

BIOLOGICAL AND CLINICAL DEFINITION OF A HIGHLY SENSITIZED PATIENT

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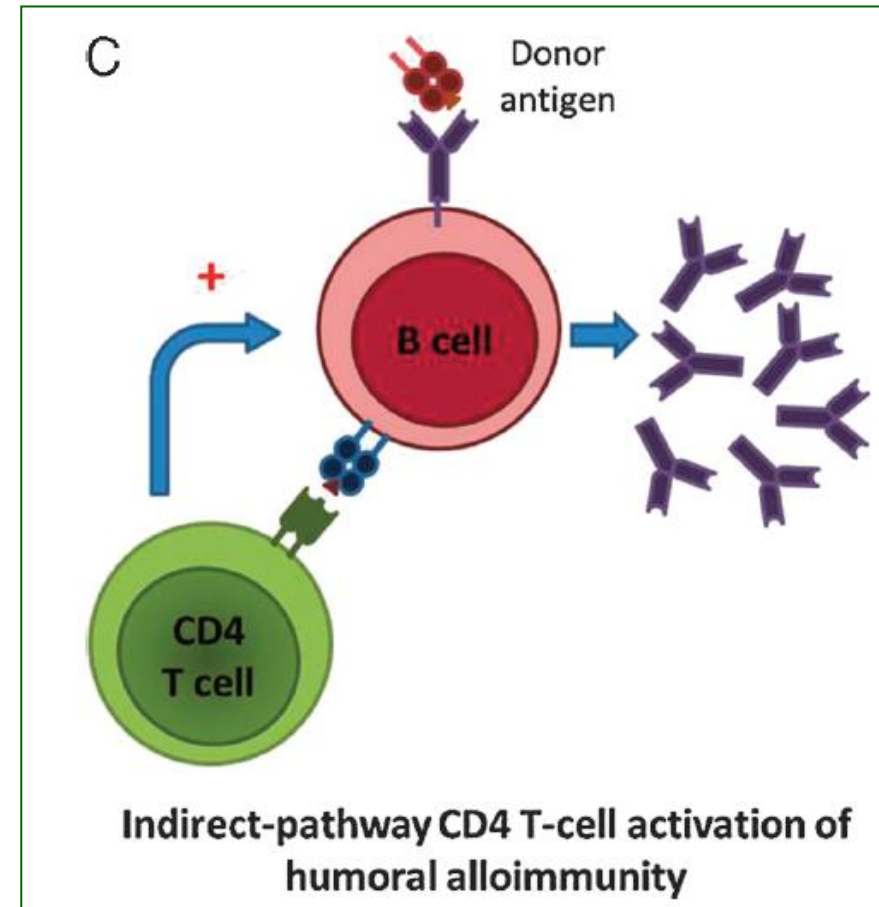
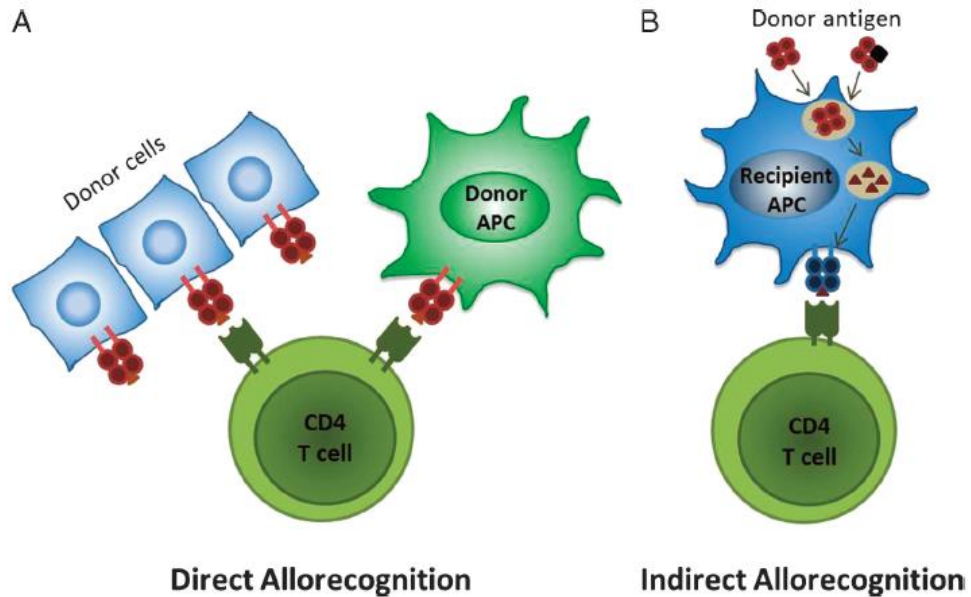
Hospital Clínic de Barcelona

17º Congreso SCT

23/03/2023

Antigenic Allorecognition

Sensitization to non-self HLA molecules (Transplant, Transfusion, Pregnancy)



