Solid Organ Naklinde İmmünolojik Hasar Mekanizmaları

Dr. Hüseyin Töz

Acıbadem Kent Hastanesi, İzmir

9. Ulusal Transplantasyon İmmunolojisi ve Genetiği Kongresi

18-21 Nisan 2024, Antalya

10:30-11:30	**Kliniğin Transplant İmmünolojisine Bakışı**
	Oturum Başkanları: Oğuz Söylemezoğlu, Hüseyin Tutkak
10:30-10:50	Solid Organ Naklinde İmmünolojik Hasar Mekanizmaları **Hüseyin Töz**
10:50-11:10	T ve B Hücreleri Dost mu, Düşman mı? **Mehmet Taşdemir**
11:10-11:30	ABO Uyumsuz Nakillerde İmmünolojik Yaklaşım **Tolga Yıldırım**

Long-term outcomes following acute rejection in kidney transplant recipients

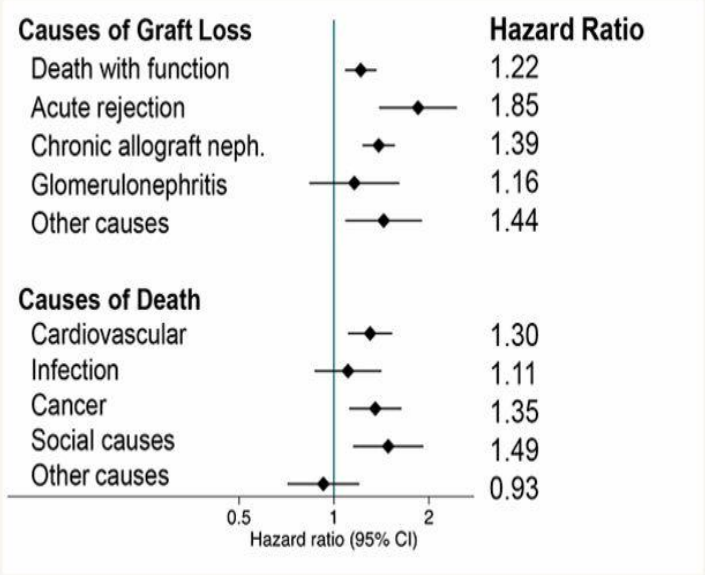
ANZ DATA
AUSTRALIA & NEW ZEALAND DIALYSIS & TRANSPLANT REGISTRY

13614 KTRs 1997-2017
2906 with early acute rejection (AR in 1st 6mth) **%21,3**

Comparison of AR vs no AR:
- Graft survival
  - Causes of graft loss
- Patient survival
  - Causes of death

Models adjusted for era, donor, recipient, immune risk and DGF

Association between early AR and late outcomes for KTRs



KTRs with early AR are at increased risks of death, from CV disease and cancer, and graft failure, from chronic allograft nephropathy and late AR.

doi: 10.1681/ASN.2018111101

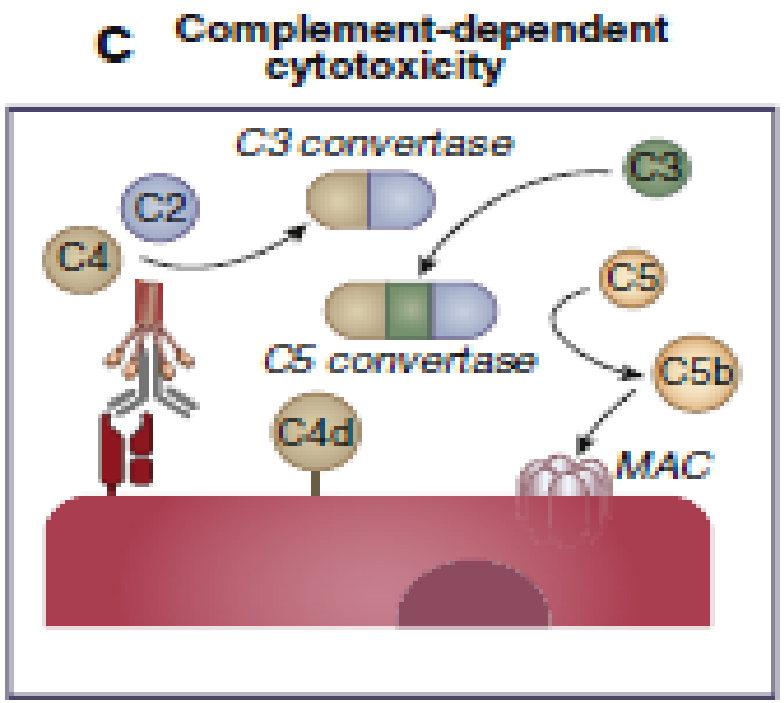
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Sellares J. Am J Transplant 2012	Chand S. Plos One 2016
74 greft kaybı %64 AR(hepsi AMR) %18 GN %7 PVAN %11 medikal, cerrahi	171 greft kaybı % 30 IFTA (1/4 ü TCMR ilişkili) % 28 AMR % 22 rekurren hastalık % 14 TCMR % 5 PVAN
Bx 2004-2008 yılları arasında biyopsi olan	2008-2014 yılları arasında greft kaybı olan

Antikorlar

Anti HLA Antikorları
Sensitizasyon, De novo

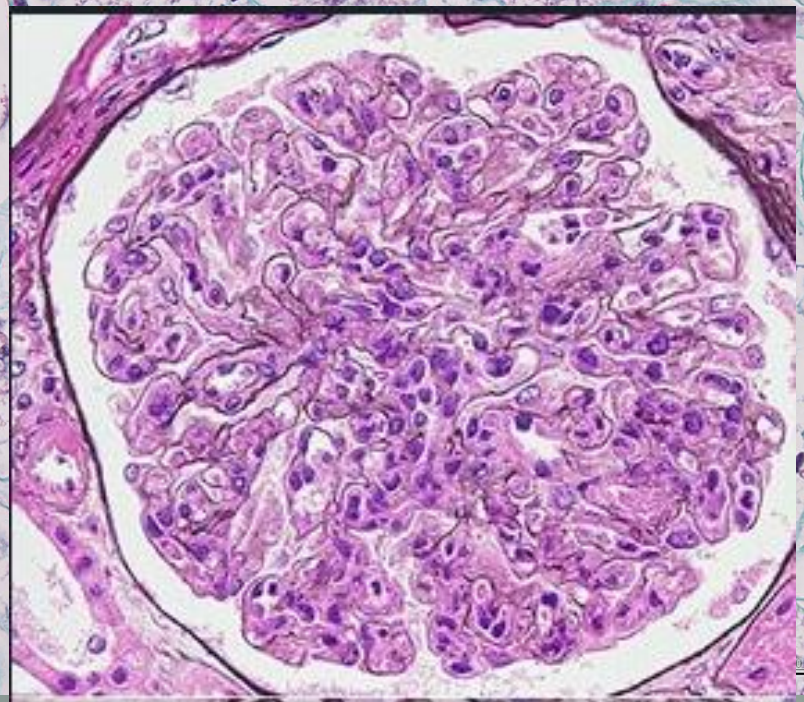
Endotel üzerinde antijenler

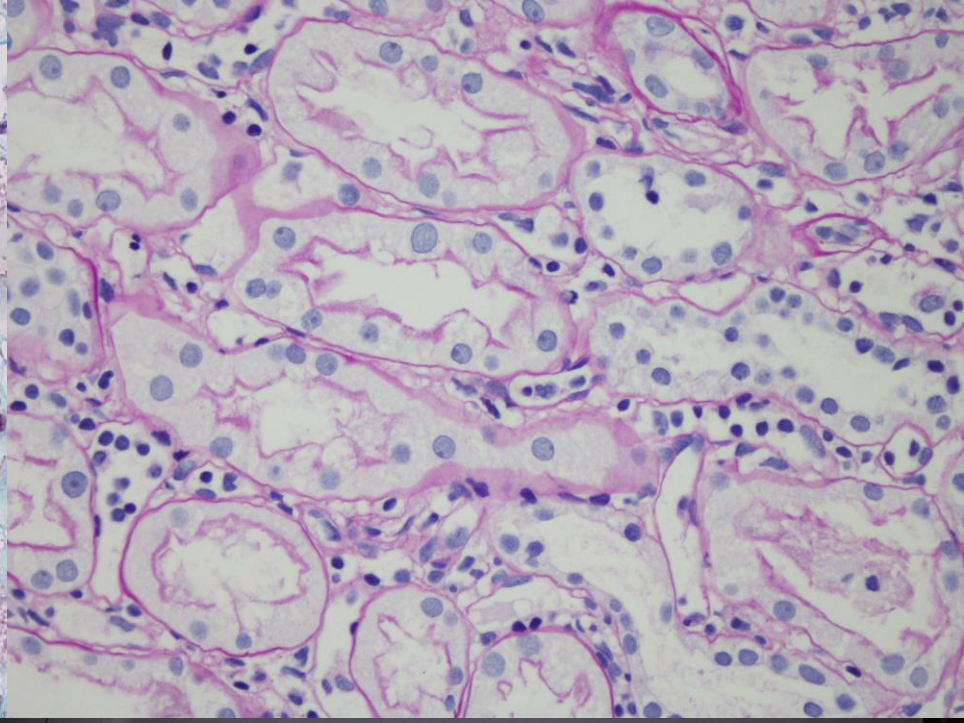


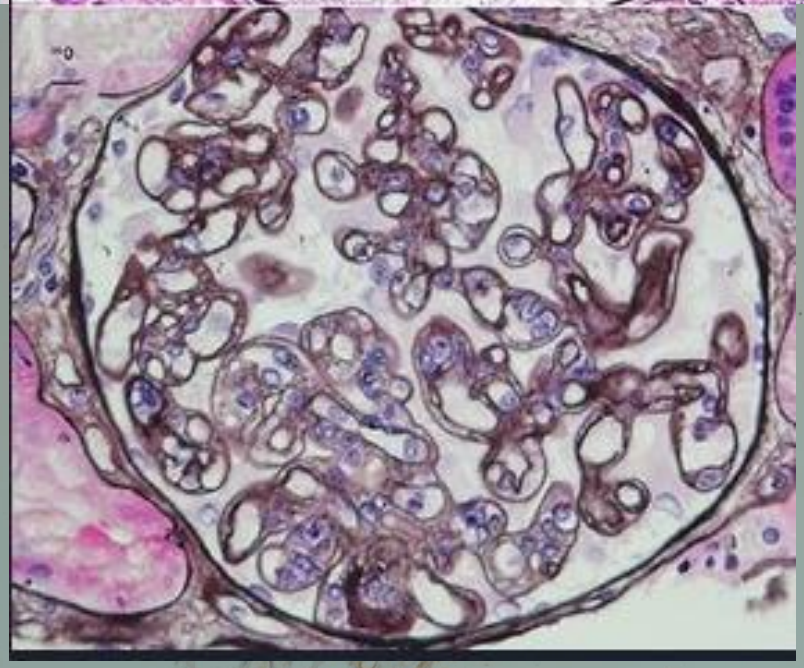
Yan ürün: C4d

Peritubular kapillaritis
Glomerulitis
Vaskulit, TMA

Intertitial infiltrasyon
ödem







Class II Single Antigen Results

Batch ID: 14092017-SNG2

Patient Name: EMRE AKAY 21/08/17
Sample ID: 14092017-9
Lot ID: 3005161 3005159-SA2
Patient HLA Type:

Patient DOB:
Draw Date:
Expiration Date: 15.12.2017

Donor Number:
Donor Center #:

Accession #:
% PRA: 36

Report Parameters

Method Type: Standard Calculation

Positive CON MFI:	Negative CON MFI:	Antigen Adjustment:	MFI Threshold:	Analysis Mode:
16141	327		750	Manual

Antibody Assignments

Specificity	% Positive	Raw Value	MFI/LRA
DQA1*02:01	100	17041	80
DQB1*03:02	100	17041	80
DQA1*03:02	100	16146	76
DQB1*03:01	100	16146	76
DQA1*06:01	100	15473	73
DQB1*02:01	100	15174	71
DQB1*04:01	100	15162	71
DQB1*03:03	100	14977	70
DQA1*03:01	100	14533	68
DQA1*05:01	100	14496	68
DQB1*02:02	100	14496	68
DQA1*04:01	100	14301	67
DQB1*04:02	100	13956	66
DRB1*03:01	100	3254	24
DRB1*11:01	100	2450	18
DRB1*01:03	100	1686	12

Tanı

Aktif AAR:

1. **Akut doku hasarının histolojik kanıtı**,

   MVI, v, TMA

2. **Vask. endotel ile antikor etkileşimi**, en az 1 nin saptanması

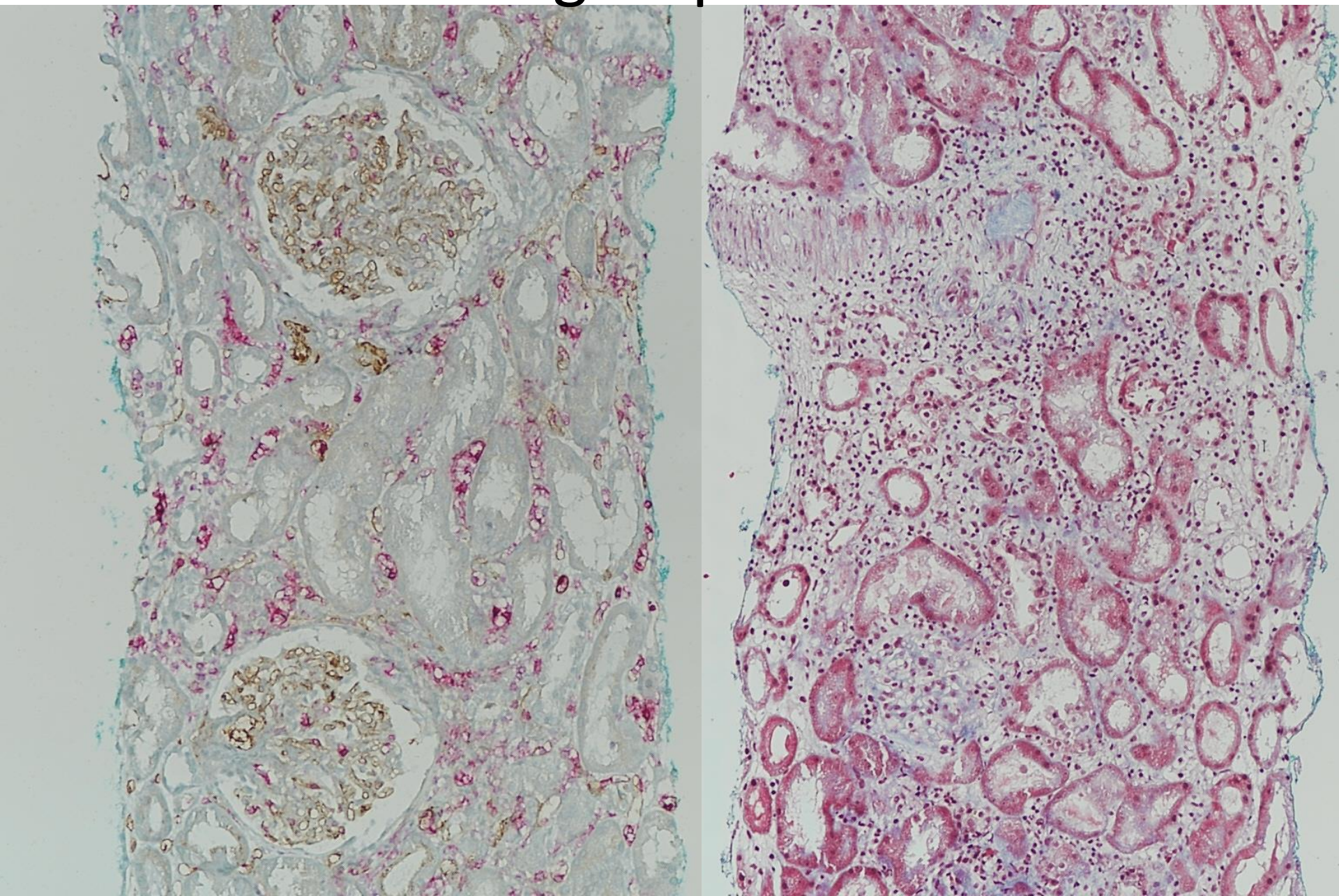
   C4d +

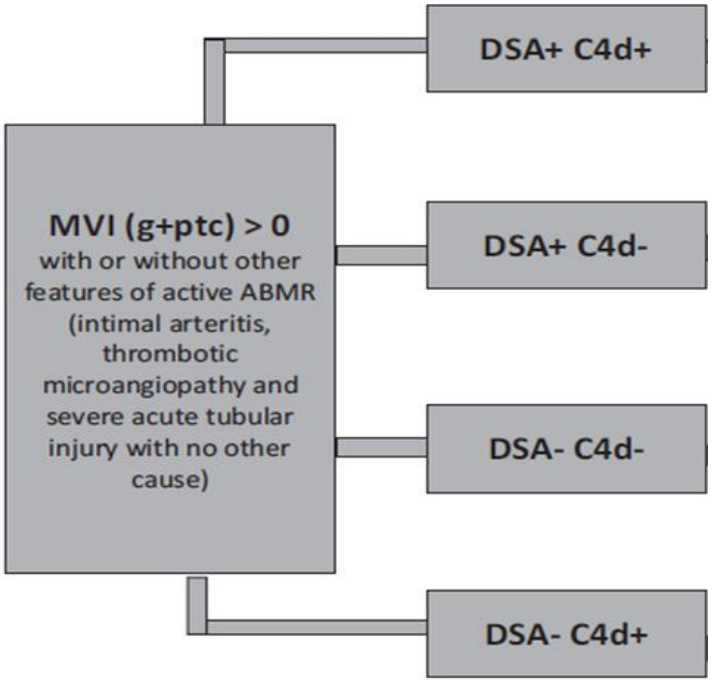
   g + ptc ≥2

3. **HLA-DSA' ların serolojik olarak gösterilmesi**,

Am J Tranplant. 2018;18:293-307

g ve ptc





*When counting MVI towards a diagnosis of ABMR, appl
present, (ii) in the presence of glomerulonephritis, glome
of borderline or TCMR, MVI needs to include an element
** Banff 2015 allowed some cases to be called "suspiciou

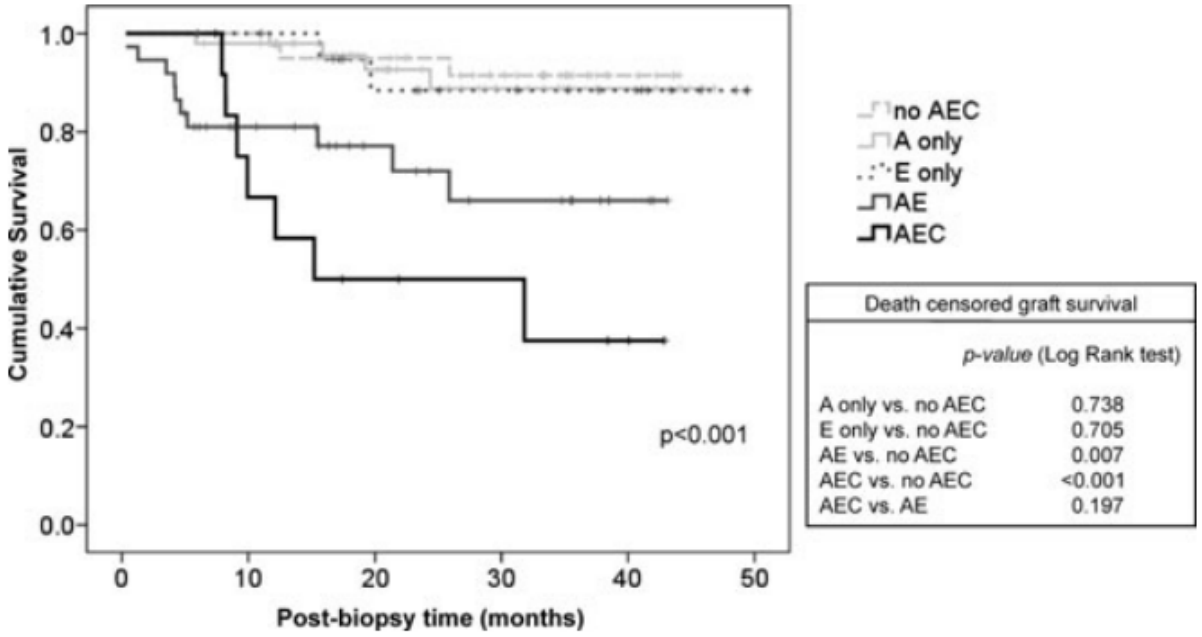
C4d negatif ABMR

- MVI + , HLA-DSA +, ama ptk ‘ de C4d negatif.
- Özellikle geç dönem, ancak erken dönemde de, ptk’de C4d nin gösterilmediği ABMR olabilir: C4d NEGATİF ABMR.
- Hem C4d pozitif, hem de negatif biyopsilerde, ABMR ile uyumlu genetik ekspresyonlar gösterildi.
- C4d pozitifliği, ABMR spektrumunun en uç noktası oalblir

- Miura M.Donor-specific antibody in chronic rejection is associated with glomerulopathy, thickening ofperitubular capillary basement membrane,but not C4d deposition. Clin Transplant 2007; 21

- Sis B, Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. Am J Transplant. 2009

Figure 9: Death censored graft survival in patients grouped according to the presence of panel reactive HLA antibody (A), C4d staining (C) and high renal ENDAT expression (E) (described in results). This divided 161 biopsies (with available C4d and antibody testing) into five groups: 13 AEC (Ab+ENDAT+C4d+), 37 AE (Ab+ENDAT+C4d-), 21 E only (Ab-ENDAT+C4d-), 50 A only (Ab+ENDAT-C4d-), 40 no AEC (Ab-ENDAT-C4d-).



Death censored graft survival	
	p-value (Log Rank test)
A only vs. no AEC	0.738
E only vs. no AEC	0.705
AE vs. no AEC	0.007
AEC vs. no AEC	<0.001
AEC vs. AE	0.197

C4d pozitif / negatif olma durumuna göre greft sağkalımı:
HLA-Antikorları ve ENDAT varsa, C4d olsun ya da olmasın , sağkalım iyi değil

Sis B. Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. Am J Transplant. 2009

Table 3

Graft Outcomes by C4d AMR Status Compared to AMR-Free Matched Controls

	Hazard of Graft Loss (95% Confidence Interval) Compared to AMR-Free Matched Controls	P-Value
C4d-Negative AMR	2.56 (1.08–6.05)	0.033
C4d-Positive AMR	3.70 (2.47–5.54)	<0.001

AMR - antibody-mediated rejection

AMR patients were matched to AMR-free controls from our institution in a 1:5 ratio on HLA-incompatibility, donor type, ABO-incompatibility, history of prior transplantation, peak PRA, and year of transplant.

Orandi BJ., Presentation and Outcomes of C4d-Negative Antibody-Mediated Rejection After Kidney Transplantation. Am J Transplant. 2016

C4d negatif ABMR

- İki ana fenotipe bakacak olursak:

- Fenotip 1: önceden duyarlı bir hastada nakil sonrası erken dönemde erken ortaya çıkar ve C4d pozitif olma olasılığı daha yüksektir.

- Fenotip: İkinci tip nakil sonrası geç gelişir ve de novo DSA gelişimine bağlıdır ve C4d negatif olması muhtemeldir.

Neden, C4d negatif

- Kullanılan fiksatif tipi ile ilgili teknik sorunlar,
  - Farklı C4d saptama yöntemleri,
  - Bazı DSA'lar tarafından kompleman aktivasyonunun zayıf olması

- ABMR'nin komplemandan bağımsız yolakları
- NK hücreleri (FcRIIA) üzerindeki Fc reseptörlerinin rolü.

Hidalgo LG.
NK cell transcripts and NK cells in kidney biopsies from patients with donor-specific antibodies: evidence for NK cell involvement
in antibody-mediated rejection.
Am J Transplant. 2010

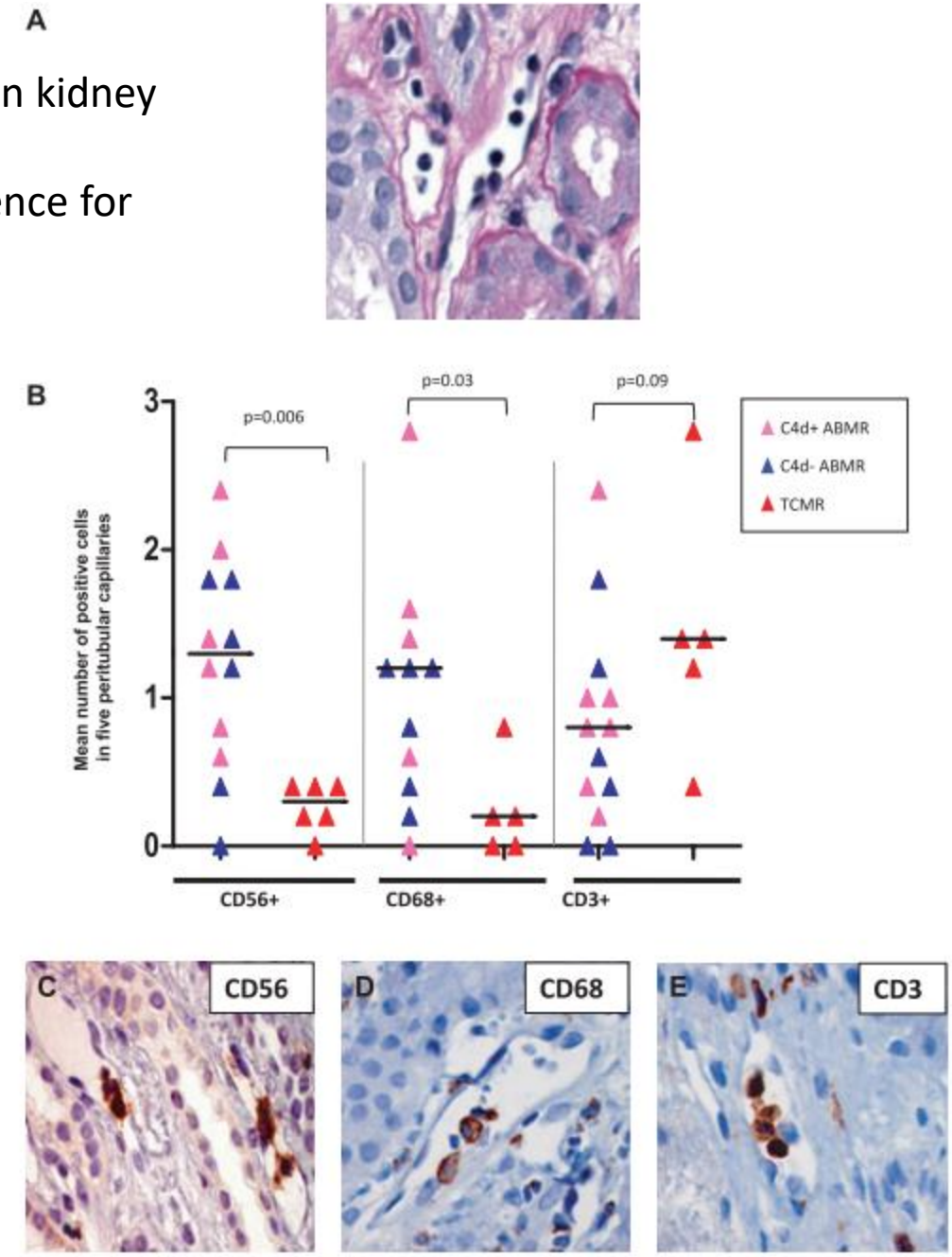
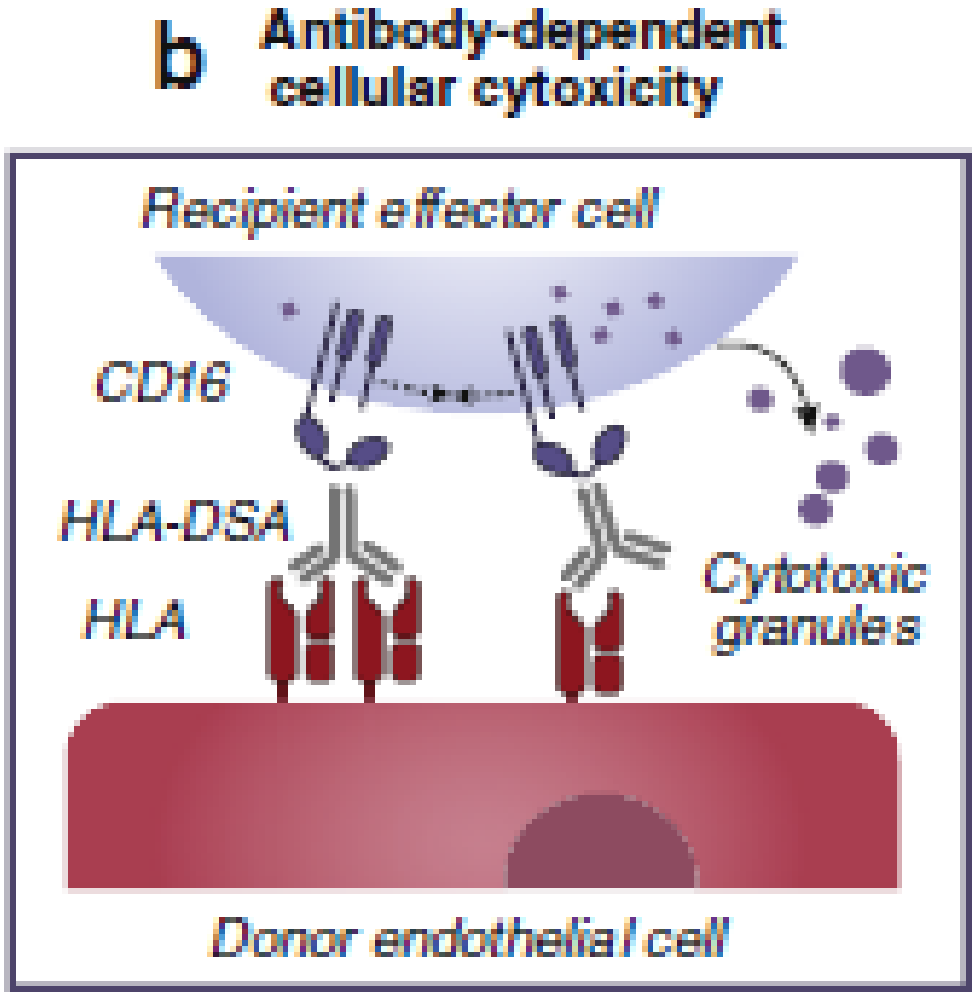


Figure 5: Intraluminal cell types in peritubular capillaries by immunohistochemistry. (A) A representative of peritubular capillaritis in a kidney transplant biopsy (periodic acid-Schiff, original magnification × 600). (B) Comparison of mean numbers of intraluminal CD56+, CD68+ or CD3+ cells in five peritubular capillaries in biopsies with antibody-mediated rejection (ABMR) versus T-cell-mediated rejection (TCMR). (C–E) Representative figures for (C) intracapillary CD56+ NK cells, (D) CD68+ macrophages or (E) CD3+ T cells (immunoperoxidase, original magnification × 600).



