KRONİK AKTİF

T-HÜCRE ARACILI REJEKSİYON

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Kidney International (2022) 101, 678–691;
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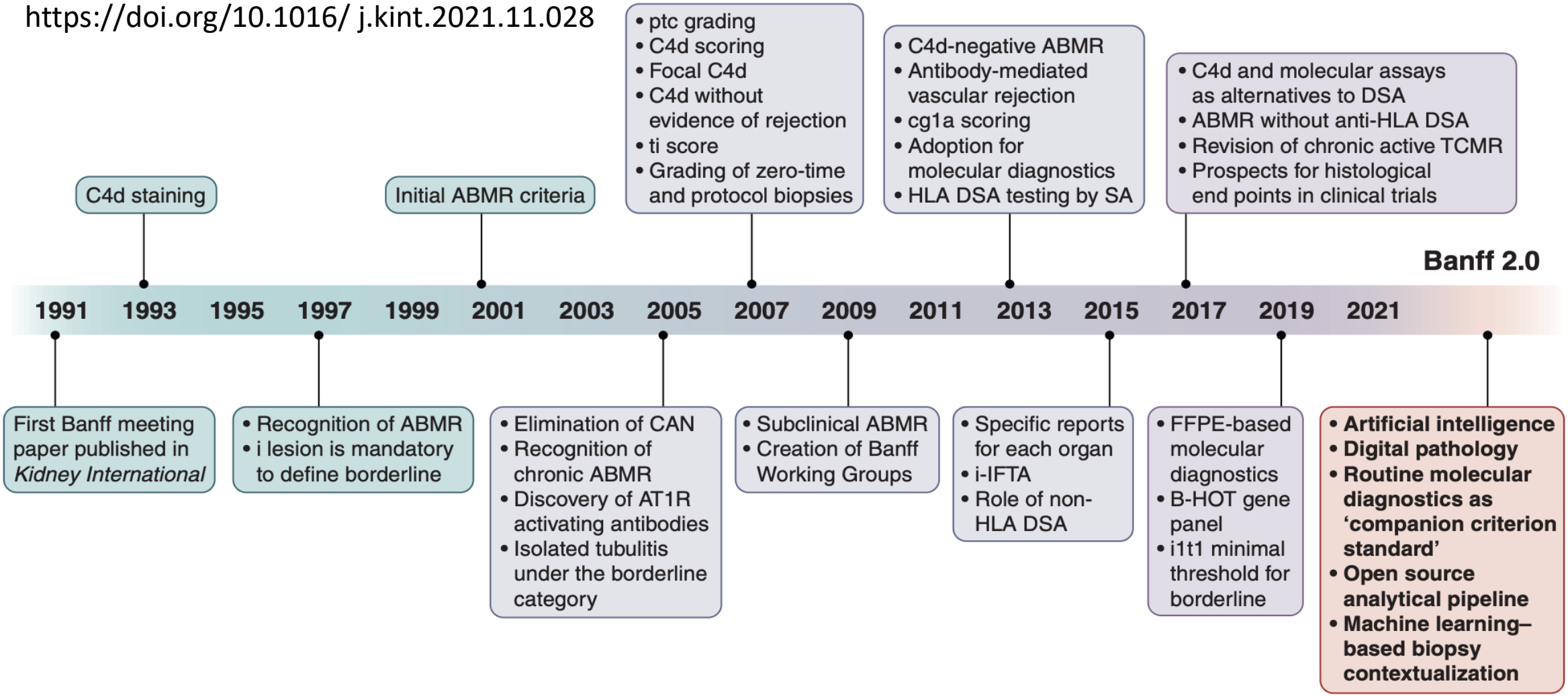

Figure 3 | Evolution of the Banff classification 1991 to 2021: important concepts and changes. ABMR, antibody-mediated rejection; AT1R, angiotensin type 1 receptor; B-HOT, Banff-Human Organ Transplant; CAN, chronic allograft nephropathy; cg, transplant glomerulopathy; DSA, donor-specific antibody; FFPE, formalin-fixed paraffin-embedded; HLA, human leukocyte antigen; i, interstitial inflammation; i-IFTA, inflammation within areas of interstitial fibrosis and tubular atrophy; ptc, peritubular capillaritis; SA, single antigen; t, tubulitis; TCMR, T cell–mediated rejection; ti, total cortical inflammation.

The Banff 97 working classification of renal allograft pathology

Lorraine C. Racusen, Kim Solez, Robert B. Colvin, Stephen M. Bonsib, Maria C. Castro, Tito Cavallo, Byron P. Croker, A. Jake Demetris, Cynthia B. Drachenberg, Agnes B. Fogo, Peter Furness, Lillian W. Gaber, Ian W. Gibson, Dennis Glotz, Julio C. Goldberg, Joseph Grande, Philip F. Halloran, H. E. Hansen, Barry Hartley, Pekka J. Hayry, Claire M. Hill, Ernesto O. Hoffman, Lawrence G. Hunsicker, Anne S. Lindblad, Niels Marcussen, Michael J. Mihatsch, Tibor Nadasdy, Peter Nickerson, T. Steen Olsen, John C. Papadimitriou, Parmjeet S. Randhawa, David C. Rayner, Ian Roberts, Stephen Rose, David Rush, Luis Salinas-Madrigal, Daniel R. Salomon, Stale Sund, Eero Taskinen, Kiril Trpkov, and Yutaka Yamaguchi

T-hücre aracılı rejeksiyon olarak adlandırmak için skarsız korteksin en az %25'inde interstisyel infiltrasyon ve en azından orta derecede tübülit

4. Acute/active rejection

Type (Grade)	Histopathological findings
IA	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross section or group of 10 tubular cells)
IB	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross section or group of 10 tubular cells)
IIA	Cases with mild to moderate intimal arteritis (v1)
IIB	Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
III	Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (v3 with accompanying lymphoctic inflammation)

İnterstisyel inflamasyonun (i); sklerotik olmayan kortikal alanlarda
Tubulitin (t) ise ve hafif atrofik tübüllerde değerlendirilmesi

Orta ve ağır atrofik tübüllerin skorlanmaya alınmaması önerilmişti.

Sklerotik kortikal parankimdeki interstisyel inflamasyon (i-IFTA)

Post –transplant böbrek ve nativ böbrekte gözlenebilen,özgül olmayan histolojik bir bulgu

- BK virus enfeksiyonu
- Piyelonefrit
- Akut Antikor Aracılı Rejeksiyon
- Rekürren glomerülonefrit
- Obstruktif sorunlar

i-IFTA ‘nin İnterstisyel inflamasyon (i-) skorunun dışında tutulması önerildi (Banff 1997)

American Journal of Transplantation 2009; 9: 1859–1867
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02727.x

Scoring Total Inflammation Is Superior to the Current Banff Inflammation Score in Predicting Outcome and the Degree of Molecular Disturbance in Renal Allografts

2004-2006 yılları arasında 129 böbrek biyopsisi retrospektif olarak değerlendirildi.

Biyopsi materyallerinde mikroarray bazlı testler (Cell-associated transcript set scores (QCAT scores) referens noktası olarak alınarak 2007 Banff (i) skoru ve toplam (i) skorunun prognoz üzerine etkisi karşılaştırıldı.

American Journal of Transplantation 2009; 9: 1859–1867
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Scoring Total Inflammation Is Superior to the Current Banff Inflammation Score in Predicting Outcome and the Degree of Molecular Disturbance in Renal Allografts

Banff t-skoru O olan (sadece atrofik olmayan tübüller) dikkate alınarak, biyopsiler QCAT skoru yüksek olanlar ve düşük olanlar olarak iki guruba ayrıldığında, Yüksek QCAT skoru olan biyopsilerin toplam i skorlarının daha yüksek olduğu saptandı.

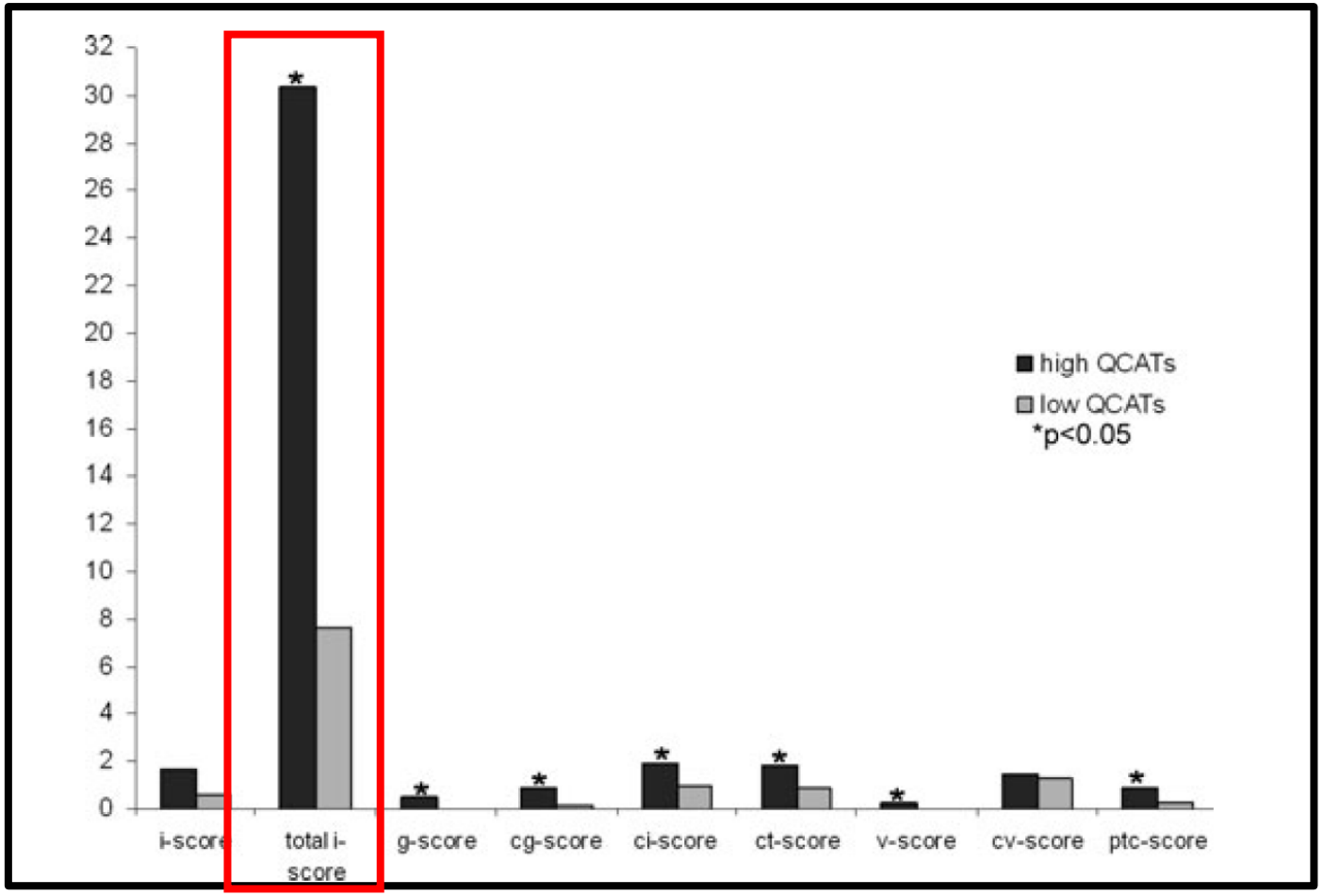

Figure 3: Comparing Banff to cases with high versus low expression of CTL-associated transcripts (QCATs). Biopsies with assigned Banff t-scores of 0 (i.e. only nonatrophic tubules were taken into account) were separated into those with high and low QCAT scores according to the threshold defined in Figure 1. Those biopsies with high QCAT scores show significantly (all $p > 0.05$, Mann–Whitney U-test) higher mean lesion scores for total i, ci, ct, v, g, cg and ptc.