Ali JM, et al. Transplantation, 2013

HLA Molecule Epitopes

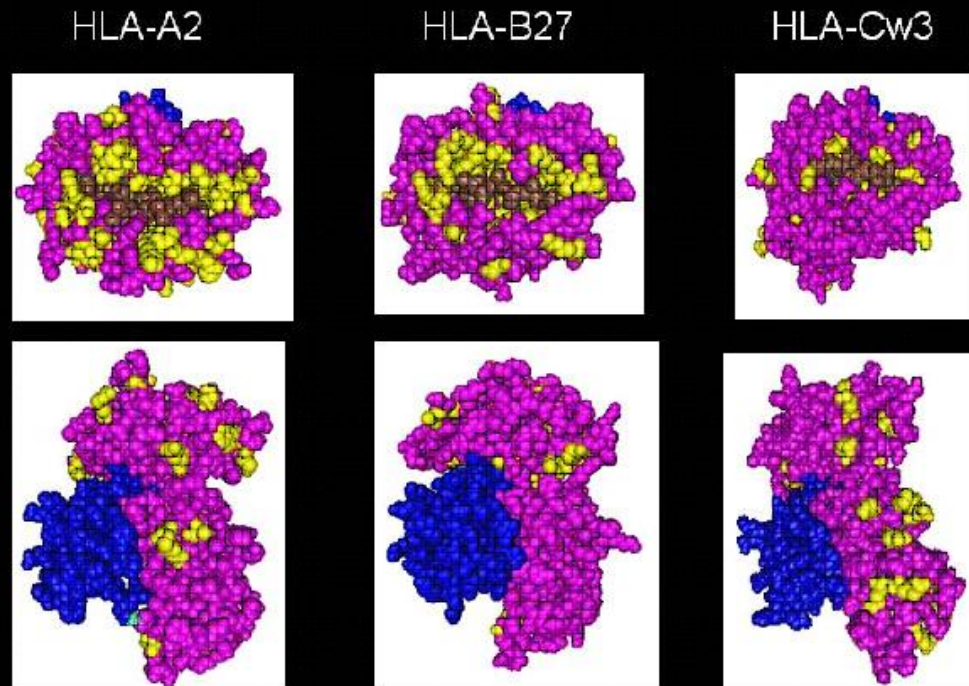


Figure 1 Polymorphic Residues on Class I Antigens

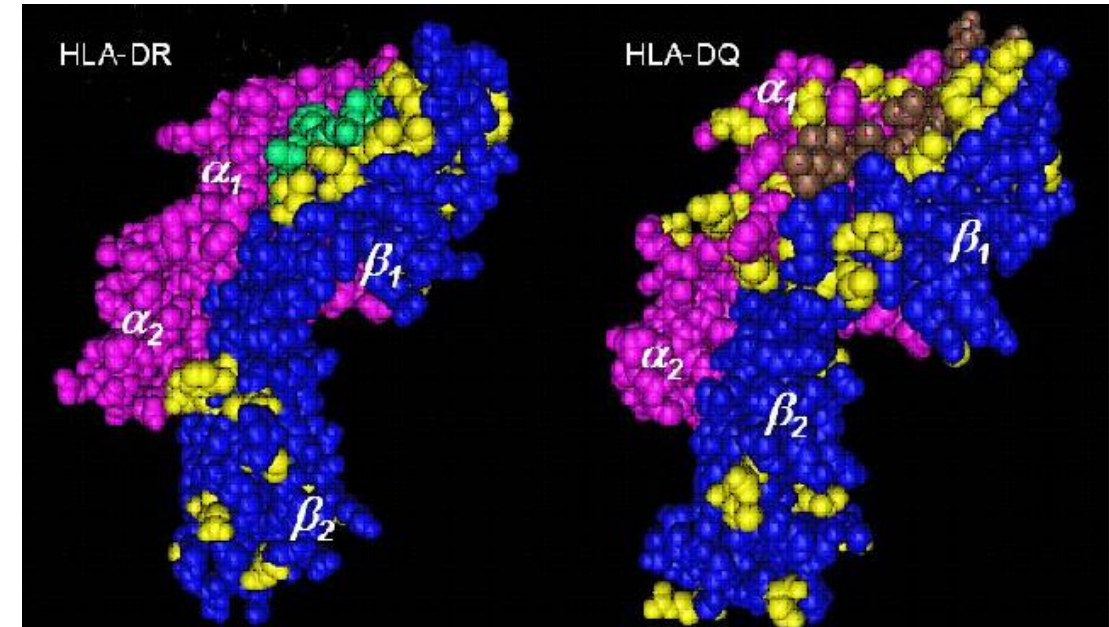


Figure 2 Topography of Polymorphic Residues on HLA-DR and HLA-DQ Molecules

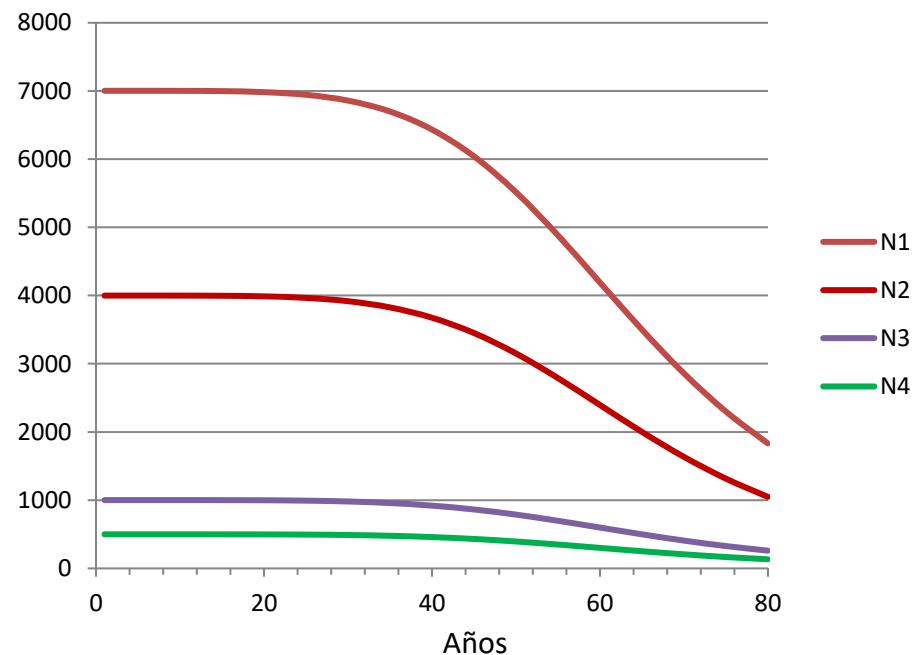
KIDNEY ALLOCATION

SCORE

Incompatibilidad HLA y edad (*)	nivel 1	$7000/(1+(edad/65)^5)$
	nivel 2	$4000/(1+(edad/65)^5)$
	nivel 3	$1000/(1+(edad/65)^5)$
	nivel 4	$500/(1+(edad/65)^5)$
	nivel 5	0
Tiempo de espera	Número días diálisis	
Diferencia edad Donante-Receptor	$-1/2 (edad D - edad R)^2$	
Límite diferencia de edad	15 años o 30 años si hiperinmunizado	
Tasa de anticuerpos (#)	$(exp(7 (PRA/100))-1) \times 3,434$	
HLA-DR Homocigoto	500	
HLA-B Homocigoto	100	

HLA Incompatibility (HLA-A,B,DRB1)

(*) Nivel de incompatibilidad	
nivel 1: 000	000
nivel 2: 0 DR y 0/1 B	100,010,110,200,210
nivel 3: (0DR y 2B) o (1DR y 0/1B)	020,120,220,001,101,201,011,111,211
nivel 4: 1DR y 2B	021,121,221
nivel 5: 2DR	002,102,202,012,112,212,022,122,222

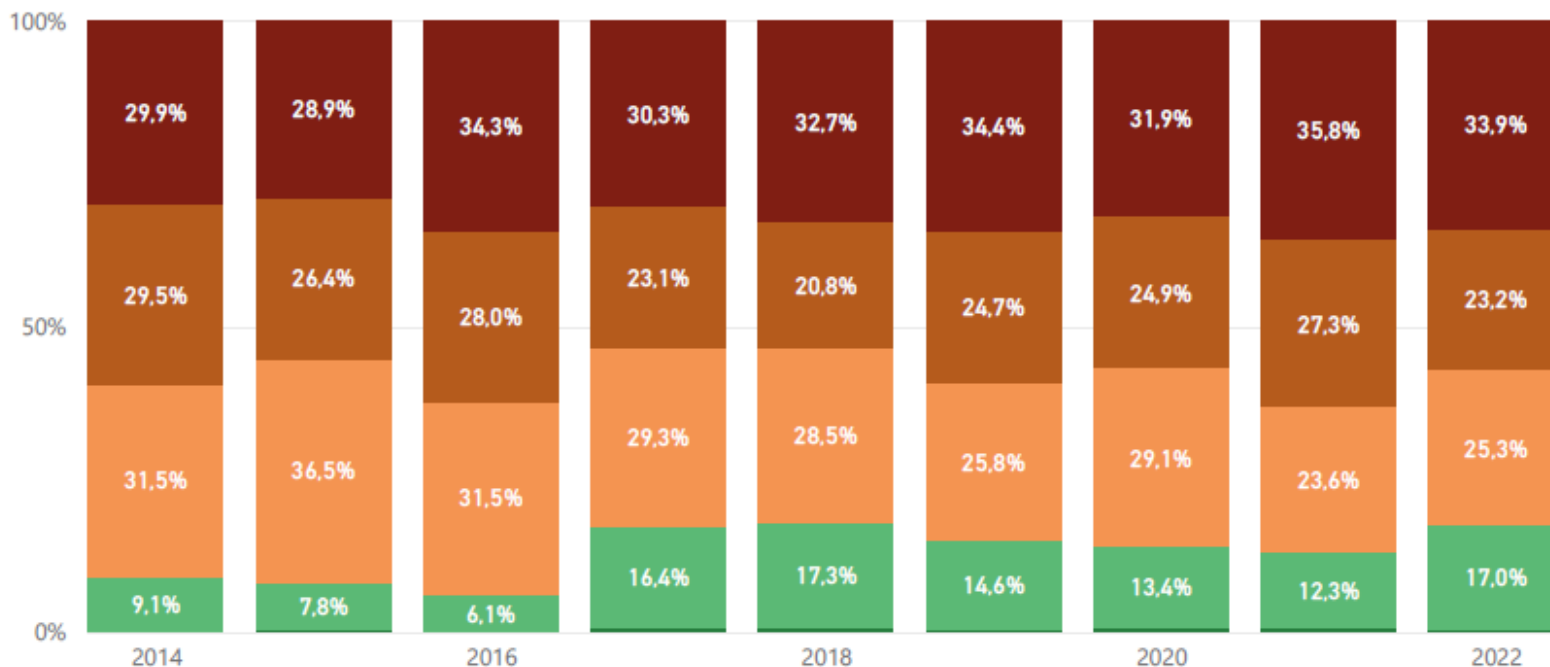


Kidney Transplantation in Catalonia - Level of HLA Incompatibility

Evolució dels TR de donant cadàver segons nivell d'incompatibilitat

● 1 ● 2 ● 3 ● 4 ● 5

TRs de gener a desembre

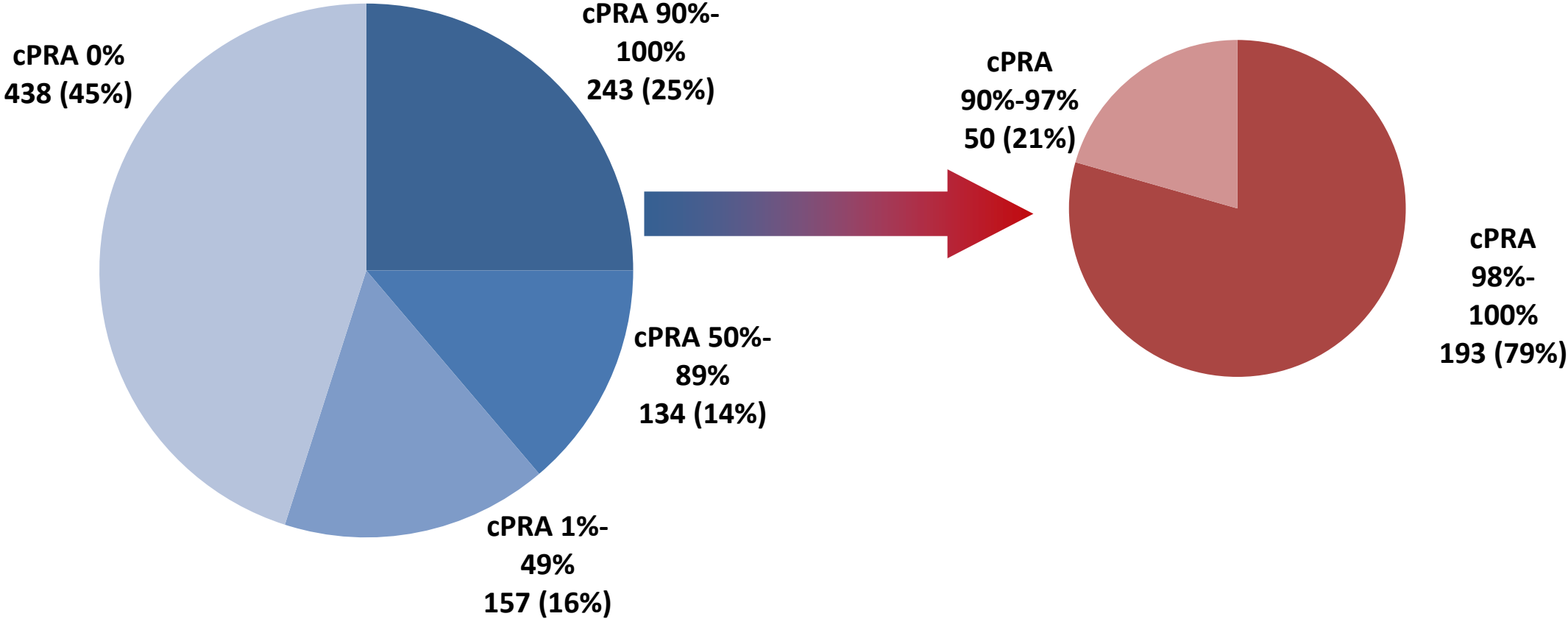


HLA-A,B,DRB1 Incompatibility

(*) Nivel de incompatibilidad	
nivel 1: 000	000
nivel 2: 0 DR y 0/1 B	100,010,110,200,210
nivel 3: (0DR y 2B) o (1DR y 0/1B)	020,120,220,001,101,201,011,111,211
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Kidney transplant patients waiting list in Catalonia

Total transplant candidates (14/04/2021): **972** (314 patients with 1 or more previous TXs)



HIGHLY SENSITIZED PATIENT



PATIENT WITH A HIGH NUMBER OF PREFORMED ALLOANTIBODIES (anti-HLA)

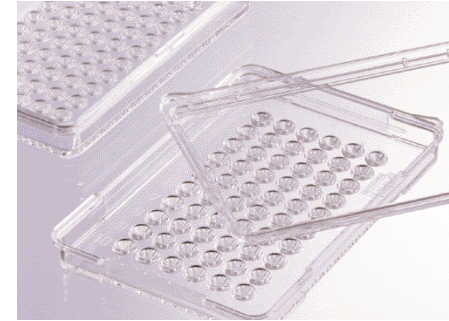
BUT...

- Which technique has been used to determine the alloantibodies?
- Which tool has been used to calculate the level of sensitization?
- Which is the level to consider a patient as highly sensitized?