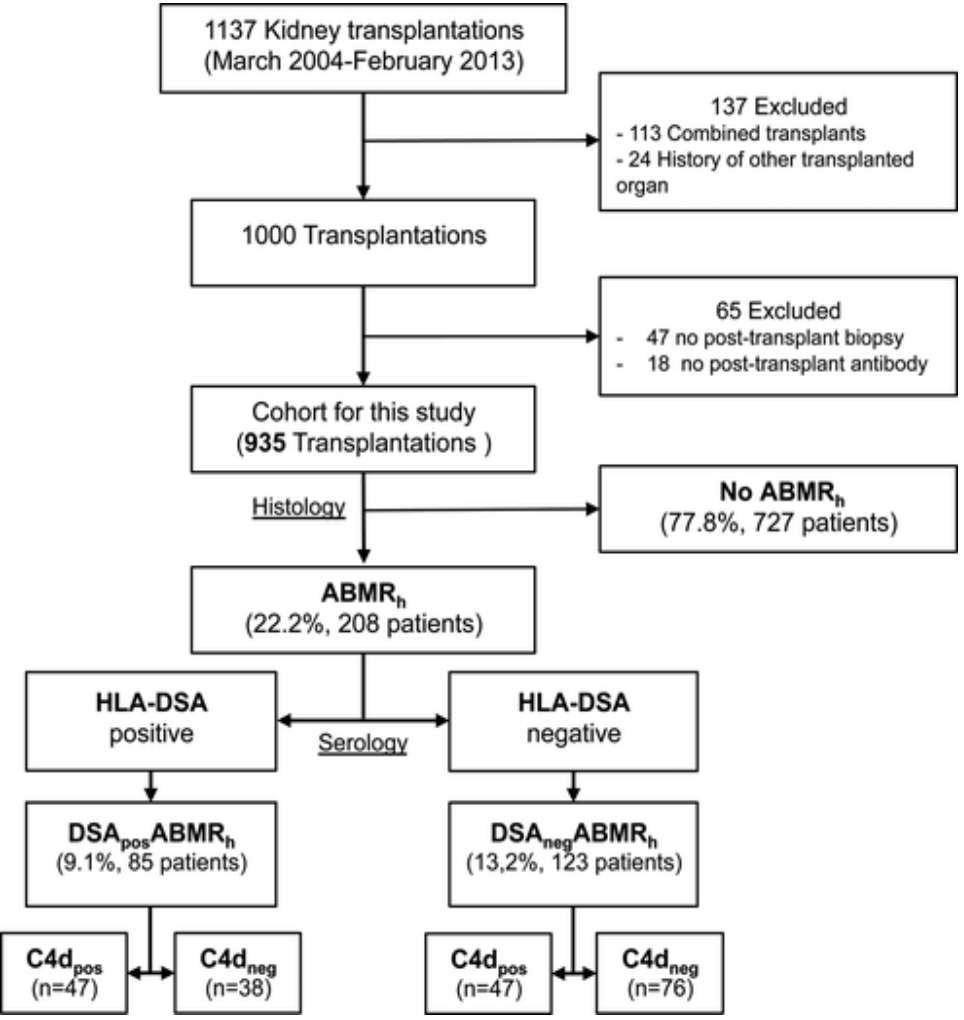
HLA-DSA veya başka bir antikorun, donör endoteline bağlanması ===
NK hücre, monosit ve makrofaj, nötrofil aktivasyonuna ve sitotoksik granül salınmasına neden olur.

- HLA-DSA ile ilgili sorunlar:
  - Tetkik istenmemesi
  - Lojistik
  - HLA lab ile iletişimsizlik
  - Verici doku tipi bilinmemesi, eksik bilinmesi
  - Maliyet / geri ödeme
  - HLA-DSA eşik değer (STAR önerisi 1400)

Am J Transplant. 2019 Mar;19(3):763-780. doi: 10.1111/ajt.15074. Epub 2018 Sep 28.

Histological picture of antibody-mediated rejection without donor-specific anti-HLA antibodies: Clinical presentation and implications for outcome.

Senev A[1,2], Coemans M[1], Lerut E[3], Van Sandt V[2], Daniëls L[2], Kuypers D[1,4], Sprangers B[1,4], Emonds MP[1,2], Naesens M[1,4].



$ABMR_h$: ilk 2 histolojik kriteri karşılaması

- akut doku hasarı
  (g > 0, ptc > 0, veya v > 0)
- vasküler endotel ile antikor ilişkisi
  (C4d > 0 veya g + ptc ≥ 2))

İndex biyopsi ve takip biyopsisi yapılmış.
(3458 Protokol bx + 387 Endikasyon bx)

MVI +, DSA -	MVI +, DSA +	DSA +, rej yok
25	155	228
MVI skoru yüksek, C4d poz daha az		
Greft kaybı %48	Greft kaybı %38	

- MVI poz olup, DSA neg olan hastalarda da prognoz, MVI poz, DSA poz kadar olumsuz

- Parajuli S. Clinical Significance of Microvascular Inflammation in the Absence of Anti-HLA DSA in Kidney Transplantation. Transplantation. 2019

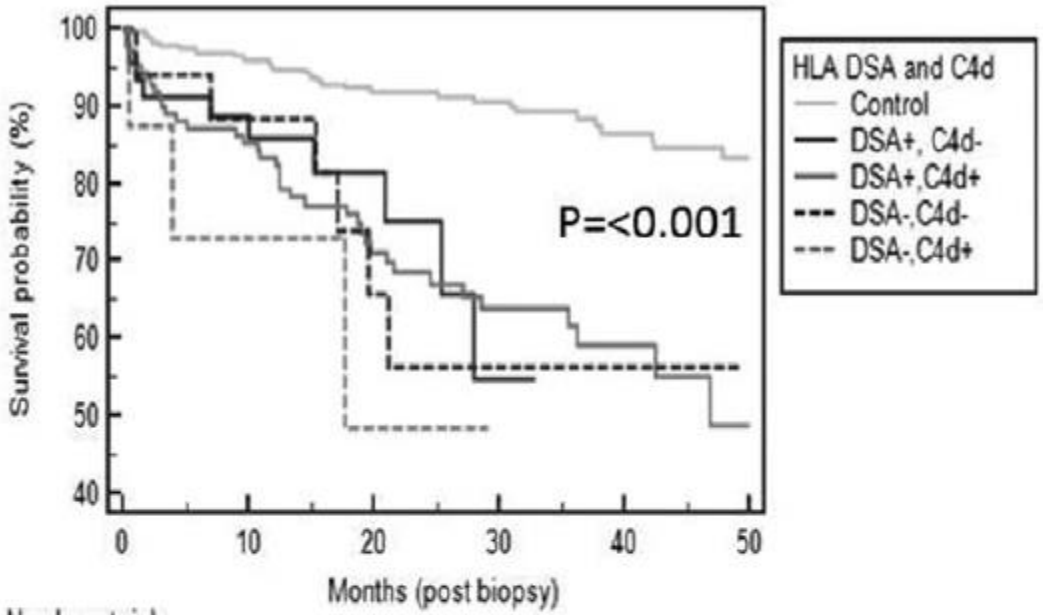


FIGURE 2. No difference in death-censored graft survival based on C4d and DSA status. DSA, donor-specific antibody

Parajuli S. Clinical Significance of Microvascular Inflammation in the Absence of Anti-HLA DSA in Kidney Transplantation. Transplantation. 2019

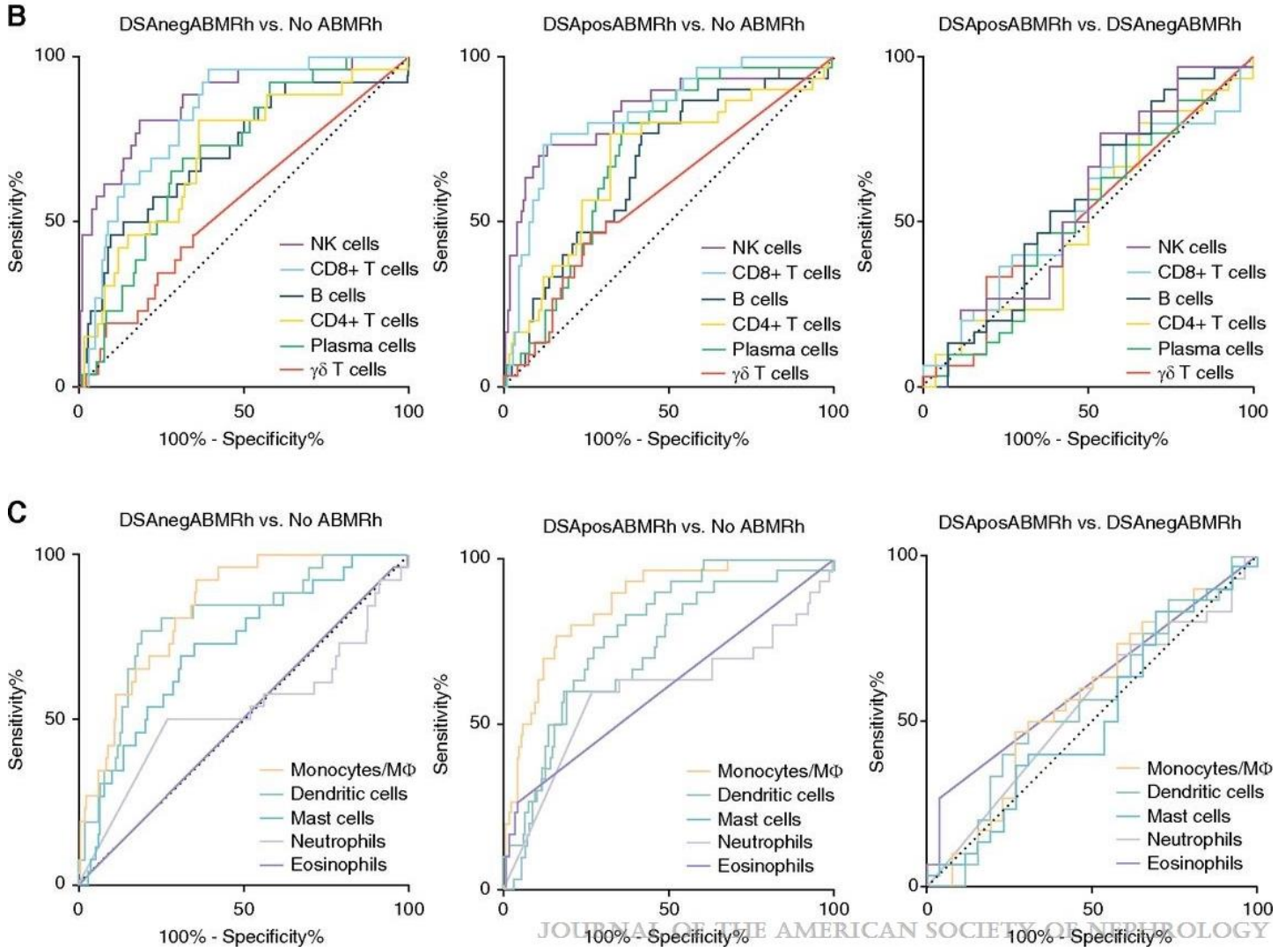
- HLA-DSA negatif olup ABMRh olan hastalarda, doku transkriptleri, HLA-DSA pozitif ABMRh olanlara benzer mi ??

Transcriptional Changes in Kidney Allografts with Histology of Antibody-Mediated Rejection without Anti-HLA Donor-Specific Antibodies

Callemeyn J. 2020

- 224 biyopsi, 56 ABMR == 26 HLA DSA var, kalanlarda yok.

- ABMRh olan biyopsilerde **IFN-gamma, NK ve endotel hücre aktivasyon yolaklarına** ait transkriptlerde artış var..
- Bu artışlar, **HLA-DSA pozitif yada negatif olanlarda farklı değil. , ayrıca infiltrasyondaki lökosit dağılımı da benzer**
- HLA-DSA statusu farklılığa neden olmuyor,
- Farklılık yaratan, TCMR eşlik edip etmemesi



Transcriptional Changes in Kidney Allografts with Histology of Antibody-Mediated Rejection without Anti-HLA Donor-Specific Antibodies Journal of the American Society of Nephrology31(9):2168-2183, September 2020.

Early acute anti-HLA antibody-negative microvascular rejection of kidney transplants is associated with preformed IgG antibodies against diverse glomerular endothelial cell antigens

- 38 hasta,
- ilk 3 ay içerisinde g+ptc >=3 (MVI, vaskulit, intertisyel hemoraji, TMA)

- Antikorlar:
  - AT1R
  - endothelin-1 type A
  - Anti-MICA
  - Ayrıca 62 non-HLA antijene yönelik antikor paneli

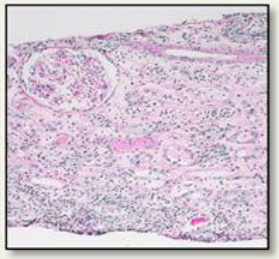
- Endotel hücre cross match
- Genetik analiz

J Am Soc Nephrol 2019

Early acute anti-HLA antibody-negative microvascular rejection of kidney transplants is associated with preformed IgG antibodies against diverse glomerular endothelial cell antigens

METHODS

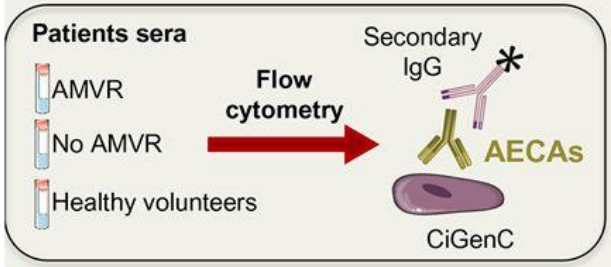
Acute microvascular rejection (AMVR) :



- ✓ Acute rejection during the first 3 months
- ✓ g+ptc≥3
- ✓ No anti-HLA-DSA

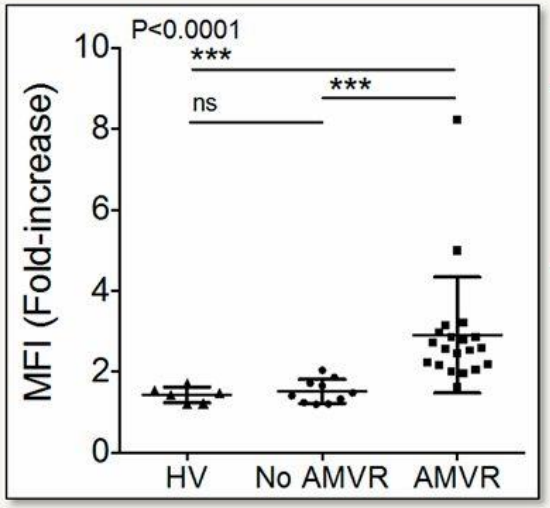
↳ **Previously identified AECAs, including polyreactive Abs, were tested**

↳ **Endothelial crossmatch** using immortalized glomerular endothelial cells (CiGEnCs) as target



↳ **Integrated analysis**
(Protein arrays and transcriptomic data)

OUTCOME



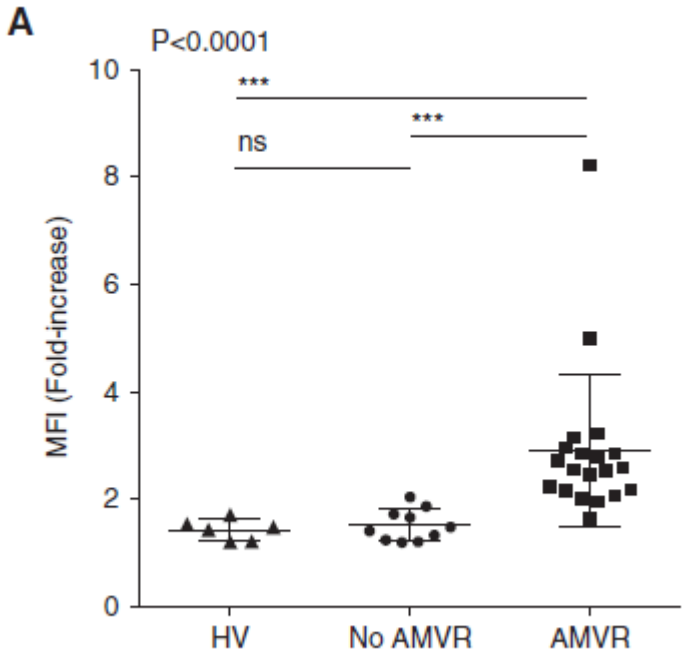
- ✓ Early AMVR is associated with preformed IgG antibodies against glomerular endothelial antigens.
- ✓ A new endothelial crossmatch assay using CiGEnCs identified a common IgG response discriminating patients with AMVR from stable kidney transplant recipients.
- ✓ Combined transcriptomic and proteomic approaches identified new targets of non-HLA antibodies with little redundancy among individuals.