American Journal of Transplantation 2009; 9: 1859–1867
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doi: 10.1111/j.1600-6143.2009.02727.x

Scoring Total Inflammation Is Superior to the Current Banff Inflammation Score in Predicting Outcome and the Degree of Molecular Disturbance in Renal Allografts

Total kortikal inflamasyon skoru (Ti skoru) ile mikroarray testleri arasında güçlü bir ilişki saptandı.

Total kortikal inflamasyon skoru (**Ti skoru)** graft prognozunu belirlemede i skoruna göre daha belirleyicidir.

Published in final edited form as:
Am J Transplant. 2010 September ; 10(9): 2066–2073. doi:10.1111/j.1600-6143.2010.03240.x.

Inflammation in Areas of Tubular Atrophy in Kidney Allograft Biopsies: A Potent Predictor of Allograft Failure

Roslyn B. Mannon[1], Arthur J. Matas[2], Joseph Grande[3], Robert Leduc[4], John Connett[4], Bertram Kasiske[5], J. Michael Cecka[6], Robert S. Gaston[1], Fernando Cosio[7], Sita Gourishankar[8], Phil Halloran[8], Lawrence Hunsicker[9], and David Rush[10] for the DeKAF Investigators

Sklerotik kortikal alanlarda inflamasyon , tübülit bulguları ve tübüler atrofi arasında ciddi korelasyon mevcut ($p<0.0001$).

(1)i-IFTA ve atrofik alanlarıdaki tübülit (t-IFTA) graft sağkalım ile ilişkilidir.
(2) i-IFTA'nın şiddetinin artması, giderek kötüleşen graft sağkalımıyla ilişkili bulundu.
(3) i-IFTA, biyopsi sırasındaki serum kreatinin, interstisyel fibroz (ci), tübüler atrofi (ct), C4d boyama, ve DSA varlığı göz önüne alınarak değerlendirildikten sonra bile graft yaşam süresi ile ilişkili bulundu .

Published in final edited form as:
Am J Transplant. 2010 September ; 10(9): 2066–2073. doi:10.1111/j.1600-6143.2010.03240.x.

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İnterstisyel Fibrozis ve Tübüler Atrofi alanlarındaki inflamasyon skoru **(i-IFTA)** graft kaybının bağımsız ve en önemli belirleyicisidir.

Böbrek allograft biyopsilerinde **i-IFTA'nın** dahil edilmesi daha iyi prognostik bilgi sağlayabilir

Bu inflamatuar hücrelerin karakterizasyonu ve uygun tedavi, geç dönemde iyileşme sağlayabilir.

Meeting Report

doi: 10.1111/ajt.14107

The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology

Bu nedenle, 2015 Banff toplantısında i-IFTA'nın yarı niceliksel bir ölçekte (0-3)) derecelendirilmesine yönelik kriterler kabul edildi, ancak i-IFTA 'nın TCMR tanısında dikkate alınması sonucuna varılmadı.

Category 4: TCMR

Acute TCMR Grade	IA. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of moderate tubulitis (t2)
	IB. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of severe tubulitis (t3)
	IIA. Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and tubulitis
	IIB. Severe intimal arteritis comprising >25% of the luminal area (v2) with or without interstitial inflammation and tubulitis
	III. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
Chronic active TCMR	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima); note that such lesions may represent chronic active ABMR as well as TCMR; the latter may also be manifest in the tubulointerstitial compartment

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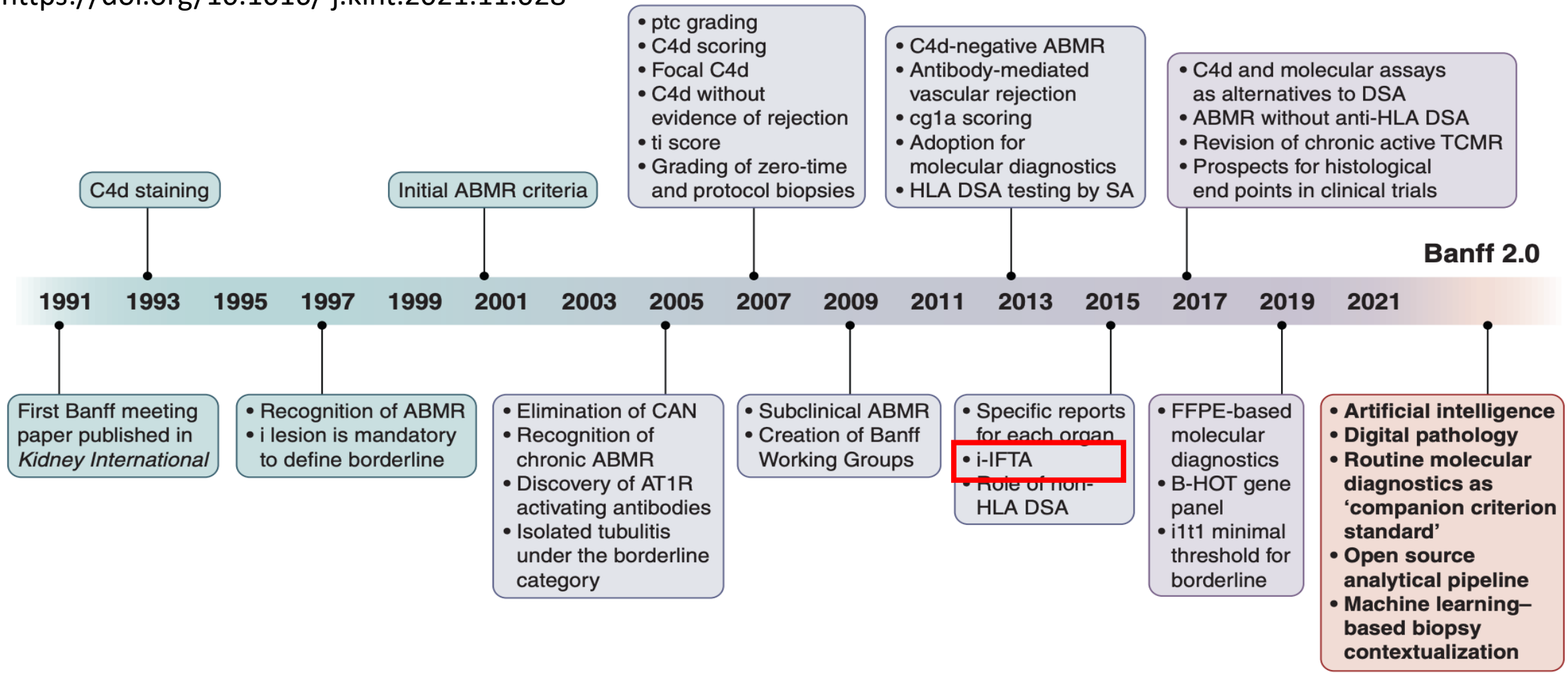

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Received: 9 July 2017 | Revised: 22 October 2017 | Accepted: 22 October 2017
DOI: 10.1111/ajt.14565

ORIGINAL ARTICLE

AJT

T cell–mediated rejection is a major determinant of inflammation in scarred areas in kidney allografts

Carmen Lefaucheur[1,2] | Clément Gosset[3] | Marion Rabant[4] | Denis Viglietti[1,2] | Jérôme Verine[3] | Olivier Aubert[2] | Kevin Louis[2] | Denis Glotz[1,2] | Christophe Legendre[2,5] | Jean-Paul Duong Van Huyen[2,4] | Alexandre Loupy[2,5]

Amaç: Böbrek alıcılarında klinikohistolojik fenotipleri ve i -IF/TA'yı etkileyen faktörleri belirlemek.

- 1539 böbrek alıcısı, 1. yıl allograft protokol biyopsilerinde
- 2260 hastada ilk 1 yılda yapılan endikasyon biyopsisi
- i-IF/TA ve atrofik tübüllerde tübülit (t-IF/TA) değerlendirildi

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Transplantasyondan 1 yıl sonra ;
*946 hastada (%61,5) interstisyel fibrozis/tübüler atrofi (IF/TA Banff derecesi > 0)
*394'ünde **(%41,6) i-IF/TA**

i-IF/TA

- t-IF/TA (P < .001)
- interstisyel inflamasyon (P < 0,001)
- tübülit (p< 0,001)
- toplam inflamasyon (P < 0,001)
- tübüler atrofi(P = 0,02)
- interstisyel fibrozis (P < 0,001)
- peritübüler kapillarit (P < 0,001),

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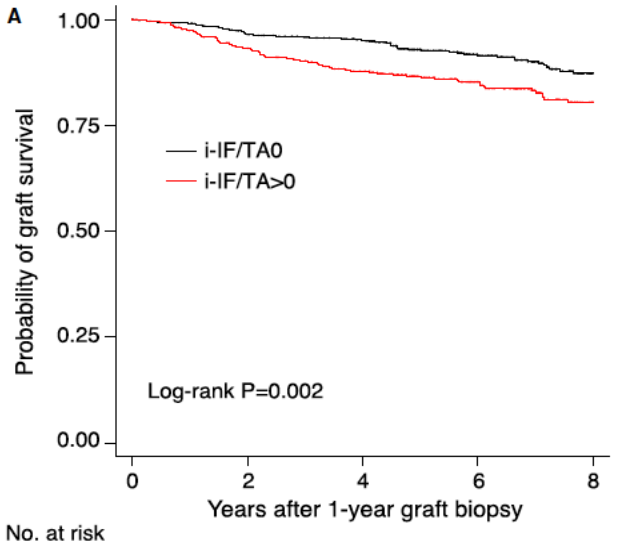
i-IF/TA'nin Bağımsız Belirleyicileri:

- Geçirilmiş T hücre aracılı rejeksiyon(TCMR)
- BK virüsü nefropatisi
- Steroid tedavisi
- Kalsinörin inhibitör tedavisi
- MMF tedavisi
- HLA mismatch