TECHNIQUES TO DETERMINE THE PRESENCE OF ALLOANTIBODIES

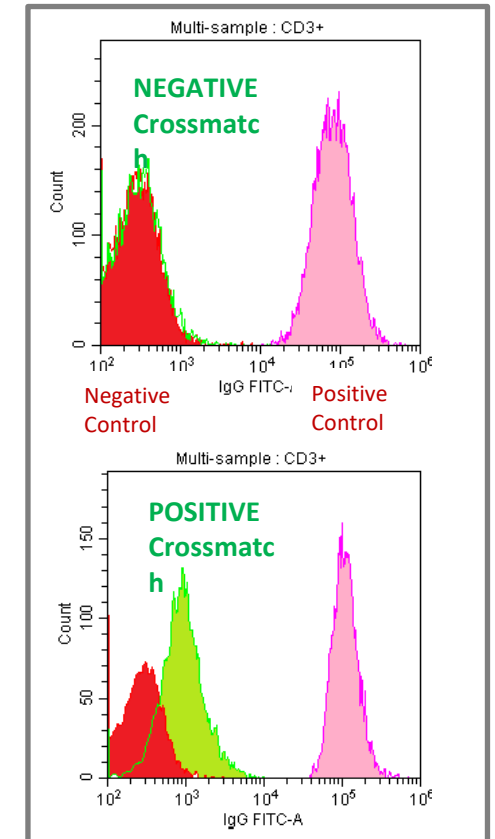
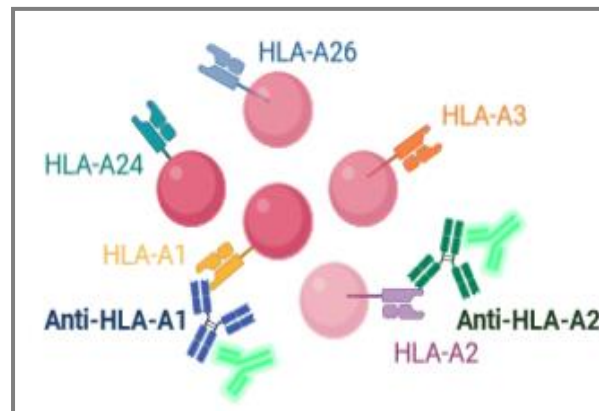
- CDC-PRA: percentage of panel donors reactive with the patient serum in CDC.

Highly sensitized patient: CDC-PRA >80-85%.



- Flow Cytometry Crossmatch (FCXM):
More sensitive. Also detects non-complement fixing antibodies.
Detects DSA, not anti-HLA specificity.

- Solid phase (Single Antigen Bead array assay):
More sensitive than CDC and FCXM.
Clinical relevance of low MFI positive results still not clear.
Allows calculation of PRA: cPRA (also cRF, vPRA).



Calculated PRA

Assessment of the degree of sensitization based on:

- The antibody specificities present in the patient
- The HLA phenotypes of the donor population

Probability that a patient has HLA antibodies against a donor derived from the actual organ donor population.

LHC - Laboratori
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CPRA value will depend on the tool used:

- Diverse reference donor population
- Precision of calculation (decimals)
- HLA loci taken in consideration
- Level of resolution of HLA typing

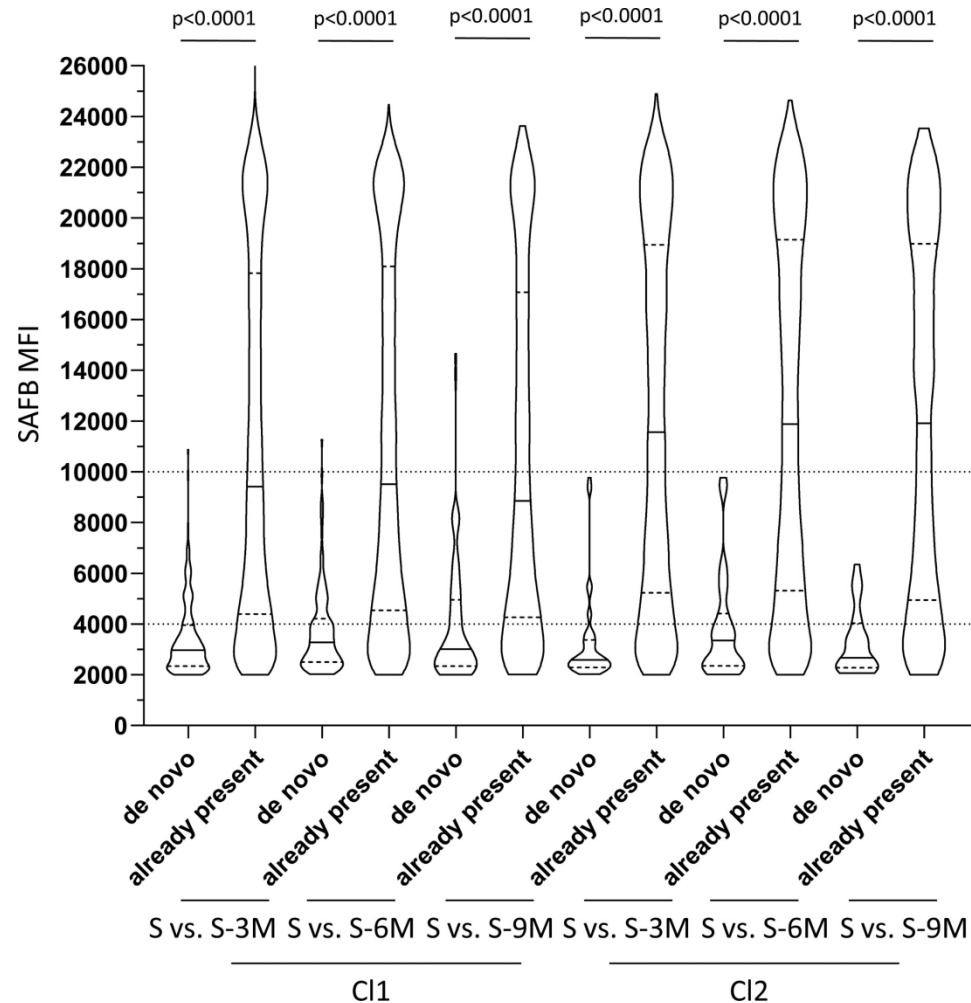
Reference Donor Pool					
HLA-A		HLA-B		HLA-DRB1	
A*01	A*24	B*51	B*15	DRB1*10	DRB1*14
A*26	A*29	B*44	B*-	DRB1*01	DRB1*13
A*29	A*32	B*44	B*49	DRB1*01	DRB1*04
A*24	A*25	B*14	B*44	DRB1*04	DRB1*-
A*29	A*33	B*14	B*57	DRB1*01	DRB1*14
A*01	A*02	B*27	B*-	DRB1*04	DRB1*11
A*02	A*29	B*44	B*-	DRB1*07	DRB1*-
A*23	A*32	B*35	B*44	DRB1*07	DRB1*13
A*02	A*30	B*38	B*51	DRB1*04	DRB1*07
A*26	A*29	B*38	B*15	DRB1*16	DRB1*13
A*29	A*32	B*07	B*44	DRB1*04	DRB1*07
A*01	A*02	B*08	B*49	DRB1*07	DRB1*03
A*03	A*25	B*41	B*-	DRB1*16	DRB1*13
A*02	A*24	B*35	B*15	DRB1*04	DRB1*11
A*02	A*30	B*51	B*39	DRB1*01	DRB1*11
A*02	A*03	B*08	B*27	DRB1*03	DRB1*15
A*02	A*23	B*39	B*44	DRB1*15	DRB1*16
A*01	A*23	B*44	B*45	DRB1*03	DRB1*01
A*24	A*-	B*44	B*07	DRB1*15	DRB1*03
A*01	A*24	B*08	B*15	DRB1*01	DRB1*03
A*02	A*30	B*13	B*35	DRB1*03	DRB1*07
A*01	A*02	B*08	B*63	DRB1*03	DRB1*04
A*02	A*25	B*18	B*35	DRB1*14	DRB1*15
A*11	A*26	B*51	B*40	DRB1*01	DRB1*11

Different programs/countries use diverse cPRA cut-offs to consider a patient as highly sensitized

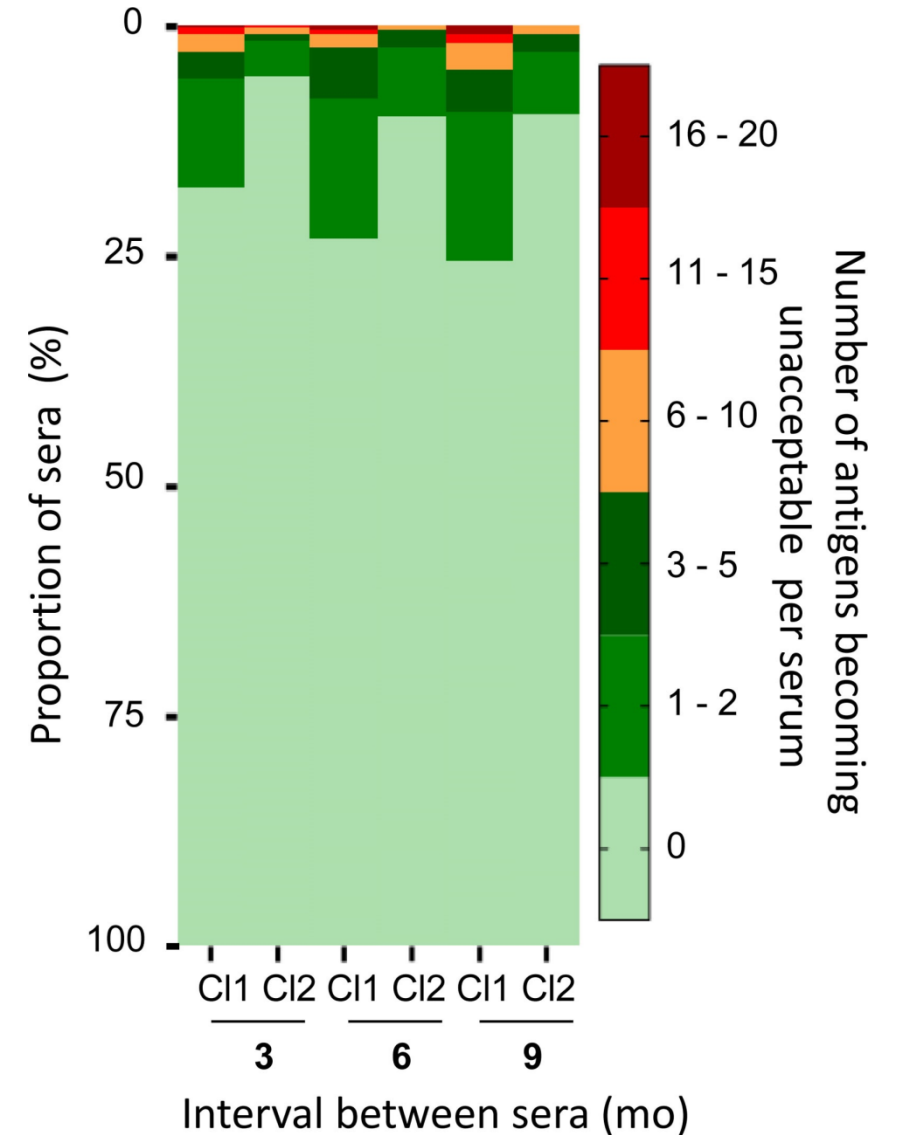
- Spain: PATHI (Plan Nacional de Acceso al Trasplante Renal para pacientes hiperinmunizados) cPRA \geq 98% (in addition in Catalonia: HiperCat cPRA \geq 90%)
- Eurotransplant: Acceptable Mismatch Program, cPRA >85% and in dialysis for at least 2 years.
- UK: Absolute priority for those with cRF 100%, matchability score 10, waiting time >7 years
- France: “Hyperimmunisés à antigènes permis” program (HAP) cPRA>85%
- Scandiatransplant acceptable mismatch program (STAMP): cPRA>80%
- Italy: cPRA>90% and >8 years in dialysis.
- USA: Kidney Allocation System (KAS) cPRA \geq 98%

