Nephrology and Transplantation Department
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Donor Specific Antibody (DSA)

The Devil in Detail

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Disclosure

No Conflict of Interst •

Outlines

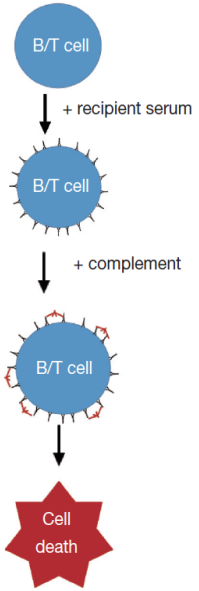
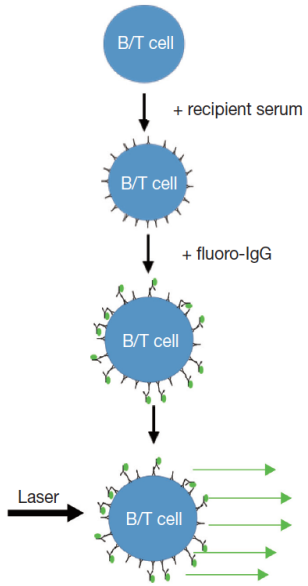
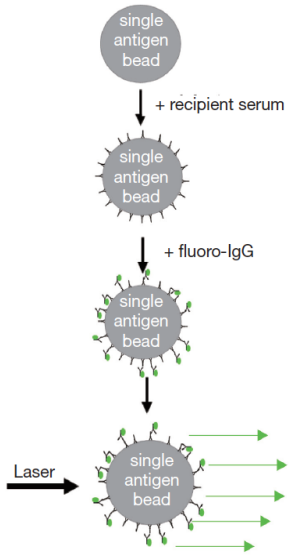
- Introduction; DSA in Kidney Transplant
- DSA Pathogenesis
- DSA Classes and Specificity
- Complement binding DSA
- DSA IgG Subclasses
- DSA and C4d Deposition

What is anti-HLA antibody?

- Anti HLA antibody resulting from the exposure of an individual's immune system to non-self HLA
  - Transfusion
  - Transplantation
  - Pregnancy
- DSA can be pre-formed or de novo

HepatoBiliary Surg Nutr 2019;8(1):37-52

How are DSA detected?

Antibody test methods	CDC cross match	Flow cross match	Solid phase single antigen assay
Diagram of protocols			
Usage of test	Usually pre-transplant	Usually pre-transplant	Both pre- and post-transplant
Antigen source	Native antigens on donor lymphocytes	Native antigens on donor lymphocytes	Purified single antigens on beads
Antibody detected	Cytotoxic, complement fixing IgG and IgM, donor specific	Donor specific IgG	IgG anti-HLA antibodies in general
Antibody specificity determined	No	No	Yes (HLA)
Quantitation	Scale 1-8 binary	Semi-quantitative	Semi-quantitative
Sensitivity	Low	Intermediate	High
Repeatability	Low	Low to intermediate	High
Requirement for live cells	Yes	Yes	No

HepatoBiliary Surg Nutr 2019;8(1):37-52

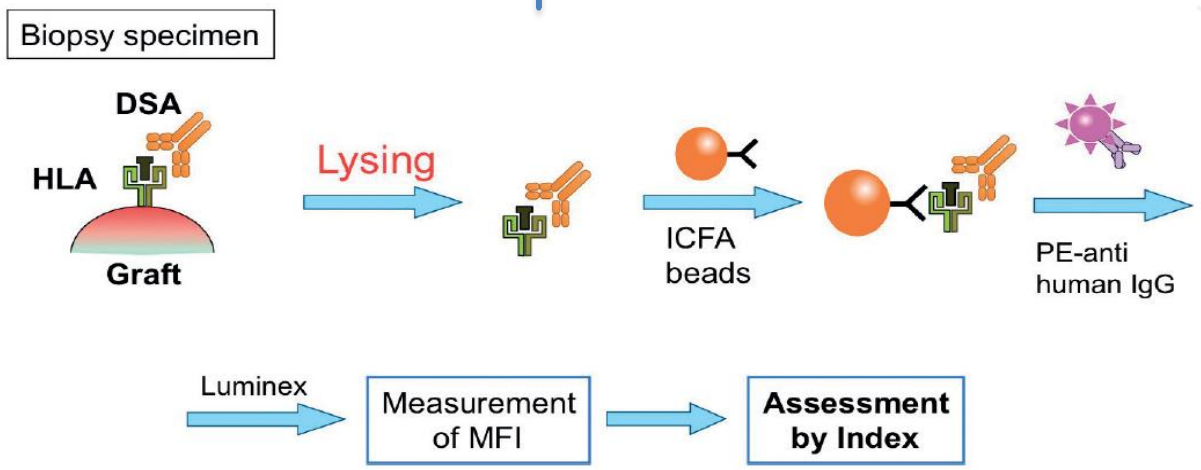
Donor-Specific Anti-HLA Antibodies in Organ Transplantation: Transition from Serum DSA to Intra-Graft DSA

Graft ICFA to predict pathological AMR; 100% sensitivity and 92.9% specificity

Graft ICFA

Indicate that g-DSA causes microcirculation lesions and high g-DSA means chronic allograft damages

Kidney



http://dx.doi.org/10.5772/intechopen.79846

What are the consequences of DSA in transplantation?

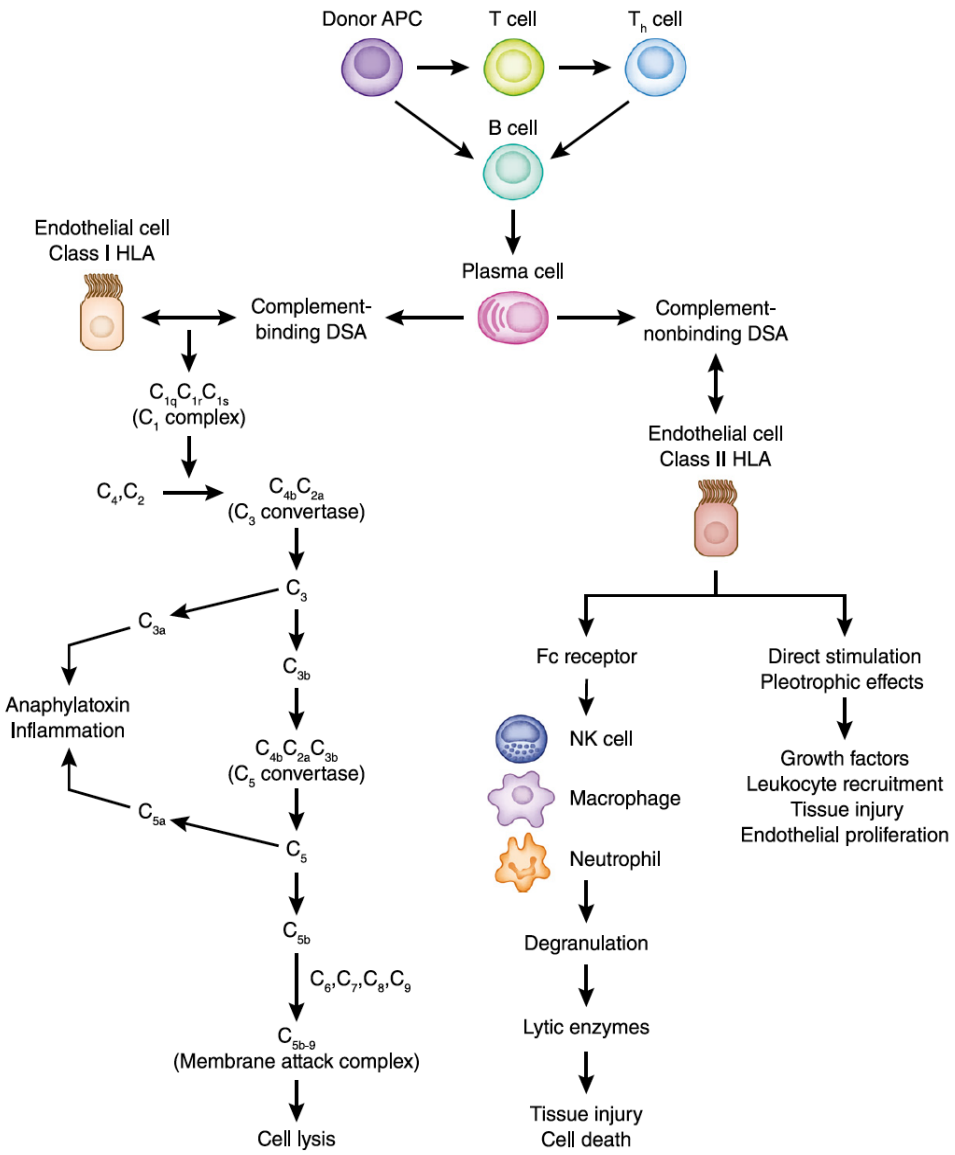
- ***Complement activation***
- ***Antibody dependent cell mediated cytotoxicity (ADCC)***
- ***Modification of the vascular endothelium***
- ***Accommodation***

HepatoBiliary Surg Nutr 2019;8(1):37-52

REVIEW

Donor-Specific Antibodies in Kidney Transplant Recipients

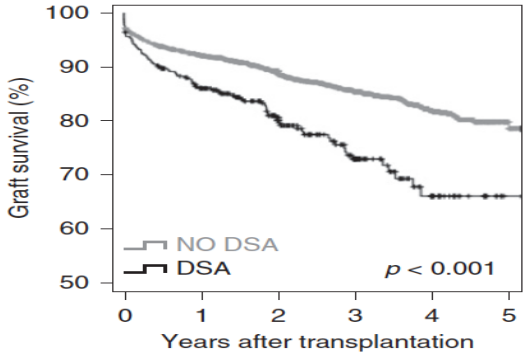
	Class 1 Donor-Specific Antibodies	Class 2 Donor-Specific Antibodies
HLA		
Antigens	A, B, and C	DR, DQ, and DP
Epitopes location	α-chain	α- and β-chains
Expression	All nucleated cells	Antigen-presenting cells
Preformed donor-specific antibodies		
Important	Very	Less
Positive crossmatch	T cells	B cells
Transplant decision	No transplant	Permissible
***De novo* donor-specific antibodies**		
Detection	Sooner	Later
IgG subclasses	IgG1, IgG3	IgG2, IgG4
Complement binding	Strong	Weak/no
Frequency	Fewer	Common, especially DQ
Antibody-mediated rejection		
Phenotypes	Acute	Chronic, subclinical
Presentation	Early	Later
Graft dysfunction	Rapidly	Slowly
C4d deposit	Positive	Negative
Treatment	More responsive	Less responsive
Graft loss	Early	Later



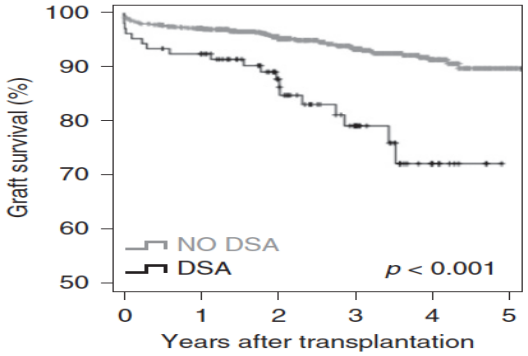
Clin J Am Soc Nephrol 13: 182–192, 2018.

Preformed Donor-Specific HLA Antibodies in Living and Deceased Donor Transplantation

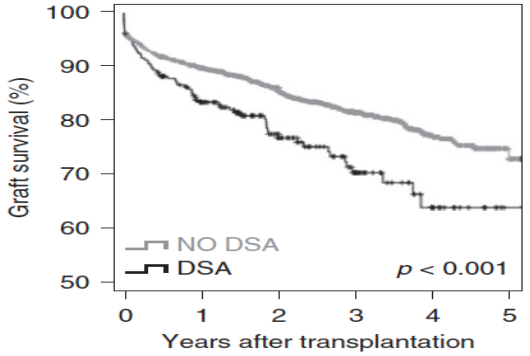
A Multicenter Study



No DSA, n	3765	3241	2179	1297	584	101
DSA, n	367	296	190	110	46	7

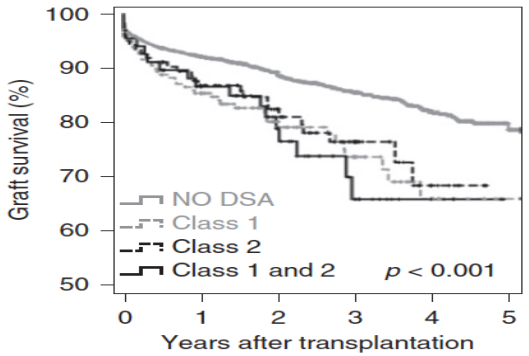


	1218	1119	1389	125	231	42
	106	97	65	39	14	2



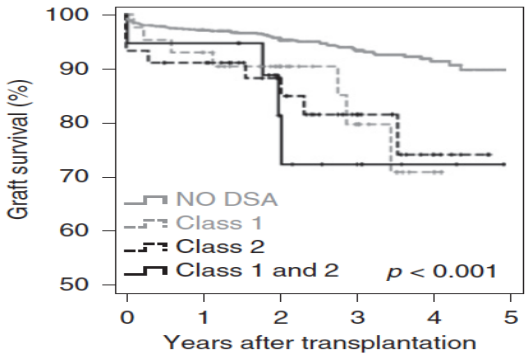
	2547	2122	1389	800	353	59
	261	199	125	71	32	5

D



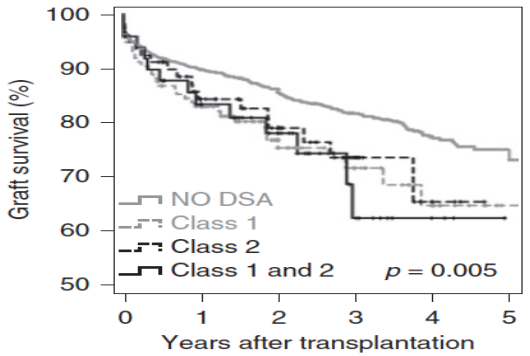
No DSA, n	3766	3242	2180	1298	584	101
Class 1, n	184	146	89	55	27	4
Class 2, n	114	94	63	38	14	3
Class 1 and 2, n	68	55	37	16	5	0

E



	1218	1119	790	497	231	42
	45	41	28	16	5	1
	43	39	27	17	7	1
	18	17	10	6	2	0

F



	2548	2123	1390	801	353	59
	139	105	61	39	22	3
	71	55	36	21	7	2
	50	38	27	10	3	0

CJASN 14: 1056–1066, July, 2019

A

Preformed DSA were associated with an increased risk for graft loss in kidney transplantation, which was greater in living than in deceased donation. Even weak DSA<3000 MFI were associated with worse graft survival. This association was stronger in living than deceased donation.

Table 2. Multivariable Cox regression models for graft survival

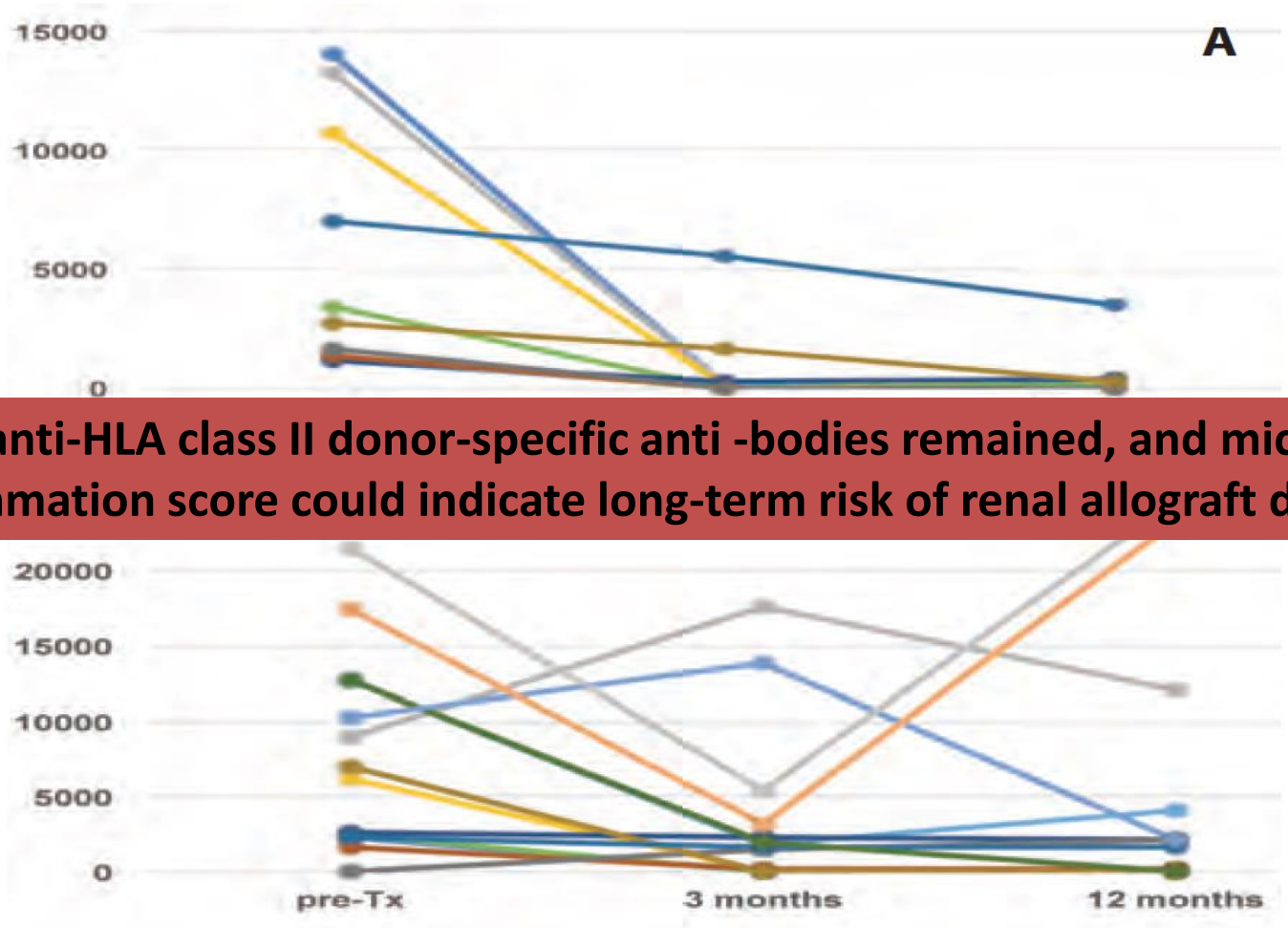
Variable	Hazard Ratio (95% CI)	*P* Value
Overall graft survival for living donors[a]		
Pretransplant donor-specific antibodies	2.53 (1.49 to 4.29)	<0.001
Pretransplant desensitization		
ABO-incompatible transplantation	2.09 (1.33 to 3.27)	0.001
Desensitization in ABO-compatible transplantation	1.68 (0.78 to 3.58)	0.18
Time on dialysis, per year	1.15 (1.05 to 1.27)	0.004
Number of HLA-A/B/DR-mismatches, per mismatch	1.19 (1.03 to 1.37)	0.02
Overall graft survival for deceased donors[b]		
Pretransplant donor-specific antibodies	1.59 (1.21 to 2.11)	0.001
Patient age, per year	1.02 (1.01 to 1.03)	<0.001
Kidney Donor Risk Index (11)	1.85 (1.53 to 2.23)	<0.001

	0	1	2	3	4	5
	Years after transplantation					
No DSA, n	1218	1119	790	497	231	42
DSA<3000, n	59	55	35	19	7	1
DSA≥3000, n	47	42	30	20	7	1

	0	1	2	3	4	5
	Years after transplantation					
	2547	2122	1389	800	353	59
	146	107	68	37	17	1
	115	92	57	34	15	4

CJASN 14: 1056–1066, July, 2019

Living-Donor Kidney Transplant With Preformed Donor-Specific Antibodies



Most anti-HLA class II donor-specific anti -bodies remained, and micro vascular inflammation score could indicate long-term risk of renal allograft dysfunction

Yoshihiro Itabashi et al/Experimental and Clinical Transplantation (2019) 1: 43-49