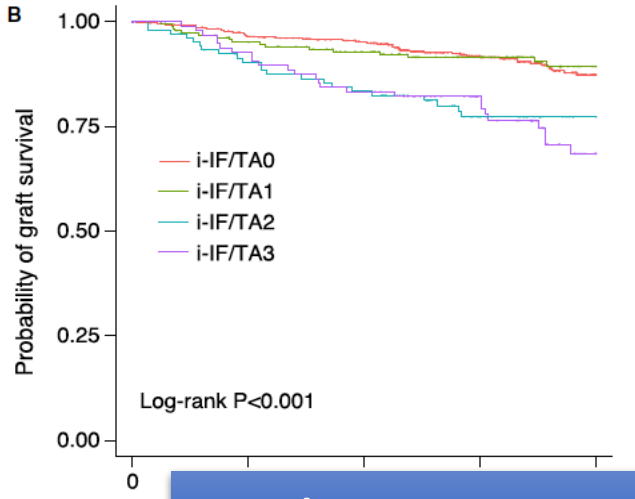
TABLE 4 Determinants of i-IF/TA at 1 year after transplantation: multivariable model

	Number of patients	Number of events	OR	95% CI	*P*
First-y T cell–mediated rejection					
No	798	306	1	-	
Yes	142	85	2.73	[1.87-3.97]	<.001
First-y BK virus–associated nephropathy					
No	914	373	1	-	
Yes	26	18	3.25	[1.38-7.67]	.007
Six-mo steroid therapy					
No	103	50	1	-	
Yes	837	341	0.64	[0.42-0.98]	.039
Six-mo calcineurin inhibitor therapy					
No	51	29	1	-	
Yes	889	362	0.47	[0.26-0.84]	.011
Six-mo IMPDHi therapy					
No	50	29	1	-	
Yes	890	362	0.46	[0.25-0.84]	.011
HLA-B mismatch (per 1-unit increment)	940	391	1.29	[1.06-1.59]	.012
HLA-DR mismatch (per 1-unit increment)	940	391	1.23	[1.01-1.50]	.044



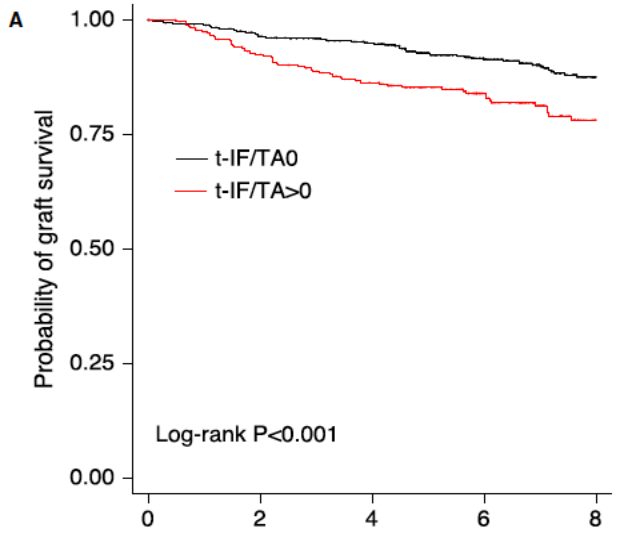
No. at risk

i-IF/TA0	552	511	470	295	133
i-IF/TA>0	394	353	313	223	115



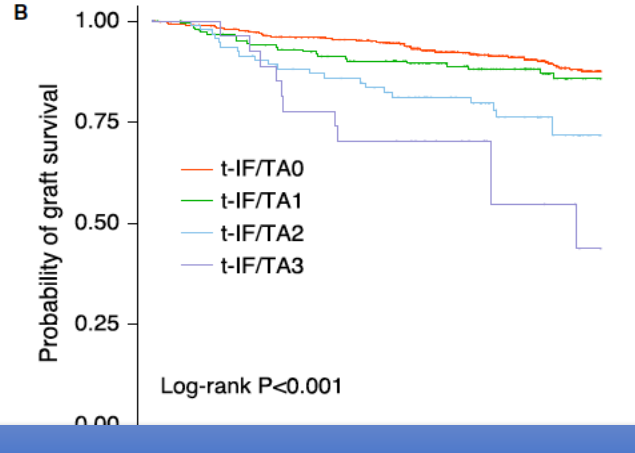
No. at risk

i-IF/TA0	552				
i-IF/TA1	189	172	151	114	61
i-IF/TA2	105	92	83	52	32
i-IF/TA3	100	89	79	57	22



No. at risk

t-IF/TA0	629	584	537	352	174
t-IF/TA>0	317	280	246	166	74



t-IF/TA0	629	584	537	352	174
t-IF/TA1	193	173	156	109	51
t-IF/TA2	97	83	71	48	20
t-IF/TA3	27	24	19	9	3

FIGURE 4 Kidney allograft survival according to the presence

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8 yıllık graft yaşam süresi

*i-IF/TA (+) hastalarda 70.8%

*i-IF/TA (-) hastalarda 83.5%, (P = 0.038)

i-IF/TA kronik aktif TCMR ‘nın önemli bir bulgusu olabilir.

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DOI: 10.1111/ajt.14609

ORIGINAL ARTICLE

AJT

The causes, significance and consequences of inflammatory fibrosis in kidney transplantation: The Banff i-IFTA lesion

Brian J. Nankivell[1] | Meena Shingde[2] | Karen L. Keung[1] | Caroline L-S. Fung[2] | Richard J. Borrows[1] | Philip J. O'Connell[1] | Jeremy R. Chapman[1]

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DOI: 10.1111/ajt.15862

ORIGINAL ARTICLE

AJT

Inflammation in areas of fibrosis: The DeKAF prospective cohort

Arthur J. Matas[1] | Erika S. Helgeson[2] | Robert Gaston[3] | Fernando Cosio[4] | Roslyn Mannon[3] | Bertram L. Kasiske[5] | Lawrence Hunsicker[6] | Sita Gourishankar[7] | David Rush[8] | J Michael Cecka[9] | John Connett[2] | Joseph P. Grande[4]

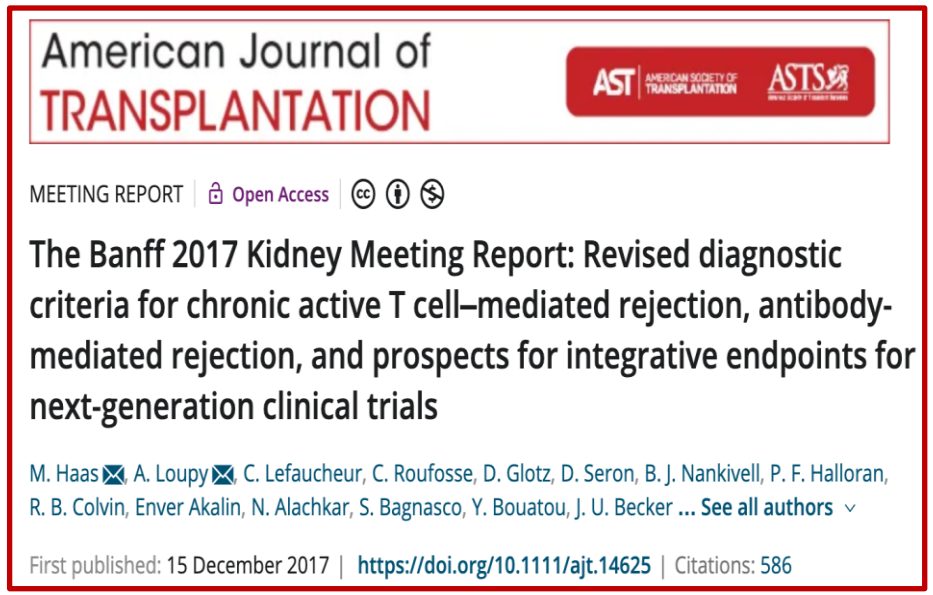
- i-IFTA daha önceki akut TCMR epizodlarıyla ilişkilidir.
- Yetersiz immünsüpresyonun bir belirtisi olabilir .
- Eş zamanlı tübülit gözlendiğinde i-IFTA'nın greft sağkalımı üzerinde daha olumsuz etkisi vardır.
- i-IF/TA kronik aktif TCMR 'nun önemli bir bulgusu olabilir.

ORIGIN

Mole
with

Philip F.
Katelynn S. Madill-Thomsen[2] | Martina Mackova[1] | Konrad S. Famulski[1]

Kronik Aktif T-Hücre Aracılı Rejeksiyon (CA-TCMR)



American Journal of TRANSPLANTATION

MEETING REPORT | Open Access

The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell–mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials

M. Haas, A. Loupy, C. Lefaucheur, C. Roufosse, D. Glotz, D. Seron, B. J. Nankivell, P. F. Halloran, R. B. Colvin, Enver Akalin, N. Alachkar, S. Bagnasco, Y. Bouatou, J. U. Becker ... See all authors

First published: 15 December 2017 | https://doi.org/10.1111/ajt.14625 | Citations: 586

Sklerotik kortikal parankimde (IFTA) **inflamasyon** (**i-IFTA)** ve tubulit (2017 Banff*)

IFTA **:** Areas of İntertisyel fibrozis ve tubular atrofi

i-IFTA: *i**nflammation** in areas of interstitial fibrosis and tubular atrophy*

*Haas M, Am J Transplant. 2018

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https://doi.org/10.1016/ j.kint.2021.11.028