European Guideline for the Management of Kidney Transplant Patients With HLA Antibodies: By the European Society for Organ Transplantation Working Group Mamode et al. Transpl Int, 2022.

Stability of Anti-HLA Sensitization Profiles in Highly Sensitized Kidney Transplantation Candidates: Toward a Rational Serological Testing Strategy.
 Wojciechowski et al. Transplantation 2022.

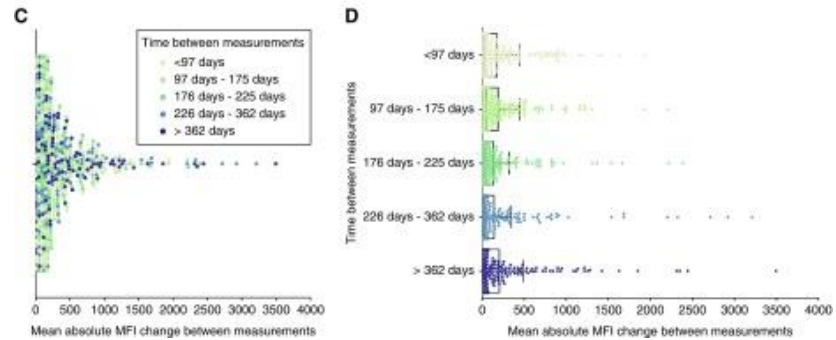
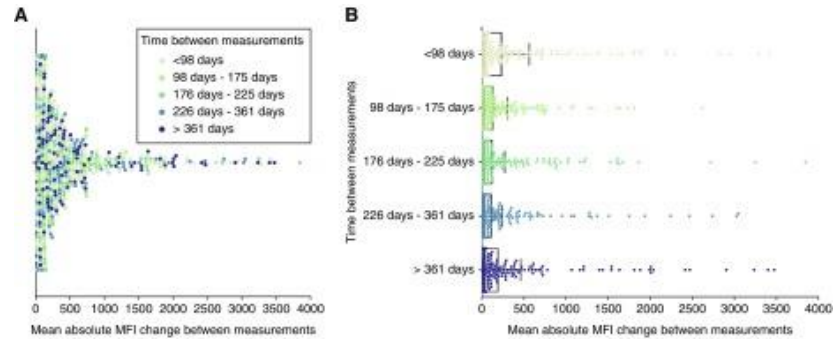


220 HS patients (cPRA ≥ 85%)



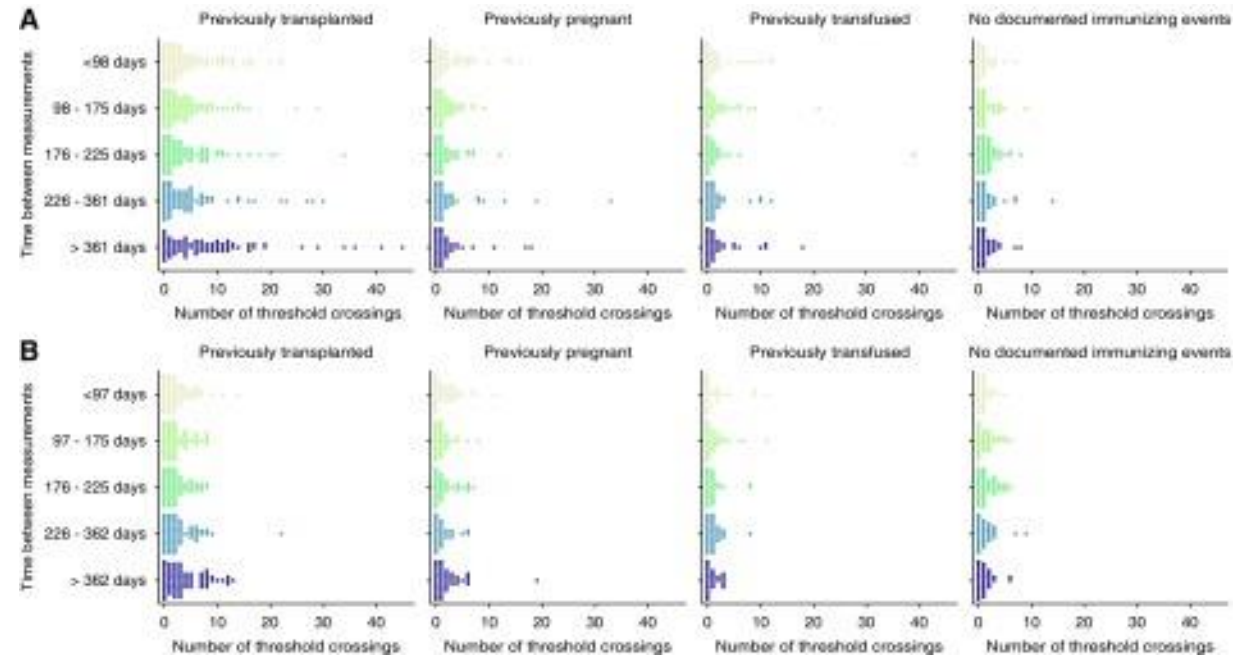
MFI variability is, on average, not affected by the interval between measurements

Class I



Mean of the absolute MFI change between consecutive SAB measurements

The alloimmunization history (immunizing events) affects pretransplant MFI variability



Number of MFI crossings over the 1000 MFI threshold

Pretransplant Kinetics of Anti-HLA Antibodies in Patients on the Waiting List for Kidney Transplantation. Togninalli et al. J Am Soc Nephrol 2019

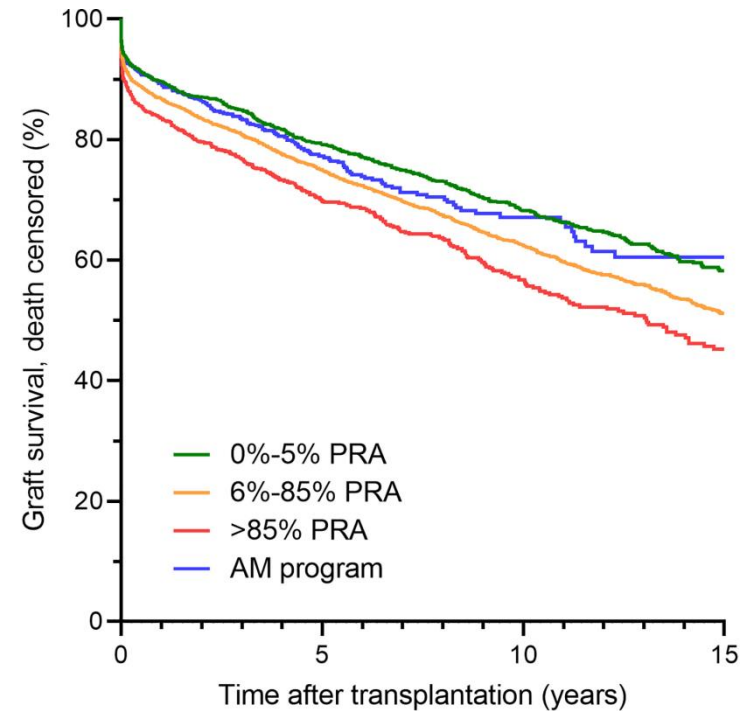
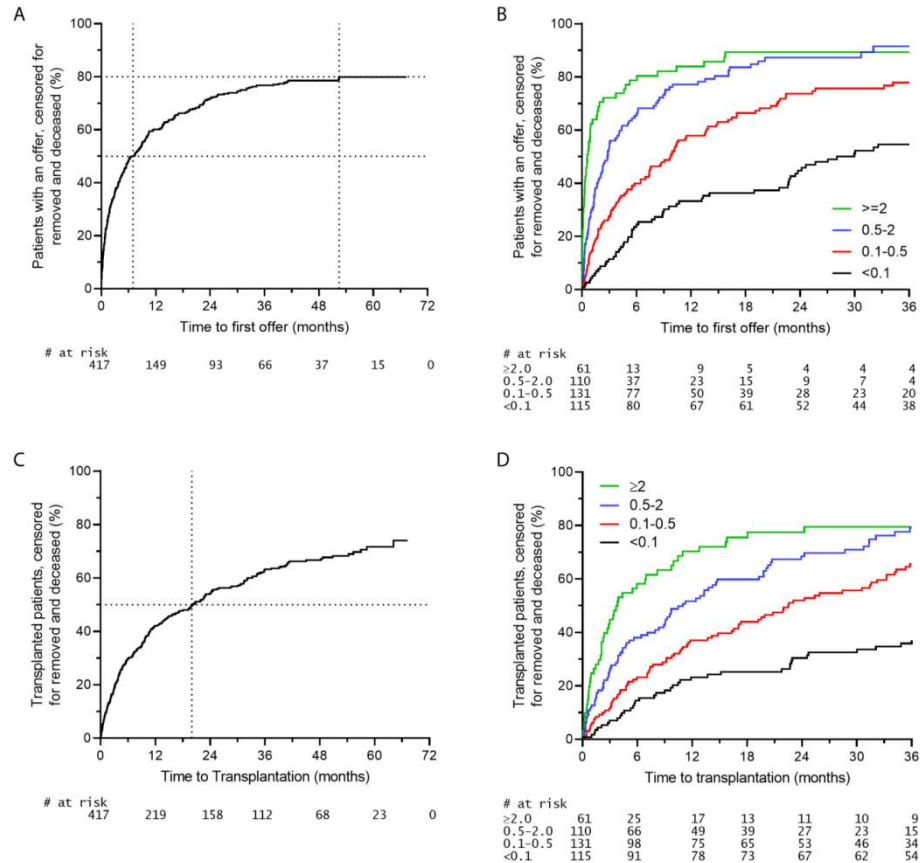
HIGHLY SENSITIZED PATIENT

From a clinical perspective:

- Transplant candidate patient with a low probability to find a compatible donor.
- High AMR risk due to the potential presence of DSA?
- Worst clinical transplant outcome?