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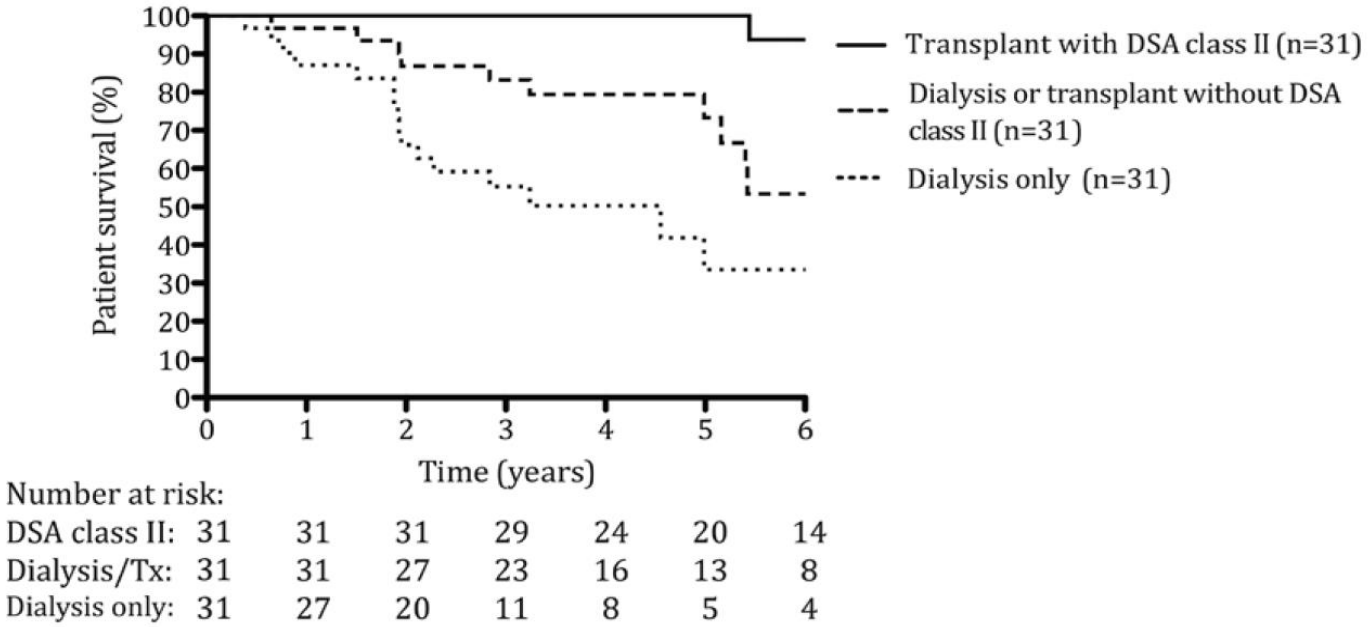
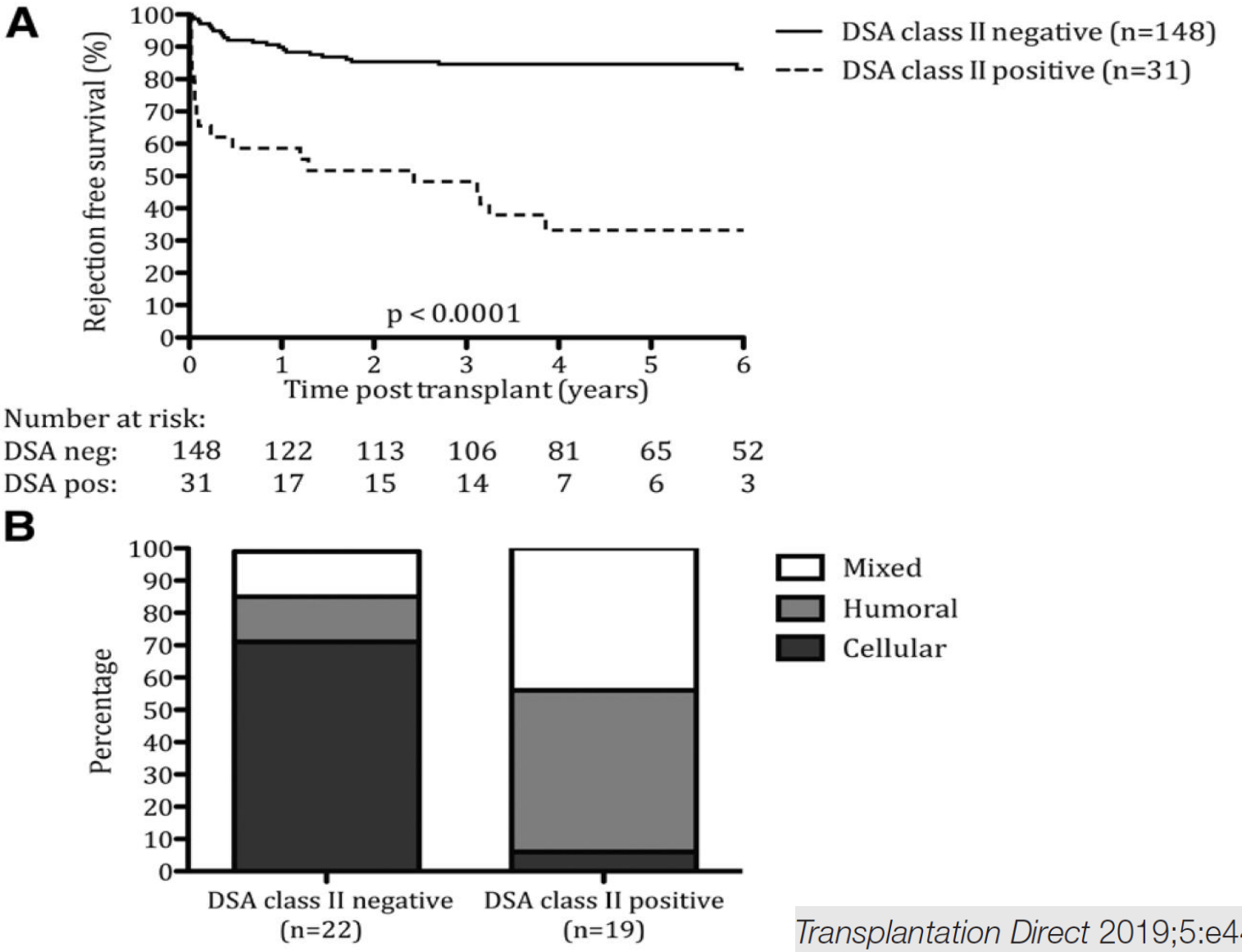
Preformed Donor-specific Antibodies Against HLA Class II and Graft Outcomes in Deceased-donor Kidney Transplantation

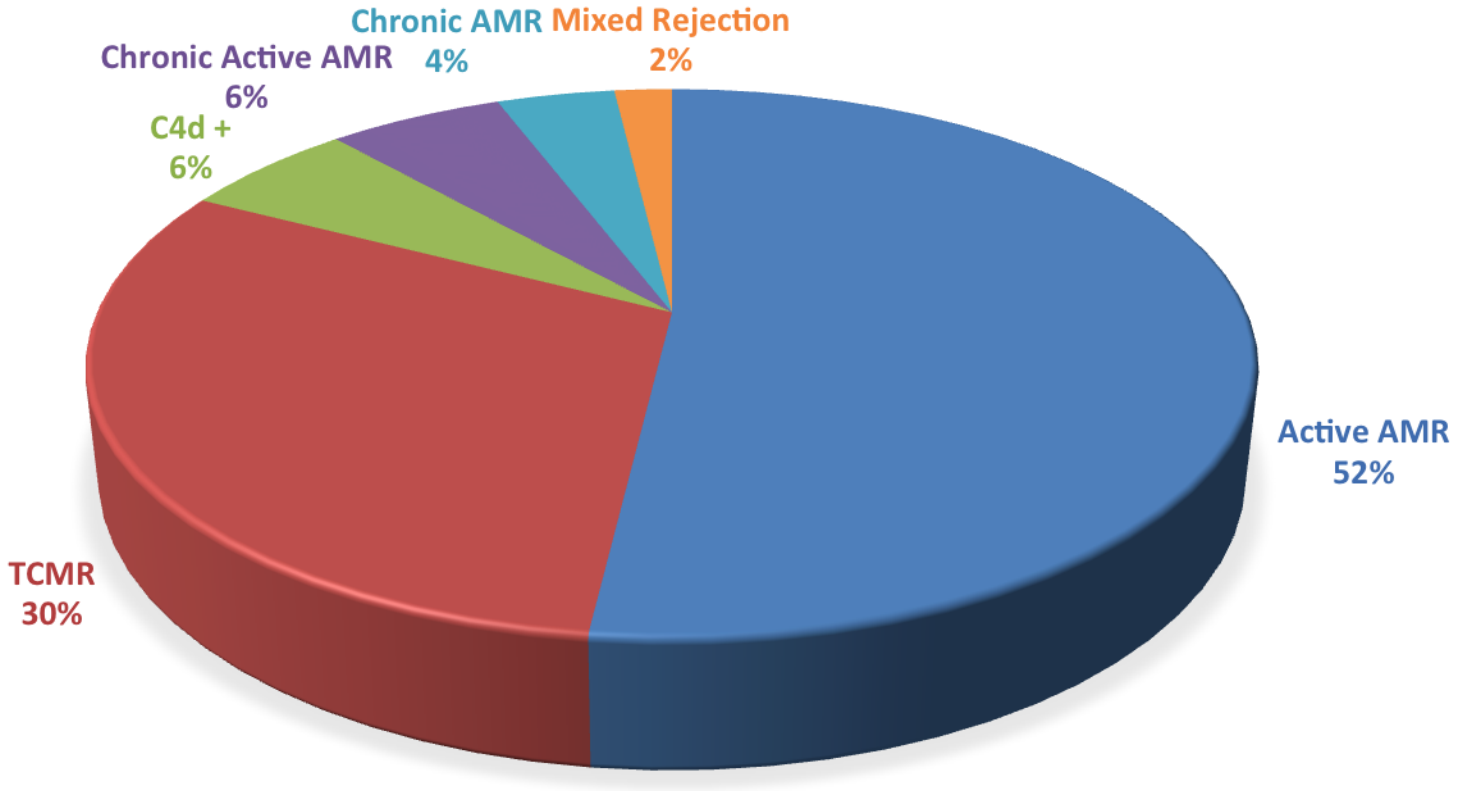


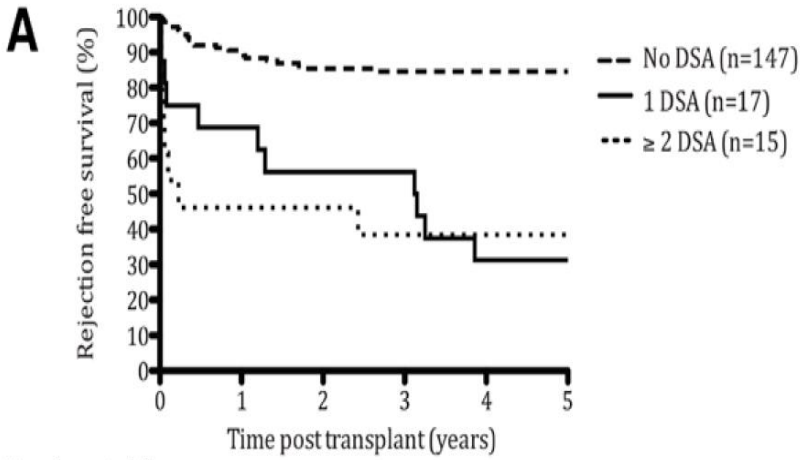
Transplantation Direct 2019;5:e446



Transplantation Direct 2019;5:e446

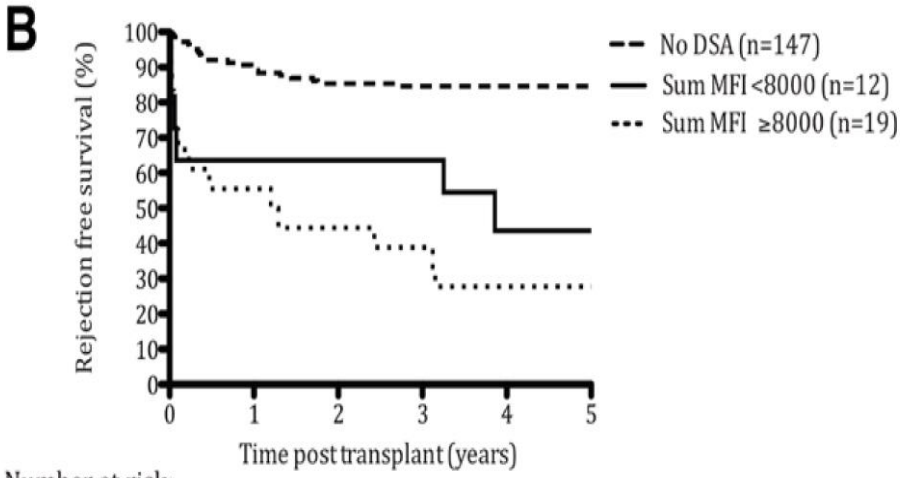
Distribution of Rejection (First post-transplantation year)





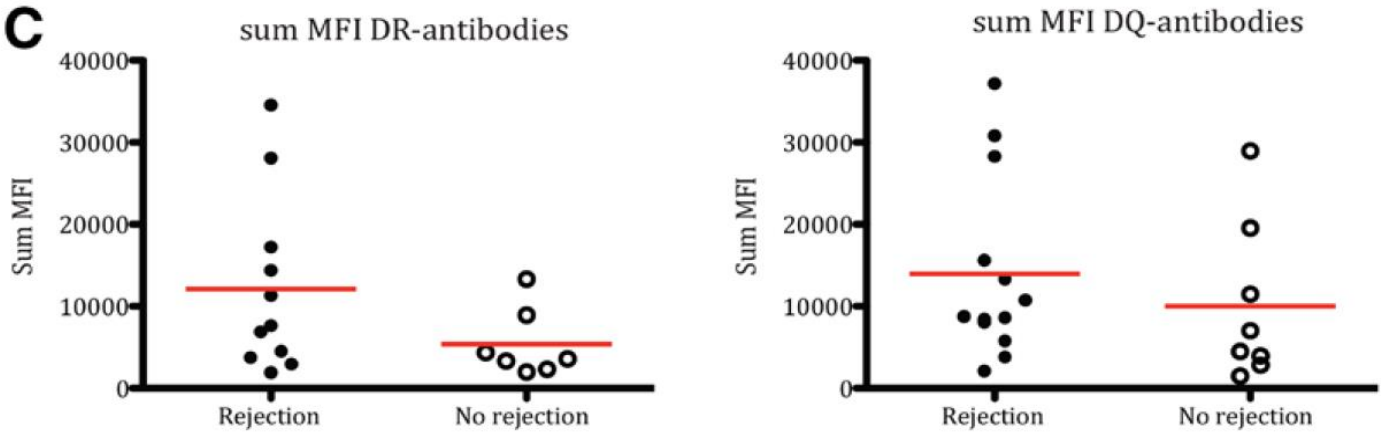
Number at risk:

No DSA:	148	122	113	106	81	65
1 DSA:	17	11	9	9	5	5
≥2 DSA:	14	6	6	5	2	1



Number at risk:

No DSA:	148	123	95	72	62	62
ΣMFI <8000:	12	7	7	7	4	4
ΣMFI ≥8000:	19	10	8	7	3	2



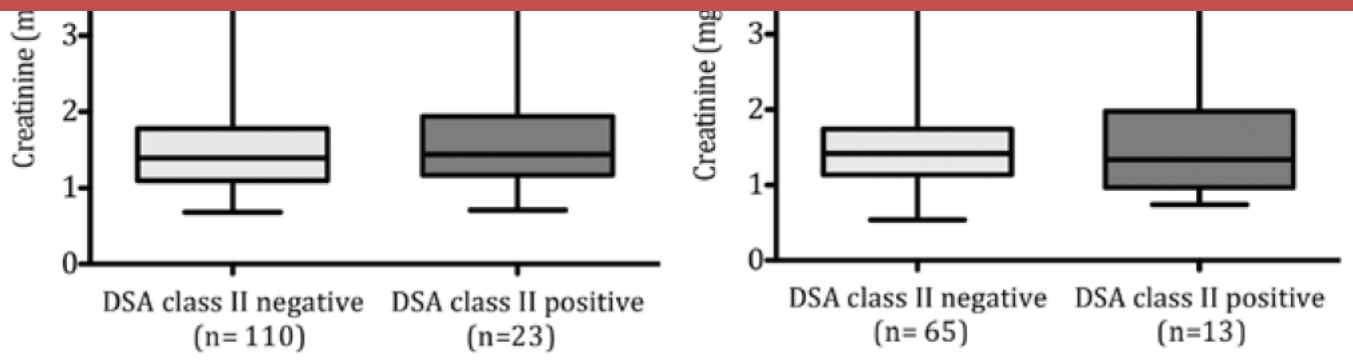
Transplantation Direct 2019;5:e446

Eplet mismatch in patients with DSA class II before transplant, with and without episode of rejection

ePmm, mean ± SD	Rejection, n = 19	No rejection, n = 10	*P*
Total	47 ± 17	47 ± 21	0.98
DR	20 ± 14	20 ± 9	0.73
DQ	25 ± 9	27 ± 14	0.66

DSA, donor-specific antibody; ePmm, eplet mismatch.

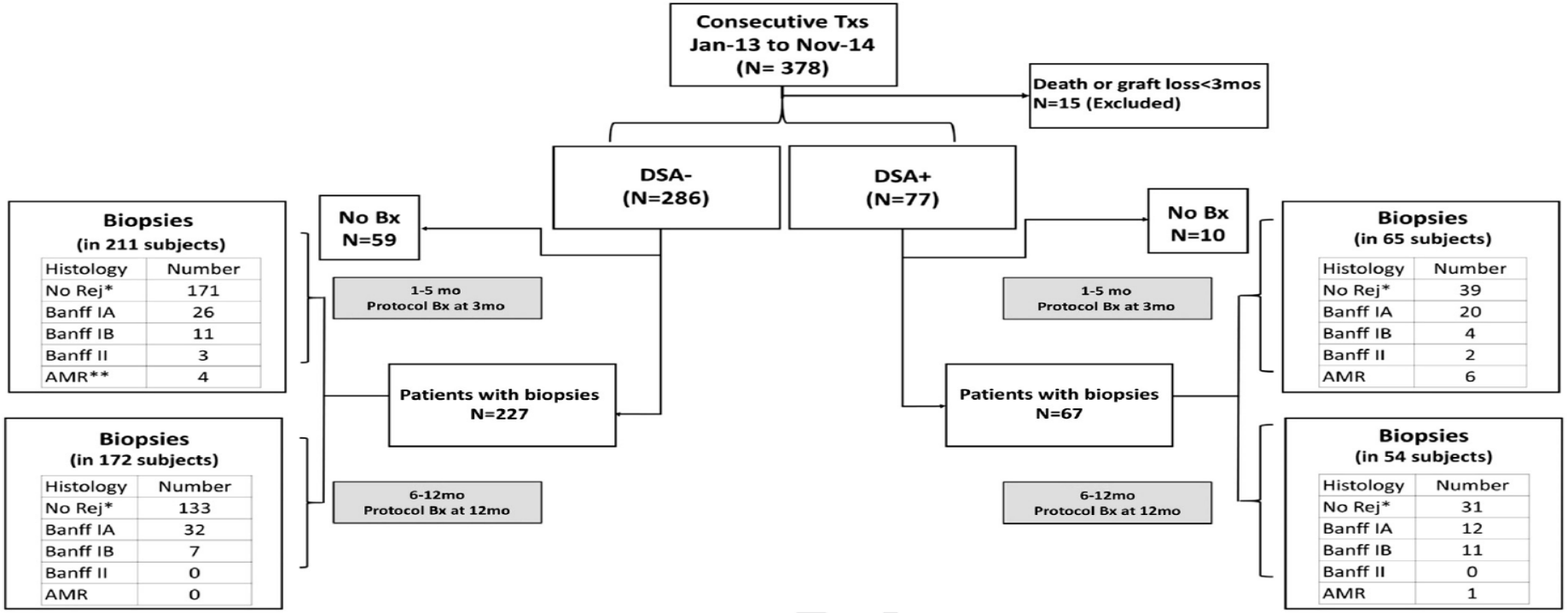
For highly sensitized patients, deceased-donor kidney transplantation with DSA class II yields a survival benefit over prolonged waiting time on dialysis. Instead of listing DSA class II as unacceptable antigens, an individual approach with further immunologic risk assessment is recommended.