CONCLUSIONS

A new endothelial crossmatch assay, combined with transcriptomic and proteomic analyses, revealed that prior to transplantation, patients with AMVR carried unknown anti-endothelial cell antibodies in their sera that specifically targeted the glomerular microvascular endothelium.

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

doi: 10.1681/ASN.2018080868



GEC e yönelik preforme IgG Antikor reaktivitesi saptandı.

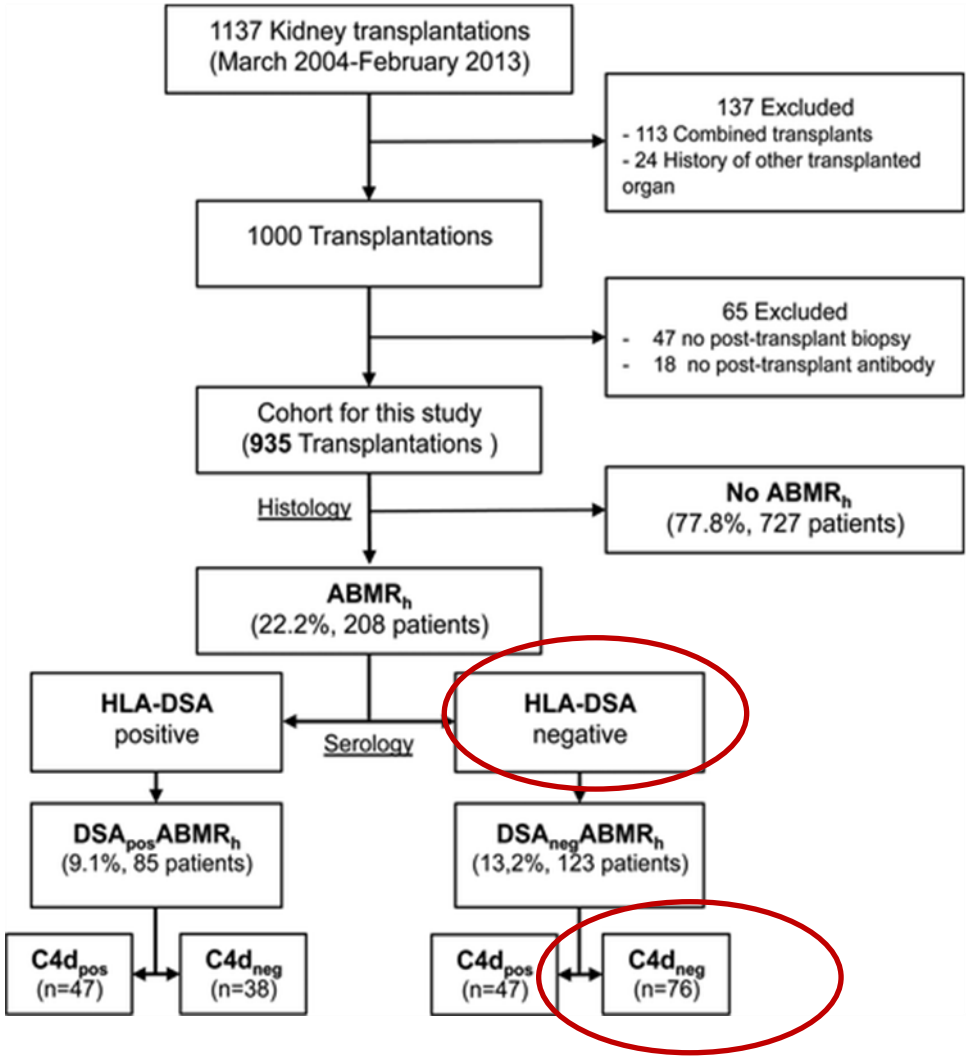
GEC kullanarak yapılan endotelyal XM de IgG yanıtı saptandı.

Transcriptomic and proteomic analizde glomeruler endotel hücrelerinde non-HLA antikorların yeni bir hedefi saptandı.

In vitro **hücre bazlı yöntemler**, rejeksiyon risk değerlendirmesini iyileştirebilir

- Bu çalışmada, AT1R ak, ETAR ak ve natural ak çalışıldı.
- AMVR ile net bir ilişkisi gösterilmedi.
- Ancak, özellikle AT1R ak ile ETAR ak arasında anlamlı bir korelasyon saptandı:
- Bazı hastalarda geniş çaplı bir oto-immun yanıt olabilir.

- Her hastaya ait *autoantibody signature* olabilir, SDBH; bazı proteinlerin salınımına - self antijen olarak algılanıp oto-ak üretimine neden olabilir.



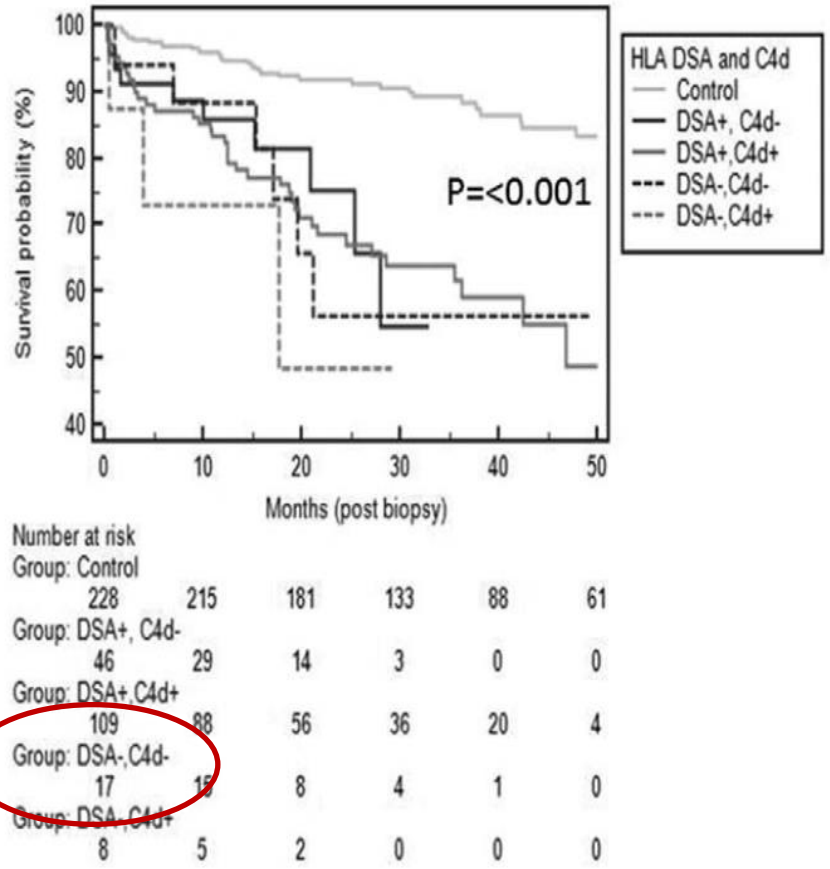


FIGURE 2. No difference in death-censored graft survival based on C4d and DSA status. DSA, donor-specific antibody.

DSA neg, C4d neg, ama MVI pozitif == mikrovasküler rejeksiyon

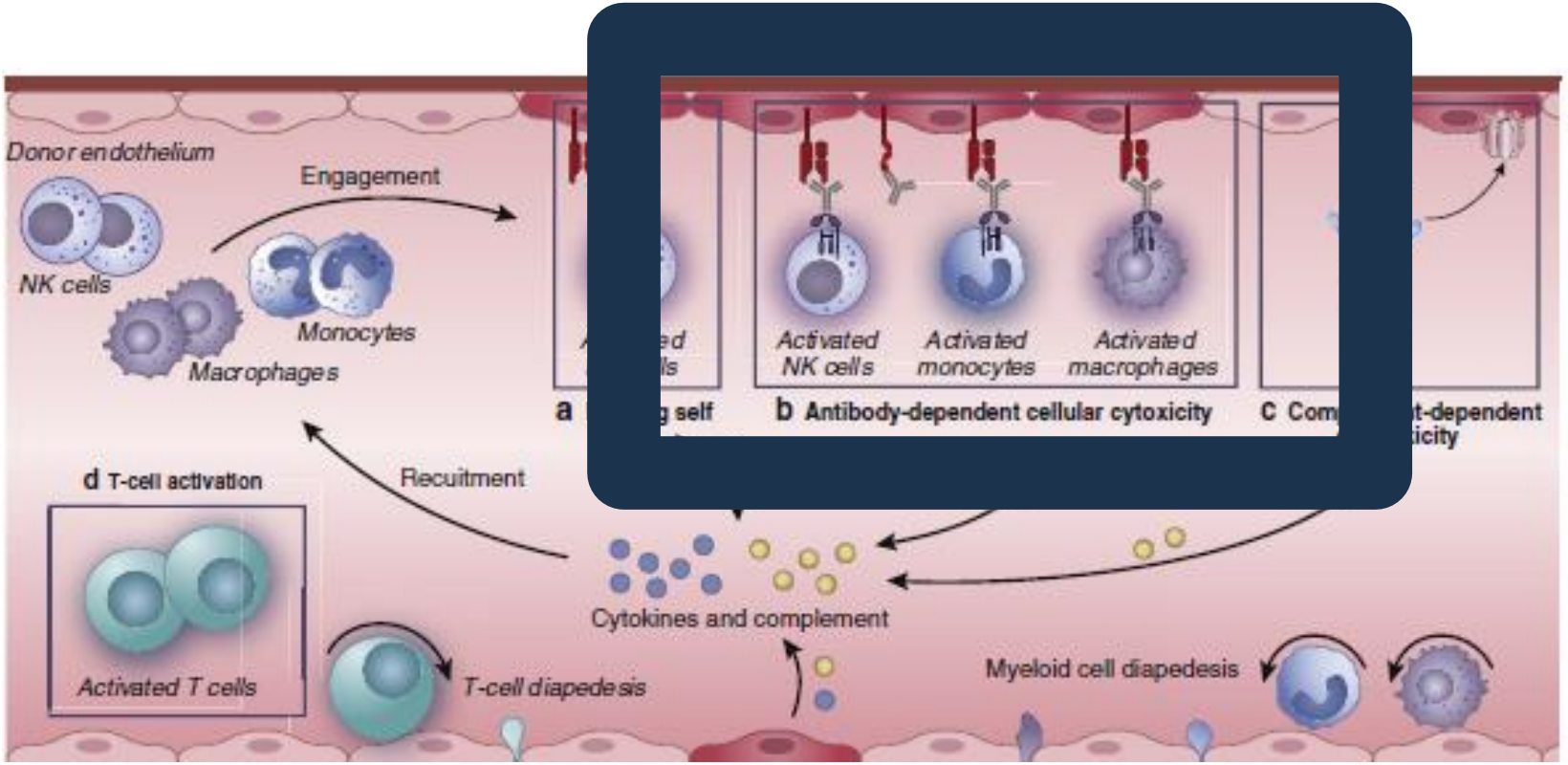
- Anti-HLA ak dışında, Saptanamayan bir humoral etiyoloji
  - ADCC mekanizması ile ilşkili genler devrede
  - nonHLA ak, Genomik mismatch

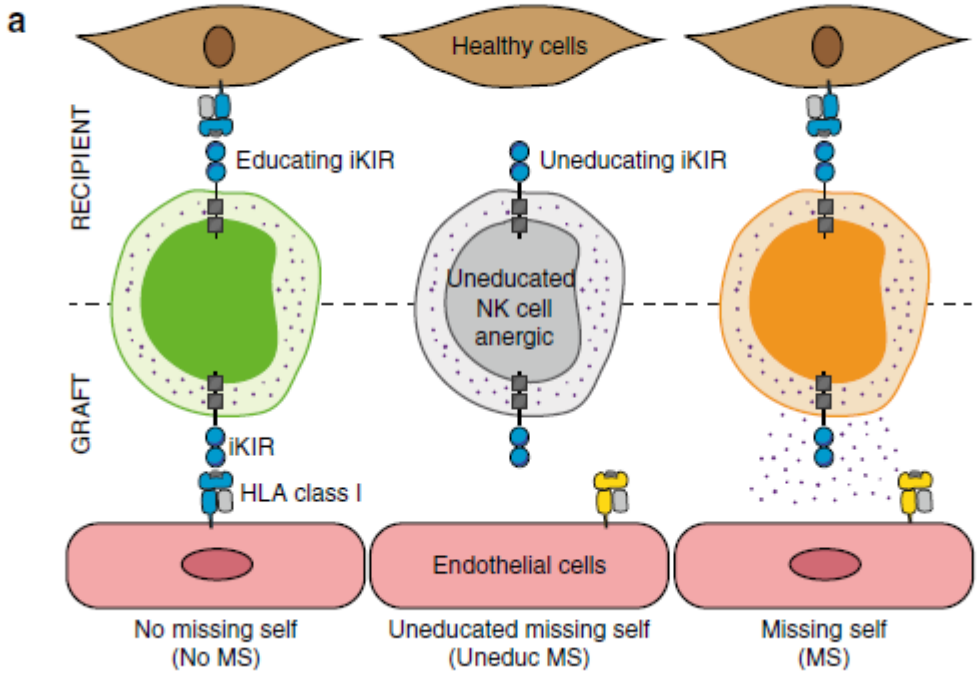
- Yine de anti-HLA ak sorumlu olabilir
  - Dolaşımda saptanamıyor ama grefftte absorbe, greft içindeki lenfoid organlarda absorbe
  - Dolaşımda antikor saptanamamasına rağmen, mB hücre aktivasyonu saptanabiliyor = non-circulating anti-HLA ab