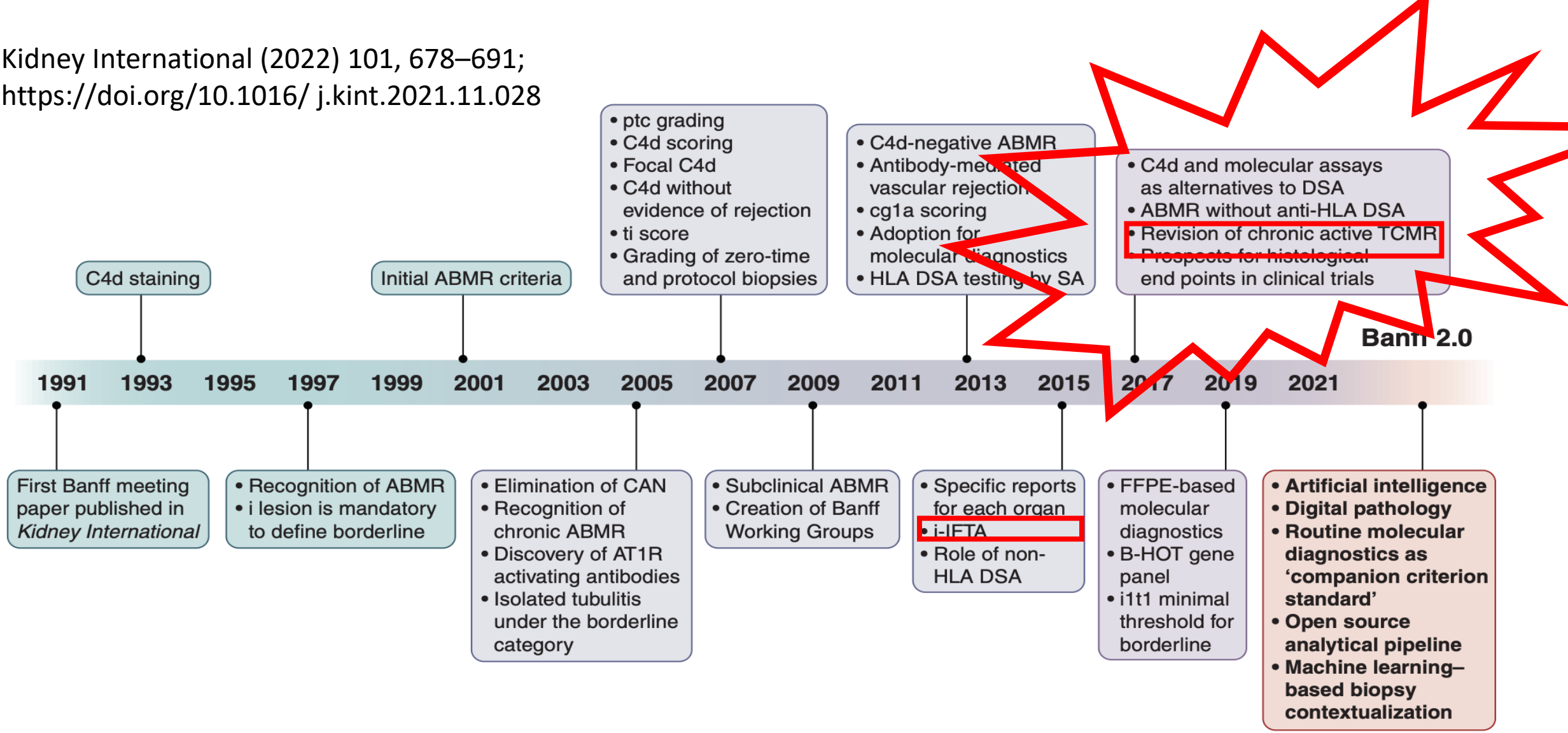

Figure 3 | Evolution of the Banff classification 1991 to 2021: important concepts and changes. ABMR, antibody-mediated rejection; AT1R, angiotensin type 1 receptor; B-HOT, Banff-Human Organ Transplant; CAN, chronic allograft nephropathy; cg, transplant glomerulopathy; DSA, donor-specific antibody; FFPE, formalin-fixed paraffin-embedded; HLA, human leukocyte antigen; i, interstitial inflammation; i-IFTA, inflammation within areas of interstitial fibrosis and tubular atrophy; ptc, peritubular capillaritis; SA, single antigen; t, tubulitis; TCMR, T cell–mediated rejection; ti, total cortical inflammation.

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First published: 15 December 2017 | https://doi.org/10.1111/ajt.14625 | Citations: 586

Akut olandan farkı sklerotik parankimde İnflamasyonun değerlendirilmesi

Total kortikal alandaki interstisyel inflamasyon (Ti skor) skoru)

Sklerotik kortikal alandaki interstisyel inflamasyon (i-IFTA skoru)

i-IFTA, O Kortikal alanın <5%
i-IFTA1, Kortikal alanın %6 – 25'i
i-IFTA2, Kortikal alanın 26%-50'si
i-IFTA3, Kortikal alanın >50%

TABLE 5 (Continued)

Chronic Active TCMR	
Grade IA	Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with moderate tubulitis (t2) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out
Grade IB	Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with severe tubulitis (t3) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out
Grade II[1]	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)

Received: 3 January 2020 | Revised: 24 February 2020 | Accepted: 10 March 2020

DOI: 10.1111/ajt.15898

MEETING REPORT

AJT

The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell– and antibody-mediated rejection

Alexandre Loupy[1*] | Mark Haas[2*] | Candice Roufosse[3] | Maarten Naesens[4,5] |

t-IFTA: interstisyel fibrozis alanlarındaki tübülit

*Tek başına (t) skorunun graft prognozunda etkisi olmadığı kanıtlandığı için,
t-IFTA; inflamasyon olan tübüllerin lokasyonunu ayırd edebilmek için eklendi.

*Sadece **Skarlı korteksteki** tübüllerdeki inflamasyonu gösteriyor.

.

Chronic active TCMR[e]

Grade IA: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND > 25% of total cortical parenchyma (ti2 or ti3) with moderate tubulitis (t2 or **t-IFTA2**) involving 1 or more tubules, not including severely atrophic tubules[d]; other known causes of i-IFTA should be ruled out

Grade IB: Interstitial inflammation involving >25% of sclerotic cortical parenchyma (i-IFTA2 or i-IFTA3) AND > 25% of total cortical parenchyma (ti2 or ti3) with severe tubulitis (t3 or **t-IFTA3**) involving 1 or more tubules, not including severely atrophic tubules[d]; other known causes of i-IFTA should be ruled out

Grade II: Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima). This may also be a manifestation of chronic active or chronic ABMR or mixed ABMR/TCMR

**Loupy A, Am J Transplant. 2020

Kronik Aktif T-Hücre Aracılı Rejeksiyon (CA-TCMR)

- Kronik aktif T Hücre Aracılı Rejeksiyon tanısı ve derecelendirilmesinde;
  - *Total kortikal parankim interstisyel inflamasyon skoru : **Ti**
  - *Sklerotik kortikal alanın interstisyel inflamasyon skoru: **i-IFTA**
  - *İnterstisyel fibrozis alanlarındaki tübülit **(t-IFTA)**
  - *Fibrointimal arteriyel kalınlaşma **(v)**
  - *Vasküler fibröz intima kalınlaşma **(cv)**

- Kronik allograft arteriopati (Grade II CA-TCMR), eşzamanlı bir kronik AAR yada mix AAR/CATCMR bulgusu olabilir.

- Bu durumda eş zamanlı iki farklı tip rejeksiyondan söz edilebilir. Fakat bulgular Kronik aktif T CMR kriterlerini dolduruyorsa, yalnızca kronik aktif T-Hücre aracılı rejeksiyon tanısı konulmalıdır

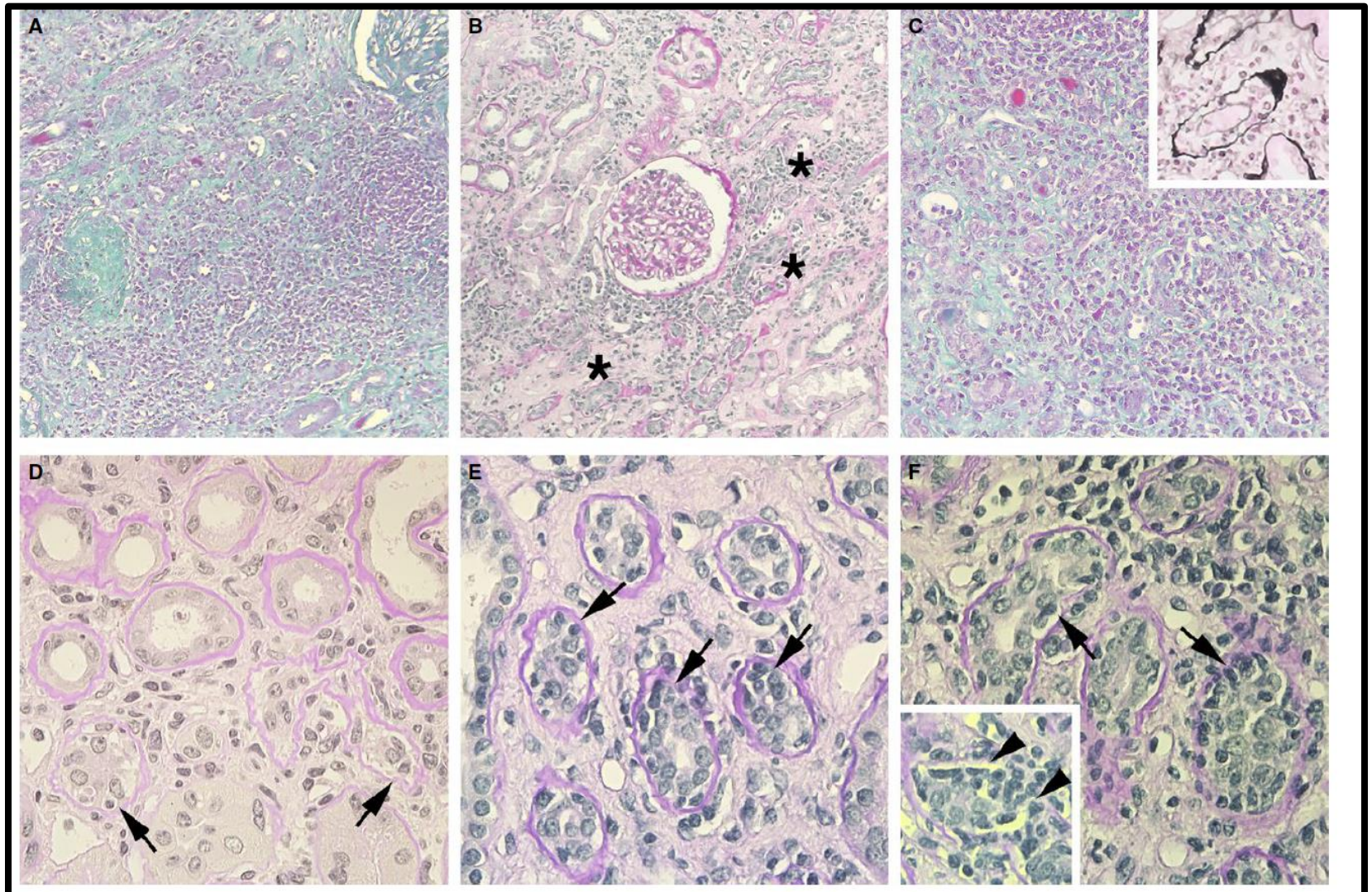


FIGURE 2 Pathological features of i-IF/TA and t-IF/TA. (A-C) Morphological features of i-IFTA defined by the presence of interstitial inflammation in area of interstitial fibrosis. In i-IFTA, presence of foci of tubulitis in atrophic tubules (asterisks and insert). A and C (trichrome stain, original magnification ×100 and ×150, respectively); B (periodic acid–Schiff stain, original magnification ×100); and C (insert, silver stain). (D-F) t-IFTA lesions. (D) t-IFTA1 characterized by foci with 1 to 4 leukocytes per atrophic tubular cross-section (arrows, original magnification ×400). (E) t-IF/TA2 characterized by foci with 5 to 10 leukocytes per atrophic tubular cross-section (arrows, original magnification ×400). (F) t-IF/TA3, characterized by foci with >10 leukocytes per atrophic tubular cross-section (arrows, original magnification ×400), or tubular basal membrane rupture in atrophic tubules (between arrowheads, insert). i-IF/TA, inflammation in fibrosis areas; t-IF/TA, tubulitis in atrophic tubules

A ve B grade IA: orta tubulit (t2)