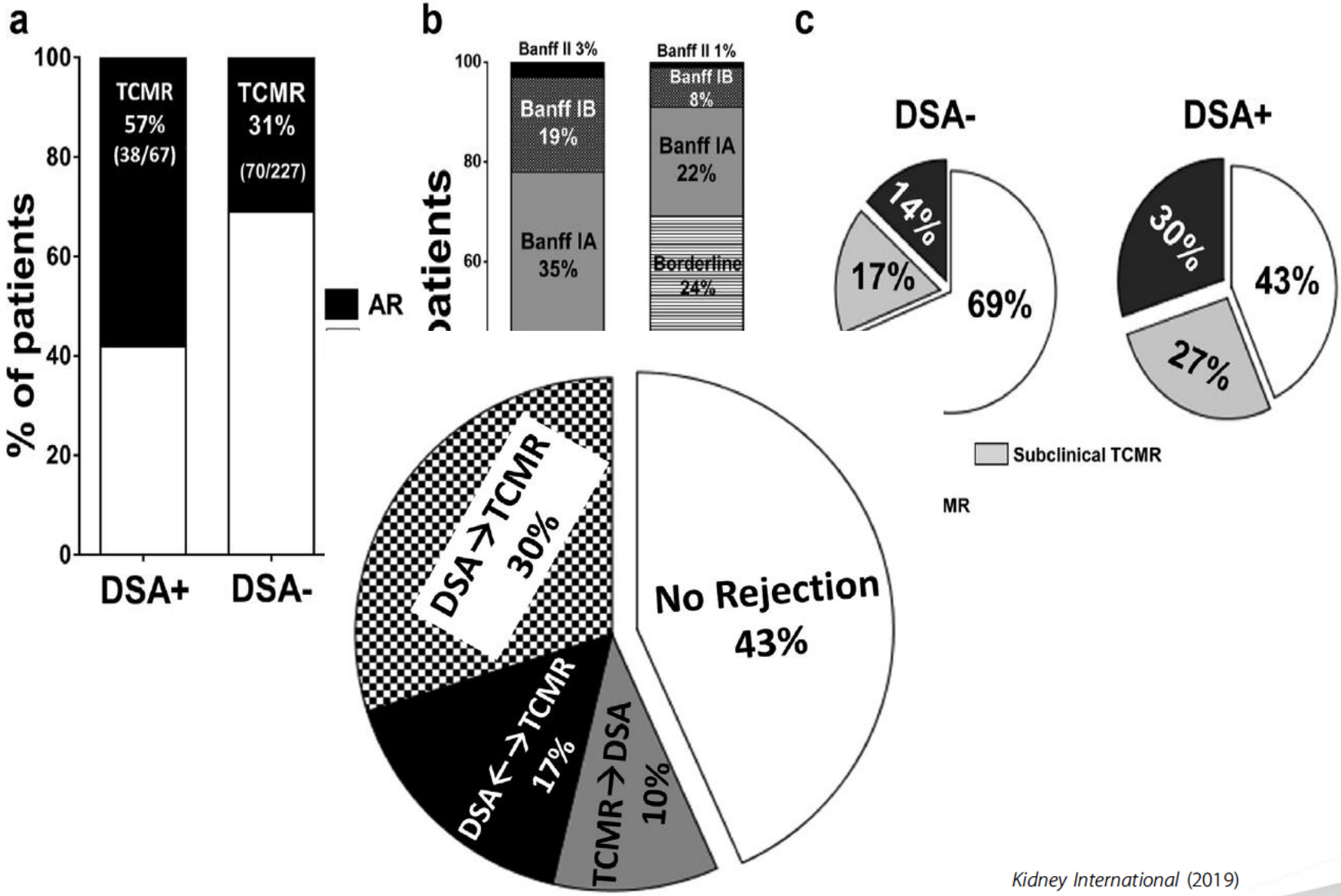


Transplantation Direct 2019;5:e446

Post-transplant donor specific antibody is associated with poor kidney transplant outcomes only when combined with both T-cell–mediated rejection and non-adherence

Kidney International (2019)





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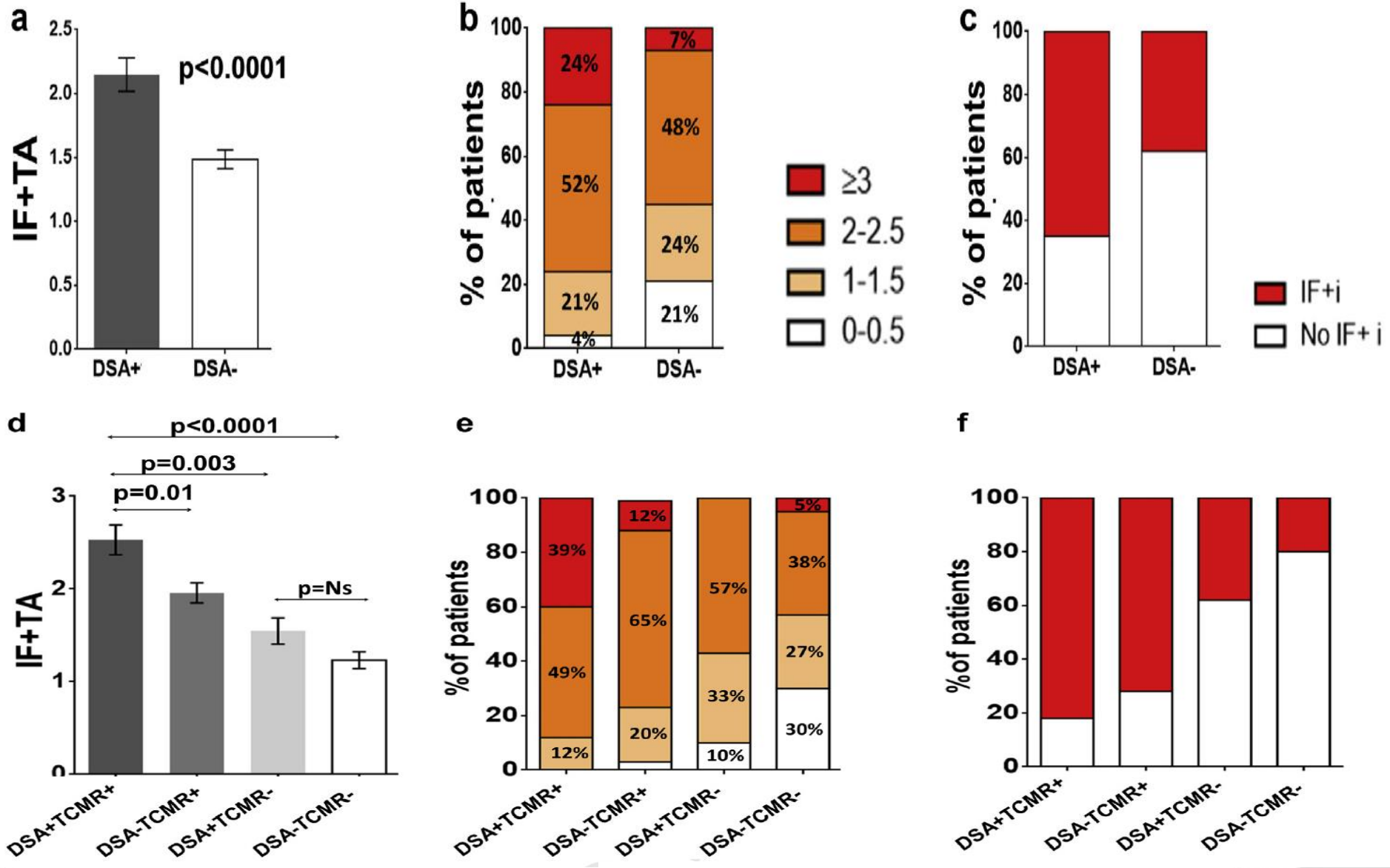


Kidney International (2019)

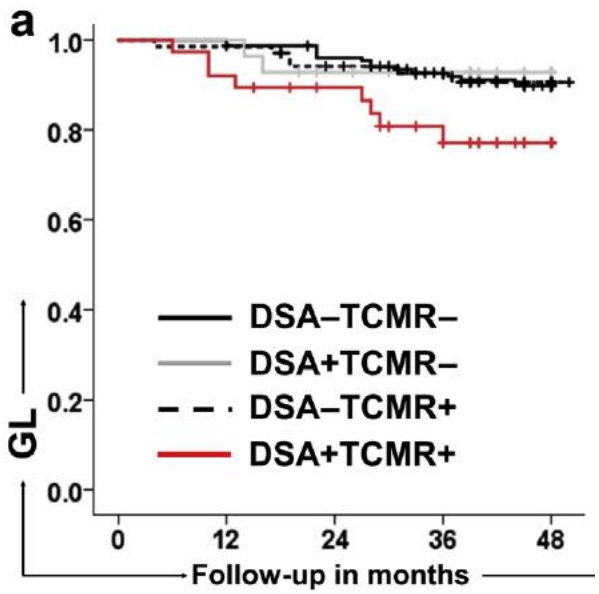


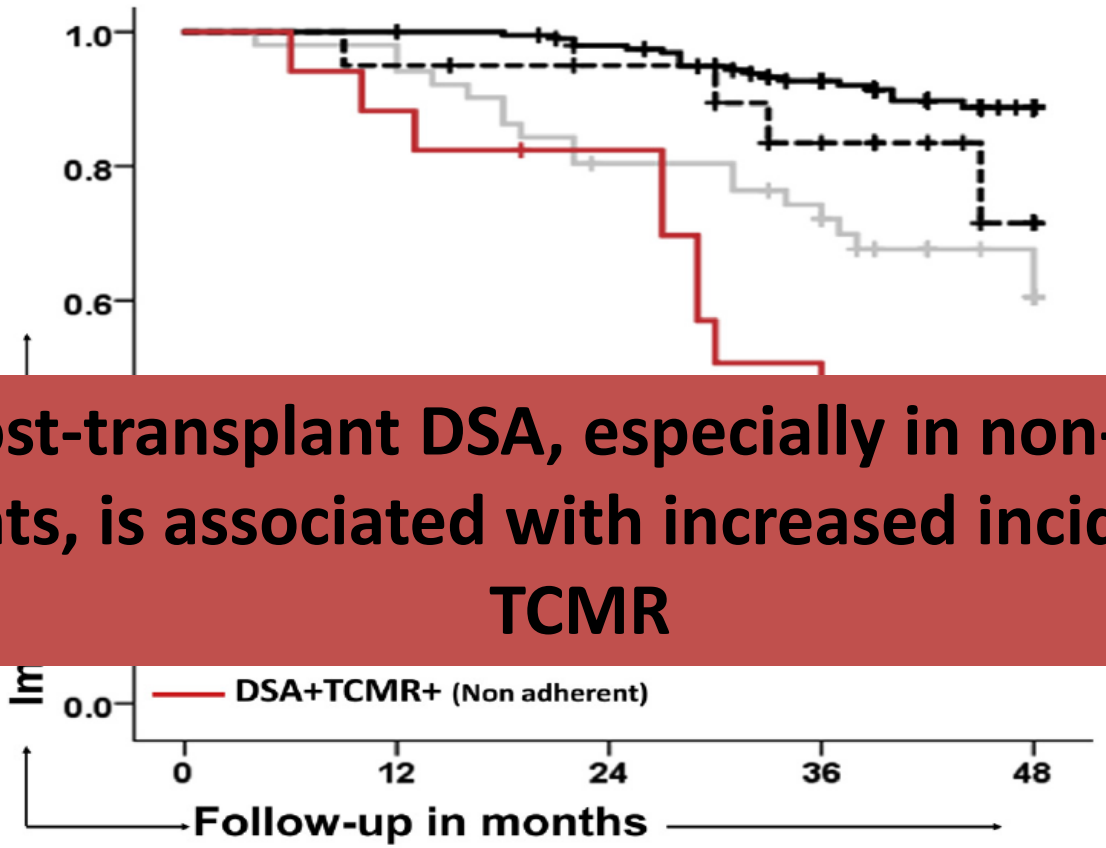
Table 2 | Univariate and multivariate analyses for graft loss and impending graft loss at 4 years

	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical variables	**Univariate analysis**		**Multivariate analysis**	
Recipient age	1.01 (0.99–1.02)	0.4		
Gender (male%)	0.7 (0.4–1.2)	0.2		
Non-Caucasian ethnicity	1.2 (0.7–2.3)	0.4		
Primary renal disease				
HTN	Ref			
DM	0.95 (0.3–2.6)	0.9		
Glomerular[a]	0.6 (0.2–2.0)	0.4		
Inherited/congenital[b]	0.2 (0.02–1.5)	0.1		
Others[c]	0.4 (0.2–1.5)	0.2		
Donor age	1.03 (0.99–1.06)	0.1		
Donor type				
DBD vs. live	1.7 (0.9–3.1)	0.1	1.5 (0.8–2.9)	0.2
DCD vs. live	2.4 (1.1–5.0)	0.03	1.9 (0.9–4.2)	0.1
Retransplant	1.0 (0.5–2.0)	0.99		
HLA mismatch	1.2 (1.04–1.4)	0.01	1.1 (0.95–1.3)	0.1
DGF	2.3 (1.3–4.1)	0.005	1.5 (0.8–2.9)	0.2
DSA and TCMR groups				
DSA−TCMR−	Ref		Ref	
DSA−TCMR+	1.2 (0.6–2.5)	0.6	0.6 (0.2–2.2)	0.5
DSA+TCMR−	0.8 (0.2–2.6)	0.7	1.1 (0.5–2.2)	0.8
DSA+TCMR+	**3.6 (1.9–6.7)**	**0.0001**	**2.3 (1.1–4.9)**	**0.03**
ABMR	1.7 (0.5–5.4)	0.4		
3-mo serum creatinine	1.6 (1.1–2.3)	0.009	1.3 (0.9–1.9)	0.2

Kidney International (2019)

Table 3 | Univariate and multivariate analysis for DSA with rejection within 1 year after transplant

Characteristics (clinical vari			OR (95% CI)	*P* value	OR (95% CI) Multivariate analysis	*P* value
Number						
Mean recipient age (yr)					95 (0.92–0.98)	0.001
Gender (male%)						
Ethnicity (Caucasian%)						
Primary renal disease						
Hypertension						
Diabetes						
Glomer[illegible][a]						
Inherit[illegible]						
Others						
Mean						
Living						
Retran						
KDPI >						
PRA-I ≥ 70%						
PRA-II ≥ 70%						
HLA Class I mismatch					1 (2.1–4.5)	<0.0001
Thymoglobulin induction (%						
Cold ischemia time (min)						
DGF (yes) %	32	17	2.2 (1.04–4.7)	0.04	3.7 (1.3–10.3)	0.01
CNI-IPV	36.9 ± 16.7	27.2 ± 10.6				
CNI-IPV >35%	45.9	20.7	3.3 (1.6–6.6)	0.001	2.5 (1.1–6.5)	0.04
3-mo serum creatinine (mg/dl)	1.72 ± 0.7	1.53 ± 0.6	1.6 (0.95–2.6)	0.08	1.9 (0.99–3.6)	0.06



Early post-transplant DSA, especially in non-adherent patients, is associated with increased incidence of TCMR

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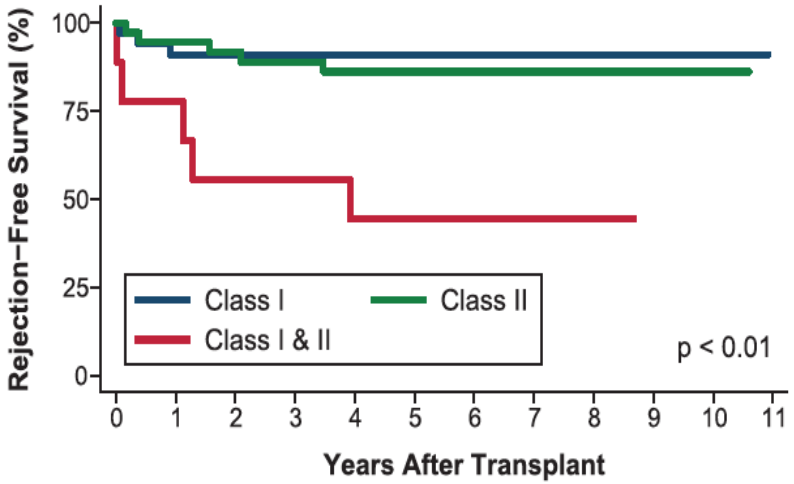
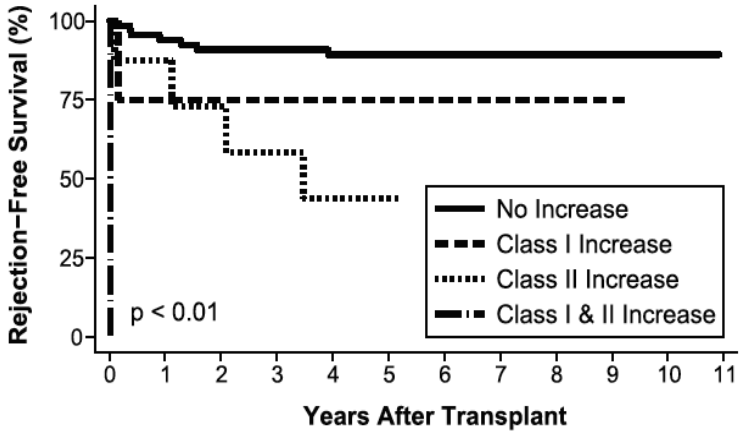
Class and Kinetics of Weakly Reactive Pretransplant Donor-specific HLA Antibodies Predict Rejection in Kidney Transplant Recipients

Rejection-Free Survival by Pre-Transplant DSA Class



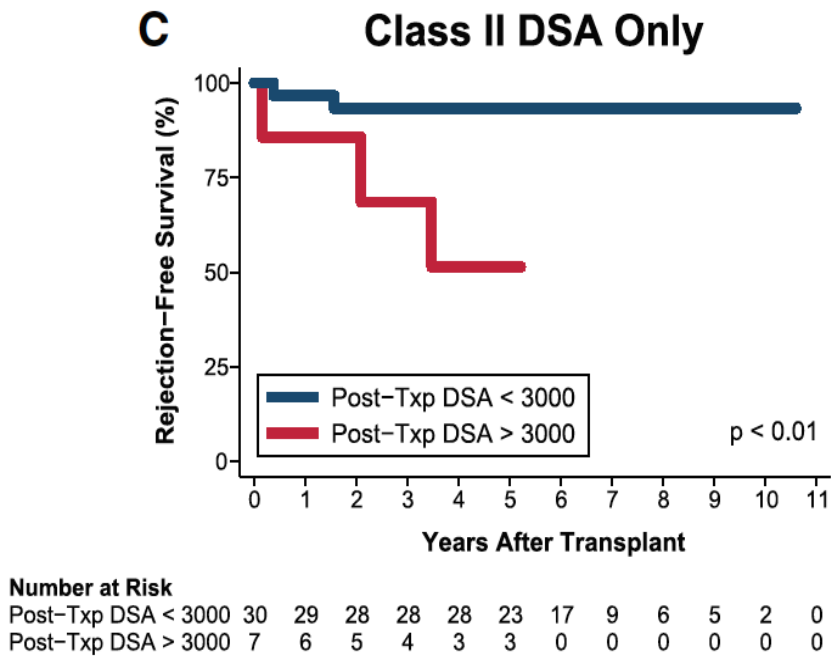
Number at Risk												
Class I	34	30	28	27	26	14	10	6	2	2	1	0
Class II	37	35	33	32	31	26	17	9	6	5	2	0
Class I and II	9	7	5	5	4	3	3	2	1	0	0	0

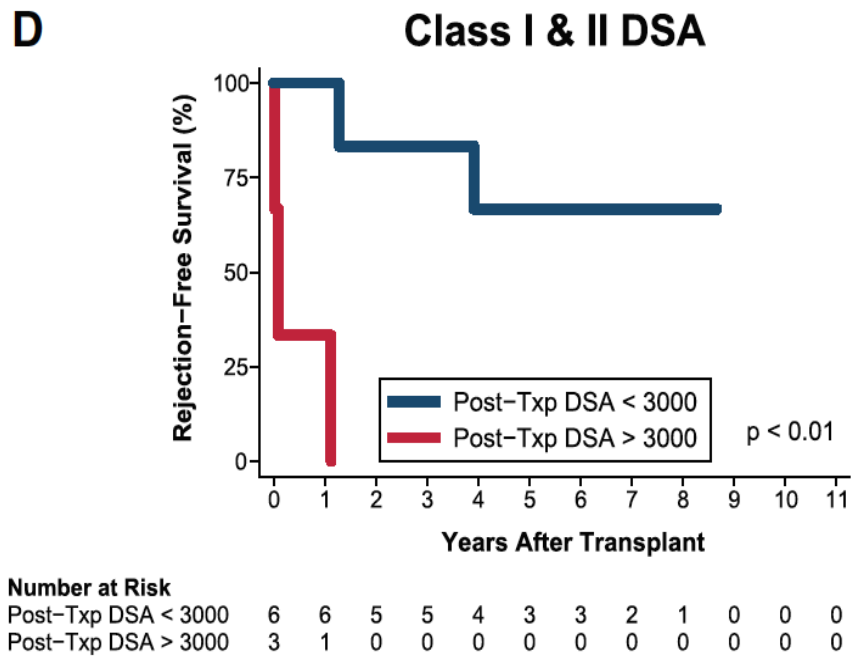
Effect of Post-Transplant DSA Increase



Number at Risk												
No Increase	67	62	58	57	55	38	29	16	8	6	3	0
Class I	4	3	3	3	3	2	1	1	1	1	0	0
Class II	8	7	5	4	3	3	0	0	0	0	0	0
Class I & II	1	0	0	0	0	0	0	0	0	0	0	0

(*Transplantation Direct* 2019;5: e478;





Pretransplant DSA class and DSA kinetics after transplantation are useful prognostic indicators in patients with weak DSA reactivity. These results identify a small, high-risk patient group that warrants aggressive posttransplant DSA monitoring and may benefit from alternative donor selection.

