were corrected for donor and recipient sex, donor and recipient age, recipient race, recipient body mass index, donor type, cold ischaemia time, repeat transplantation, and pretransplant HLA antibodies (absence; non-DSA HLA antibodies; DSA).

Table S5: **Univariable and multivariable HR for dnDSA class II occurrence**

Patients grouped according to different HLA levels (2-digit and 4-digit) of molecular mismatches in HLA DQB_1 and DQA_1 loci (n=926).

HLA mismatches	Patients at risk	Events	Univariable HR (95% CI)	p value	Multivariable† HR (95% CI)	p value
DQA_1 (2-digit)						
0 mismatch	519	9	1	..	1	..
1 mismatch	395	24	4·30 (1·99–9·28)	<0·001	4·62 (2·09–10·20)	<0·001
2 mismatches	12	1	5·84 (0·74–46·30)	0·09	9·73 (1·12–84·65)	0·04
DQA_1 (4-digit)						
0 mismatch	260	4	1	..	1	..
1 mismatch	562	26	3·12 (1·09–8·94)	0·03	2·79 (0·96–8·14)	0·06
2 mismatches	104	4	3·11 (0·78–12·45)	0·11	3·27 (0·79–13·50)	0·10
DQB_1 (4-digit)						
0 mismatch	235	2	1	..	1	..
1 mismatch	559	25	5·47 (1·30–23·09)	0·02	5·07 (1·19–21·63)	0·03
2 mismatches	132	7	7·64 (1·59–36·82)	0·01	8·27 (1·69–40·46)	0·01

†Multivariable models were corrected for donor and recipient sex, donor and recipient age, recipient race, recipient body mass index, donor type, cold ischaemia time, repeat transplantation, and pretransplant HLA antibodies (absence; non-DSA HLA antibodies; DSA).

***Table S6*: The number of biopsies per patient and rejection subtypes (n=883)**

		# ABMR n (%)	# TCMR n (%)	# TCMR including borderline changes n (%)	# Any rejection n (%)
One biopsy per patient (62)	First biopsy	6 (9·7)	8 (12·9)	15 (24·2)	16 (25·8)
Multiple biopsies per patient (821)	First biopsy	61 (7·4)	144 (17·5)	216 (26·3)	239 (29·1)
	Repeated biopsies	147 (5·9)	161 (6·5)	391 (15·7)	486 (19·5)

ABMR=antibody-mediated rejection. TCMR=T cell–mediated rejection. Any rejection = ABMR and/or TCMR.

Table S7: Effects of number of HLA antigen and total eplet mismatches and antibody-verified eplet mismatches per locus on kidney allograft histology (n=926).

(Any rejection; ABMR; TCMR grade I–III; TCMR including borderline changes.) The estimates and confidence bounds were based on separate logistic mixed models with random intercepts, a linear fixed and random effect of time, corrected for donor/recipient sex, donor/recipient age, recipient race, recipient body mass index, donor type, cold ischaemia time, repeat transplantation, and pretransplant HLA antibodies/DSA. All post-transplant biopsies (n=3372) were used for these analyses.