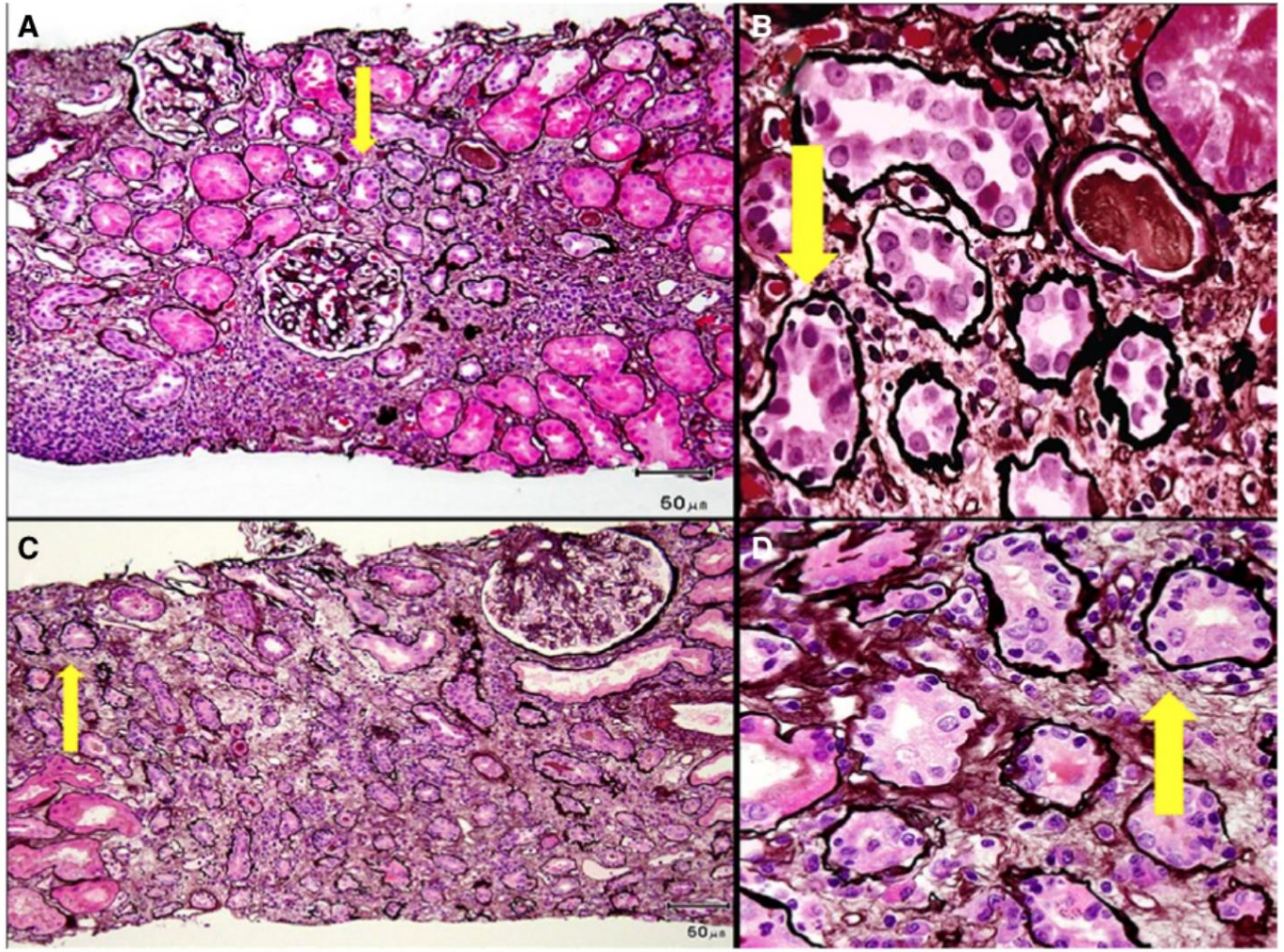
Her durumda ciddi i-IFTA mevcut

inflamatuar hücreler,

interstisyel ödem,

interstisyel fibrosis,

tubuler atrofi



Lenfositler yoğun

Lenfositler ve plazma hc yoğun

C ve D grade IB: ağır tubulit (t3)

Patogenez

- Patogenez net olarak belli değil
- Düşük immunsupresyon ile ilişkiden bahsediliyor → CA-TCMR
- Siklosporin yerine **takrolimus** kullanımı i-FTA oranını azaltmış
- Geçirilmiş Akut T-hücre aracılı rejeksiyon ?
- Antikor Aracılı Rejeksiyon ?
- Efektör Bellek T hücrelerinin rolü ?
- HLA uyumsuzluğu ? DSA varlığı ?
- AT1R-Ab ?

Nephrol Dial Transplant (2016) 31: 2131–2142
doi: 10.1093/ndt/gfw245
Advance Access publication 1 July 2016

ndt
Nephrology Dialysis Transplantation

Original Articles

Potential role of effector memory T cells in chronic T cell-mediated kidney graft rejection

Amaç: Biyopsi materyallarinden faydalanarak kronik TCMR için transkriptomik profili çıkartarak spesifik bir gen ekspresyonunu araştırmak ve akut TCMR ile karşılaştırmak.

- İtalya'da 5 farklı merkezden 1-6 yıllık eski biyopsi materyalleri
- DSA negatif
- 2013 Banff tanımlarıyla akut ve kronik TCMR—3 patolog sınıflaması
- 14 kronik ve 10 akut TCMR hastası
- 52 kadaverik donor (Orta dereceli kronik lezyonları olan IS almayan kişiler, nakilden hemen önce biyopsi alınmış)

- Biyopsi materyalilerinden microarray
  - RNA ekstraksiyonu→Mikroarray analizi→Real time PCR→Confocal laser scanning microscopy

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ndt
Nephrology Dialysis Transplantation

Original Articles

Potential role of effector memory T cells in chronic T cell-mediated kidney graft rejection

- Mikroarray sonuçlarında izleyen gruplara göre validasyon yapılmış
  - Kronik TCMR (n=5), akut TCMR (n=6),
  - PO 3. ayda protokol biyopsi yapılan ve normal greft fonksiyonu bulunan (n=4)
  - KNİ toksisitesi (n=8)
  - Kadaverik donor (n=6)

- Kontrol grubu: 52 kadaverik donörden doku örneği

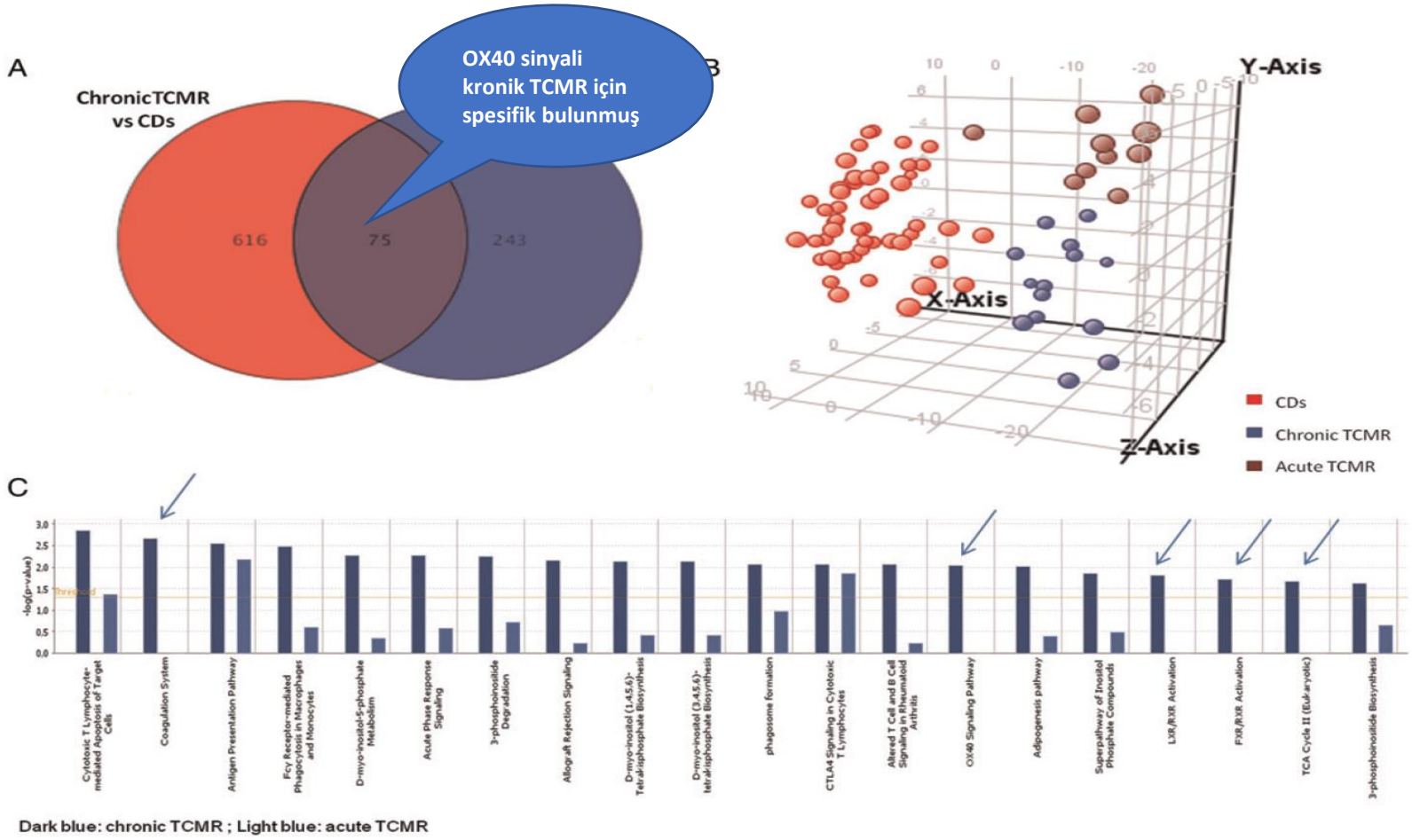

FIGURE 1: (**A**) Venn diagram showing shared and specific genes for chronic TCMR and acute TCMR in kidney biopsy samples. All modulated genes were characterized by FDR <0.05 and a FC ≥1.5 compared with CD biopsy samples. (**B**) Three-dimensional PLS discrimination analysis showed different spatial representation of chronic TCMR, acute TCMR and CDs. (**C**) Shared pathways in chronic and acute TCMR. Pathways characterizing only chronic TCMR are indicated by the arrows: coagulation system, OX40 signalling, LXL/RXR activation, FXF/RXR activation and the TCA cycle.