(*Transplantation Direct* 2019;5: e478;

frontiers in Immunology

ORIGINAL RESEARCH
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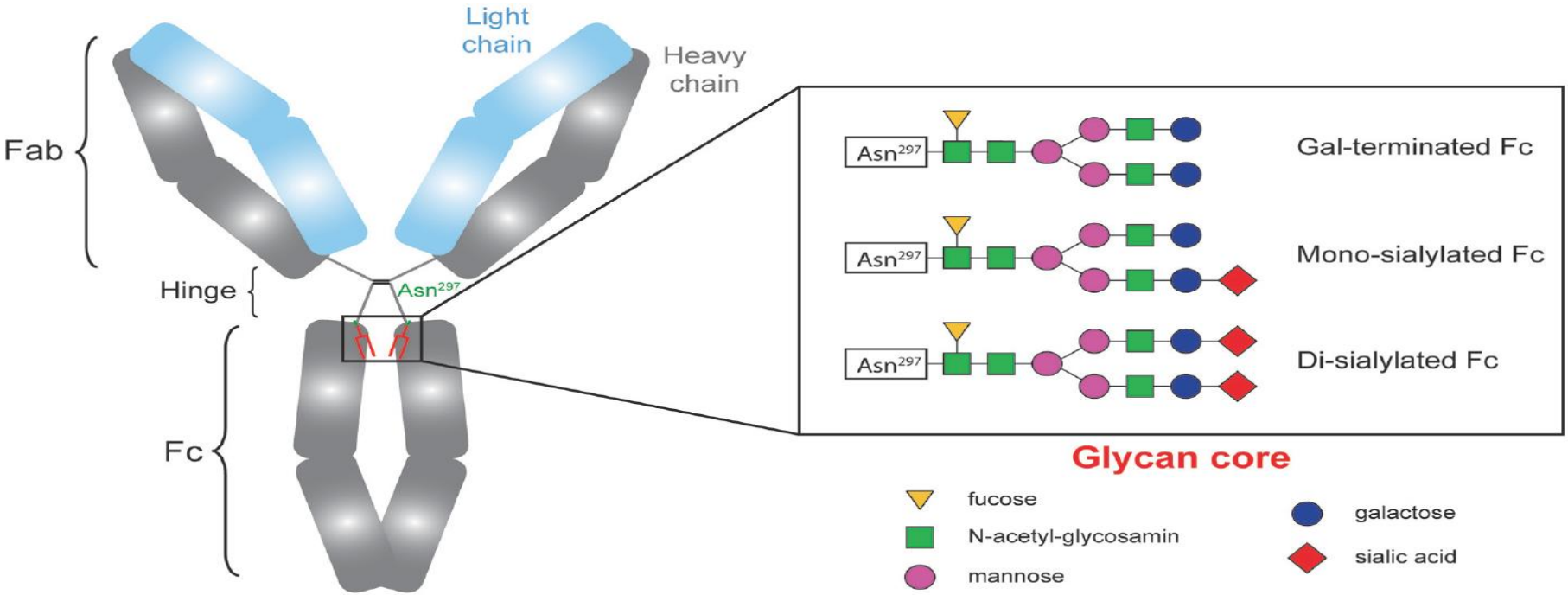
Highly Variable Sialylation Status of Donor-Specific Antibodies Does Not Impact Humoral Rejection Outcomes



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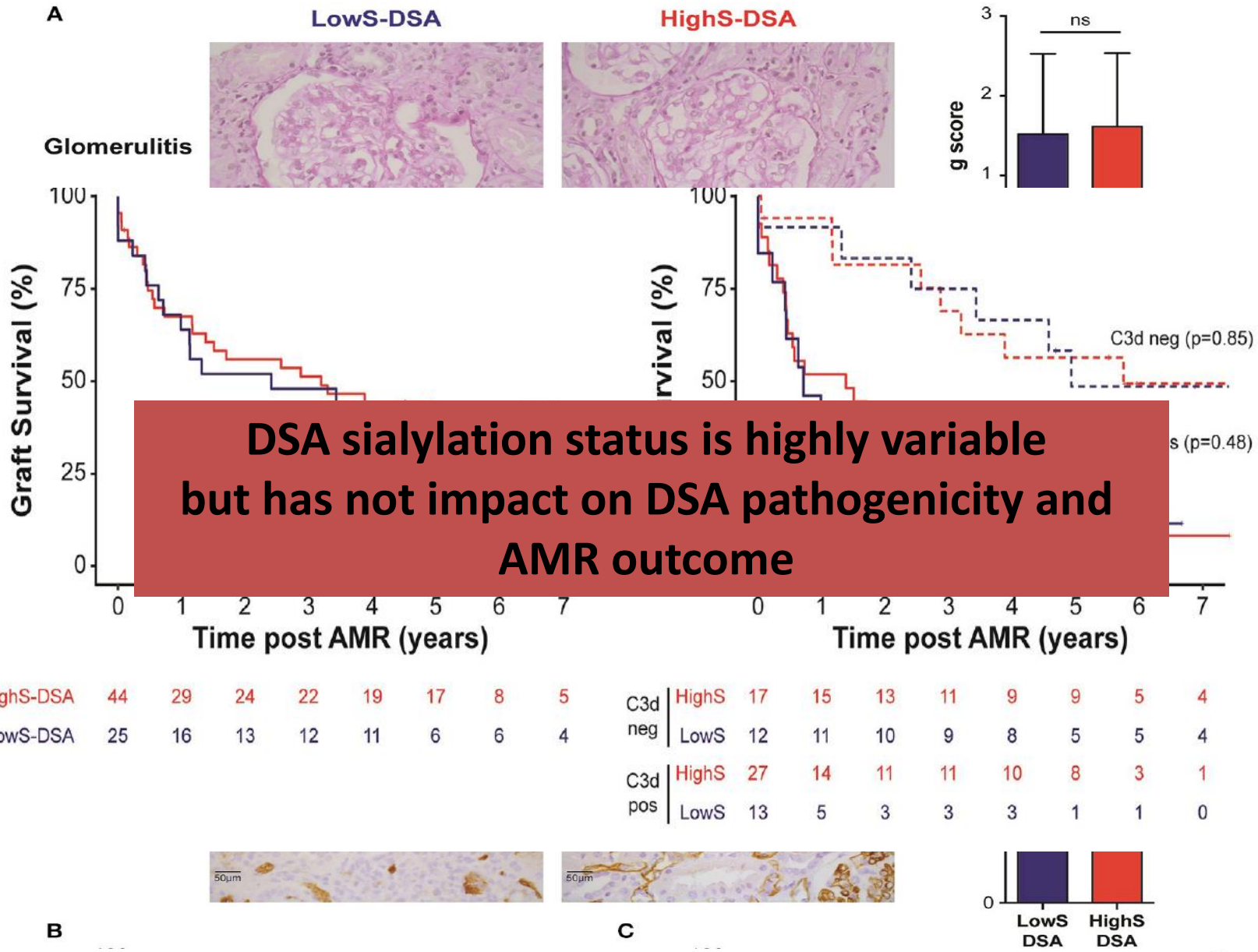
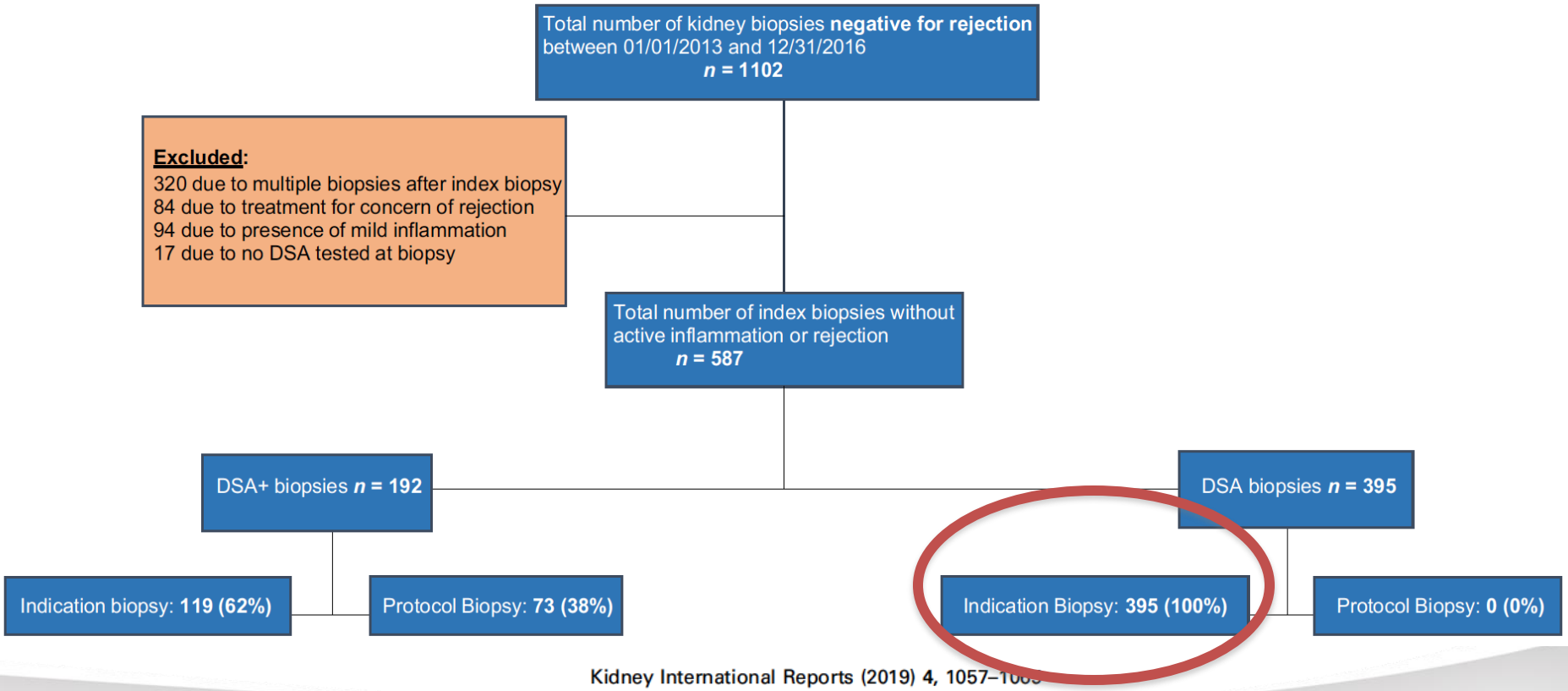
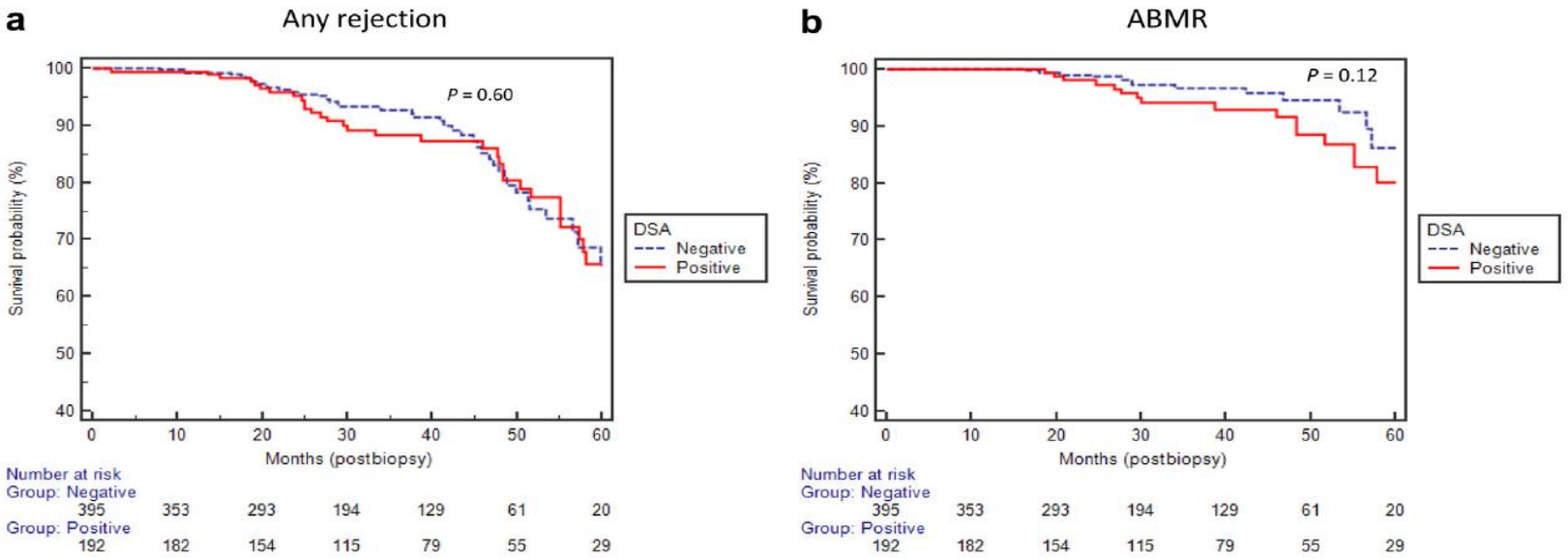


DSA sialylation status is highly variable but has not impact on DSA pathogenicity and AMR outcome

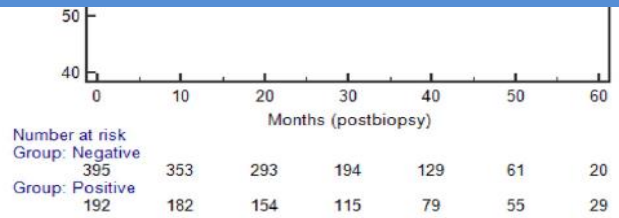
Donor-Specific Antibodies in the Absence of Rejection Are Not a Risk Factor for Allograft Failure



Kidney International Reports (2019) 4, 1057–1065



When categorized based on the MFI, there were 51 patients with MFI <500, 34with MFI 500 to 1000, 27 with MFI >1000 to 2000, and 80 with MFI >2000 at time of biopsy. There was no difference in the risk of subsequent rejection in this subgroup compared with the DSA group (P . 0.52)



Kidney International Reports (2019) 4, 1057–1065

KI REPORTS
KIReports.org

How Do We Interpret the Presence of Donor-Specific Antibodies When There Is No Rejection?

How can we incorporate these results into clinical practice?

Patients with preformed DSA but negative biopsies may have a course that is similar to those without antibodies but the immunology of these antibodies and recent findings suggest that such patients **should be followed more closely** for the possibility of developing rejection .

Kidney Int Rep (2019) **4,** 1040–1042;

Donor-specific antibodies detected by single antigen beads alone can help risk stratify patients undergoing

iii Comparison of RMM-DSA-, RMM+DSA- and RMM+DSA(RMM)+, $p = .019$

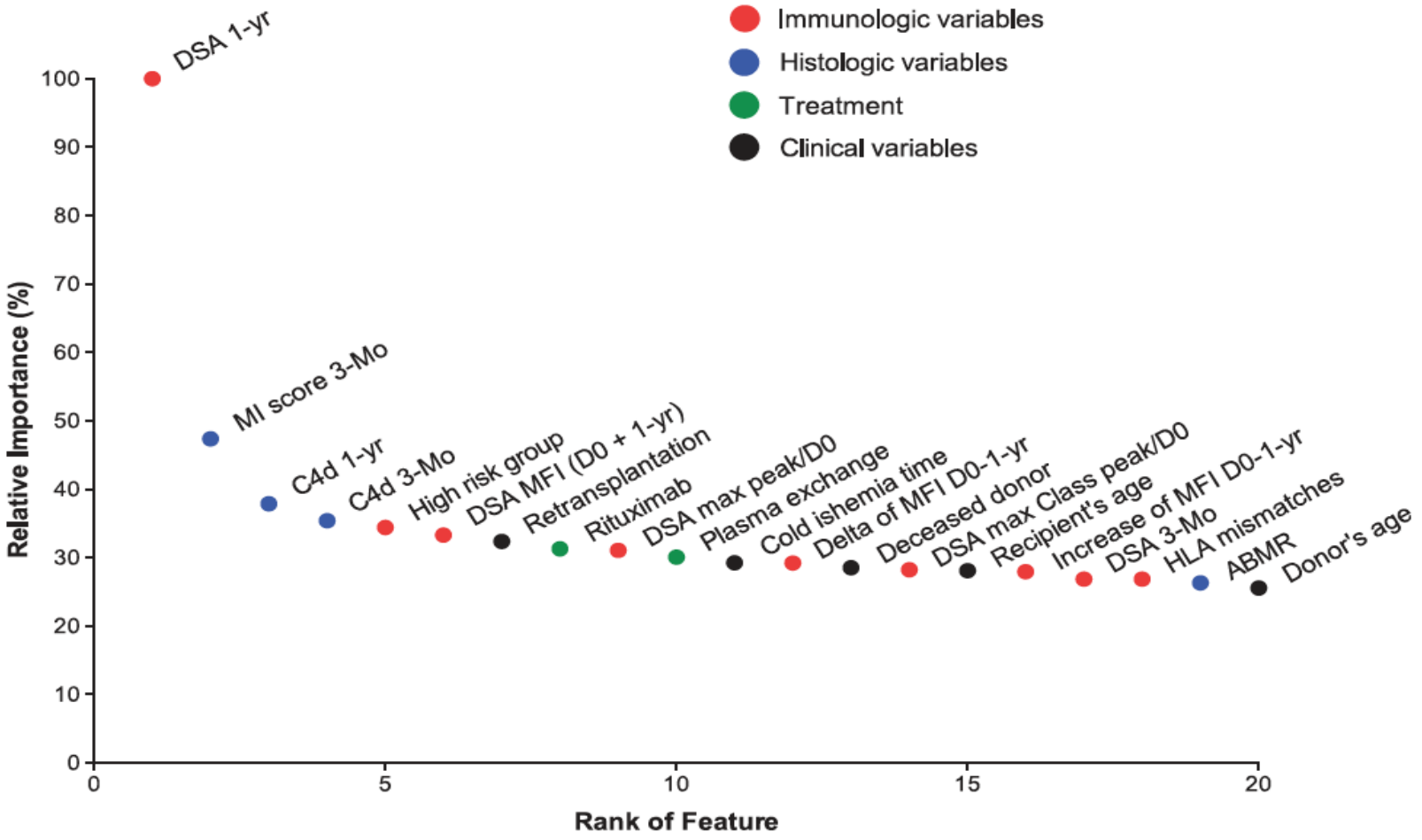
iii Comparison of RMM-DSA-, RMM+DSA- and RMM+DSA(RMM)+, $p<0.0001$

Patients with preformed DSA against an RMM were independently at risk of antibody-mediated rejection(H R 8.70 [3.42-22.10], P < .0001) and death-censored allograft loss (HR 3.08 [1.17-8.14],P = .023). In addition, prior transplant nephrectomy was also associated with allograft failure, whereas receiving a retransplant that was matched at HLA class II was associated with a favorable outcome.