EUROTRANSPLANT ACCEPTABLE MISMATCH PROGRAM

Recipients in dialysis for at least 2 years and with a PRA >85%

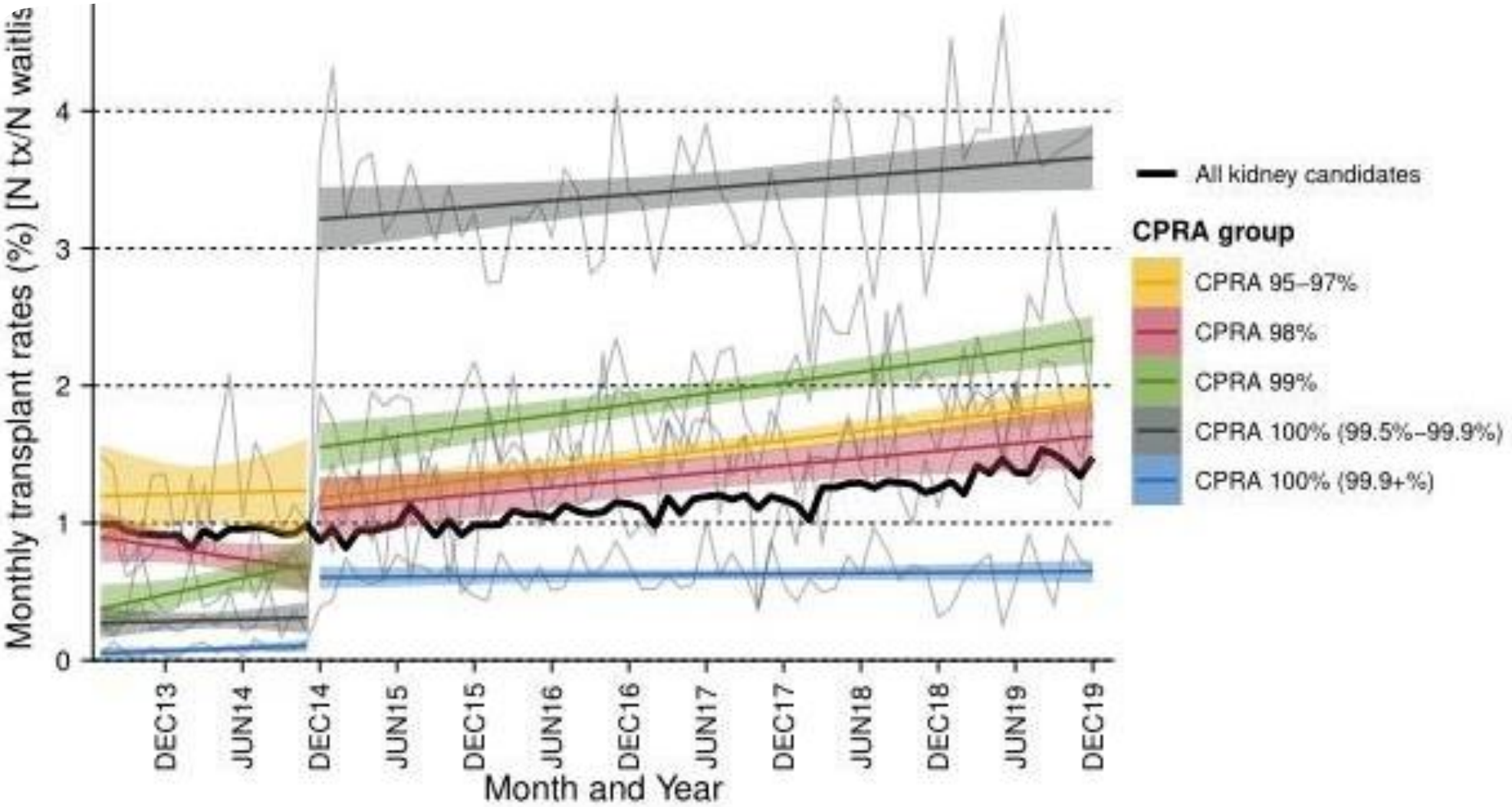


# at risk				
0%-5% PRA	2357	1061	580	204
6%-85% PRA	4575	2105	1121	443
>85% PRA	1295	436	218	83
AM program	1017	299	96	35

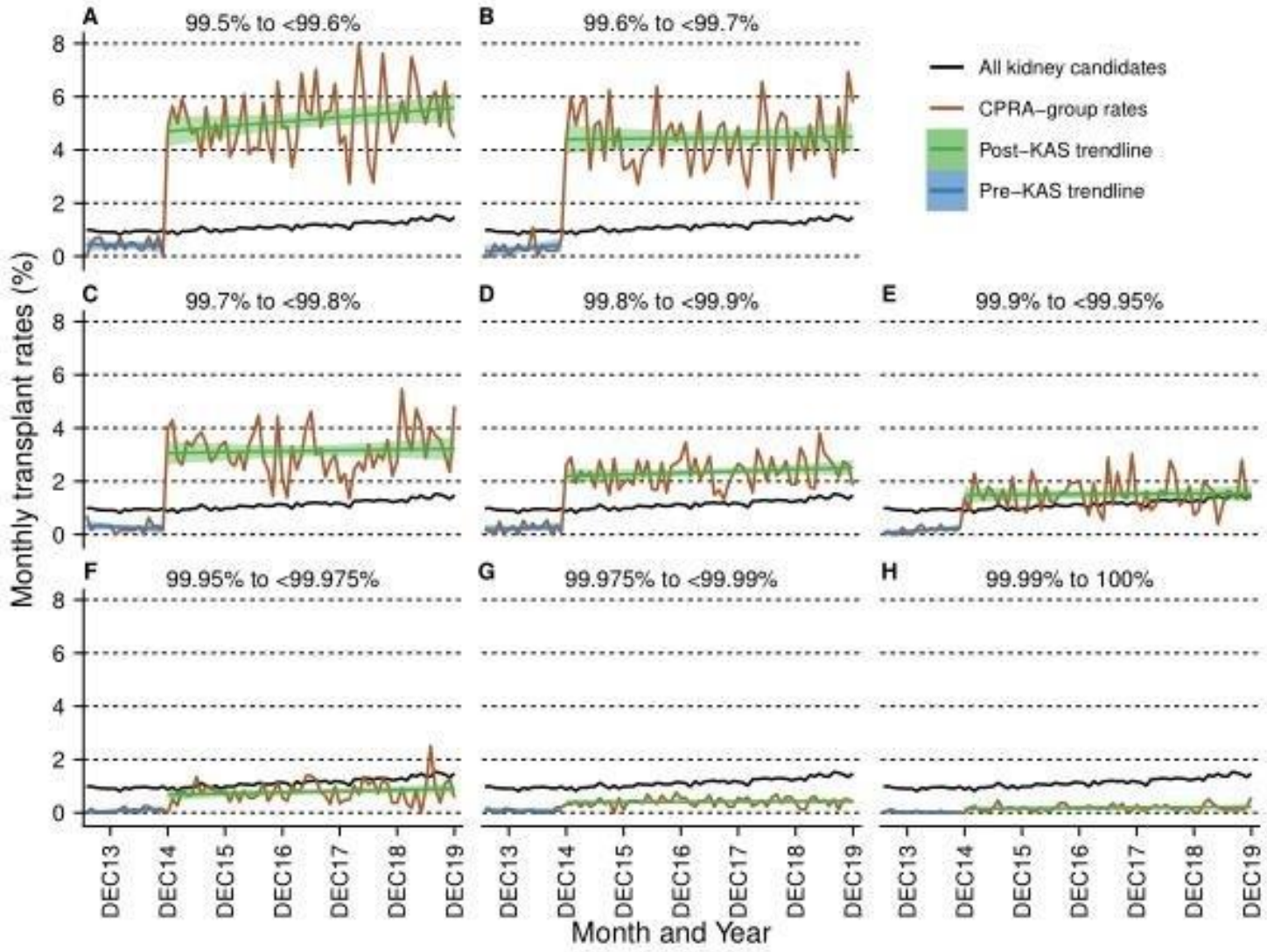
**Calculated Donor Frequency
(based on patient typing, ABO
and acceptable antigens)**