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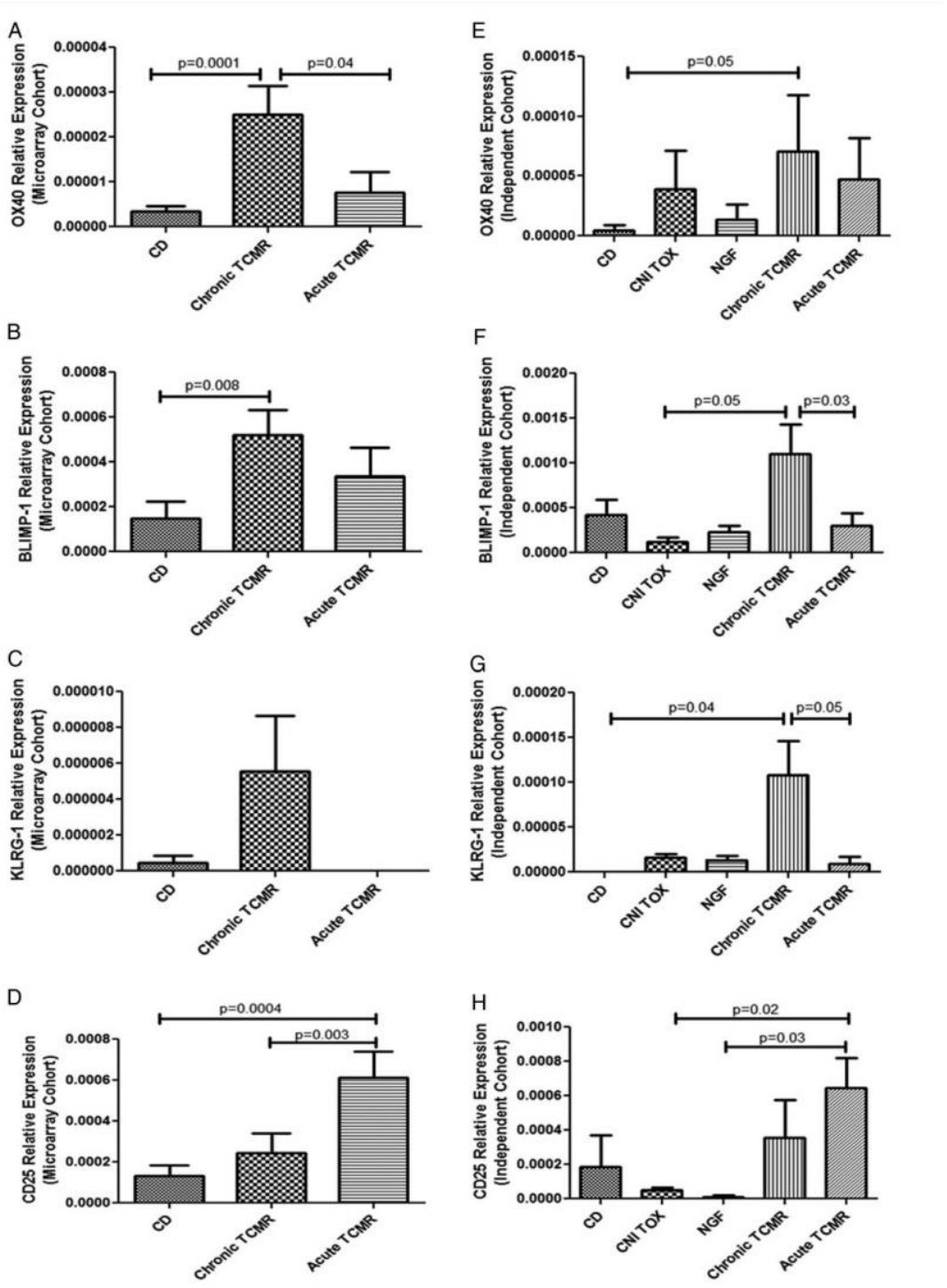
Original Articles

Potential role of effector memory T cells in chronic T cell-mediated kidney graft rejection

SONUÇLAR

- **OX40 sinyali kronik TCMR için spesifik bulunmuş**
  - **OX40 sinyali** $CD8^+$ effektör bellek T lenfositlerin üretiminde önemli
  - Bu sinyal ile **KLRG-1, BLIMP-1** ekspresyonu
  - $CD8^+$ effektör bellek T lenfositler kronik TCMR da rol alıyor (akut da değil)
  - OX40 bloke edecek tedaviler ileride de umut verici olabilir.

KLRG-1:KILLER CELL LECTIN-LIKE RECEPTOR G1
BLIMP-1:B LYMPH CYTE-INDUCED MATURATION PROTEİN 1



Tedavi

Survey conducted by Transplantation Society and CyberNephrology online forum

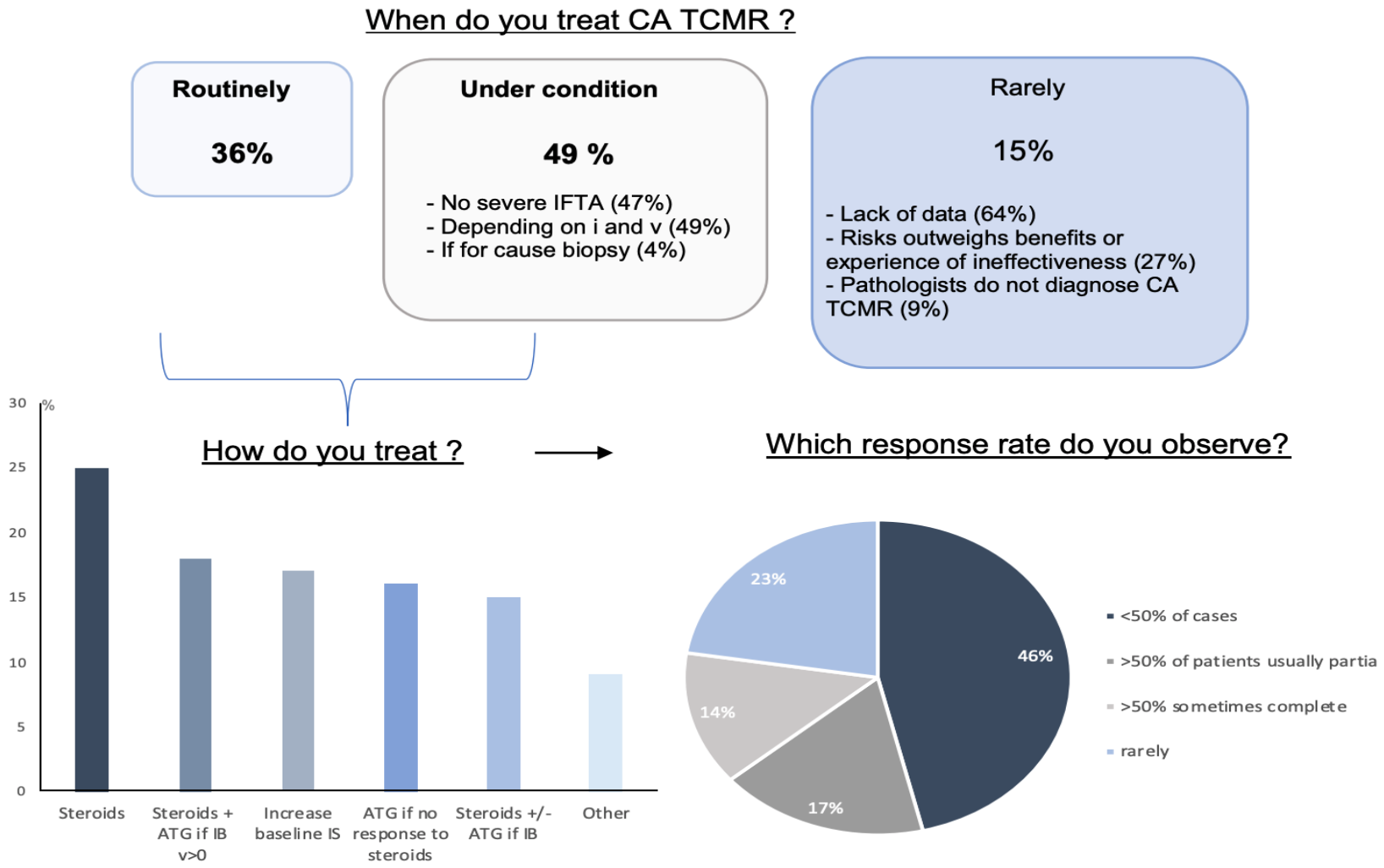


FIGURE 1 Responses to TTS survey regarding the management of chronic active (CA) TCMR: of the 128 respondents to this survey, 47 (37%) were from Europe, 26 (20%) from Asia, 23 (18%) from the United States and Canada, 18 (14%) from Latin America, 9 (7%) from the Middle East and Africa, and 5 (4%) from Australia and New Zealand. Sixty-five percent of centers performed <100 renal transplantations annually; 12% performed >200. At all but 12% of centers, biopsies were read by a renal or transplant pathologist

Chronic active T cell–mediated rejection is variably responsive to immunosuppressive therapy

see comm

Vanderlene L. Kung[1], Rana Sandhu[2], Mark Haas[1] and Edmund Huang[2]

- Tek merkezli, retrospektif çalışma, %67 kadaverik donor, %14 LUD
- %21 alıcıda önceki graft yetersizliği var (≳1)
- %55 hastada geçmişinde biyopsi kanıtlı akut rejeksiyon atağı (TCMR ve ABMR) ve %30'unda DSA pozitifliği saptanmış
- Akut TCMR vakası yok
- 48 hasta (CA-TCMR), 44'üne tedavi verilmiş
  - Pulse steroid veya ATG veya birlikte
- Hastaların transkripsiyonel profili çıkarılmış (RNA ekstraksiyonu) ve immunohistokimyasal yöntemle mast hücreleri gösterilmiş (anti-CD117 boyası ile)

Yanıt:

Parsiyel: GFR de %50-90 düzelme

Tam: GFR de >%90 düzelme

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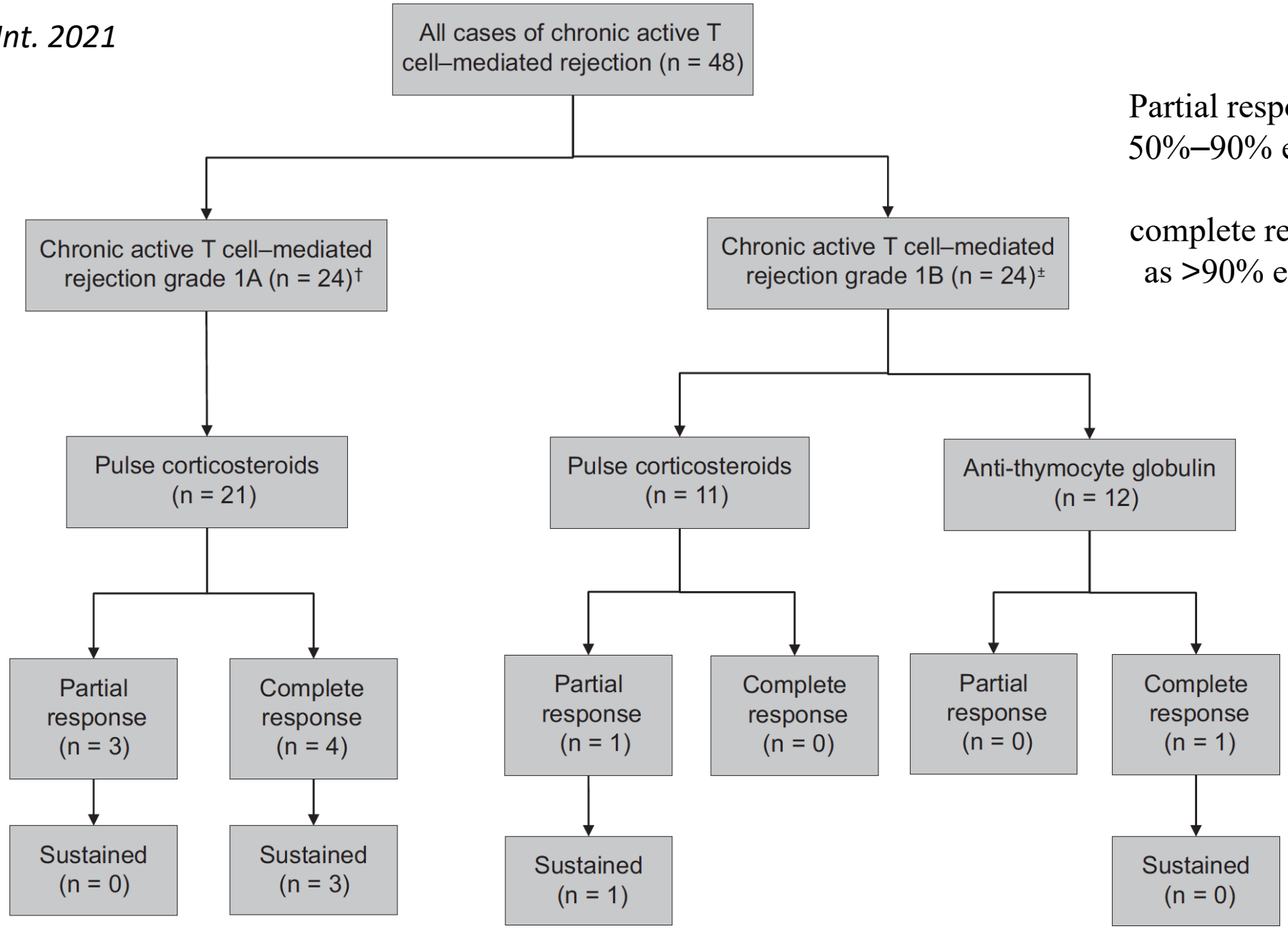


Partial response defined as 50%–90% eGFR recovery and complete response defined as >90% eGFR recovery.

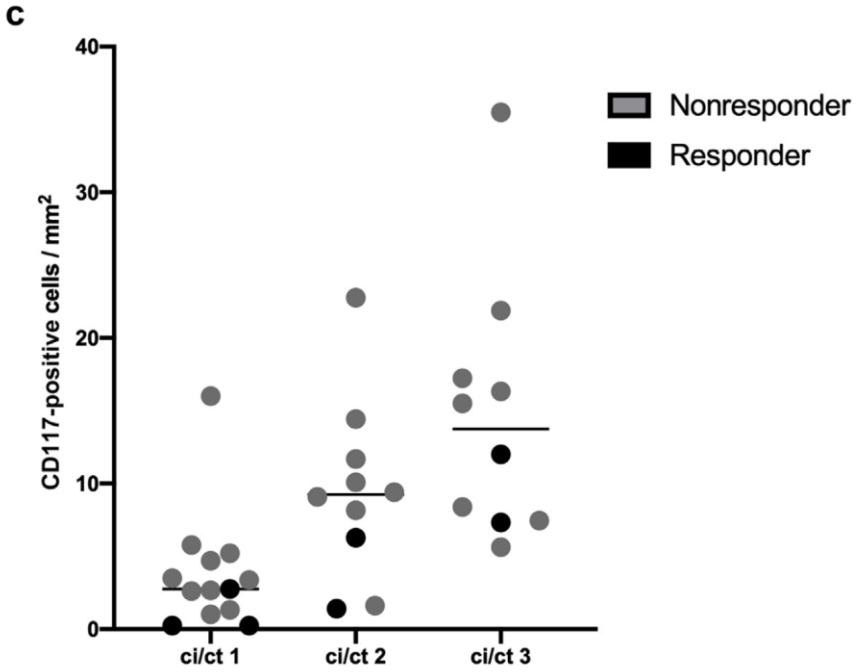
Figure 1 | Flowchart illustrating chronic active T cell–mediated rejection (CA TCMR) treatment and outcomes. †Three patients with CA TCMR 1A were not treated. ±One patient with CA TCMR 1B was not treated.

Chronic active T cell–mediated rejection is variably responsive to immunosuppressive therapy

see comm

Vanderlene L. Kung[1], Rana Sandhu[2], Mark Haas[1] and Edmund Huang[2]

- Histolojik değişiklikler tedaviye yanıtta çok anlamlı farklı değil
- Ama yanıtlar parankimal skar derecesi ile yakın ve tubulit derecesi ile kısmi ilişkili
- Grade 1B grubunda olan hastalarda yanıtsızlık daha sık
- Artmış **allograft mast hücreleri** ve **lipid metabolizma değişimi** tedaviye direnci etkiliyor
- CA-TCMR olguları homojen değil ve bir grubu tedaviden fayda görebiliyor



Kung V, Kidney Int. 2021

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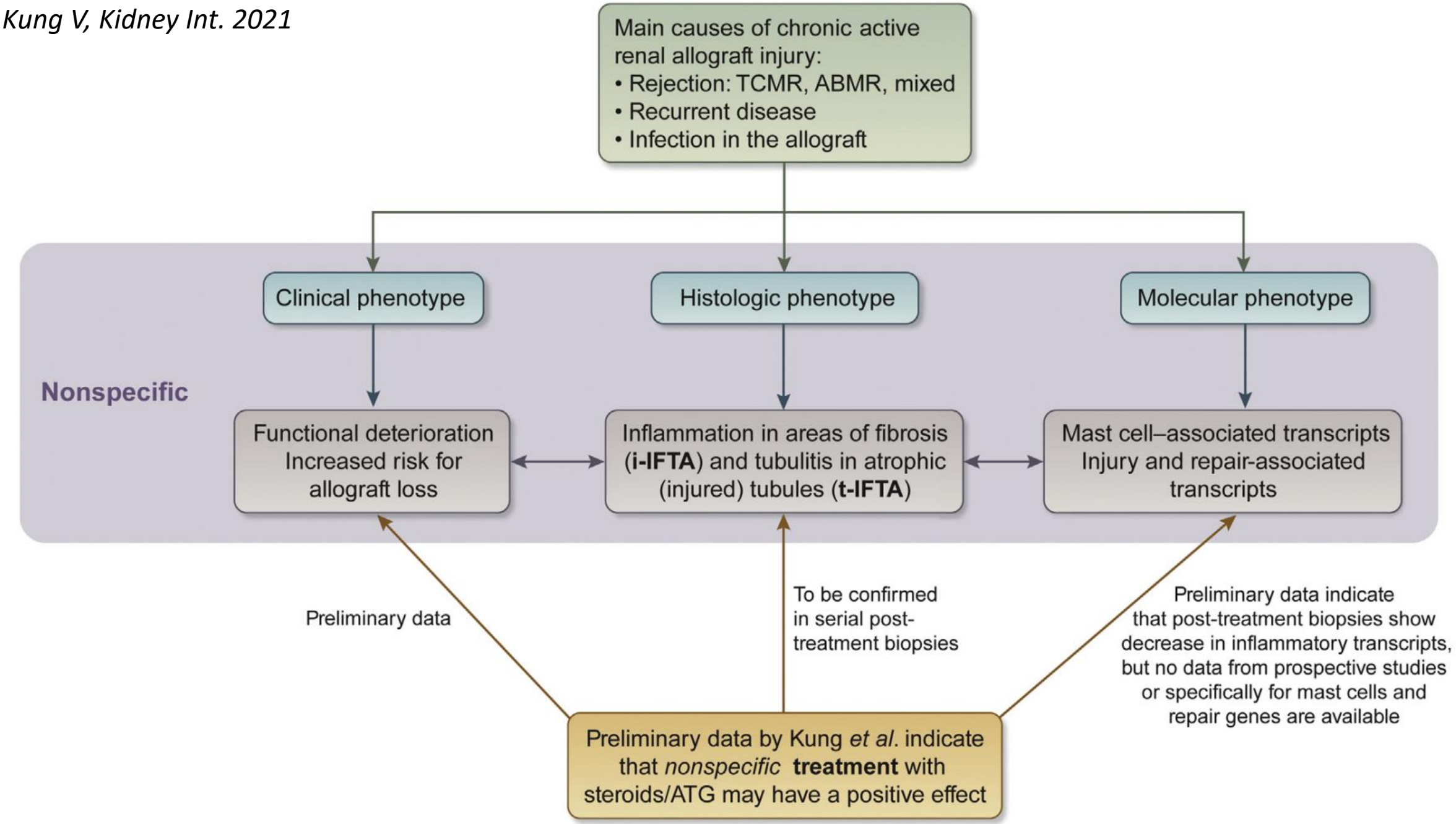

Chronic active T cell–mediated rejection is variably responsive to immunosuppressive therapy.

Case selection

- Retrospective single institution review
- 44 cases of treated, pure CA TCMR without antibody-mediated rejection or intimal arteritis

Primary observation

20% of patients responded (had ≥50% eGFR recovery at 4 weeks post initiation of immunosuppressive therapy)

Possible features of immunosuppressive therapy resistant CA TCMR

Histology → Severe tubulitis

Transcriptional profiling → Increased mast cells and altered fatty acid metabolism

CONCLUSION:
CA TCMR is not a homogenous entity, and in a subset of cases, improvement in kidney function can be achieved with immunosuppressive therapy.

kidney INTERNATIONAL ISN

Kung et al, 2021

> Nephrology (Carlton). 2022 Jul;27(7):632-638. doi: 10.1111/nep.14048. Epub 2022 May 1.