RMM-	124	93	67	43	27	15	3	0
RMM+	55	38	26	17	11	8	3	0

RMM+	124	83	62	41	26	14	3	0
	55	33	22	13	9	7	3	0

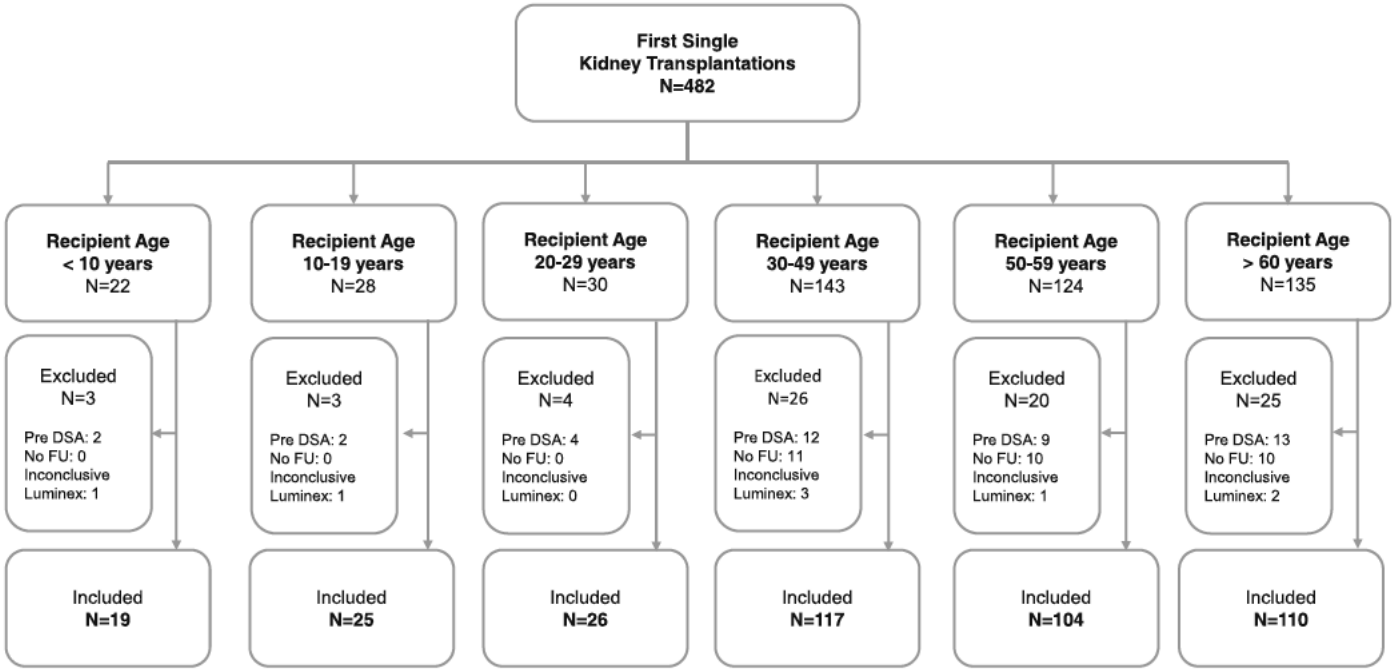
Lo Pat The in



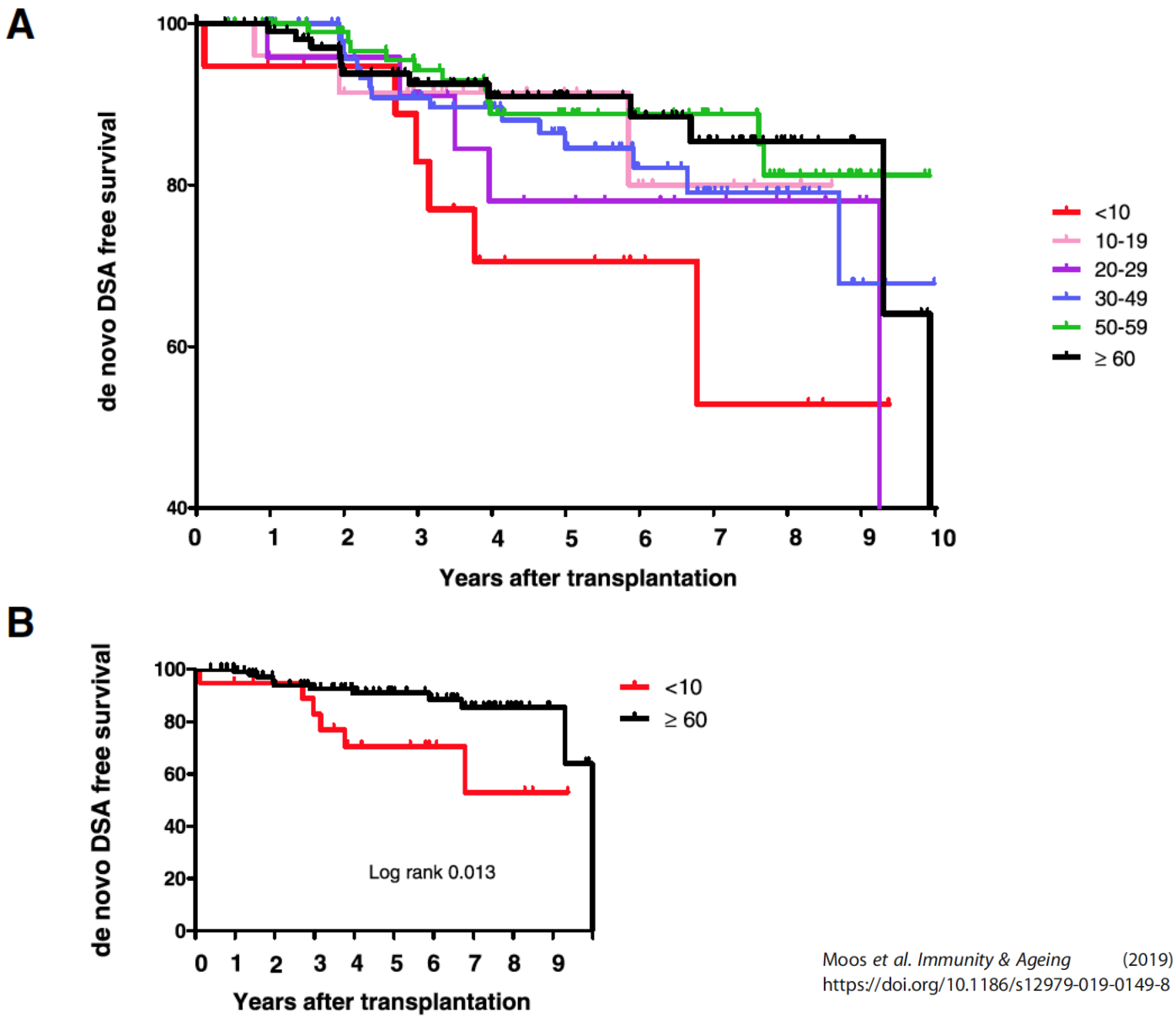
(*Transplantation* 2017;101: 2440–2448)

Age-associated decrease in de novo donor-specific antibodies in renal transplant recipients reflects changing humoral immunity

Seraina von Moos[1*†], Gesa Schalk[2†], Thomas F. Mueller[1†] and Guido Laube[2†]



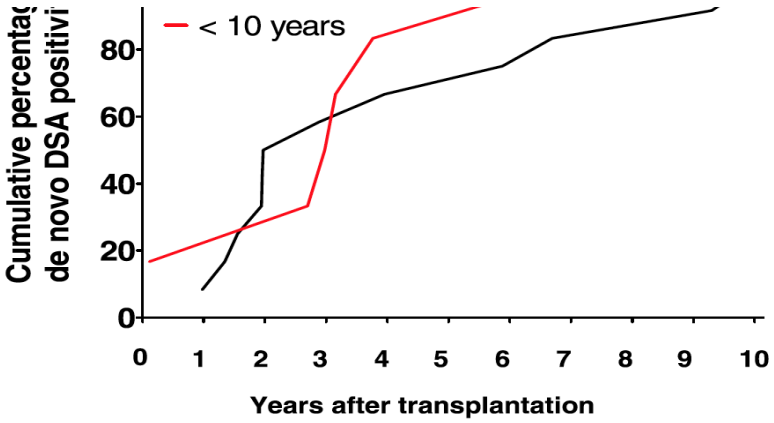
Moos *et al. Immunity & Ageing* (2019) 16:9
https://doi.org/10.1186/s12979-019-0149-8

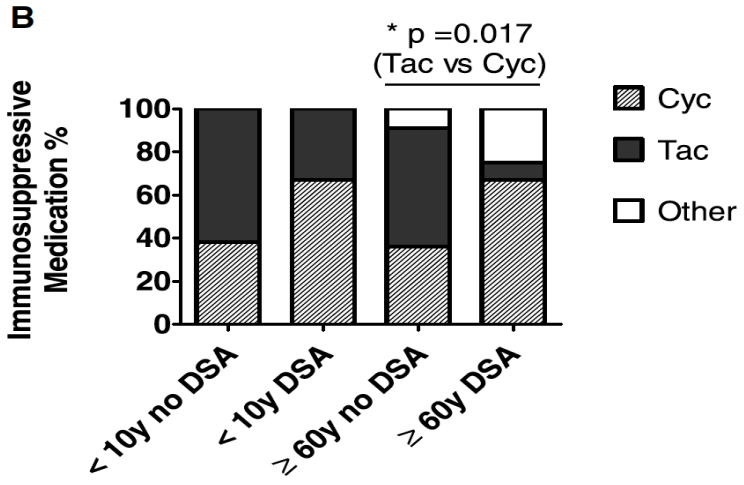


Moos *et al. Immunity & Ageing* (2019) 16:9
https://doi.org/10.1186/s12979-019-0149-8

Table 2 Risk of development of *dn*DSA in different age groups

	Children < 10y	Adolescent 10-19y	20-29y	30-49y	50-59y	Old ≥ 60y
Cumulative prevalence dnDSA	32% (6/19)	12% (3/25)	19% (5/26)	13% (15/117)	11% (11/104)	11% (12/110)
Hazard ratio, p	–	HR 0.42 $p = 0.205$	HR 0.52 $p = 0.312$	HR 0.35 $p = 0.088$	HR 0.18 p = 0.014	HR 0.21 p = 0.022





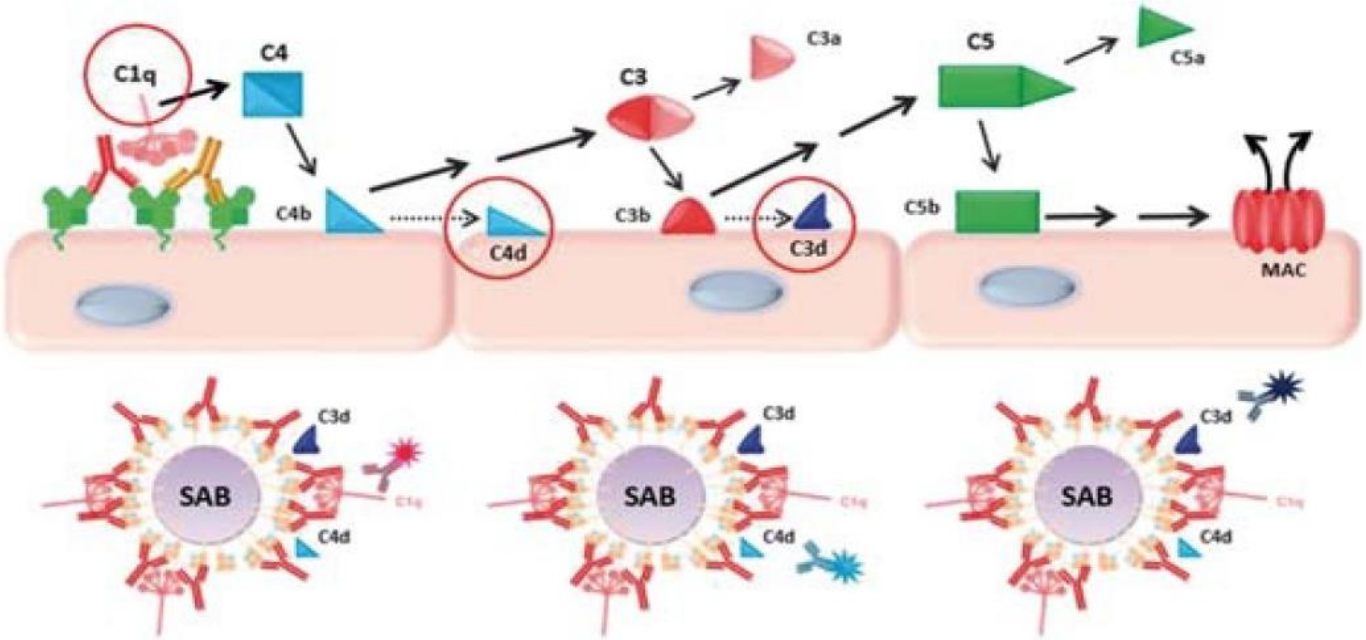
Older kidney transplant recipients have a lower risk of developing dnDSA ,pointing towards reduced humoral immune reactivity with increasing age.

Adjustment in immunosuppression?

Moos *et al. Immunity & Ageing* (2019) 16:9
https://doi.org/10.1186/s12979-019-0149-8

Clinical Utility of Complement Dependent Assays in Kidney Transplantation

James H. Lan, MD, FRCP(C), D(ABHI)[1] and Kathryn Tinckam, MD, MMSc, FRCPC[2]



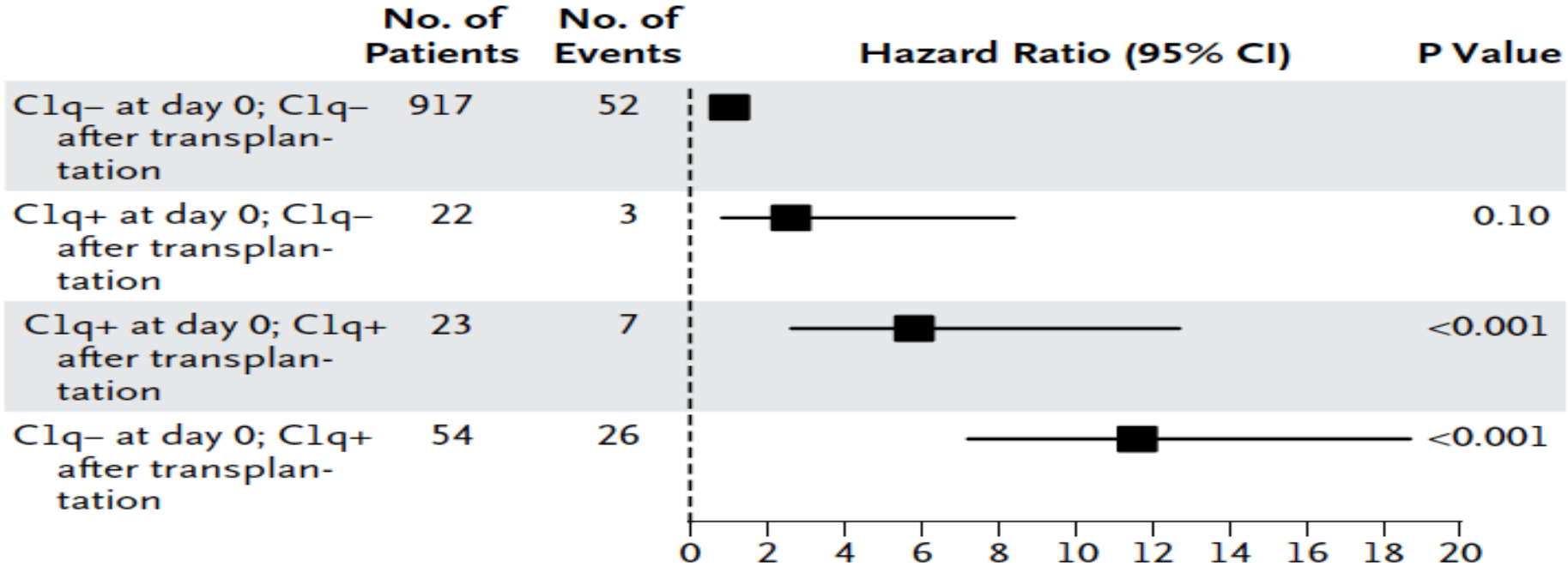
	C1q Assay	C4d Assay	C3d Assay
Complement source	Purified exogenous C1q	Normal human serum	Normal human serum
Reagent	Anti-C1q antibody	Anti-C4d antibody	Anti-C3d antibody

Transplantation ■ January 2018 ■ Volume 102 ■ Number 1S

ORIGINAL ARTICLE

Complement-Binding Anti-HLA Antibodies and Kidney-Allograft Survival

C Risk of Kidney-Allograft Loss According to C1q Status



N Engl J Med 2013;369:1215-26.

C1q-binding donor-specific antibody assays help define risk and prognosis in antibody-mediated rejection

Kidney International (2018) **94,** 657–659

Emanuele Cozzi[1] and Luigi Biancone[2,3]

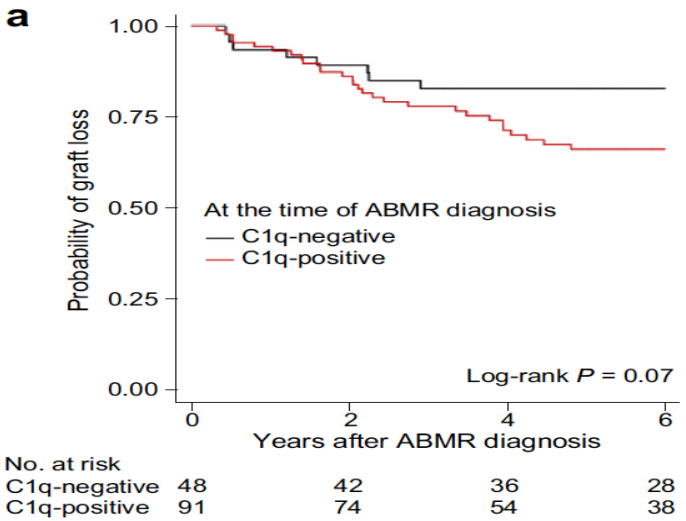
- Patients with C1qfl DSAs at the time of AMR have a poorer graft function, worse histological score, and higher mean MFI values .
- C1q positivity at the time of post treatment evaluation was associated with poor graft recovery and failure to improve the score of acute histological lesions.
- The post treatment C1qfl status was associated with time to renal loss, independently of graft function, histology, and other DSA characteristics.