Heidt et al. Front Immunol, 2021

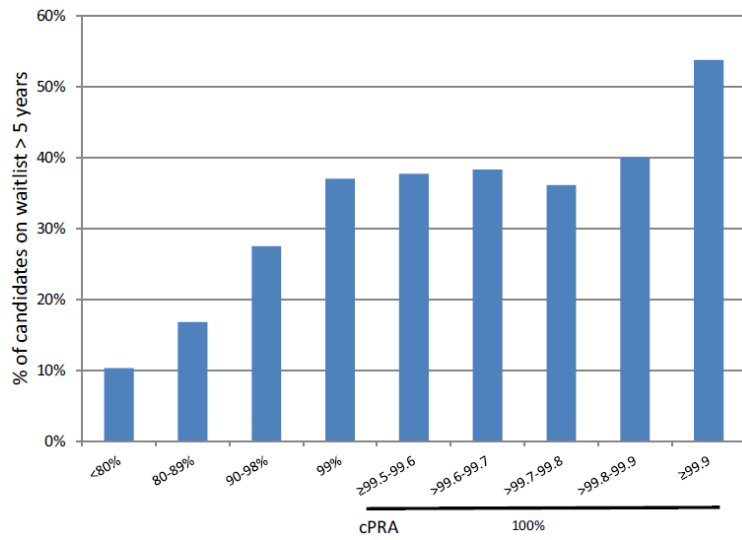
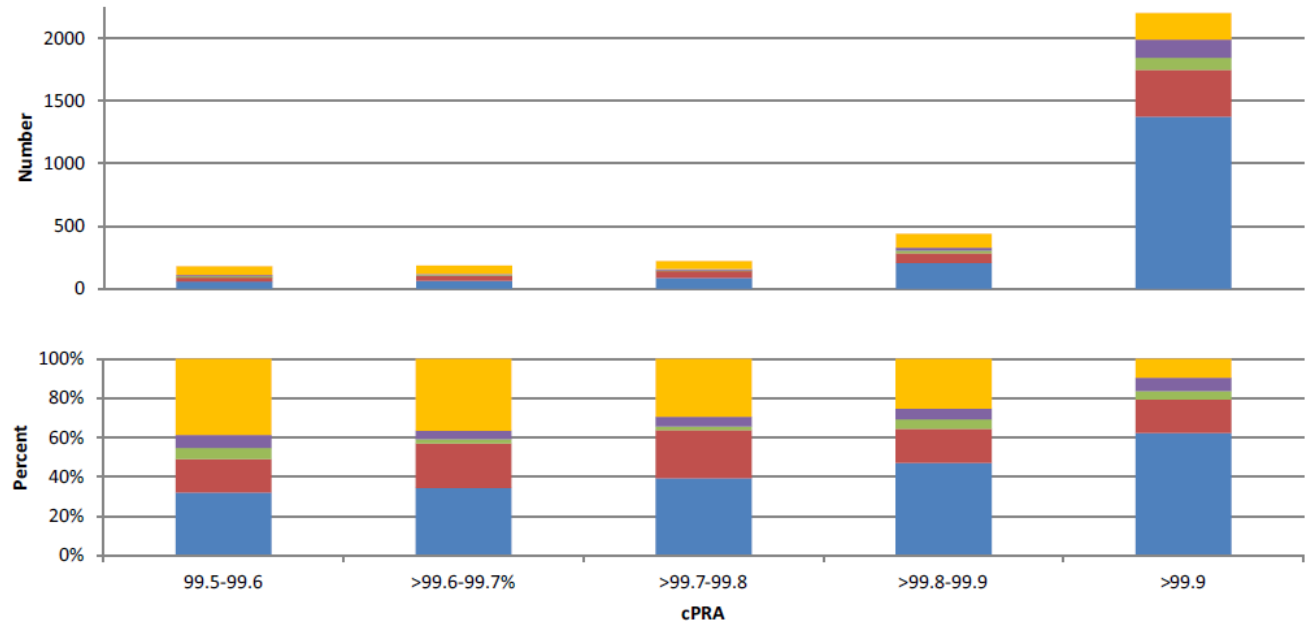
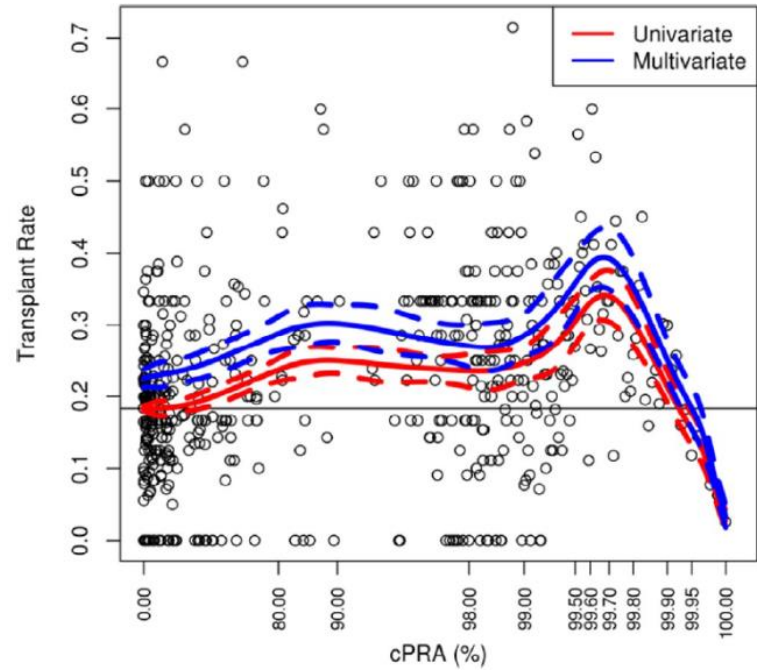
US Kidney Allocation System (KAS)



US Kidney Allocation System (KAS)

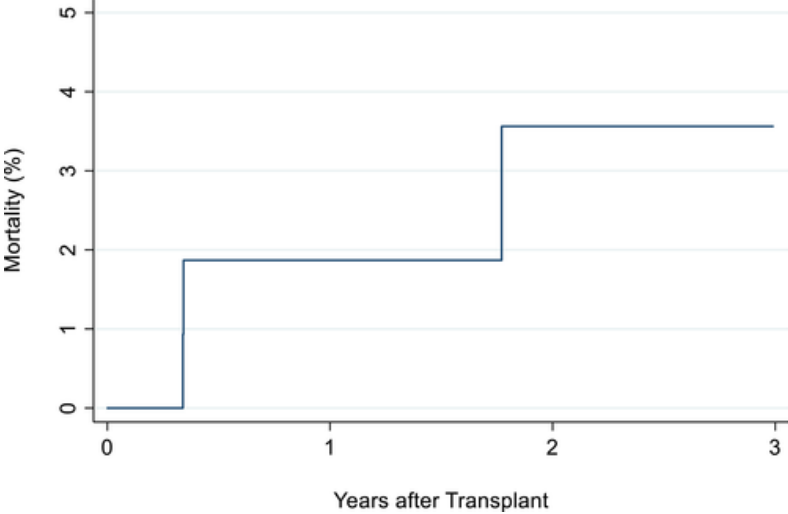


Low access to transplantation for highly sensitized patients

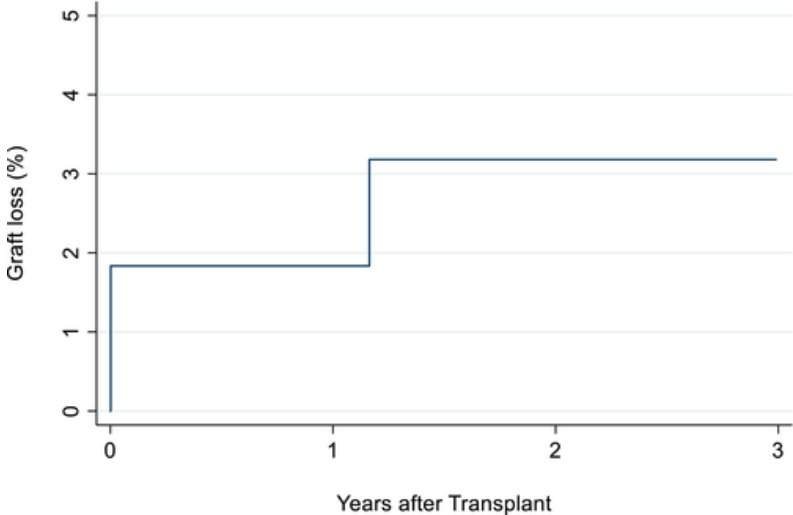


	N=181	N=186	N=221	N=441	N=2204
Transplanted N(%)	70(38.7)	68(36.6)	65(29.4)	112(25.3)	213(9.7)
Waitlist Removal N(%)	12(6.6)	8(4.3)	11(5.0)	24(5.4)	146(6.6)
Death N(%)	10(5.5)	4(2.2)	4(1.8)	21(4.8)	95(4.3)
Still Waiting Inactive N(%)	31(17.1)	42(22.6)	54(24.4)	77(17.4)	376(17.1)
Still Waiting Active N(%)	58(32.0)	64(34.4)	87(39.4)	207(46.9)	1374(62.3)

Mortality, death-censored graft failure and long-term graft function for cPRA 100% recipients under the Kidney Allocation System

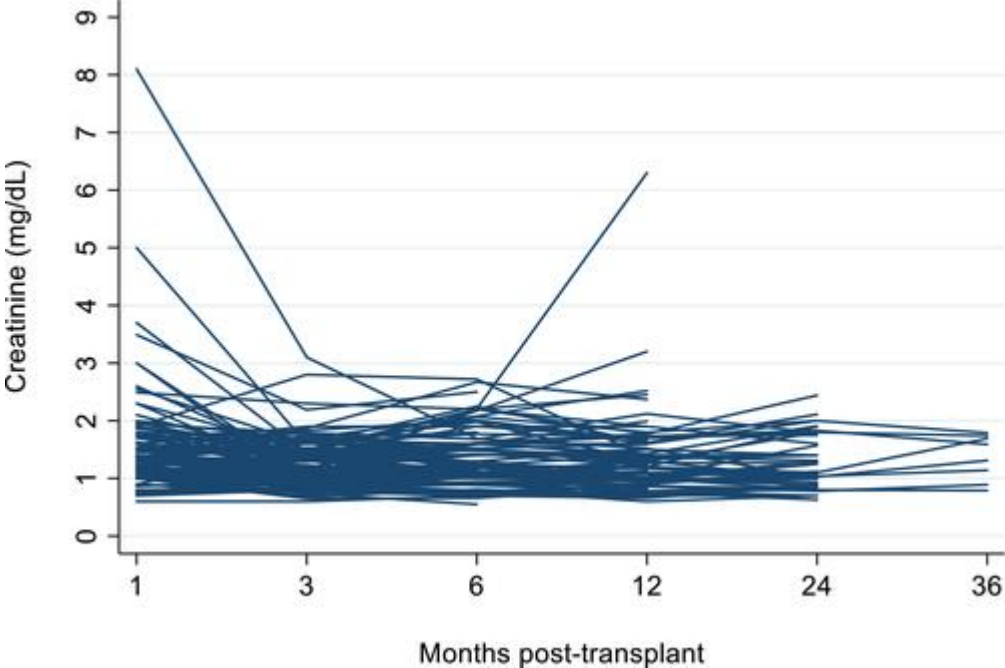


The 1-y incidence of **mortality** was 1.9%, and the 3-y incidence was 3.6%.