- Ya da antikordan bağımsız mekanizmalar

Rejeksiyonda innate immun sistem

- NK, mono/makrofajlar


Donor endothelium
Engagement
NK cells
Monocytes
Macrophages
Activated NK cells
Activated monocytes
Activated macrophages
b Antibody-dependent cellular cytoxicity
d T-cell activation
Recuitment
Activated T cells
T-cell diapedesis
Cytokines and complement
Myeloid cell diapedesis



nature COMMUNICATIONS

ARTICLE

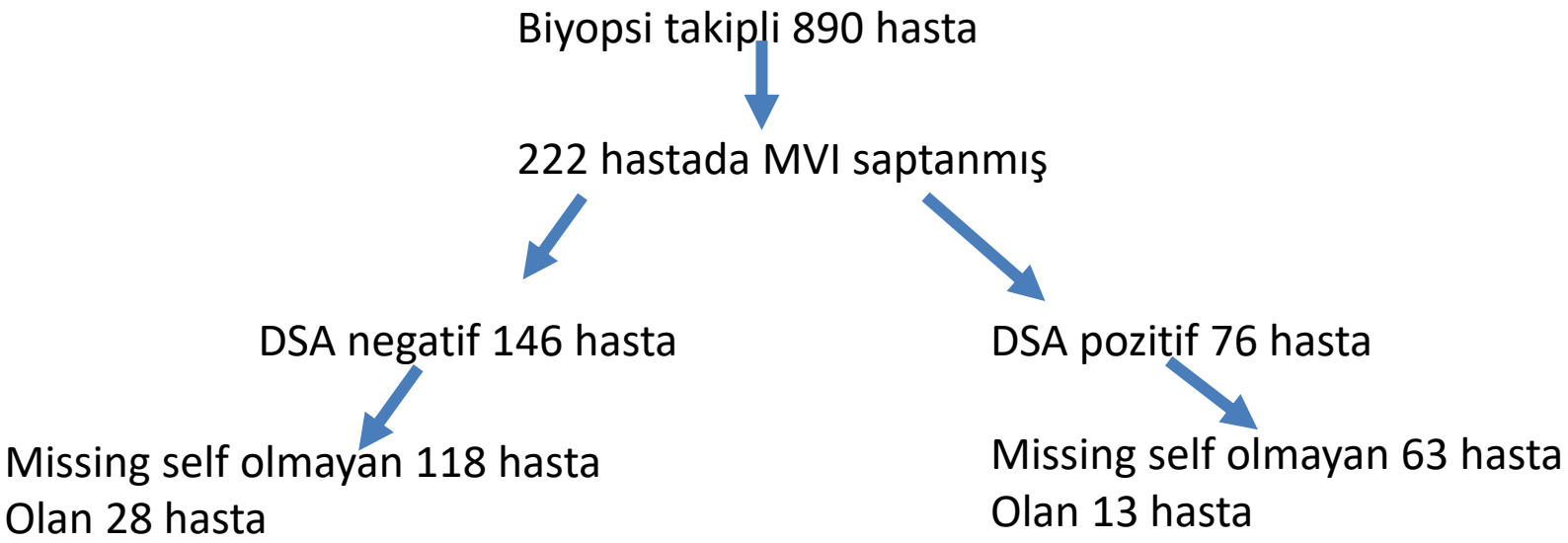
https://doi.org/10.1038/s41467-019-13113-5 OPEN

Missing self triggers NK cell-mediated chronic vascular rejection of solid organ transplants

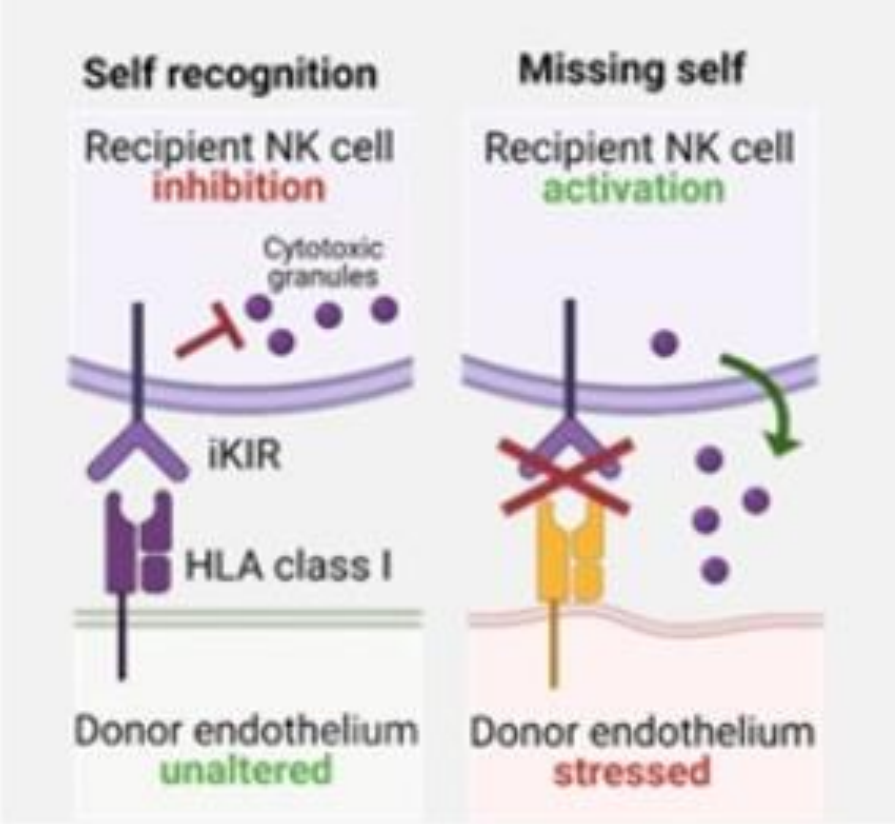
2019

Alice Koenig[1,2,3], Chien-Chia Chen[1], Antoine Marçais[1], Thomas Barba[1,2,3], Virginie Mathias[1,4], Antoine Sicard[1,2,3], Maud Rabeyrin[5], Maud Racapé[6], Jean-Paul Duong-Van-Huyen[6], Patrick Bruneval[6], Alexandre Loupy[6], Sébastien Dussurgey[7], Stéphanie Ducreux[1,4], Vannary Meas-Yedid[8], Jean-Christophe Olivo-Marin[8], Héléna Paidassi[1], Romain Guillemain[9], Jean-Luc Taupin[10,11,12], Jasper Callemeyn[13,14], Emmanuel Morelon[1,2,3], Antonino Nicoletti[12,15], Béatrice Charreau[16], Valérie Dubois[1,4], Maarten Naesens[13,14], Thierry Walzer[1,17], Thierry Defrance[1,17] & Olivier Thaunat[1,2,3]*

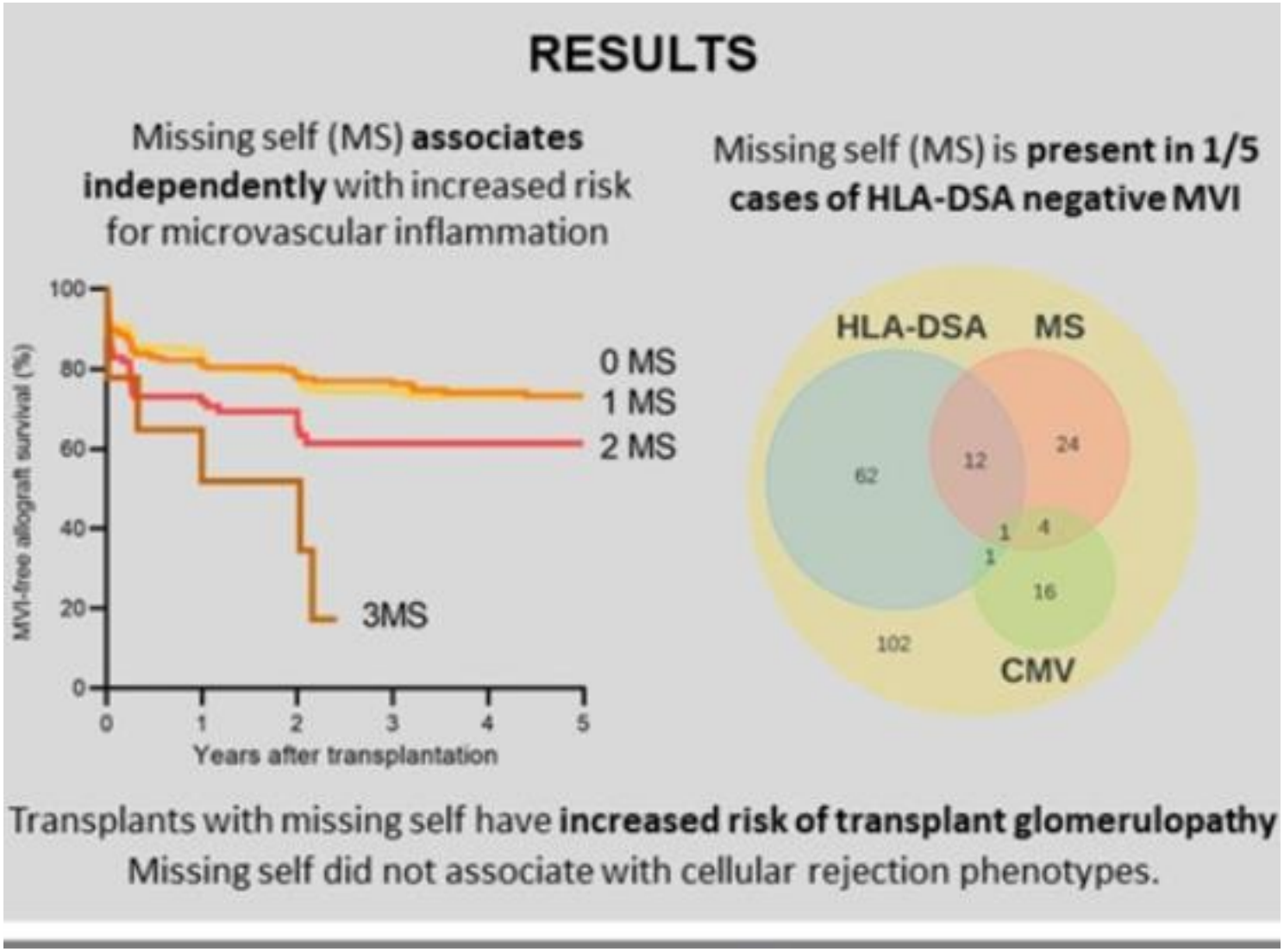
Missing Self–Induced Microvascular Rejection of Kidney Allografts: A Population-Based Study



Missing Self-Induced Microvascular Rejection of Kidney Allografts: A Population-Based Study. J Am Soc Nephrol. 2021

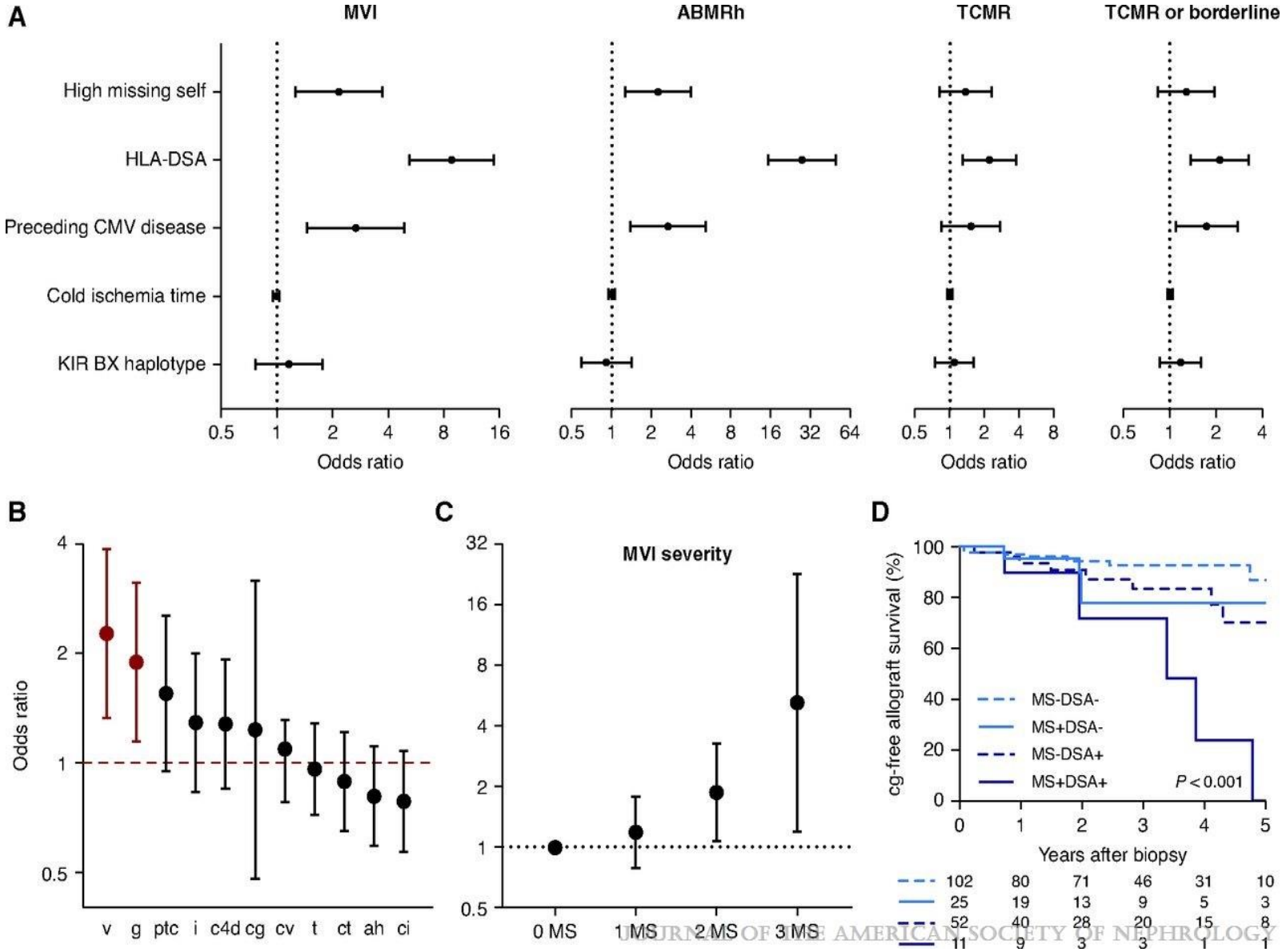


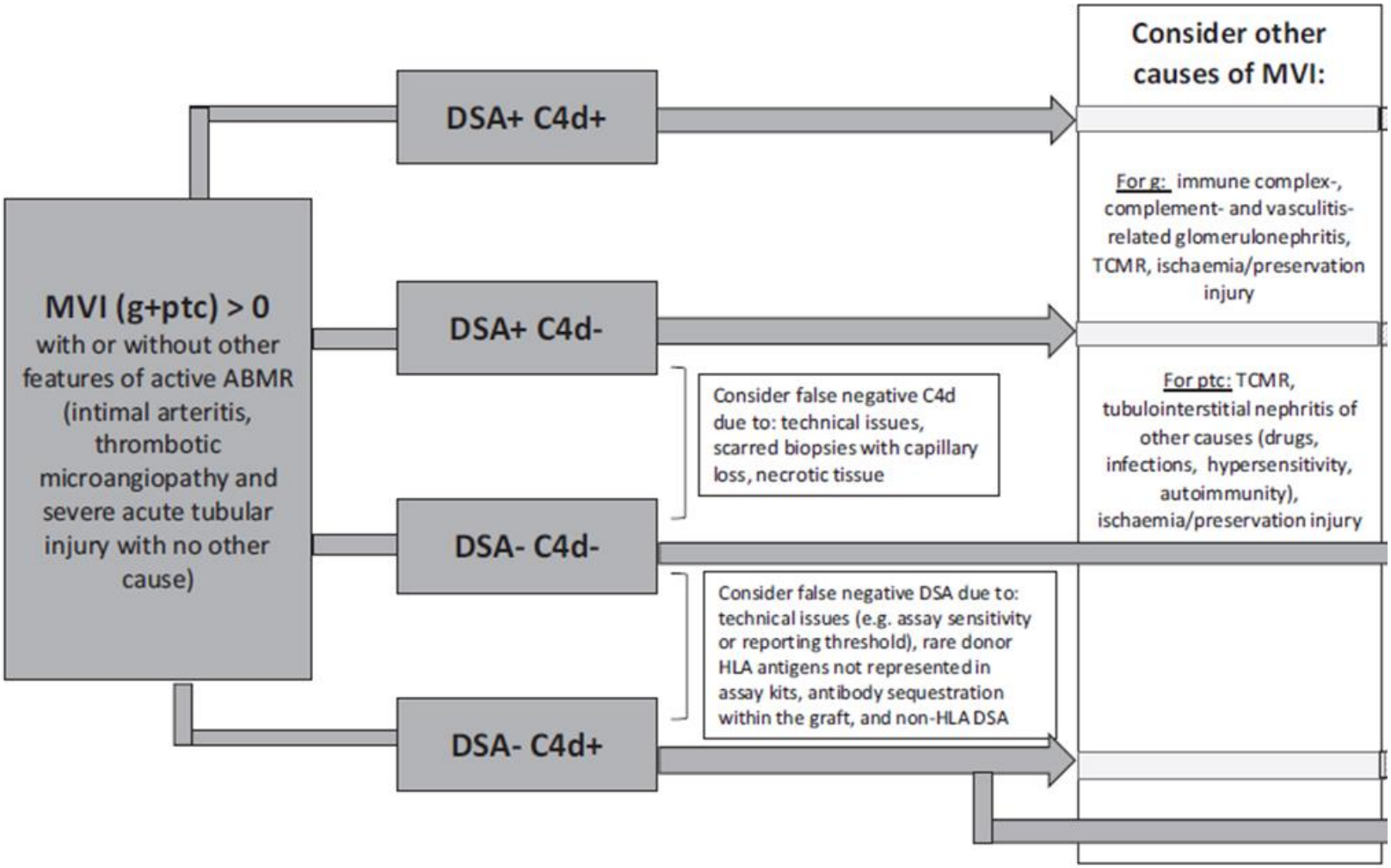
Missing Self-Induced Microvascular Rejection of Kidney Allografts: A Population-Based Study. J Am Soc Nephrol. 2021



Missing Self-Induced Microvascular Rejection of Kidney Allografts: A Population-Based Study. J Am Soc Nephrol. 2021

Figure 3.