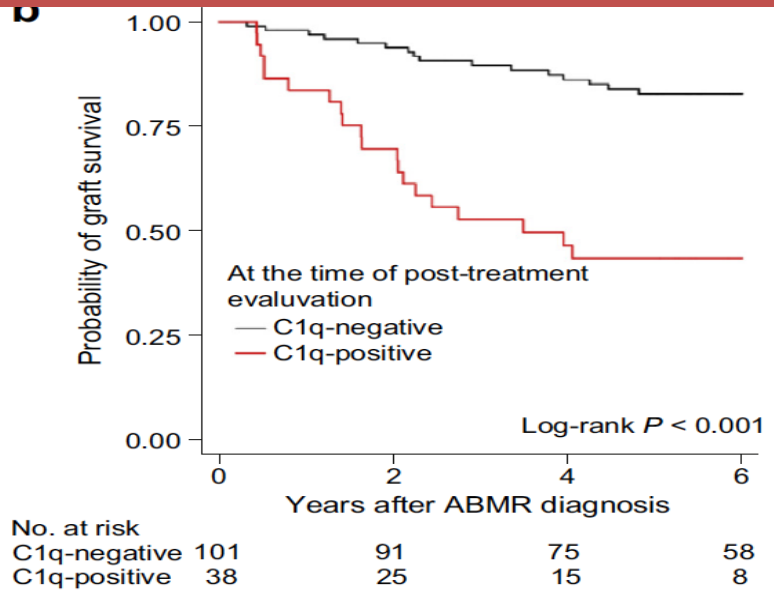
C1qfl DSA; one of the strongest determinants of long-term graft loss currently in our hands

Complement-binding anti-HLA antibodies are independent predictors of response to treatment in kidney recipients with antibody-mediated rejection

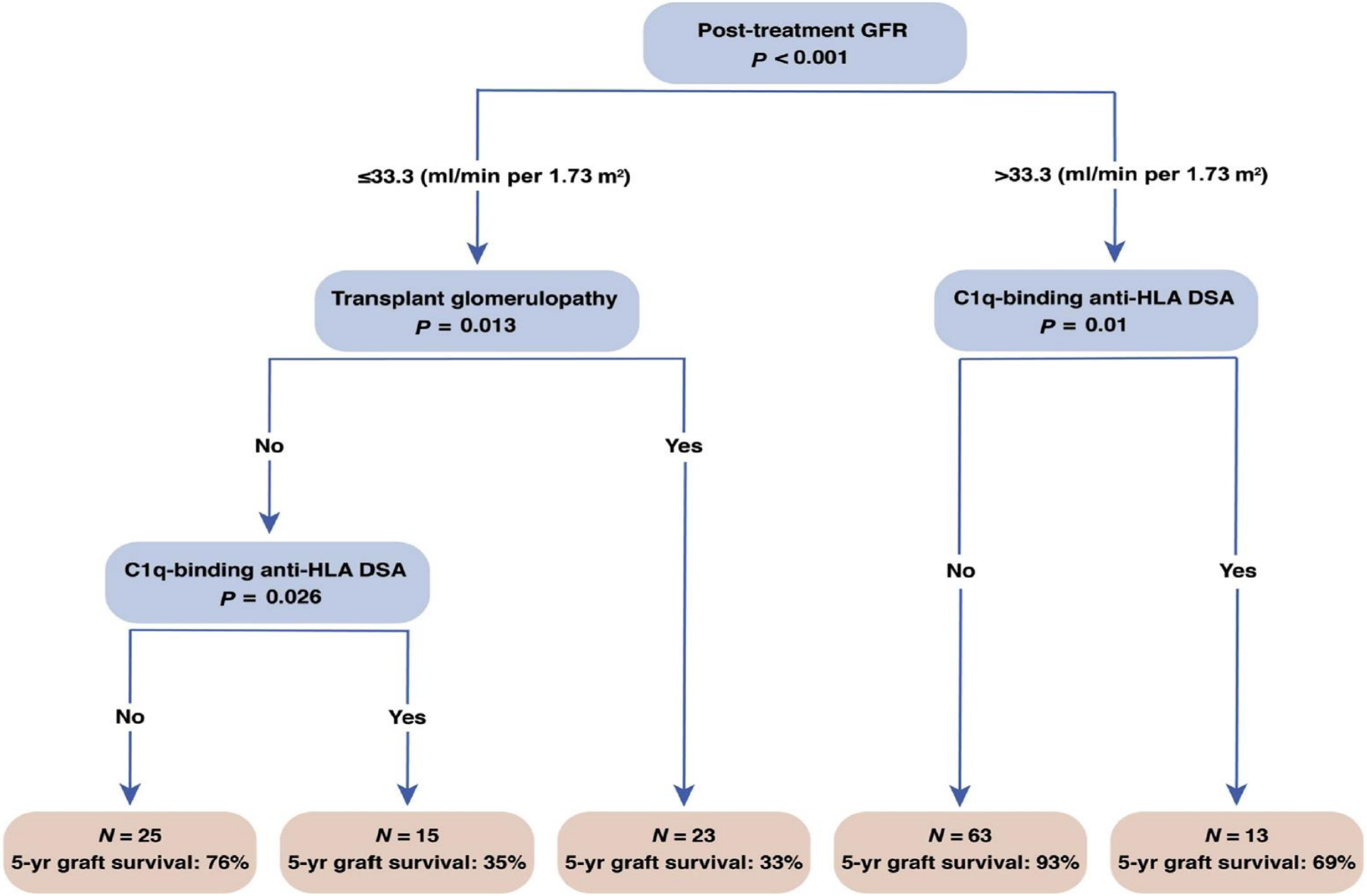
see commentary on page 657

In patients with AMR, persistence of C1qfl DSAs not withstanding an aggressive antirejection treatment is associated with a significantly worse outcome compared with that observed in AMR patients who convert to C1q-DSAs





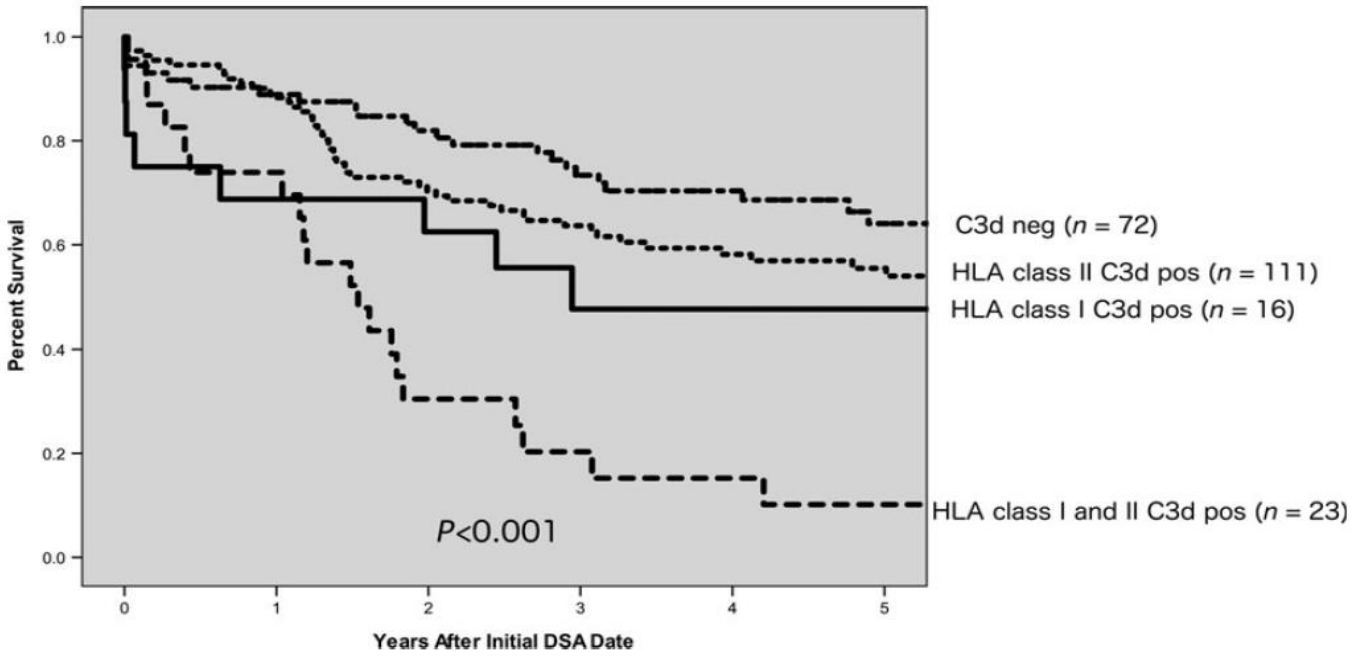
Kidney International (2018) **94,** 773–787;



Kidney International (2018) **94,** 773–787;

The recipients that had C3d binding DSA had a significantly higher incidence of antibody-mediated rejection and any rejection. They also had significantly lower kidney survival, with the lowest survival in those that had both anti-HLA class I and class II C3d binding DSA.

Ronald P Pelletier[1], Ivan Balazs[2], Pat Adams[3], Amer Rajab[1], Nicholas R DiPaola[4] & Mitchell L Henry[1]



Transplant International 2018; 31: 424–435

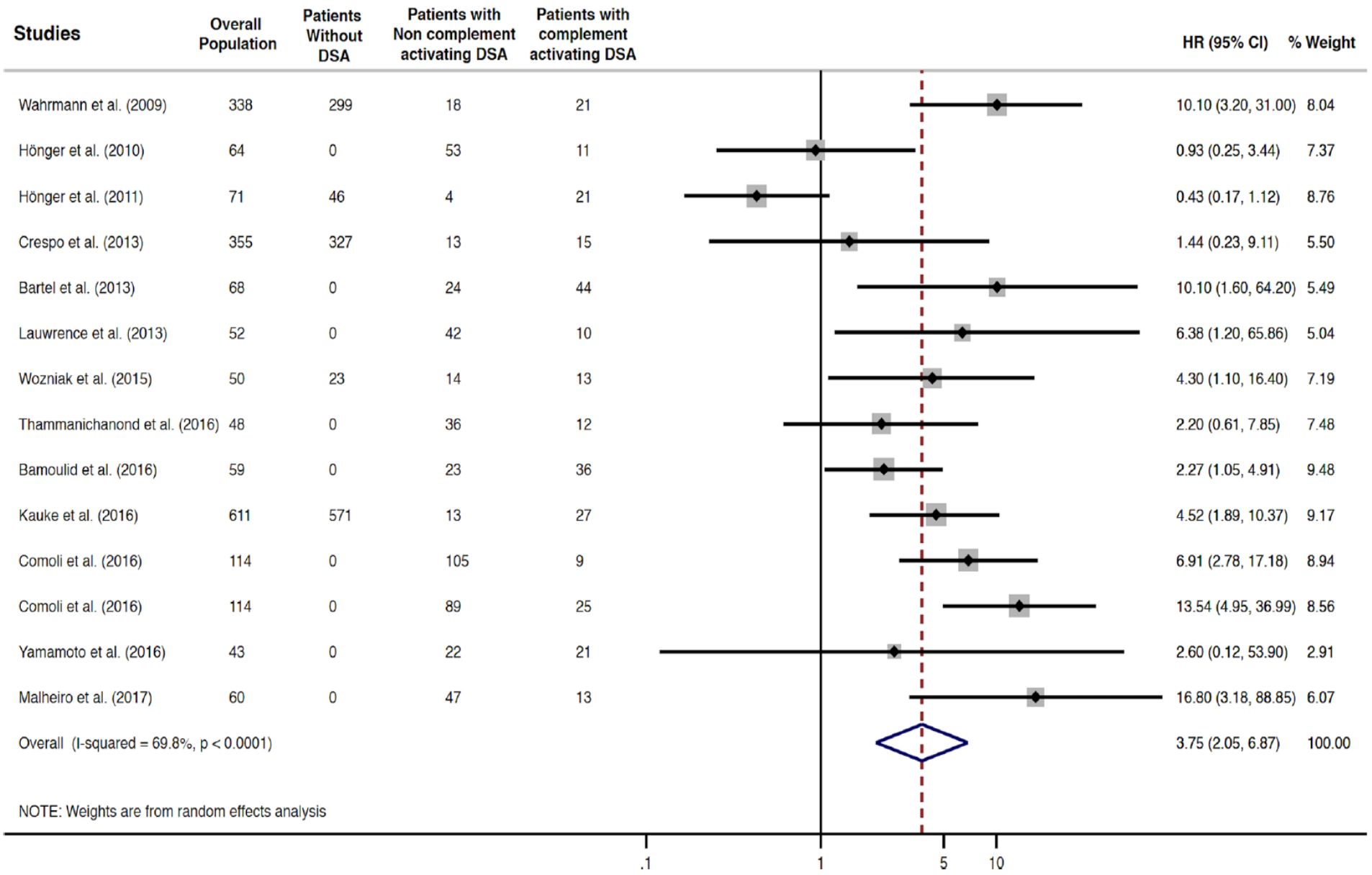
ORIGINAL ARTICLE

Failure to remove *de novo* donor-specific HLA antibodies is influenced by antibody properties and identifies kidney recipients with late antibody-mediated rejection destined to graft loss – a retrospective study

The poor prognosis of late AMR is related to deterioration of graft function prior to treatment and failure to remove C3d binding and/or high-MFI DSAs

HLA DQ+	0.413	1.8	0.4–7.3
HLA DQ−*			
C1q+	0.710	0.8	0.2–3.1
C1q−			
C3d+	<0.05	10.1	1.5–68.3
C3d−			
Mean fluorescence intensity (MFI) >10 000	<0.05	5.7	1.2–27.1
MFI ≤ 10 000			

Transplant International 2019; 32: 38–48



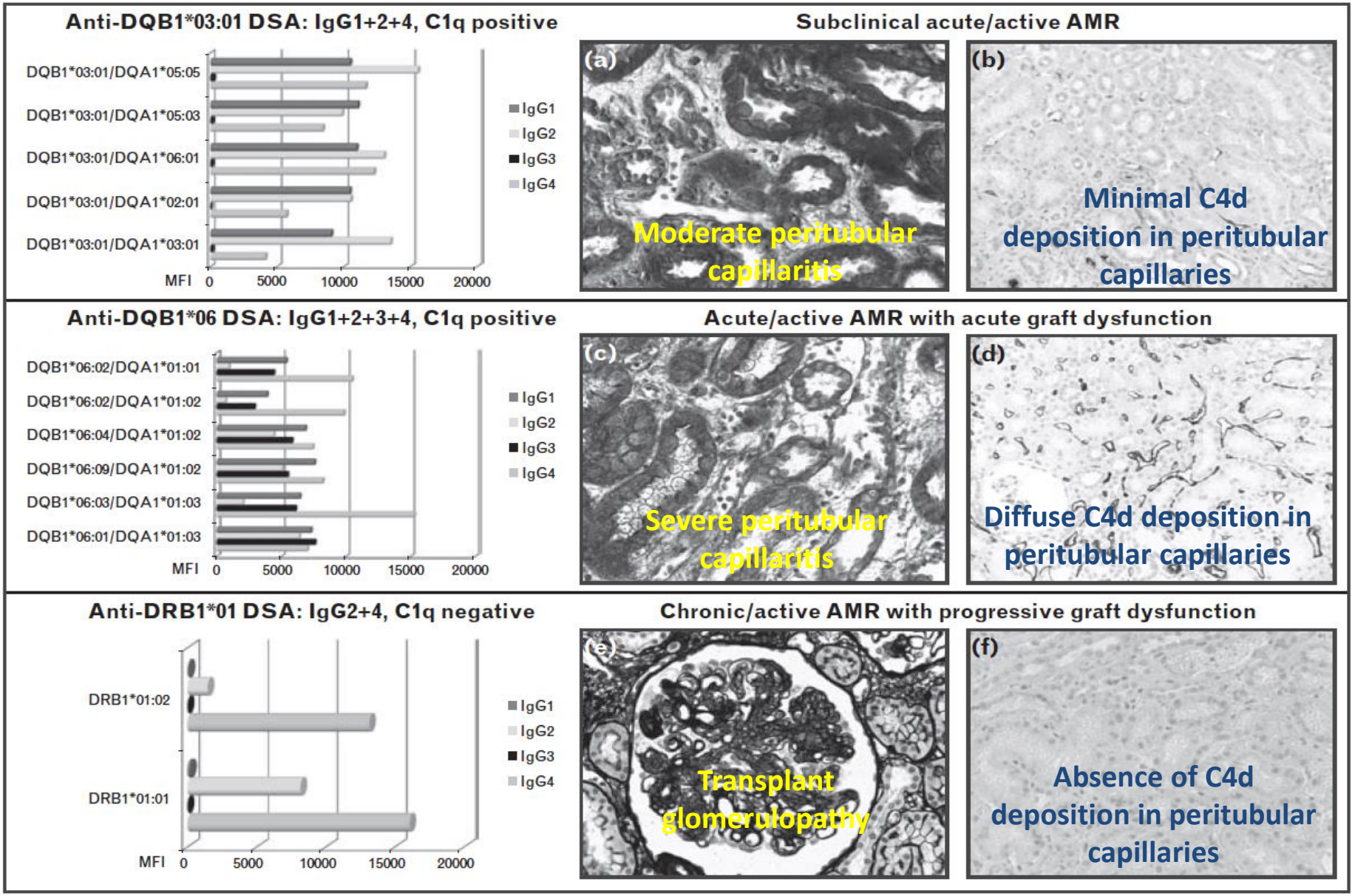
REVIEW

CURRENT OPINION

Evidence for an important role of both complement-binding and noncomplement-binding donor-specific antibodies in renal transplantation

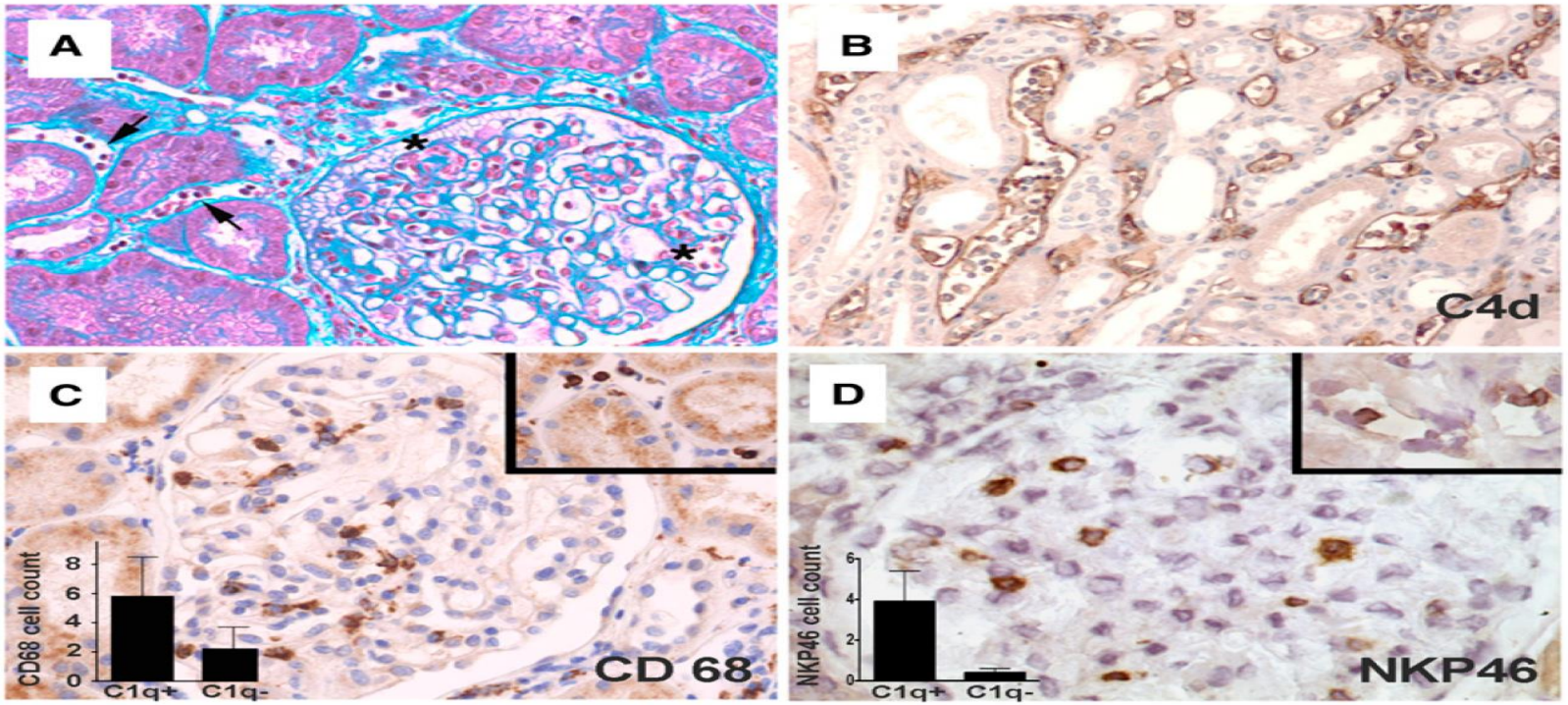
Denis Viglietti[a,b], *Carmen Lefaucheur*[a,b], *and Denis Glotz*[a,b]