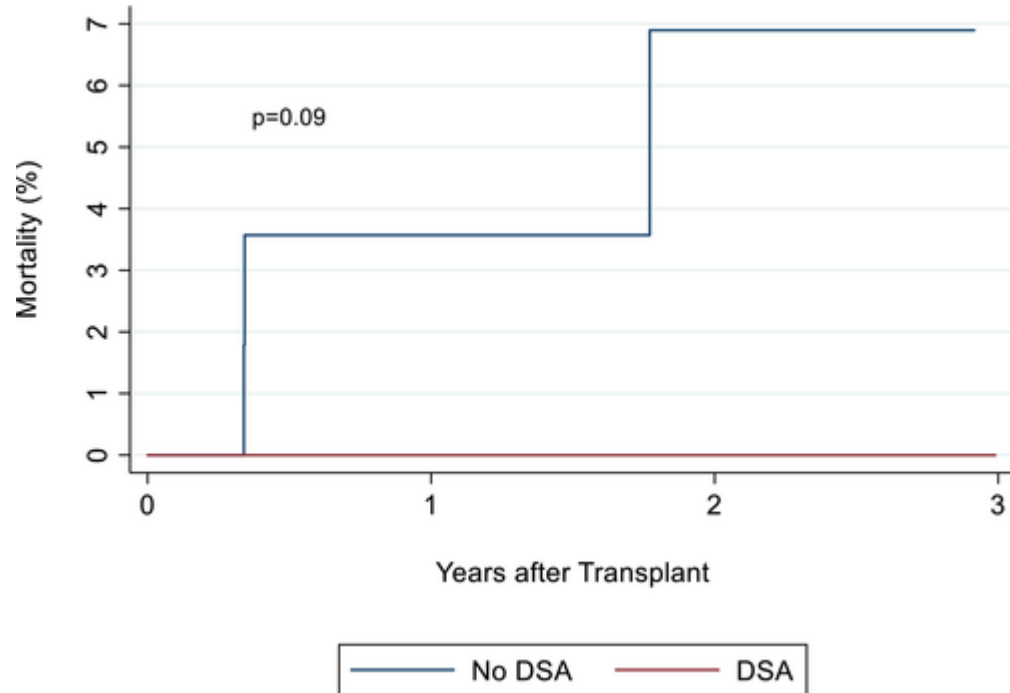
The 1-y incidence of death-censored **graft failure** was 1.8%, and the 3-y incidence was 3.2%.

109 cPRA 100% DDKT recipients
Single center
3-y period (2014-2017)



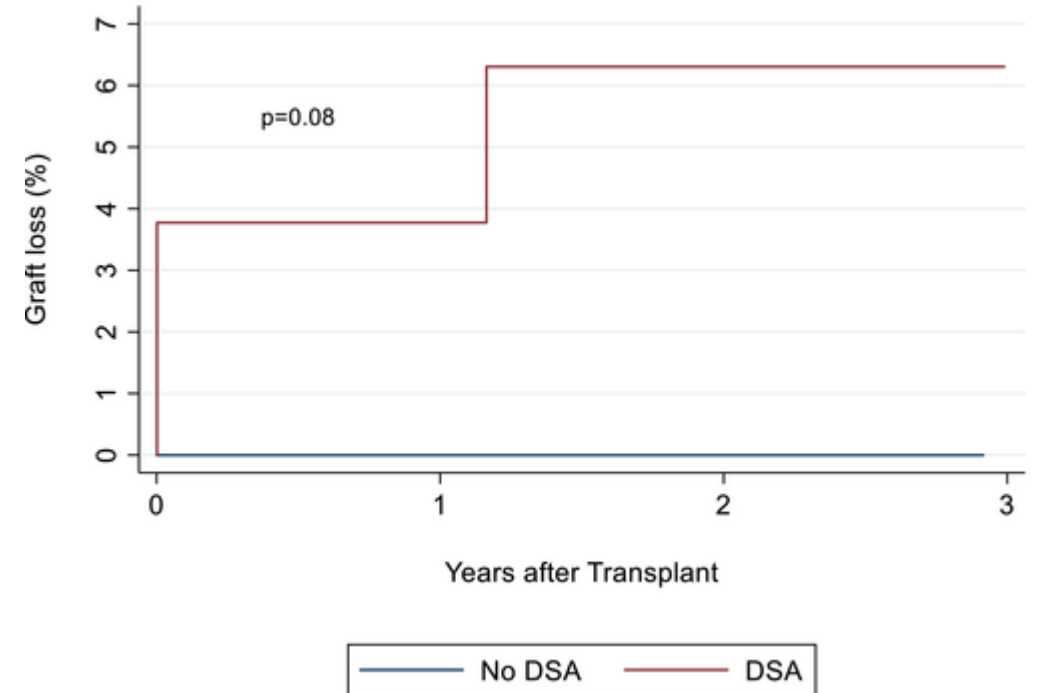
Long-term graft function

Mortality and death-censored graft failure for recipients with DSA compared with recipients without DSA



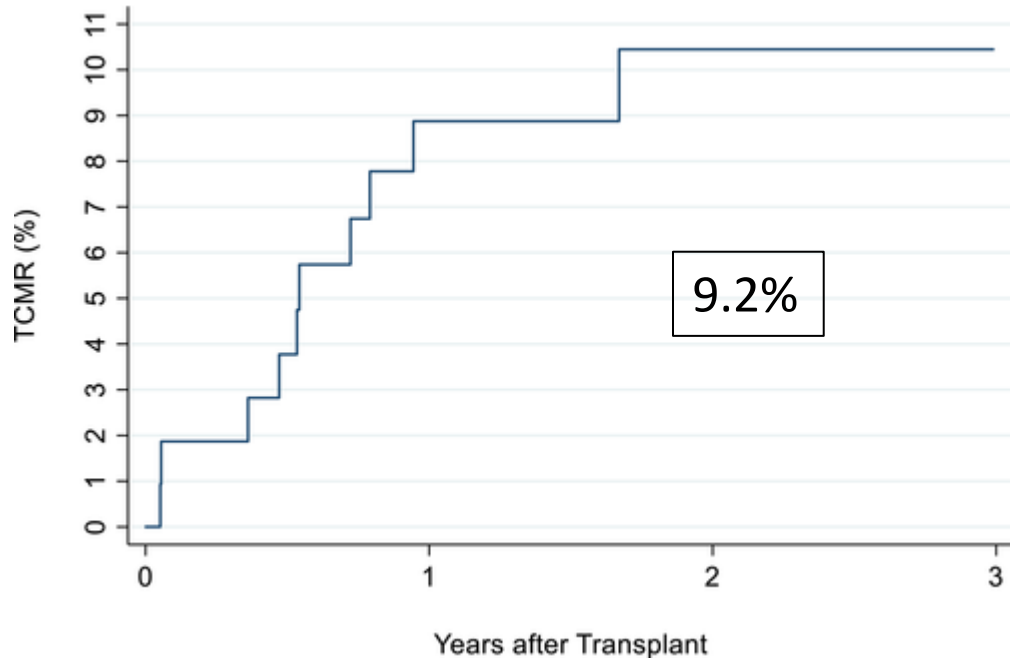
No statistically significant differences in **mortality** for recipients with DSA compared with recipients without DSA, although the point estimate for 3-y mortality was lower for recipients with DSA (0% vs 6.9%, $P = .09$).

Recipients with DSA (n = 53) vs recipients without pretransplant DSA (n = 56)

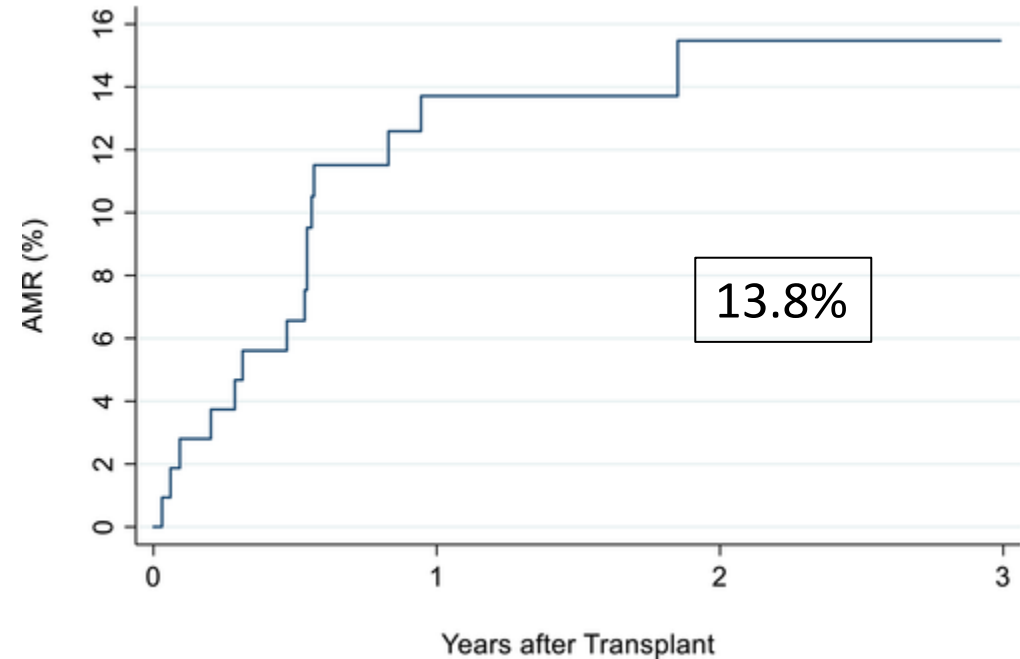


No statistically significant differences in death-censored **graft failure** for recipients with DSA compared with recipients without DSA, although the point estimate for 3-y death-censored graft failure was higher for recipients with DSA (6.8% vs 0%, $P = .08$).

Relatively low incidence of TCMR and AMR for cPRA 100% recipients under the Kidney Allocation System



40% were grade 1A, 10% were grade 1B, 40% were grade 2A, and 10% were grade 2B. There were no grade 3 rejection episodes.



Six of the episodes (40%) were C4d positive, whereas the remaining 9 episodes (60%) were C4d negative.