	Any rejection		ABMR		TCMR I–III		TCMR including borderline changes	
HLA mismatches	**Odds ratio (95% CI)**	**p value**	**Odds ratio (95% CI)**	**p value**	**Odds ratio (95% CI)**	**p value**	**Odds ratio (95% CI)**	**p value**
Antigen (split level)								
HLA-ABDR (0–6)	1·15 (1·03–1·27)	0·01	1·18 (0·90–1·55)	0·24	1·11 (0·98–1·27)	0·10	1·15 (1·04–1·27)	0·01
HLA-ABDRDQ (0–8)	1·16 (1·07–1·26)	<0·001	1·25 (1·00–1·57)	0·05	1·15 (1·04–1·28)	0·01	1·16 (1·07–1·26)	<0·001
A locus								
0	1	..	1	..	1	..	1	..
1	0·80 (0·59–1·09)	0·16	1·51 (0·70–3·26)	0·30	1·34 (0·91–1·96)	0·14	0·80 (0·60–1·09)	0·16
2	1·00 (0·70–1·43)	0·99	1·21 (0·48–3·06)	0·68	1·00 (0·64–1·58)	1·00	1·02 (0·72–1·44)	0·91
B locus								
0	1	..	1	..	1	..	1	..
1	1·32 (0·94–1·86)	0·11	1·66 (0·68–4·03)	0·26	1·57 (1·01–2·44)	0·04	1·32 (0·94–1·84)	0·11
2	1·41 (0·93–2·14)	0·11	1·03 (0·34–3·16)	0·95	1·19 (0·69–2·04)	0·53	1·45 (0·96–2·19)	0·08
DR locus								
0	1	..	1	..	1	..	1	..
1	1·57 (1·19–2·07)	0·002	2·18 (1·03–4·60)	0·04	1·35 (0·95–1·93)	0·09	1·56 (1·18–2·05)	0·002
2	2·60 (1·46–4·66)	0·001	3·38 (0·78–14·59)	0·10	3·16 (1·62–6·17)	<0·001	3·37 (1·91–5·92)	<0·001
DQ locus								
0	1	..	1	..	1	..	1	..
1	1·55 (1·19–2·03)	0·001	2·05 (1·02–4·14)	0·05	1·57 (1·11–2·21)	0·01	1·47 (1·13–1·92)	0·005
2	2·02 (1·26–3·25)	0·004	4·07 (1·28–12·97)	0·02	2·16 (1·23–3·80)	0·01	2·01 (1·27–3·19)	0·003
Eplet MM load								
Total eplet MM load	1·01 (1·01–1·02)	0·001	1·00 (0·99–1·02)	0·67	1·01 (1·00–1·02)	0·03	1·01 (1·00–1·02)	0·002
Antibody-verified eplets	1·03 (1·01–1·04)	<0·001	1·03 (0·99–1·07)	0·22	1·02 (1·00–1·04)	0·02	1·03 (1·01–1·04)	<0·001
A molecule	1·02 (0·98–1·06)	0·48	1·04 (0·94–1·16)	0·40	1·01 (0·96–1·06)	0·86	1·00 (0·97–1·04)	0·87
B molecule	1·05 (0·99–1·12)	0·14	1·01 (0·86–1·18)	0·92	1·00 (0·92–1·08)	0·94	1·05 (0·98–1·11)	0·16
DR molecule	1·03 (1·00–1·07)	0·09	0·94 (0·85–1·03)	0·19	1·02 (0·98–1·07)	0·38	1·04 (1·00–1·07)	0·04
DQ molecule	1·06 (1·03–1·09)	<0·001	1·12 (1·04–1·20)	0·002	1·05 (1·01–1·08)	0·006	1·05 (1·02–1·08)	<0·001

ABMR=antibody-mediated rejection. DSA=donor-specific antibodies. HLA=human leukocyte antigen. HR=hazard ratio. MM=mismatch. TCMR=T cell–mediated rejection.

Table S8: Univariable analysis of death-censored graft survival for the confounders included in the multivariable models (n=926)

Parameters	Univariable HR (95% CI)	P value
Donor age	1·02 (1·01–1·03)	0·006
Recipient age	1·01 (1·00–1·03)	0·03
Donor sex (0=female, 1=male)	0·71 (0·52–0·97)	0·03
Recipient sex (0=female, 1=male)	0·68 (0·50–0·94)	0·02
Recipient race	2·54 (1·04–6·22)	0·04
Recipient BMI	1·00 (0·96–1·03)	0·82
DCD donor	1·38 (0·80–2·38)	0·25
Living donor	0·43 (0·17–1·09)	0·08
Repeat transplantation	1·68 (1·14–2·48)	0·009
Cold ischemia time	1·02 (0·99–1·05)	0·14
Pre-transplant non-DSA HLA antibodies	1·13 (0·71–1·81)	0·60
Pre-transplant HLA-DSA antibodies	2·15 (1·41–3·28)	<0·001

***Table S9*: Harrell's C-statistics of HLA mismatch calculations for death-censored graft survival (n=926).**

	Death-censored graft survival	
HLA mismatch models	**Univariable C-statistic (95% CI)†**	**Multivariable‡ C-statistic (95% CI)†**
HLA-A/B/DR antigens	0·58 (0·52–0·63)	0·68 (0·64–0·73)
HLA-A/B/DR/DQ antigens	0·58 (0·53–0·63)	0·68 (0·64–0·73)
Total antibody-verified eplets	0·56 (0·51–0·62)	0·66 (0·63–0·72)
DQ antibody-verified eplets	0·55 (0·51–0·61)	0·66 (0·63–0·72)

†95% CIs are calculated based on 1000 bootstrapped samples. ‡Multivariable models were corrected for donor and recipient sex, donor and recipient age, recipient race, recipient body mass index, donor type, cold ischaemia time, repeat transplantation, and pretransplant HLA antibodies (absence; non-DSA HLA antibodies; DSA).