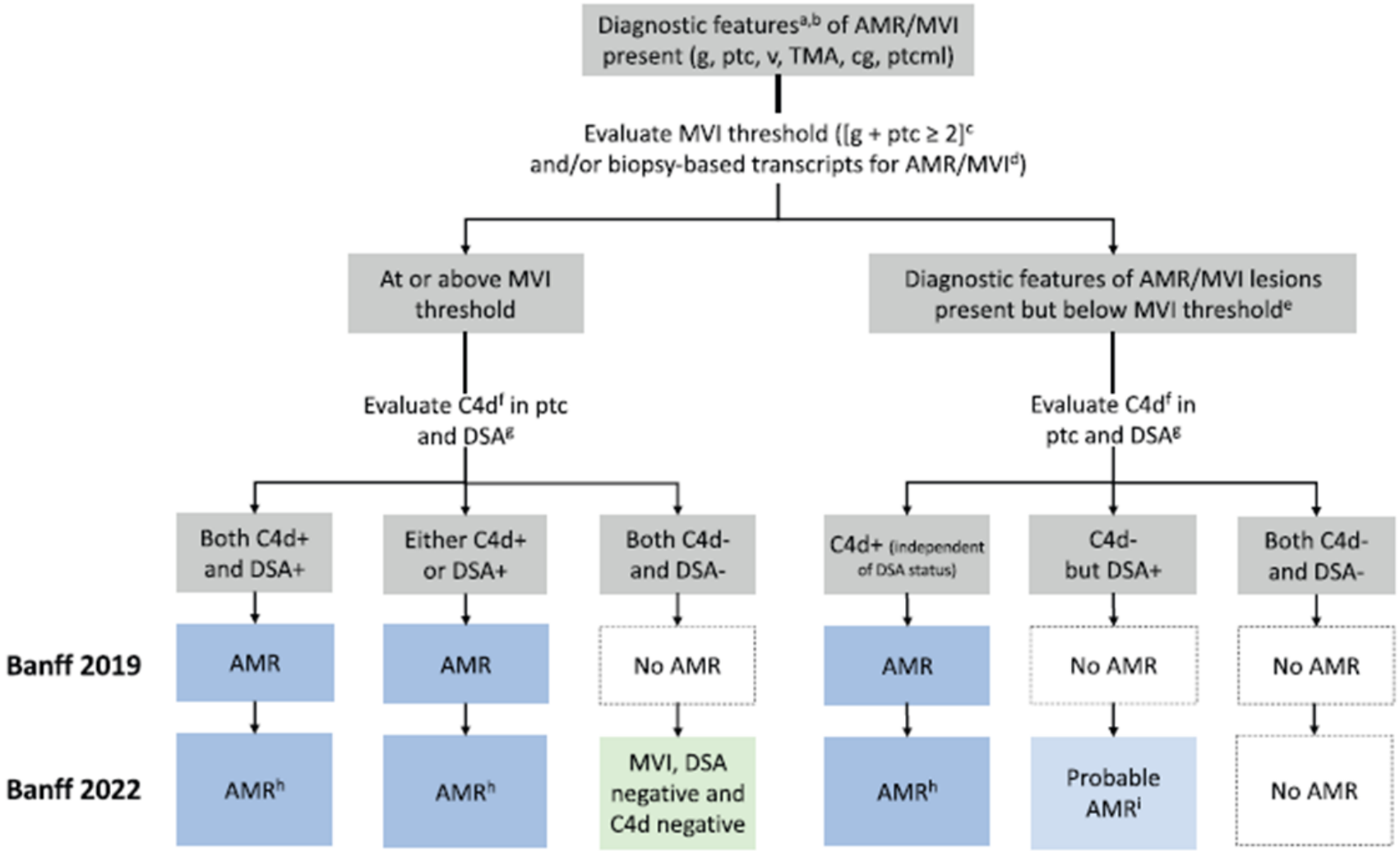




*When counting MVI towards a diagnosis of ABMR, apply all Banff 2017 rules: (i) in the absence of C4d, MVI ≥ 2 must be present, (ii) in the presence of glomerulonephritis, glomerulitis does not count towards MVI, and (iii) in the presence of borderline or TCMR, MVI needs to include an element of glomerulitis (g ≥1)

** Banff 2015 allowed some cases to be called "suspicious for ABMR"; this designation was removed in Banff 2017

American Journal of Transplantation 24 (2024) 338–349



Rejeksiyon bulgusu olmadan C4d pozitifliğinin anlamı var mı ?

- C4d skoru 2-3, i,t,g,v = 0
- ABO uyumlu tx: 5001 bx = 108 (%2.16)

- Molecular assessment of C4d-positive renal transplant biopsies without evidence of rejection.
- Kidney Int Rep. 2019;4(1):148-158

Dunn's multiple comparisons test	Adjusted *P* Value
C4d- WER vs. C4d+ WER ABOi	>0.999
C4d- WER vs. C4d+ WER	>0.999
C4d- WER vs. ABOi AbMR	>0.999
C4d- WER vs. AbMR	3.33×10^{-2}
C4d- WER vs. TCMR	>0.999
C4d- WER vs. Mixed rejection	2.14×10^{-1}
C4d+ WER ABOi vs. C4d+ WER	>0.999
C4d+ WER ABOi vs. ABOi AbMR	>0.999
C4d+ WER ABOi vs. AbMR	3.26×10^{-3}
C4d+ WER ABOi vs. TCMR	9.61×10^{-1}
C4d+ WER ABOi vs. Mixed rejection	3.57×10^{-2}
C4d+ WER vs. ABOi AbMR	>0.999
C4d+ WER vs. AbMR	8.96×10^{-5}
C4d+ WER vs. TCMR	9.11×10^{-1}
C4d+ WER vs. Mixed rejection	1.46×10^{-2}
ABOi AbMR vs. AbMR	>0.999
ABOi AbMR vs. TCMR	>0.999
ABOi AbMR vs. Mixed rejection	>0.999
AbMR vs. TCMR	>0.999
AbMR vs. Mixed rejection	>0.999
TCMR vs. Mixed rejection	>0.999

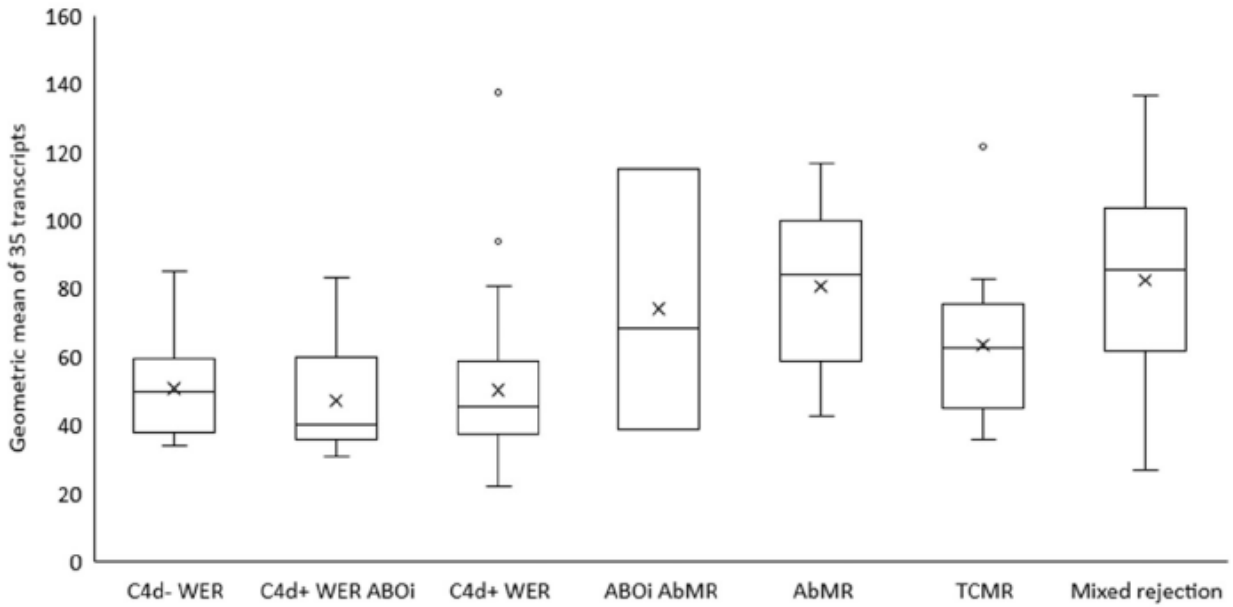
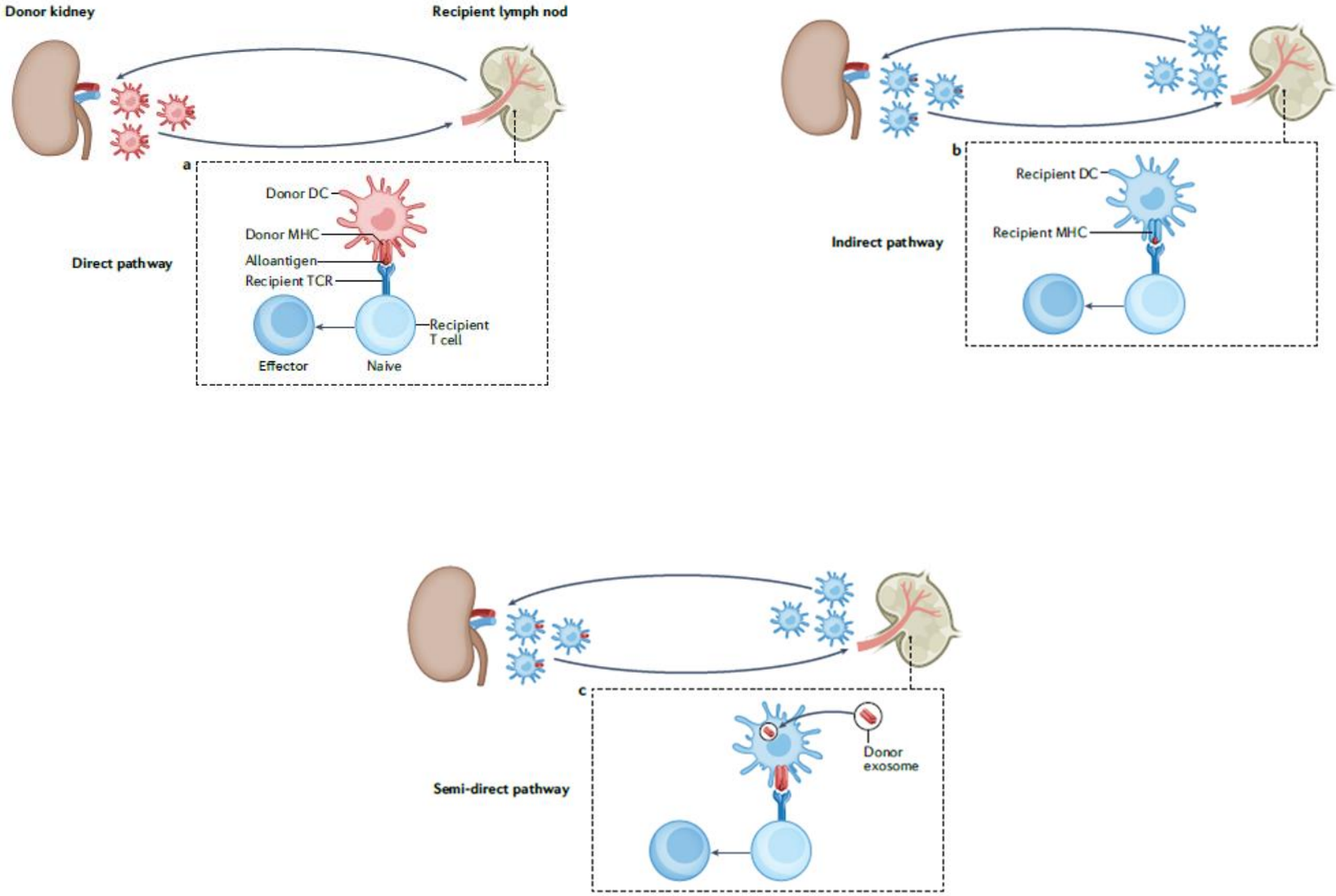


Figure 1. Antibody-mediated rejection (AbMR) gene transcript levels in different diagnostic categories. The geometric mean of the 35 AbMR-associated gene transcripts was calculated for each of the 125 samples. Median and first and third quartiles are plotted. Transcript geometric mean is elevated in AbMR samples compared with samples without evidence of rejection. ABOi, ABO-incompatible; C4d+ WER, C4d-positive biopsies without evidence of rejection; TCMR, T-cell–mediated rejection.