AMR was more common in recipients with DSA and developed in 12 recipients with DSA (22.6%) and 3 recipients without DSA (5.4%) ($P = .009$).

CATALONIA KIDNEY TRANSPLANTATION WAITING LIST

PROBABILITY OF FIRST KIDNEY TRANSPLANTATION AT 1-Y, 2-Y AND 3-Y ON DIALYSIS

		Probabilitat 1r TR cadàver						Temps mitjà en diàlisi fins el primer TR de cadàver ⁴		Primers TRs de cadàver prediàlisi ⁴	
		1r any de diàlisi ¹		2n any de diàlisi ²		3r any de diàlisi ³		n	mediana (mesos)	n	%
		n	probabilitat	n	probabilitat	n	probabilitat				
Global		3.716	24%	3.280	51%	2.847	69%	4.036	22	334	8%
Sexe	Homes	2.475	23%	2.211	50%	1.929	68%	2.668	23	216	8%
	Dones	1.241	26%	1.069	53%	918	71%	1.368	22	118	9%
Edat (anys)	0-17	83	81%	77	100%	70	100%	99	2	39	39%
	18-44	487	21%	433	50%	385	72%	562	25	22	4%
	45-64	1.607	22%	1.414	49%	1.227	69%	1.863	25	125	7%
	65-74	1.179	24%	1.047	50%	906	66%	1.195	21	107	9%
	>=75	360	26%	309	53%	259	69%	317	17	41	13%
Grup sanguini	A	1.528	35%	1.347	68%	1.165	84%	1.834	18	198	11%
	AB	164	58%	150	79%	128	93%	196	9	48	24%
	B	386	25%	341	53%	292	73%	426	22	41	10%
	O	1.636	11%	1.440	32%	1.260	53%	1.580	31	47	3%
cPRA I+II màxim	0% o no realitzat	2.260	28%	2.005	59%	1.770	76%	2.756	21	218	8%
	1-50%	699	19%	604	40%	495	62%	606	24	55	9%
	51-89%	518	15%	458	35%	396	54%	445	26	36	8%
	90-94%	62	40%	54	63%	47	84%	68	15	13	19%
	95-97%	68	24%	62	42%	55	59%	64	23	8	13%
	98-99%	64	16%	57	40%	49	66%	67	26	3	4%
	100%	45	7%	40	10%	35	29%	30	38	1	3%



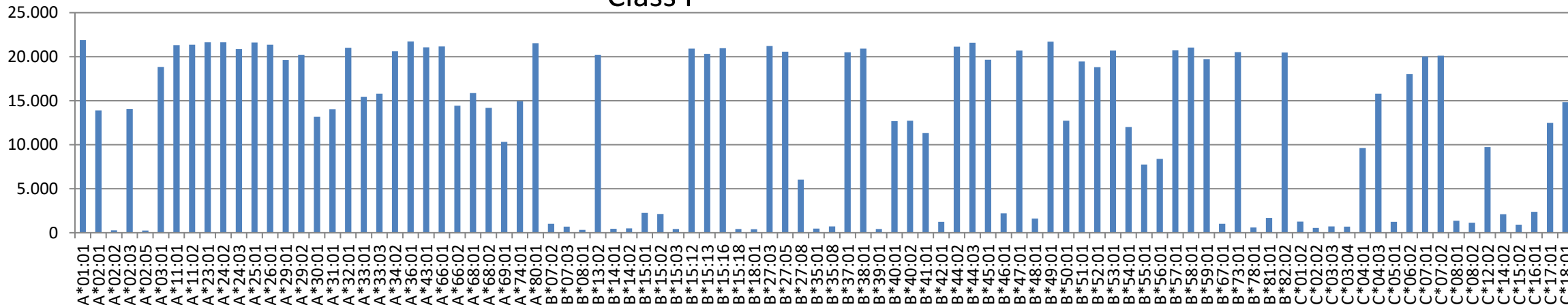
Strategies for kidney transplantation in highly sensitized transplant candidates

- Priority in deceased donor allocation systems
- Paired exchange programmes in living donor transplantation
- Desensitization

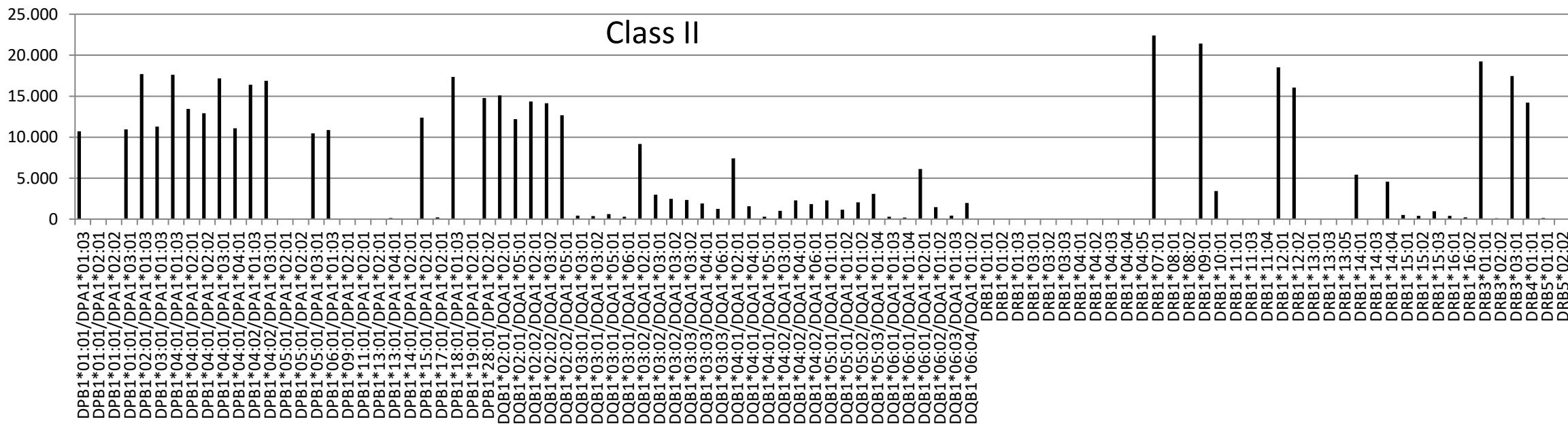
Highly sensitized patient: cPRA I 100% / cPRA II 93% / cPRA I+II 100%

MFI

Class I



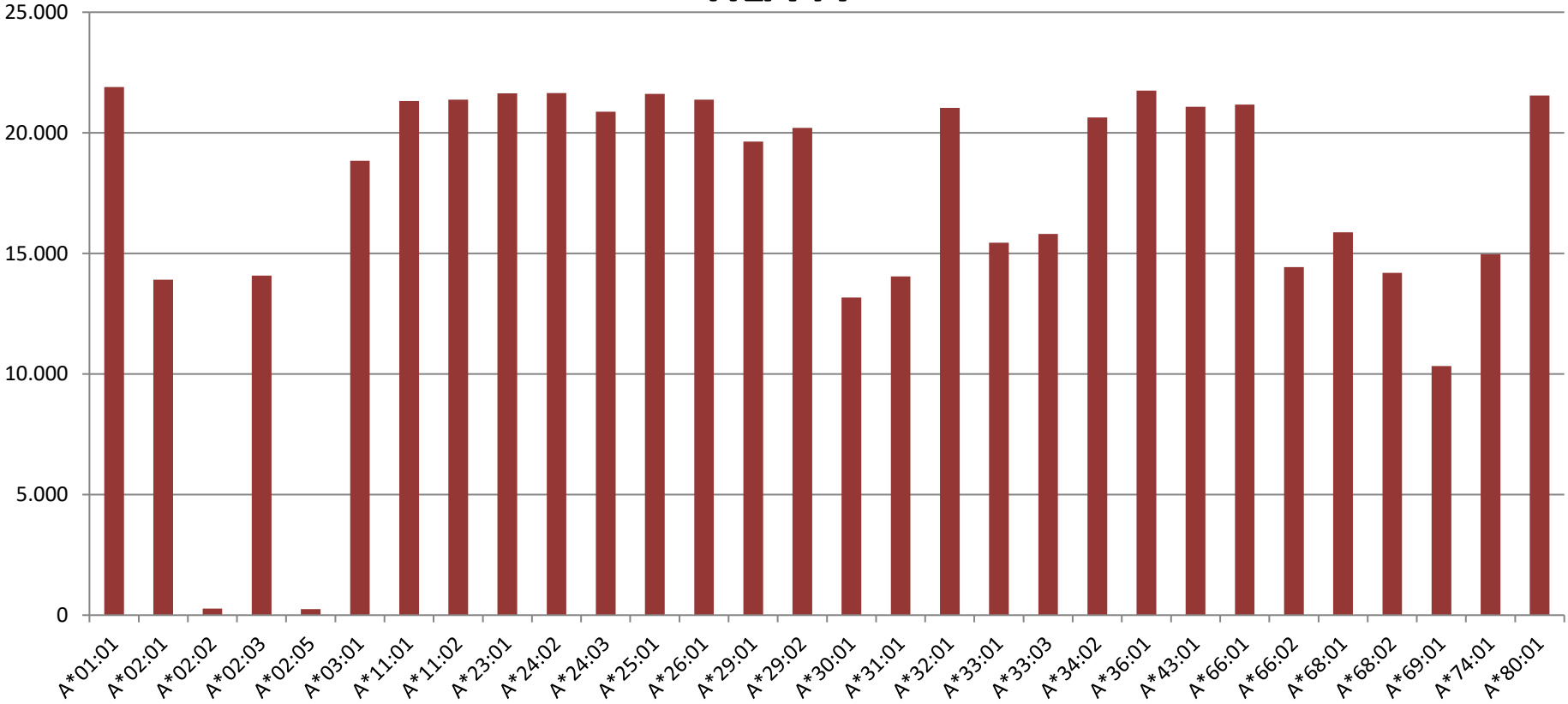
Class II



A*02:02P, A*-	B*08:01P, B*15:03P	C*02:02P, C*03:04P	DRB1*08:04P, DRB1*13:04	DRB3	DQB1*03:01P, DQB1*-	DQA1*05:01P, DQA1*-	DPB1*13:01P, DPB1*17:01P	DPA1*02:01P, DPA1*-
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MFI

HLA-A



Thank you for your attention

17º CONGRESO

BARCELONA



**22-24
marzo
2023**

**SOCIETAT
CATALANA DE
TRASPLANTAMENT**