Table S10: Univariable and multivariable HRs for composite of graft survival and 50% eGFR decline from 3 months onwards according to HLA antigen mismatches and eplet mismatch load (n=886). Analyses were landmarked at three months after transplantation. 28 patients were excluded due to graft failure within the first three months, 12 due to a missing eGFR measurement at three months.

Statistically significant associations were highlighted in yellow.

HLA mismatches	Patients at risk	Events	Univariable HR (95% CI)	p value	Multivariable* HR (95% CI)	p value
Antigen (split level)						
HLA-ABDR (0-6)	886	181	1·13 (0·99–1·29)	0·06	1·15 (1·00–1·31)	0·05
HLA-ABDRDQ (0-8)	886	181	1·11 (1·00–1·23)	0·04	1·13 (1·01–1·26)	0·03
A antigen						
0 mismatch	230	51	1	··	1	··
1 mismatch	451	84	0·91 (0·62–1·34)	0·64	0·95 (0·64–1·40)	0·78
2 mismatches	205	46	1·19 (0·77–1·85)	0·43	1·31 (0·84–2·05)	0·23
B antigen						
0 mismatch	171	31	1	··	1	··
1 mismatch	527	104	1·23 (0·79–1·91)	0·37	1·17 (0·75–1·82)	0·50
2 mismatches	188	46	1·49 (0·89–2·49)	0·13	1·34 (0·79–2·27)	0·28
DR antigen						
0 mismatch	307	57				
1 mismatch	539	110	1·22 (0·86–1·73)	0·26	1·31 (0·92–1·87)	0·13
2 mismatches	40	14	1·75 (0·83–3·71)	0·14	1·62 (0·73–3·60)	0·24
DQ antigen						
0 mismatch	345	61	1	··	1	··
1 mismatch	469	103	1·33 (0·94–1·87)	0·11	1·38 (0·98–1·96)	0·07
2 mismatches	72	17	1·23 (0·66–2·31)	0·51	1·29 (0·68–2·45)	0·44
Eplets						
Total eplets	886	181	1·01(1·00–1·02)	0·14	1·01 (1·00–1·02)	0·10
Antibody-verified eplets	886	181	1·02 (1·00–1·04)	0·03	1·02 (1·01–1·04)	0·01
A molecule	886	181	1·02 (0·97–1·07)	0·45	1·03 (0·98–1·09)	0·22
B molecule	886	181	1·08 (1·00–1·16)	0·05	1·06 (0·99–1·15)	0·11
C molecule	886	181	0·95 (0·87–1·04)	0·26	0·93 (0·85–1·02)	0·11
DR molecule	886	181	1·03 (0·99–1·08)	0·15	1·04 (0·99–1·09)	0·09
DQ molecule	886	181	1·04 (1·01–1·07)	0·02	1·05 (1·01–1·08)	0·01
DP molecule	886	181	0·99 (0·90–1·09)	0·84	1·00 (0·90–1·11)	0·94

eGFR=estimated glomerular filtration rate. HLA=human leukocyte antigen. HR=hazard ratio.

*Multivariable models were corrected for donor and recipient sex, donor and recipient age, recipient race, recipient body mass index, donor type, cold ischaemia time, repeat transplantation, and pretransplant HLA antibodies (absence; non-DSA HLA antibodies; DSA).

Table S11: **STROBE Statement—Checklist of items included in this cohort study.**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	6-9, 18-19
Study size	10	Explain how the study size was arrived at	6-9 and Supplement p1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	18-19
		(*d*) If applicable, explain how loss to follow-up was addressed	6, 18-19
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 10, 13 and Supplement p 1
		(b) Give reasons for non-participation at each stage	10, 13 and Supplement p 1
		(c) Consider use of a flow diagram	Supplement p 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	26 - 27
		(b) Indicate number of participants with missing data for each variable of interest	n/a; see item #12 (c)
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	28 - 32
		(*b*) Report category boundaries when continuous variables were categorized	n/a; see item #11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a; see item #12 (b) and #12 (e)
Discussion			
Key results	18	Summarise key results with reference to study objectives	16, 19
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16 , 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20