Bazı hastalarda, ABMR e progresyon olabilir, özellikle HLA-DSA pozitif ise.
ABMR-ilişkili transkriptker çalışılabilir

T hücrelerin rolü


Donor kidney
Recipient lymph nod
a
Donor DC
Donor MHC
Alloantigen
Recipient TCR
Recipient T cell
Effector
Naive
Direct pathway
b
Recipient DC
Recipient MHC
Indirect pathway
c
Donor exosome
Semi-direct pathway

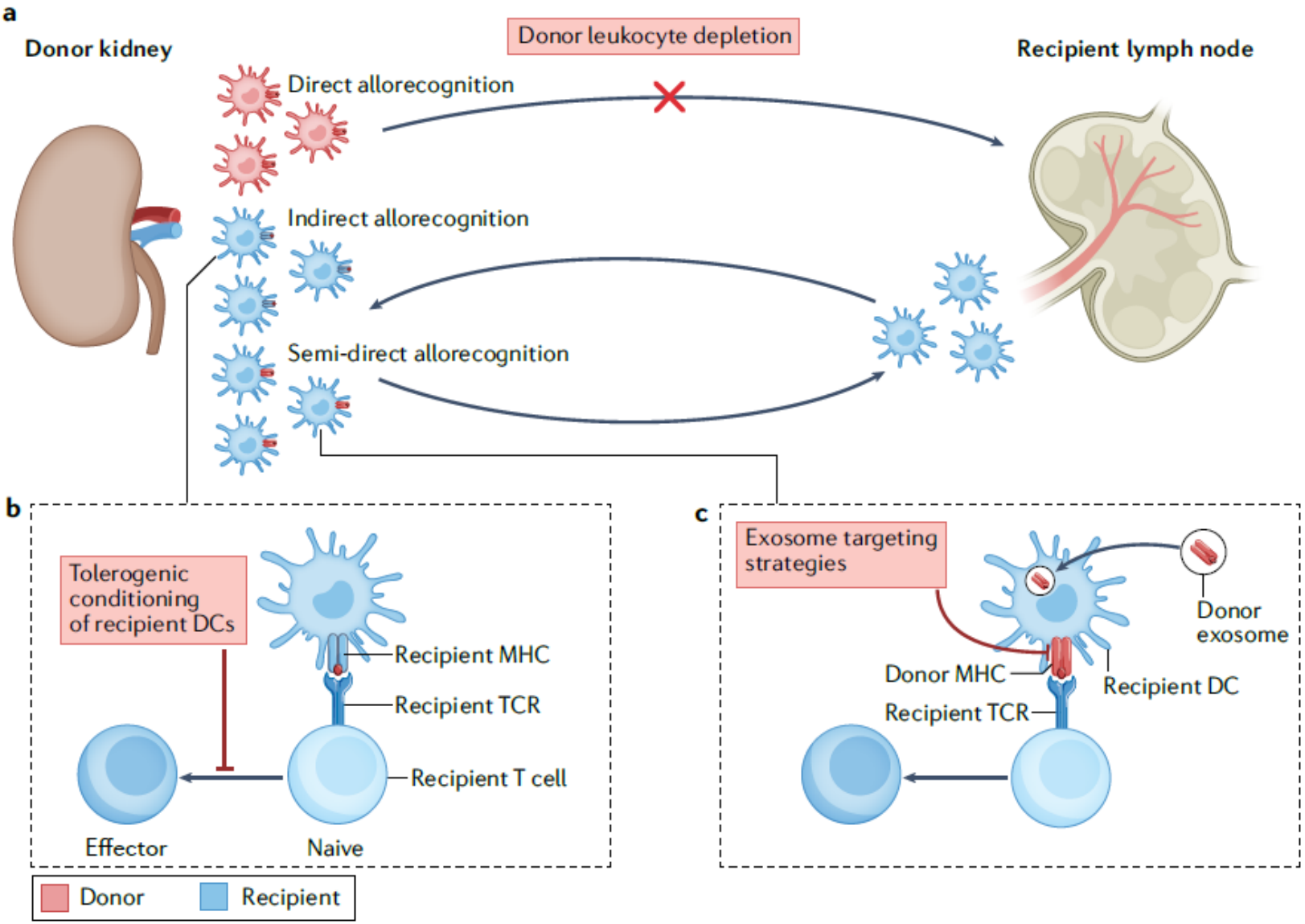


Fig. 2 | **Pathways of allorecognition and therapeutic strategies.** Different therapeutic approaches might target specific pathways of allorecognition. **a** | Strategies that target the donor dendritic cells (DCs) that drive direct allorecognition include pre-transplant donor leukocyte depletion. **b** | Strategies that target recipient DCs include pharmacological conditioning of recipient DCs in the presence of donor antigen to inhibit alloreactive T cell responses (that is, cell-based 'negative vaccination' strategies). **c** | Strategies that block the release or capture of donor exosomes might prevent semi-direct allorecognition. TCR, T cell receptor.

- Standard Tak / MMF ted rağmen:
- Endikasyon biyopsilerde %5-15,
- protokol biyopsilerde, >= Border-line == daha bile yüksek !!!

- The negative impact of T cell-mediated rejection on renal allograft survival in the modern era. Am J Transplant. 2022.

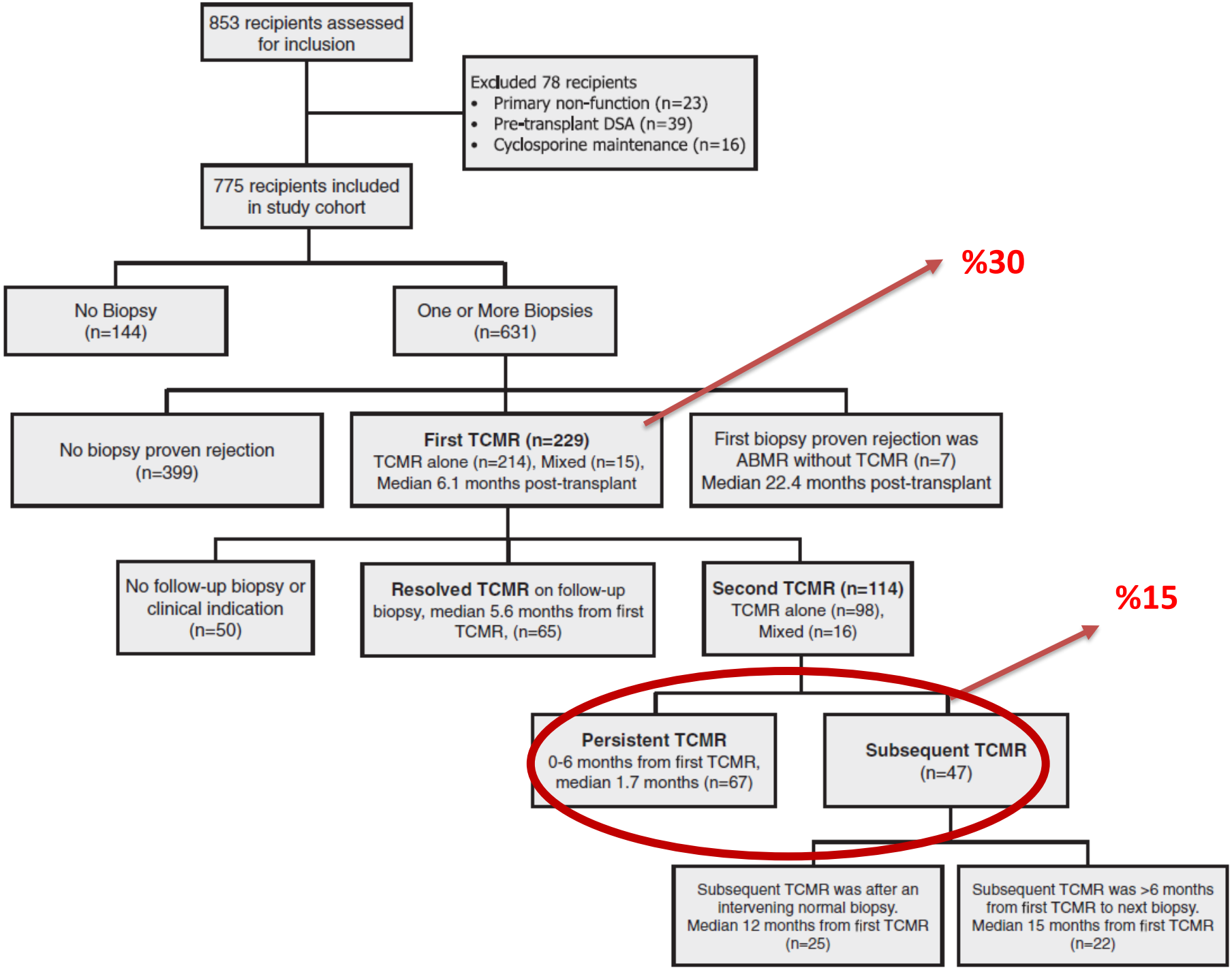

853 recipients assessed for inclusion
Excluded 78 recipients
• Primary non-function (n=23)
• Pre-transplant DSA (n=39)
• Cyclosporine maintenance (n=16)
775 recipients included in study cohort
No Biopsy (n=144)
One or More Biopsies (n=631)
%30
No biopsy proven rejection (n=399)
First TCMR (n=229)
TCMR alone (n=214), Mixed (n=15), Median 6.1 months post-transplant
First biopsy proven rejection was ABMR without TCMR (n=7)
Median 22.4 months post-transplant
No follow-up biopsy or clinical indication (n=50)
Resolved TCMR on follow-up biopsy, median 5.6 months from first TCMR, (n=65)
Second TCMR (n=114)
TCMR alone (n=98), Mixed (n=16)
%15
Persistent TCMR
0-6 months from first TCMR, median 1.7 months (n=67)
Subsequent TCMR (n=47)
Subsequent TCMR was after an intervening normal biopsy. Median 12 months from first TCMR (n=25)
Subsequent TCMR was >6 months from first TCMR to next biopsy. Median 15 months from first TCMR (n=22)

TABLE 3 Sequence of models exploring the effects of time-dependent covariates for graft loss

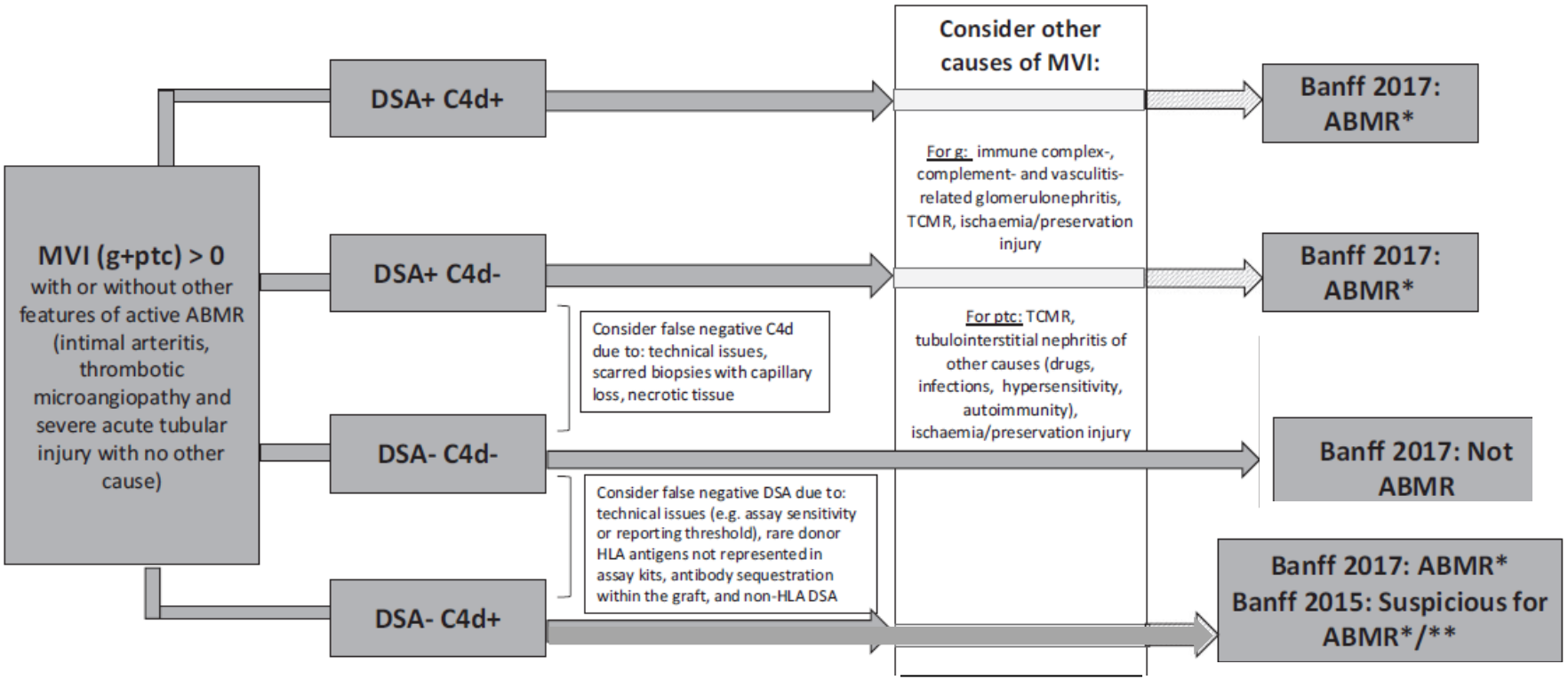
	Death-Censored Graft Loss $n = 74$ events			All-Cause Graft Loss $n = 187$ events		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Model 3						
DGF	2.19	(1.17, 4.07)	0.014	2.00	(1.38, 2.92)	<0.001
First TCMR	1.81	(0.91, 3.60)	0.09	1.18	(0.77, 1.80)	0.449
Second TCMR	2.98	(1.55, 5.75)	0.001	2.30	(1.39, 3.79)	0.001
ABMR	5.18	(2.73, 9.85)	<0.001	2.69	(1.59, 4.54)	<0.001
Sensitivity analysis by second TCMR definition						
DGF	2.19	(1.17, 4.08)	0.014	2.00	(1.37, 2.91)	<0.001
First TCMR	1.81	(0.91, 3.60)	0.09	1.18	(0.77, 1.80)	0.452
Second TCMR persistent	2.98	(1.45, 6.12)	0.003	2.38	(1.37, 4.15)	0.002
Second TCMR subsequent	2.99	(1.30, 6.87)	0.01	2.16	(1.12, 4.19)	0.022
ABMR	5.18	(2.72, 9.88)	<0.001	2.72	(1.60, 4.62)	<0.001

TCMR tanı, tedavi ve takibi önem taşımakta

SOT’da immun zararlanma

- Rejeksiyon
  - ABMR
    - HLA antikorları
    - Non-HLA antikorlar (alloantikorlar, otoantikorlar)
    - Antikordan bağımsız mekanizmalar
  - TCMR
- İskemi reperfüzyon hasarı
- Glomerulonefrit rekurrensi
- Rekurren TİN
- Enfeksiyonlar (CMV) == Pro-inflamatuvar ortam
- Beyin ölümü, hipertansif-yaşlı organ

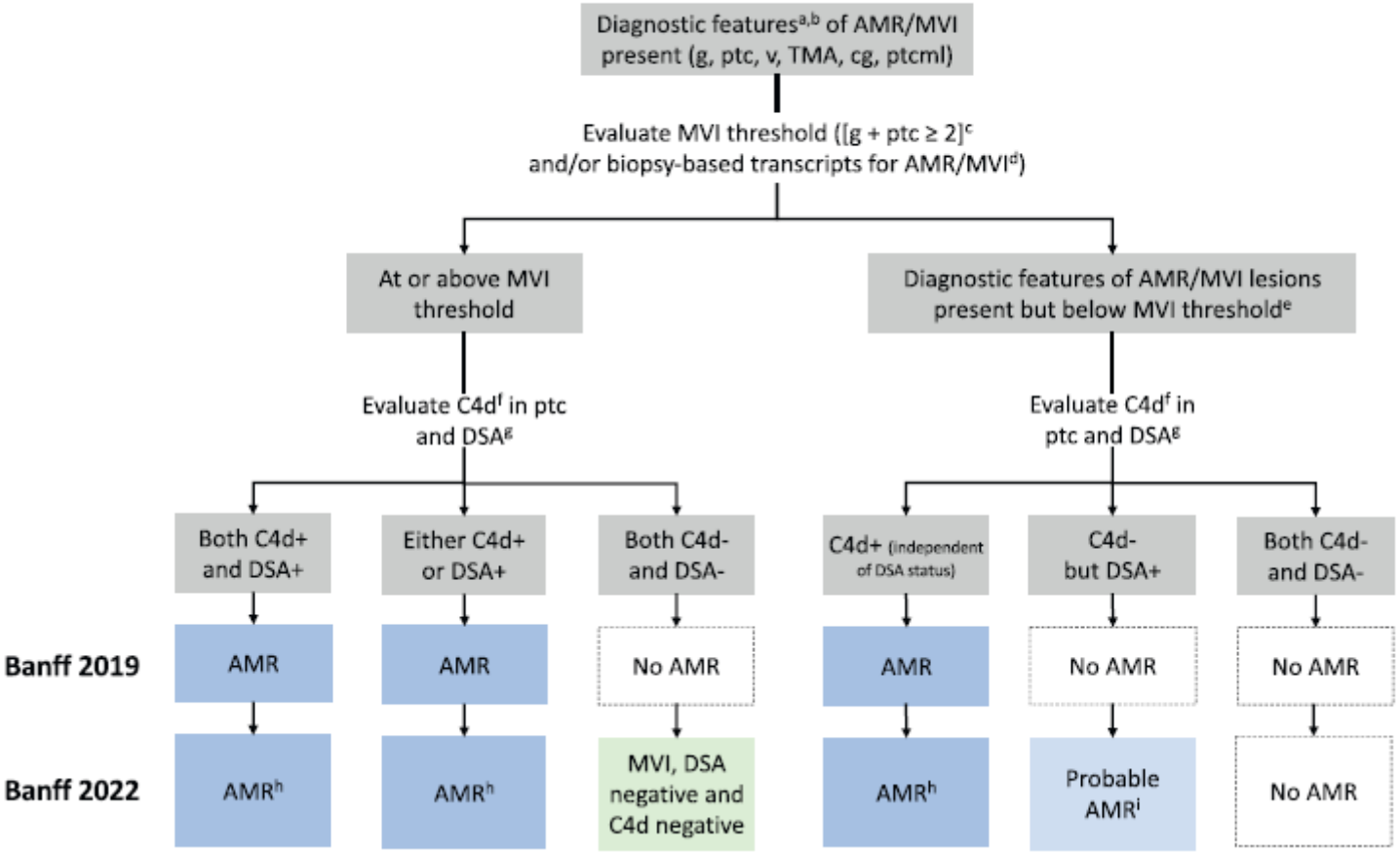
TEŞEKKÜR EDERİM.