Volume 21 • Number 4 • August 2016

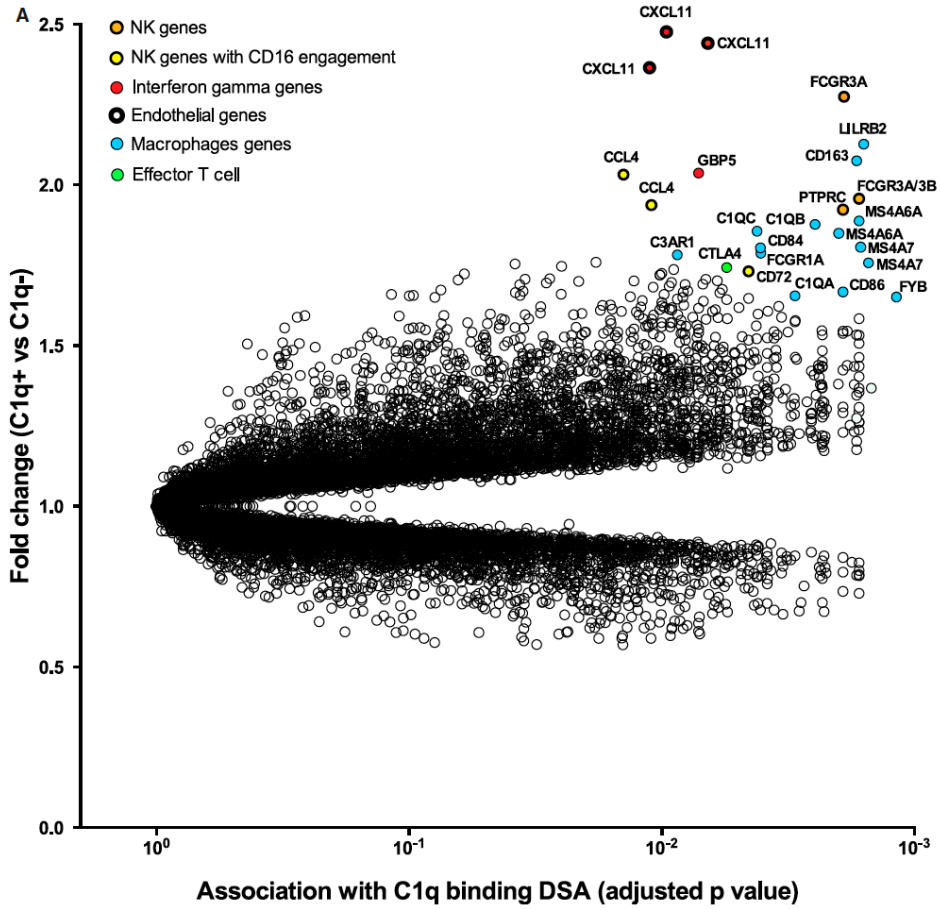


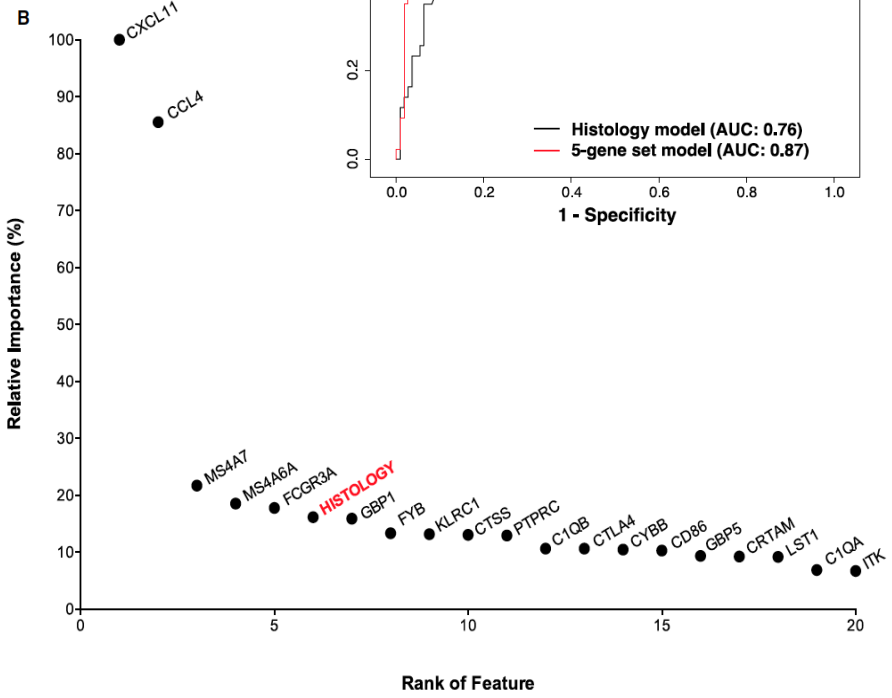
Banff diagnostic categories	Frequency (%)	Male gender (%)	Age (mean±-SD)	Creatinine (mean±-SD)	Deceased Donor (%)	Positive Anti-HLA I (%)	Positive Anti-HLA II (%)
C4d staining without evidence of rejection	9 (7.2)	55.6	39.5± 13.5	2.18±1.92	66.7	0	60
Active AMR	57 (45.6)	66.67	42.2± 14.4	2.83±1.48	63.4	48.48	63.64
Chronic active AMR	22 (17.6)	81.82	39.9± 14.7	4.01± 3	81.2	33.33	83.33
Chronic AMR	5 (4)	100	46.4± 7.5	2.76± 1.07	80	66.67	100
Suspicious for Acute TCMR	3 (2.4)	66.67	48 ± 18	1.5	100	0	0
TCMR	22 (17.6)	81.82	38± 17.7	2.96 ±1.36	50	5.88	11.76
Chronic active TCMR	1 (0.8)	100	33	5.9	80	66.67	
Mix	6 (4.8)	83.33	26.3± 9.4	3.96 ±2.91	65.7	33.78	100

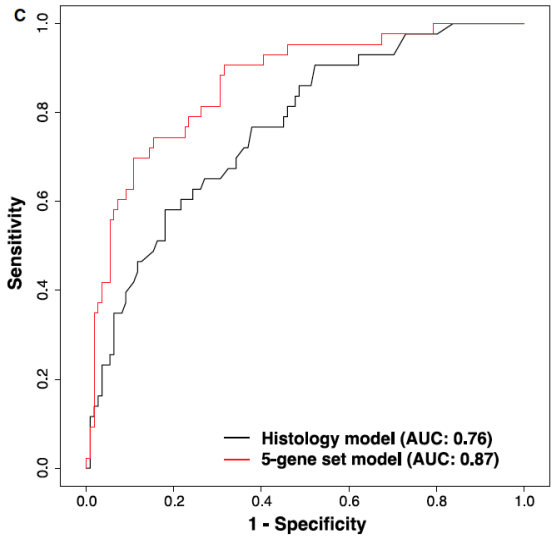
Complement-Activating Anti-HLA Antibodies in Kidney Transplantation: Allograft Gene Expression Profiling and Response to Treatment



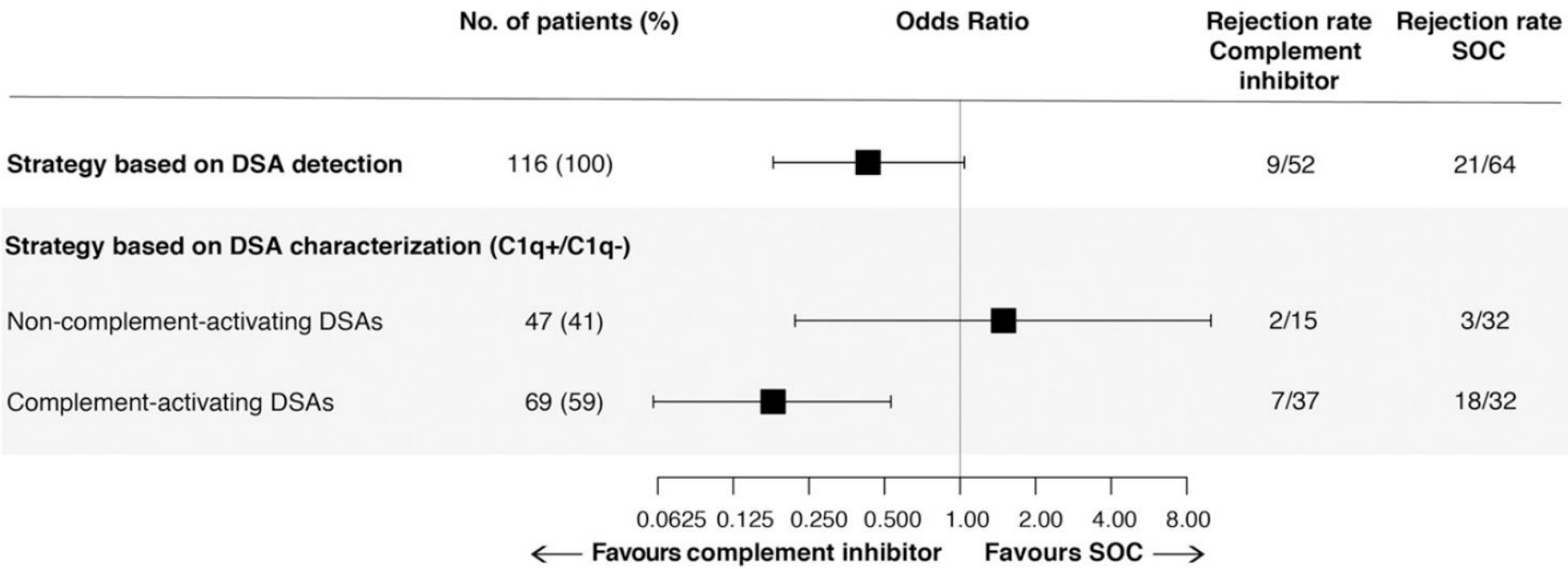
J Am Soc Nephrol **29:** 620–635, 2018







J Am Soc Nephrol **29:** 620–635, 2018

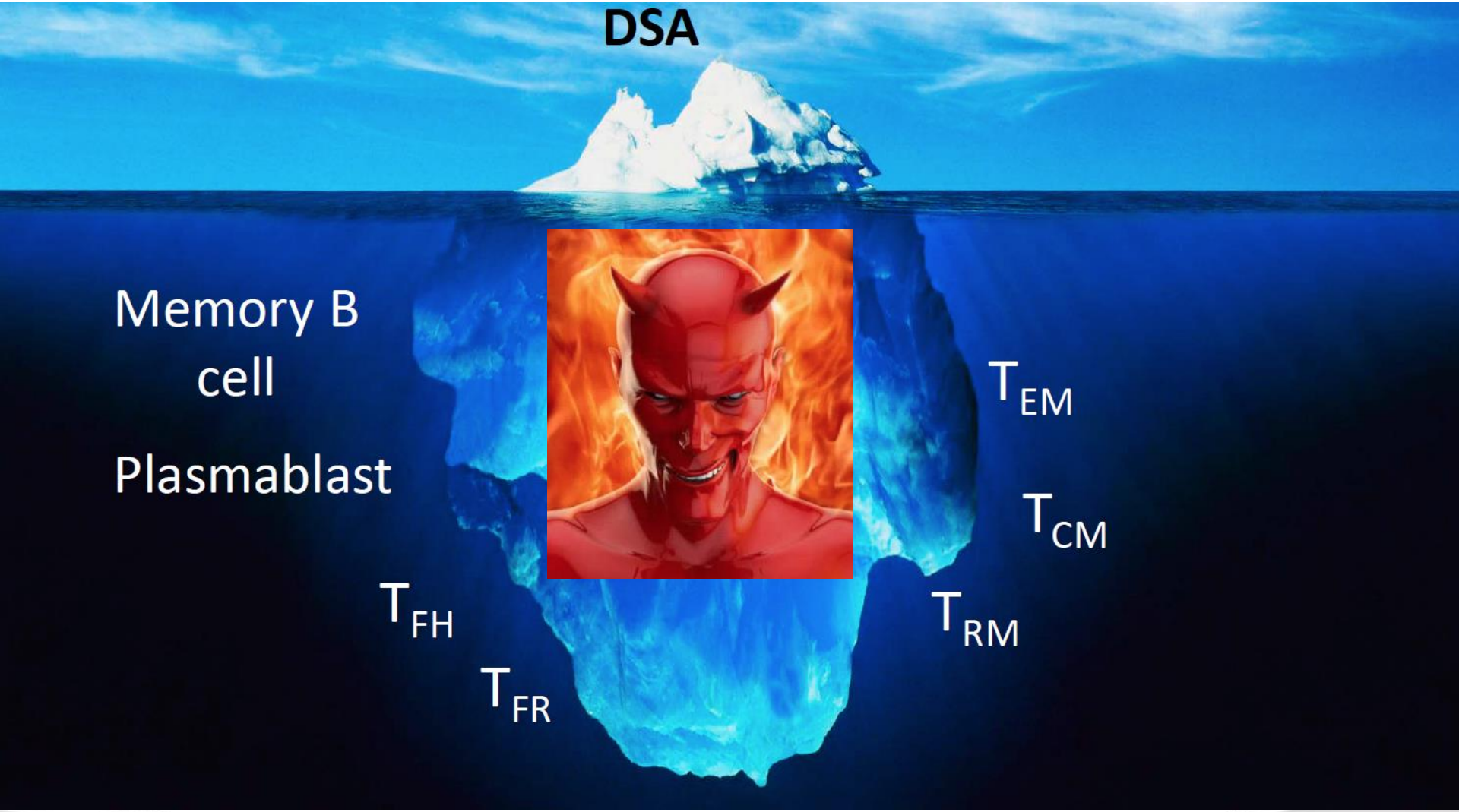


Circulating complement-activating anti-HLA DSAs are associated with a specific histomolecular kidney allograft rejection phenotype that can be abrogated by complement inhibition

J Am Soc Nephrol **29:** 620–635, 2018

Its not as easy as it looks!!!!

Moving Forward…..



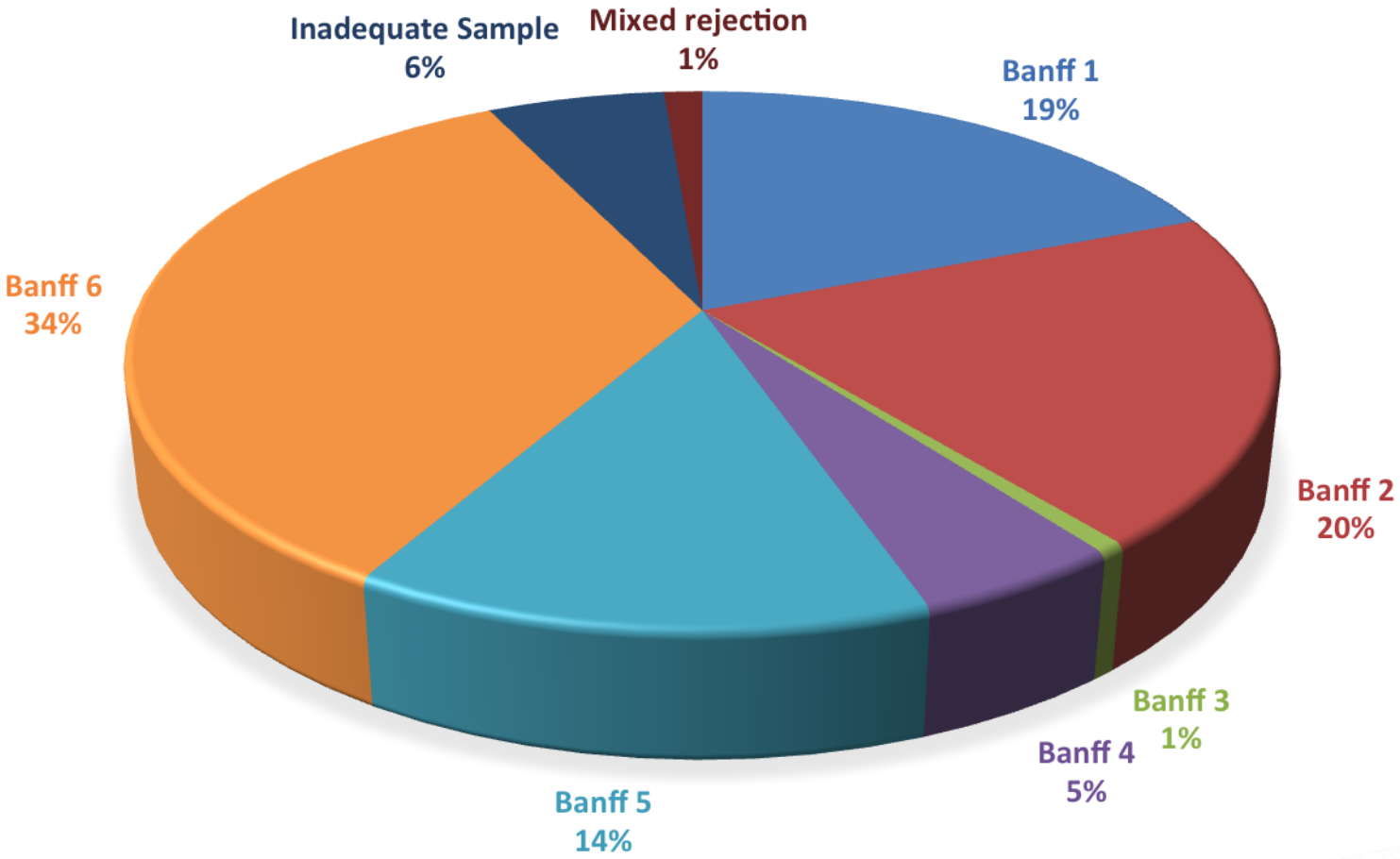

Thank You

What factors may influence the pathogenicity of HLA DSA?

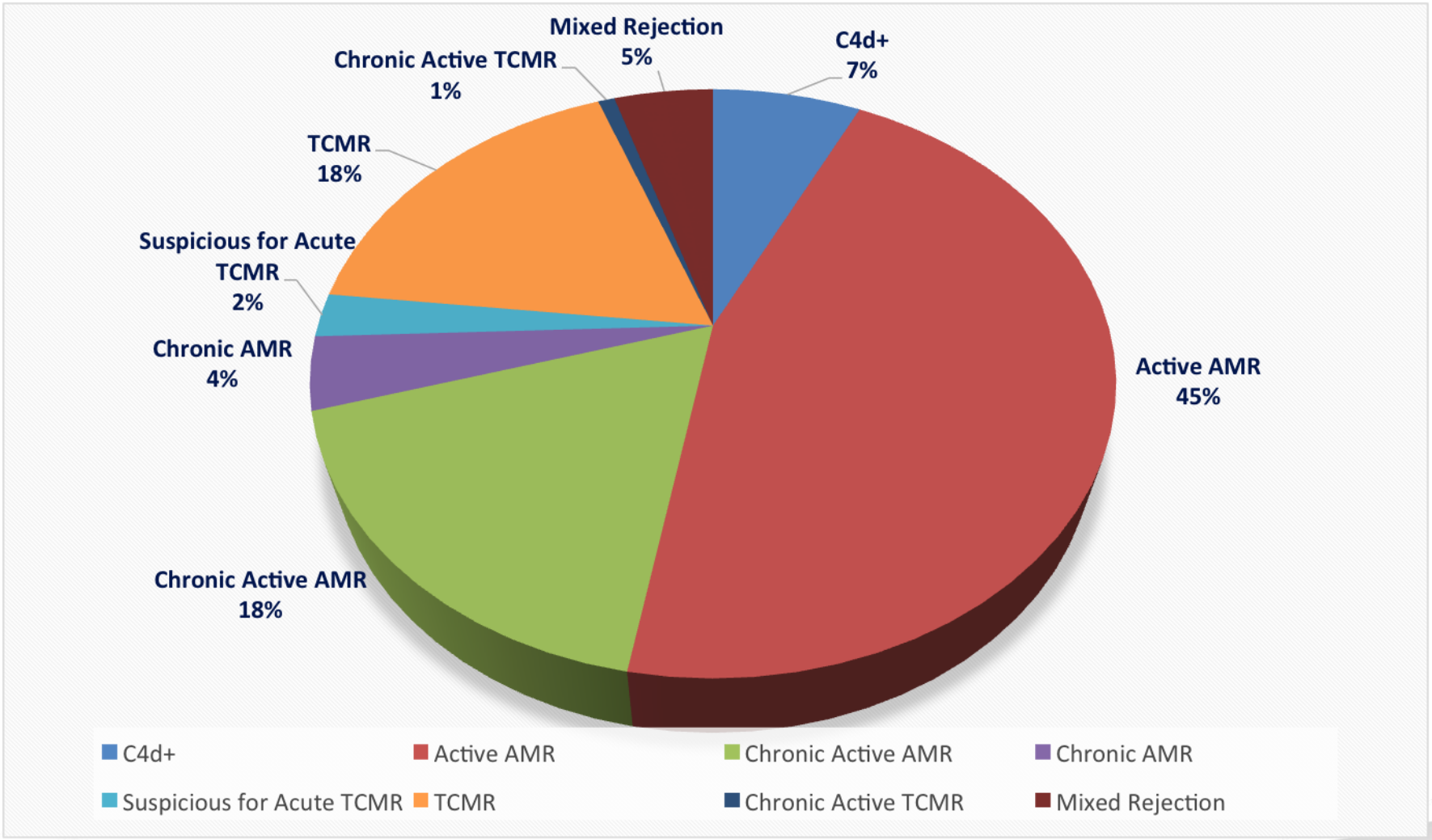
- Expression of HLA on the allograft endothelium
- Avidity of the eplet-antibody interaction
- Ability to fix complement
- Their IgG subclass