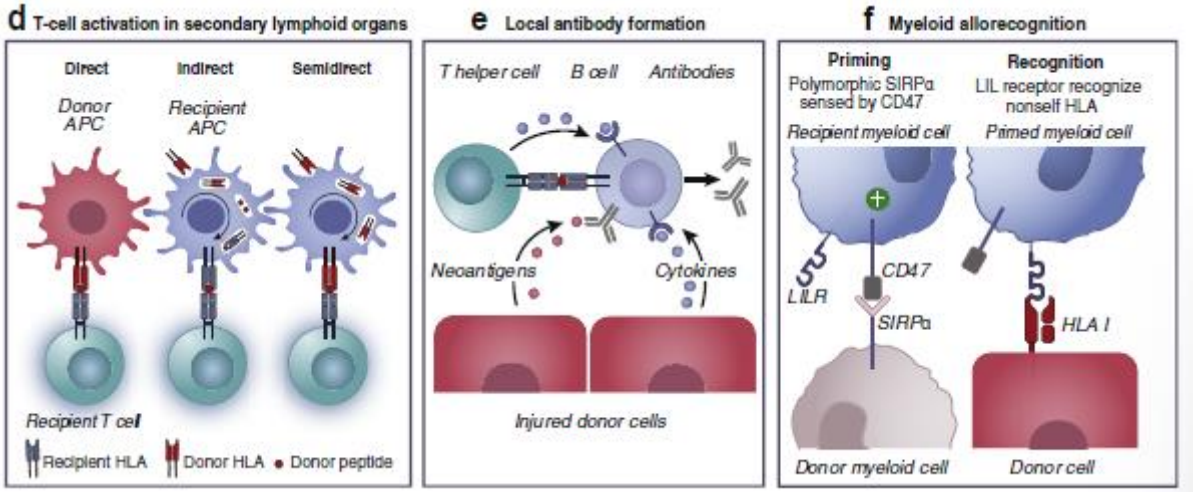


*When counting MVI towards a diagnosis of ABMR, apply all Banff 2017 rules: (i) in the absence of C4d, MVI ≥ 2 must be present, (ii) in the presence of glomerulonephritis, glomerulitis does not count towards MVI, and (iii) in the presence of borderline or TCMR, MVI needs to include an element of glomerulitis (g ≥1)

** Banff 2015 allowed some cases to be called "suspicious for ABMR"; this designation was removed in Banff 2017

American Journal of Transplantation 24 (2024) 338–349




d T-cell activation in secondary lymphoid organs
Direct
Indirect
Semidirect
Donor APC
Recipient APC
Recipient T cell
Recipient HLA
Donor HLA
Donor peptide
e Local antibody formation
T helper cell
B cell
Antibodies
Neoantigens
Cytokines
Injured donor cells
f Myeloid allorecognition
Priming
Polymorphic SIRPα sensed by CD47
Recognition
LIL receptor recognize nonself HLA
Recipient myeloid cell
Primed myeloid cell
LILR
CD47
SIRPα
HLA I
Donor myeloid cell
Donor cell

- Alıcı için: retrospektif olarak 14 KIR geni için genotipleme yapılmış (2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 2DS1,2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1) and 2 psodogen için (2DP1, 3DP1)
- Verici için:

Table S1 Definitions of epitopes, KIR haplotypes and missing self

Epitope	**Corresponding HLA antigens**
Bw4	A23, A24, A25, A32, B13, B27, B37, B38, B44, B47, B49, B51, B52, B53, B57, B58, B59, B63, B77
C1	Cw1, Cw3, Cw7, Cw8, Cw12, Cw14, Cw16
C2	Cw2, Cw4, Cw5, Cw6, Cw15, Cw17, Cw18
KIR haploptype	**Corresponding KIR genes**
BX haplotype	Presence of either KIR2DL2, KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, KIR3DS1
AA haplotype	Absence of BX haplotype-defining KIR genes
Missing self type	**Definition**
A3/11	Recipient A3 or A11 positive AND recipient KIR3DL2 positive AND donor A3 and A11 negative
Bw4	Recipient BW4 positive AND recipient KIR3DL1 positive AND donor Bw4 negative
C1/2DL2	Recipient C1 positive AND recipient KIR2DL2 positive AND donor C1 negative
C1/2DL3	Recipient C1 positive AND recipient KIR2DL3 positive AND donor C1 negative
C2	Recipient C2 positive AND recipient KIR2DL1 positive AND donor C2 negative

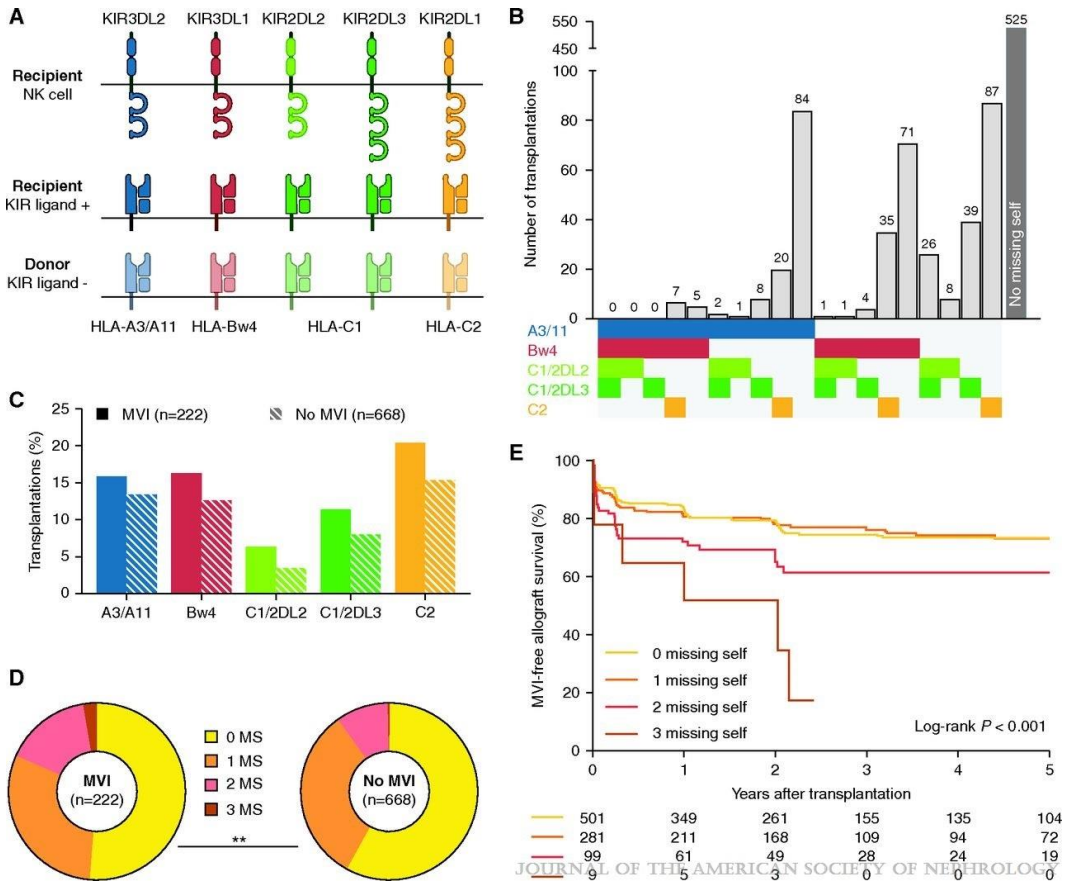
Missing Self-Induced Microvascular Rejection of Kidney Allografts: A Population-Based Study. J Am Soc Nephrol. 2021

- Missing self was defined as the absence of a corresponding donor HLA class I antigen in combination with a specific inhibitory KIR gene in an educated recipient (e.g., donor C2-/recipient 2DL1+C2+).

- “High” missing self was defined as the co-occurrence of two or more missing self types.

- Alıcı: Recipient NK cells were considered as educated for alıcıda bir inh KIR gen (2DL1, 2DL2, 2DL3, 3DL1, and 3DL2) sadece ona karşılık gelen Class I aj ile birlikte eksprese ediliyorsa alıcı NK hücreleri eğitimli.(i.e., 2DL1+/C2+, 2DL2+/C1+, 2DL3+/C1+, 3DL1+/Bw4+, 3DL2+/A3+, or 3DL2+/A11+).
- Bu durumda vericide, eğitimli alıcıcıdaki Class I aj yoksa, missing self.

Figure 1.



[Missing Self–Induced Microvascular Rejection of Kidney Allografts: A Population-Based Study]

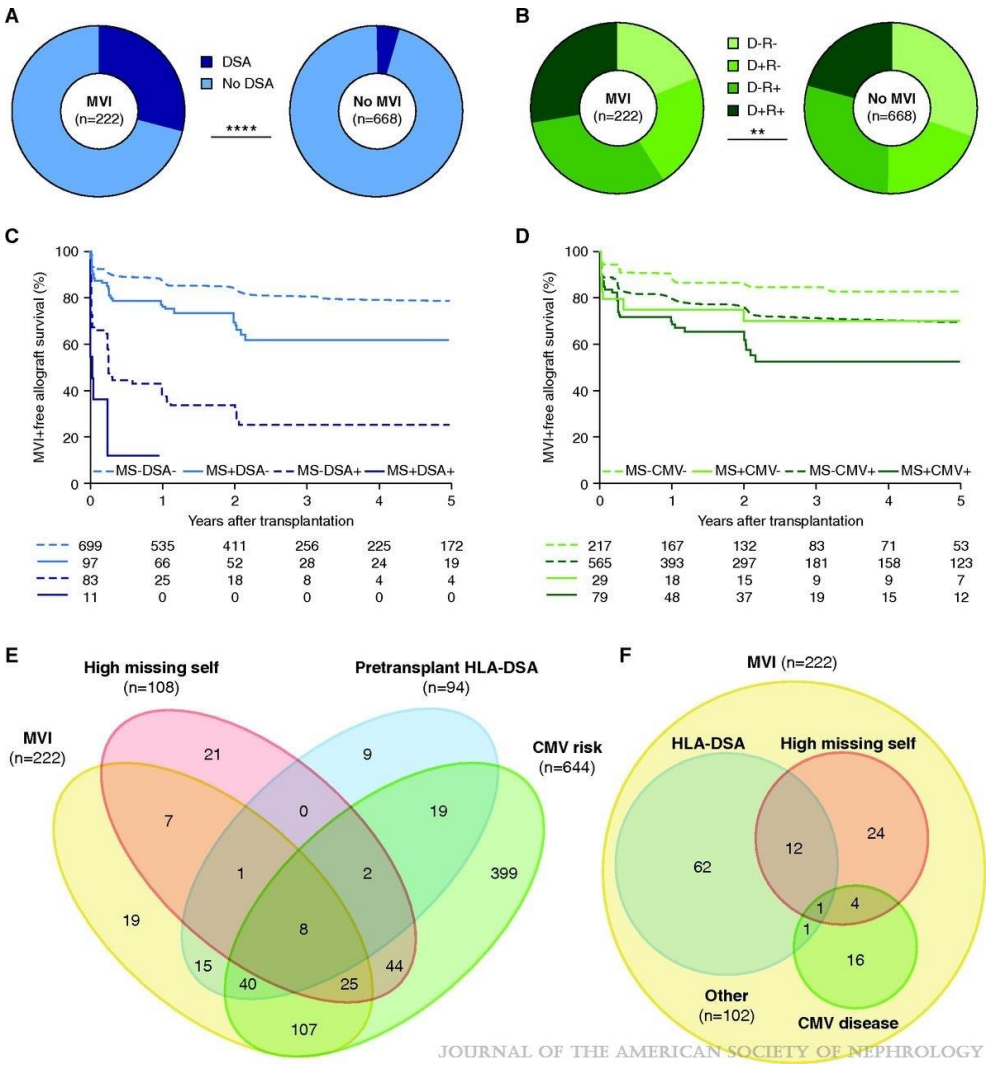
Callemeyn, Jasper; Senev, Aleksandar; Coemans, Maarten; Lerut, Evelyne; Sprangers, Ben; Kuypers, Dirk; Koenig, Alice; Thaunat, Olivier; Emonds, Marie-Paule; Naesens, Maarten

Journal of the American Society of Nephrology32(8):2070-2082, August 2021.

doi: 10.1681/ASN.2020111558

Missing self types cumulatively associate with risk of MVI. (A) Definition of missing self types. (B) Histogram of the possible combinations of missing self types within the study population (n=924). C1 and C2 missing self are mutually exclusive by definition. C1/2DL3 and C1/2DL2 indicate C1 missing self in presence of the KIR2DL2 and KIR2DL3 gene, respectively. (C) Prevalence of specific missing self types in transplantations with and without MVI during histologic follow-up after the baseline biopsy (n=890 transplantations, with 3476 posttransplant biopsies). (D) Number of missing self types in transplantations with and without MVI, chi-squared test for comparison. (E) Kaplan–Meier survival curves for incidence of MVI, censored for recipient death and allograft failure, with groups stratified according to the number of missing self types present within a donor-recipient pair. MS, missing self type. *P<0.05; **P<0.01.

Figure 2.



[Missing Self–Induced Microvascular Rejection of Kidney Allografts: A Population-Based Study]

Callemeyn, Jasper; Senev, Aleksandar; Coemans, Maarten; Lerut, Evelyne; Sprangers, Ben; Kuypers, Dirk; Koenig, Alice; Thaunat, Olivier; Emonds, Marie-Paule; Naesens, Maarten

Journal of the American Society of Nephrology32(8):2070-2082, August 2021.

doi: 10.1681/ASN.2020111558

Missing self independently associates with risk of MVI (n=890 transplantations with 3476 post-transplant biopsies). (A) Prevalence of pretransplant HLA-DSA in transplantations with and without MVI during histologic follow-up, chi-squared test for comparison. (B) Pretransplant donor/recipient CMV IgG status in transplantations with and without MVI during follow-up, chi-squared test for comparison. (C) Kaplan–Meier survival curves for incidence of MVI, censored for recipient death and allograft failure, stratified according to high versus low missing self (2–3 versus 0–1 types) and pretransplant HLA-DSA. (D) Survival curves for incidence of MVI, stratified according to high missing self and post-transplant risk for CMV disease (high risk: donor and/or recipient CMV seropositive; low risk: donor and recipient CMV seronegative). (E) Venn diagram depicting the independence of high missing self, pretransplant HLA-DSA and CMV disease risk as pretransplant predictors for MVI (occurring in n=222 transplantations), and the proportion of MVI incidence associated with each predictor. (F) Venn diagram depicting the prevalence of high missing self, prior symptomatic CMV disease and HLA-DSA, either current or previous, at the first moment of diagnosis in the 222 transplantations with MVI. MS, high missing self; +/−, CMV IgG positive/negative. **P<0.01; ****P<0.0001.