HepatoBiliary Surg Nutr 2019;8(1):37-52

Pathology Findings in 469 Transplant Biopsies



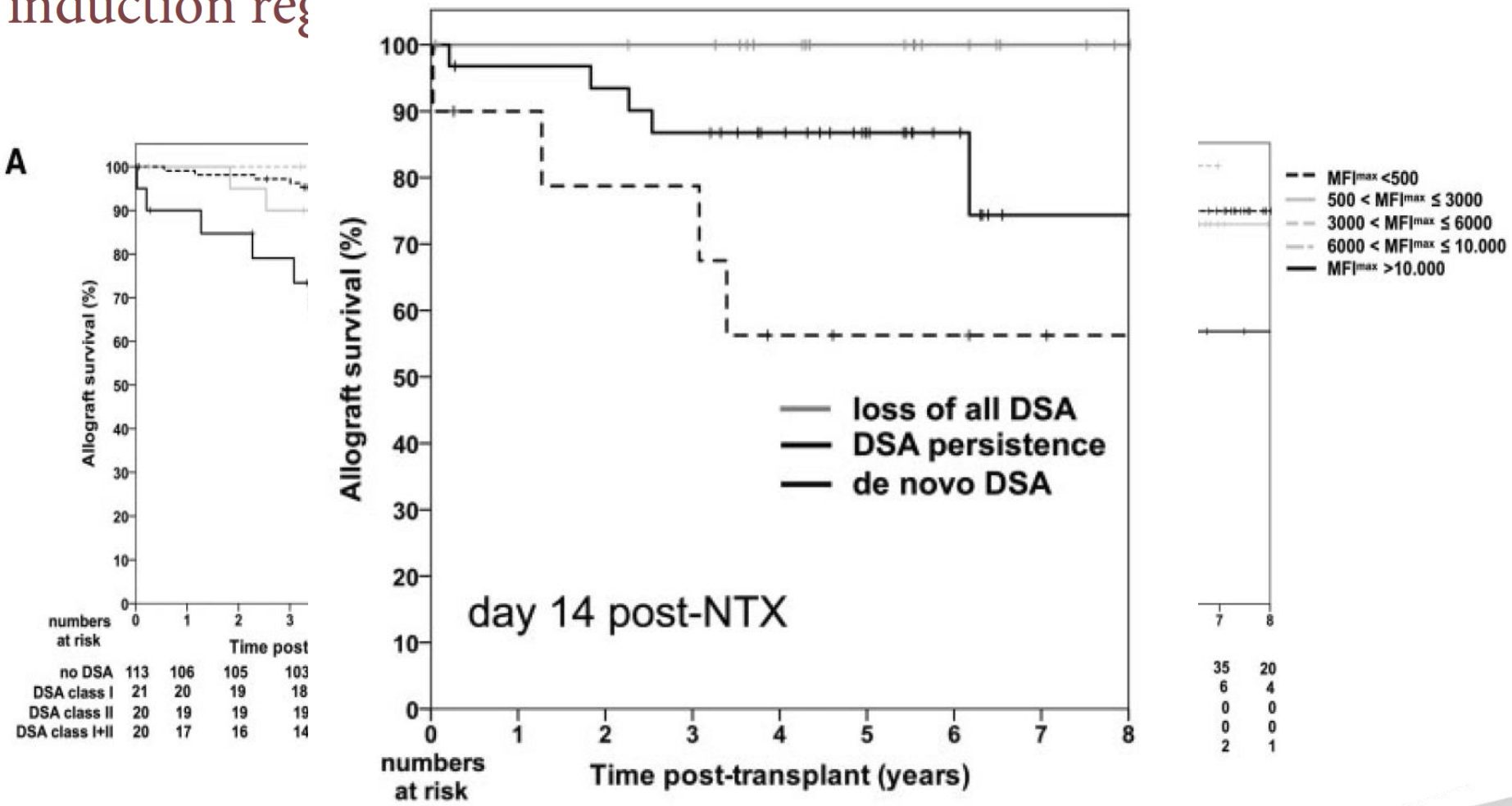
Overall Rejection Distribution



Not all DSA is the same; Risk stratification in the setting of known DSA

- Alloantibody quantification
- Single versus Multiple DSA
- Complement binding DSA
- Immunoglobulin Subclasses

Characteristics of donor-specific anti-HLA antibodies and outcome in renal transplant patients treated with a standardized induction reg



Nephrol Dial Transplant (2017) 32: 730–737

transplant donor-specific anti-human leukocyte antigen antibodies induce a wide spectrum of allograft injuries

Post

Various histologic phenotypes are associated with circulating HLADSAs;

- Acute forms of injury characterized by microcirculation inflammation with or without complement deposition in allograft peritubular capillaries
- Thrombotic microangiopathy
- Antibody-associated arteritis
- Chronic forms dominated by transplant glomerulopathy lesions and interstitial fibrosis and accelerated arteriosclerosis

Role of donor-specific anti-human leukocyte antigen antibody strength: is the mean fluorescence intensity level associated with injury phenotype?

- Several groups have demonstrated correlations between increased MFI/mean channel shift levels and increased incidences of AMR and allograft loss.

- Higher levels of circulating HLA-DSAs have also been correlated with increased micro vascular inflammation and increased C4d deposition in the peritubular capillaries of the allograft and more recently with the severity of allograft arteriosclerosis.

Role of complement-binding donor-specific anti-human leukocyte antigen antibodies

- Post transplant C1q-binding HLA-DSAs detected at 1 year after transplantation or during an episode of acute rejection in the first year after transplantation were found to be an independent determinant of allograft loss and to be associated with a 4.8-fold increase in the risk of allograft loss (Improvement of risk stratification for allograft)

- C1q-binding HLA-DSA status following transplantation was associated with allograft loss independently of the HLA-DSA MFI with an adjusted hazard ratio of 4.5

- Patients with post transplant C1q-binding HLA-DSAs exhibited a higher incidence of AMR and an increased rate of allograft injuries, including, transplant glomerulopathy, and C4d deposition in the peritubular capillaries.

Role of donor-specific anti-human leukocyte antigen antibody IgG subclass composition: are IgG subclasses associated with antibody mediated injury phenotype?

- In a study that included 125 kidney transplant recipients with post transplant HLA-DSAs that were detected within the first year after transplantation only the presences of IgG3(intense micro vascular inflammation and increased complement deposition in the allografts) and IgG4(subclinical AMR who exhibited a predominance of chronic features represented by transplant glomerulopathy and interstitial fibrosis) HLA-DSAs were informative regarding the discrimination of AMR disease phenotype, namely, acute AMR and subclinical AMR, respectively.

Relationships between donor-specific anti HLA complement-binding capacity, strength, and IgG subclass composition

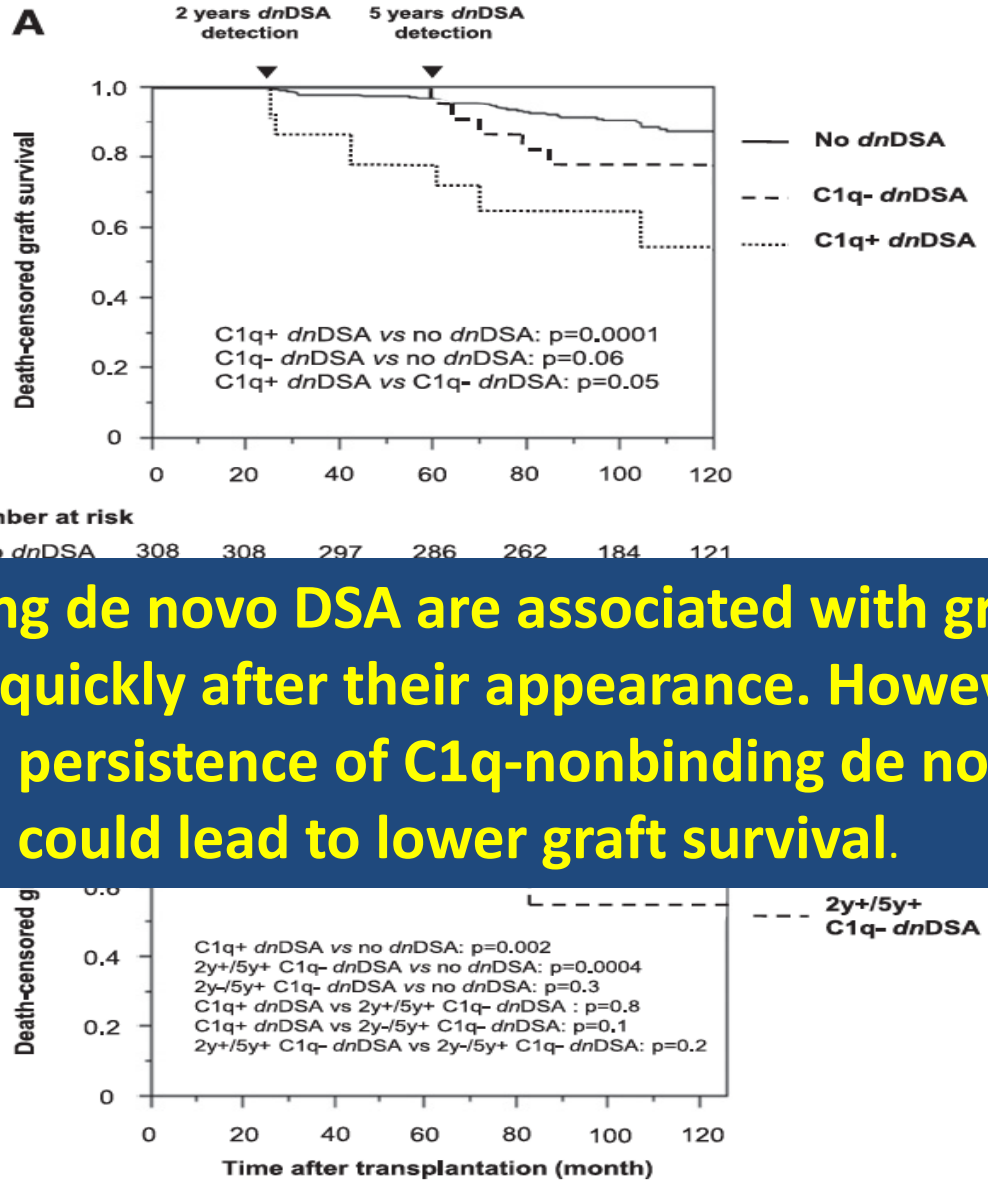
- The factors that influence C1q reactivity include the presence of complement-fixing IgG subclasses (IgG1 and IgG3), and the influence of antibody removal therapy, which can induce the loss of C1q reactivity by diminishing IgG subclass reactivity.

- C1q binding is strongly related to HLA antibody density on single-antigen beads, which is reflected by the total IgG MFI.

CLINICAL RESEARC

681/ASN.2014040326

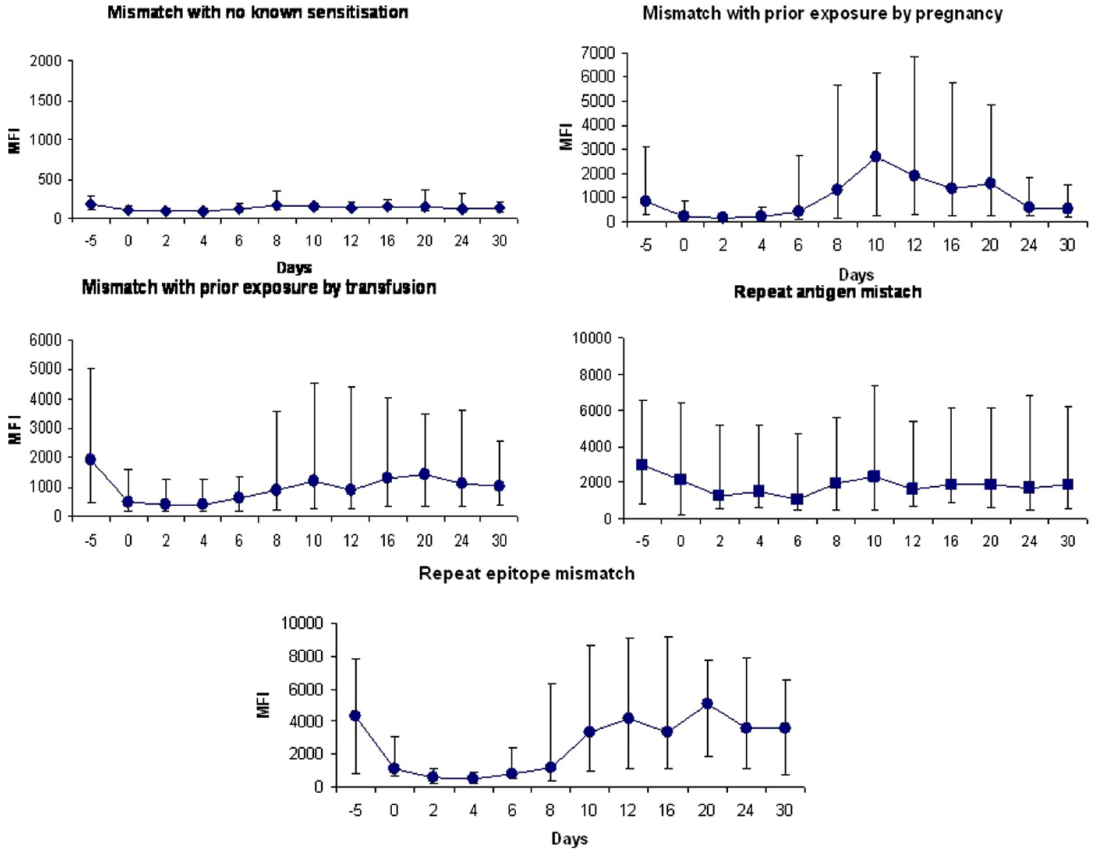
Non-Comple
Anti-HLA Ar



C1q-binding de novo DSA are associated with graft loss occurring quickly after their appearance. However, the long-term persistence of C1q-nonbinding de novo DSA could lead to lower graft survival.

Pregnancy-induced HLA antibodies respond more vigorously after renal transplantation than antibodies induced by prior transplantation

Rob Higgins [a,*], David Lowe [b], Sunil Daga [a,c], Mark Hathaway [b], C. Williams [b], F.T. Lam [a], Habib Kashi [a]



Changes in HLA-specific antibody levels by time after transplantation and mode of original sensitization;

Peak level post transplantation occurs earlier for pregnancy induced HLA-specific antibodies compared to other sensitization events and the peak rise is also statistically significant ($p < 0.0001$) compared to others

http://dx.doi.org/10.1016/j.humimm.2015.06.013

ORIGINAL ARTICLE

idney Transplants
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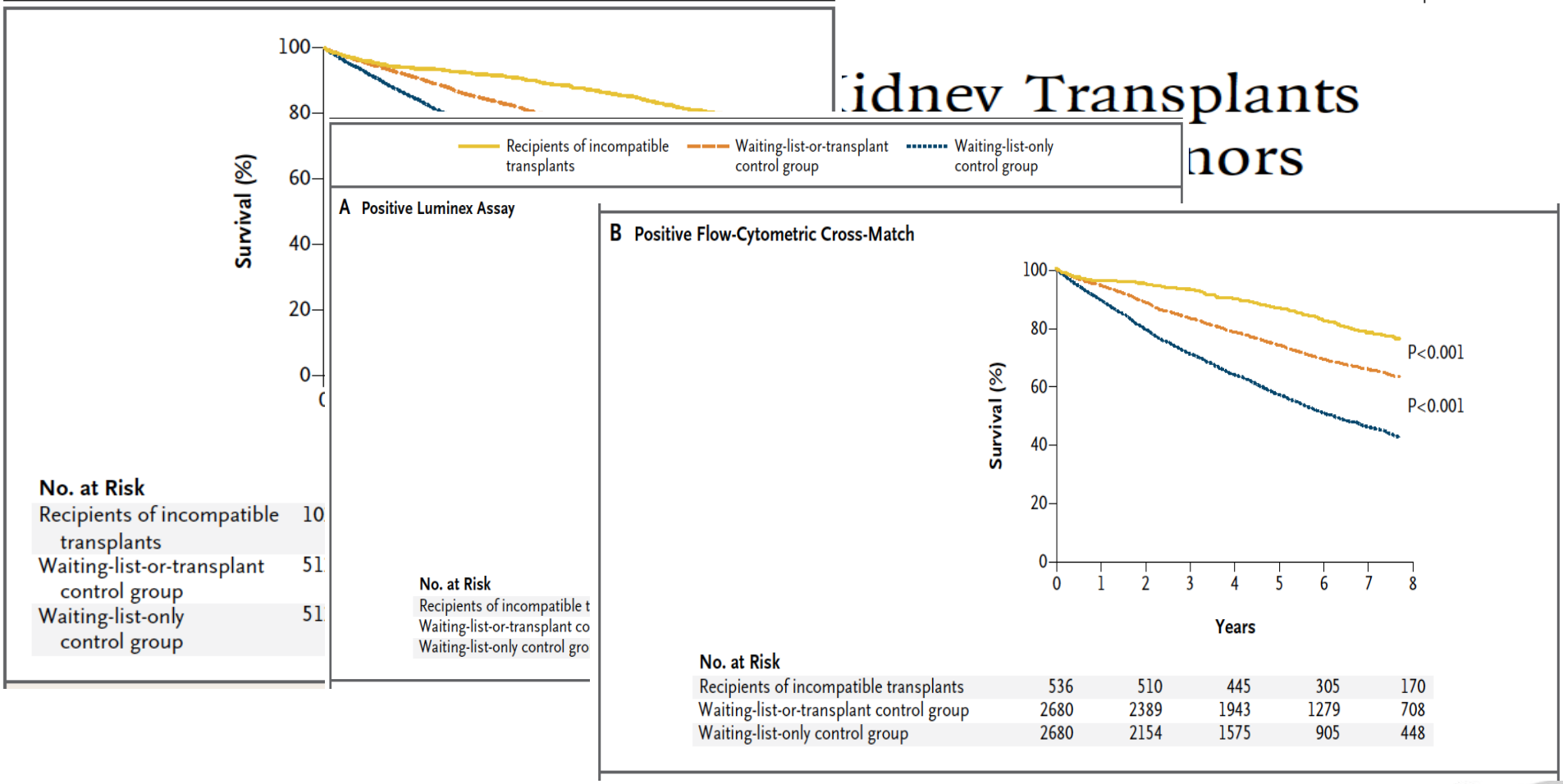

- Preformed DSA in sensitized patients [pregnancy, blood transfusion and previous transplant] can trigger hyper acute rejection, accelerated acute rejection, and early acute antibody mediated rejection.
- De novo DSA are associated with late acute antibody-mediated rejection , chronic antibody-mediated rejection, and transplant glomerulopathy.
- C1q binding DSA are closely associated with acute antibody-mediated rejection, more severe graft injuries, and early graft failure, whereas C1q nonbinding DSA correlate with subclinical or chronic antibody-mediated rejection and late graft loss.
- Complement binding IgG3 DSA are frequently associated with acute antibody-mediated rejection and severe graft injury, whereas non complement binding IgG4 DSA are more correlated with subclinical or chronic antibody mediated rejection and transplant glomerulopathy.

CJASN January 2018, 13 (1) 182-192

Variable	Univariate HR	Univariate *P*	Stepwise model HR	Stepwise model *P*
Age of recipient	1.0 (1.0, 1.0)	0.45		
Race	0.9 (0.4, 2.0)	0.86		
Deceased donor	0.9 (0.4, 1.9)	0.79		
Steroid containing immunosuppression	1.8 (0.7, 4.9)	0.22		
History of nonadherence	3.2 (1.5, 7.0)	0.002	6.5 (2.6, 15.9)	<0.0001
Prior kidney transplant	0.9 (0.3, 2.4)	0.80		
Viral infection requiring immunosuppression reduction	2.1 (0.9, 4.6)	0.07	5.3 (2.1, 13.5)	0.0004
BK nephropathy prior to DSA	1.2 (0.4, 4.1)	0.75		
C1q (MFI >1000)	5.9 (2.3, 15.6)	0		
IgG3 (MFI >1000)	3.2 (1.5, 7.0)	0.002	3.8 (1.5, 9.3)	0.0039
IgG4 (MFI >1000)	2.1 (0.8, 5.7)	0.14		
Dominant MFI (Log)	1.4 (0.46, 4)	0.57		
Number of DSA specificities	1.1 (0.9, 1.3)	0.35		
Anti-class I DSA only	0.7 (0.2, 2.1)	0.52		
Anti-class II DSA only	0.7 (0.3, 1.5)	0.36		
Both anti-class I and II DSA	2.0 (0.9, 4.3)	0.10		
Center				
Center B	–			
Center A	1.1 (0.4, 2.8)	0.86		
Center C	0.6 (0.2, 1.4)	0.22		
Time to dnDSA (years post-transplant)	1.2 (1.1, 1.3)	0.004	1.2 (1.0, 1.3)	0.01
C-stat	NA	NA	0.80	