Treatment of chronic active T cell–mediated rejection after kidney transplantation: A retrospective cohort study of 37 transplants

Hiroshi Noguchi [1], Yuta Matsukuma [2], Kaneyasu Nakagawa [2 3], Kenji Ueki [2], Akihiro Tsuchimoto [2], Toshiaki Nakano [2], Yu Sato [1], Keizo Kaku [1], Yasuhiro Okabe [1], Masafumi Nakamura [1]

- 37 hasta (2018-2020), CA-TCMR tanılı (grade (1A:1B:2) 22:10:5)
- Vakaların yarısında protokol biyopsi ile yakalama+ (3 ve 12 ay)
- 32'si tedavi edilmiş, 2 ölüm, 5 graft kaybı

TABLE 1 Clinical, pathological, and immunological findings in patients with CA-TCMR ($n = 37$)

Variable	CA-TCMR ($n = 37$)
Clinical factor	
Age at diagnosis of CA-TCMR (years)	44.2 ± 17.6
Sex (female: male)	16:21
Donor source (living)	27 (73.0%)
Primary disease (DM, CGN, other)	7:13:17
Duration of dialysis (months)	11 (0.0–40.5)[a]
HLA mismatch	2.9 ± 1.2
ABO-incompatible transplantation	10 (27.0%)
Biopsy type (indication)	18 (48.6%)
Duration after transplantation (months)	17.9 (12.4–39.9)[a]
Spot urine protein/creatinine ratio	0.22 (0.11–0.84)[a]
Estimated glomerular filtration rate (ml/min/1.73 m^2)	34.4 ± 19.1
Serum creatinine (mg/dl)	1.93 ± 0.90
Follow-up duration (months)	19.8 ± 11.6
Pathological findings: Banff lesion score (0:1:2:3)	
CA-TCMR grade (1A:1B:2)	22:10:5
ti	0:2:24:11
I	16:14:5:2
i-IFTA	1:0:9:27
t	0:1:25:11
t-IFTA	4:11:15:7
g	30:7:0:0
v	35:0:2:0
ci	1:7:15:14
ct	0:8:15:14
cg	36:1:0:0
cv	3:7:5:22
ptc	34:1:2:0
C4d	25:11:0:1
Immunological factor ($n = 33$)	
Panel reactive antibody class I (%)	0.0 (0.0–0.0)[a]
Panel reactive antibody class II (%)	0.0 (0.0–0.0)[a]
De novo donor-specific antibody	1 (3.0%)

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Variable	Univariate analysis Odds ratio
Treatment	
Increase in baseline IS alone	2.70
Steroid pulse alone	1.20
Steroid pulse + increase in baseline IS	1.78
ATG alone	0.19
ATG + increase in baseline IS	0.73

- Tedavi seçenekleri:
  - Bazal immunsupressiflerde artış (n = 4),
  - Pulse steroid (sadece) (n = 9),
  - Pulse steroid ve bazal immunsupressiflerde artış (n = 10),
  - Rabbit anti-thymocyte globulin (rATG) (sadece) (n = 4),
  - ATG ve bazal immunsupressiflerde artış (n = 5).

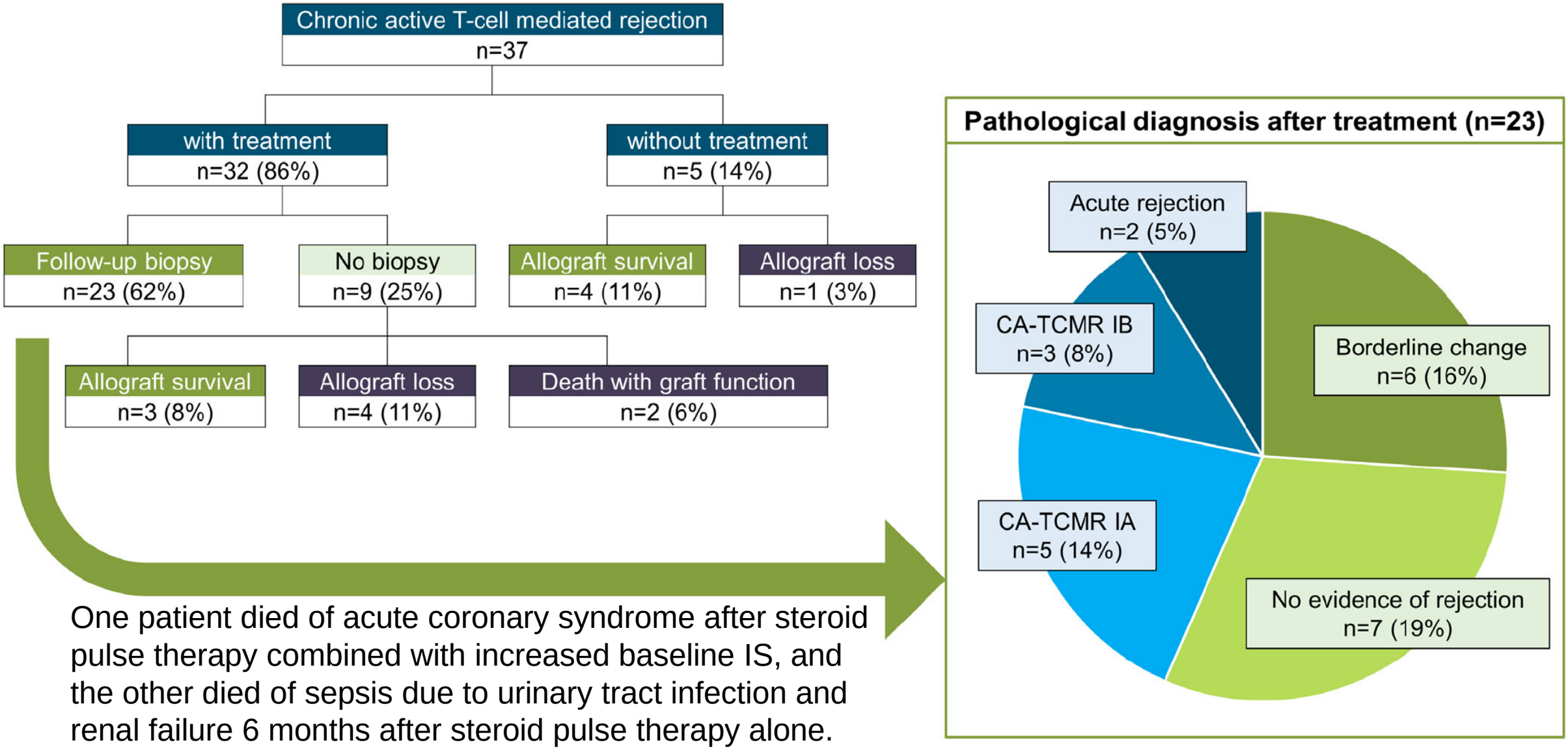

FIGURE 1 Outcome of 37 patients with chronic active T cell-mediated rejection.

> Nephrology (Carlton). 2022 Jul;27(7):632-638. doi: 10.1111/nep.14048. Epub 2022 May 1.

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- Endikasyon biyopsisi ve proteinüri, graft kaybı için risk faktörleri
- 23 hastaya takipte biyopsi tekrarı yapılmış
- Tedavi sonrası "ti", "i-IFTA", "t" ve "t-IFTA" skorlarında anlamlı düzelme olmuş
- Tedaviye cevapta proteinüri derecesi önemli

TABLE 3 Predictive factors for response to treatment in CA-TCMR ($n = 23$)

	Univariate analysis			Multivariate analysis		
Variable	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Clinical factor						
Age at diagnosis of CA-TCMR (years)	0.97	0.92–1.02	.285		ND	
Sex (female)	1.75	0.33–9.30	.509		ND	
Donor source (living)	0.25	0.01–2.12	.215		ND	
Primary disease (DM, CGN, other)			.974		ND	
Duration after transplantation (months)	1.00	0.99–1.00	.119		ND	
HLA mismatch	0.73	0.32–1.51	.399		ND	
ABO-incompatible transplantation	1.20	0.16–9.01	.859		ND	
Biopsy type (indication)	0.08	0.01–0.91	.019	0.17	0.00–6.51	.337
Spot urine protein/creatinine ratio	–	–	<.001	–	–	.001
Serum creatinine (mg/dl)	0.19	0.04–1.03	.021	1.16	0.09–15.37	.911
Pathological findings: Banff lesion score (0:1:2:3)						
CA-TCMR grade (2, 1B vs. 1A)	1.04	0.17–6.77	.968		ND	
ti	2.40	0.44–12.49	.299		ND	
i	1.25	0.41–4.09	.692		ND	
i-IFTA	0.41	0.05–1.58	.221		ND	
t	0.56	0.11–2.97	.492		ND	
t-IFTA	0.85	0.36–1.95	.703			
v	-	-	.278		ND	
ci	1.17	0.42–3.25	.768		ND	
ct	1.41	0.45–4.82	.559		ND	
cv	1.71	0.72–4.48	.230		ND	
ptc	–	–	.189		ND	
Treatment						
Increase in baseline IS alone	2.70	0.29–60.19	.401		ND	
Steroid pulse alone	1.20	0.16–10.85	.859		ND	
Steroid pulse + increase in baseline IS	1.78	0.25–12.45	.562		ND	
ATG alone	0.19	0.17–2.25	.159		ND	
ATG + increase in baseline IS	0.73	0.07–7.14	.773		ND	

Abbreviations: ATG, rabbit antithymocyte globulin; CA-TCMR, chronic active T cell-mediated rejection; CGN, chronic glomerular nephritis; CI, confidence

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- Graft kaybı olan 5 vakada endikasyon biyopsisi grubunda
- Graft kaybı nedeni progressif CA-TCMR
- Dört kişi tedavi grubunda
  - Pulse steroid (sadece), n=2
  - Pulse steroid ve bazal immunsupressiflerde artış, n=2

- Takip biyopsisi yapılan grupta graft kaybı ya da ölüm yok

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- SONUÇ:
  - Tedavi faydalı olabiliyor özellikle subklinik grupta
  - Ama graft kaybı tedavi grubunda da yüksek
  - Tedavinin graft survisini uzatmada rolü gösterilememiş (pozitif etki olsa da)

Tedavi

- i-IFTA renal dokuda **aktif devam eden** hasarlanmayı gösteriyor (IFTA dan farklı olarak)---tedavi gerekliliği ?
- Tedavisinde immunsupresyonun faydası net bilinmiyor,
- Net protokol yok
- Özellikle **grade 1B** steroidler başta olmak üzere akut TCMR tedavisine dirençli
- Biyopsi dokusundan moleküler analizler (gen ekspresyon analizleri) steroid duyarlı/dirençli grubu ayırmakta faydalı olabilir.

* Kung V, Kidney Int. 2021

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DOI: 10.1111/ajt.16093

ORIGINAL ARTICLE

AJT

Significance of revised criteria for chronic active T cell–mediated rejection in the 2017 Banff classification: Surveillance by 1-year protocol biopsies for kidney transplantation

Kaneyasu Nakagawa[1] | Akihiro Tsuchimoto[1] | Kenji Ueki[1] | Yuta Matsukuma[1] | Yasuhiro Okabe[2] | Kosuke Masutani[3] | Kohei Unagami[4] | Yoichi Kakuta[5] | Masayoshi Okumi[5] | Masafumi Nakamura[2] | Toshiaki Nakano[1] | Kazunari Tanabe[5] | Takanari Kitazono[1] | Japan Academic Consortium of Kidney Transplantation Investigators

Amaç :Banff 2017 CA -TCMR önerilerinin klinik önemini belirlemek

1. yılda protokol biyopsisi yapılmış olan ve 2015 Banff kriterlerine göre değerlendirilen 406 böbrek alıcısı geriye dönük olarak Banff 2017 kriterlerine göre 3 gözlemci tarafından yeniden değerlendirilmiş.

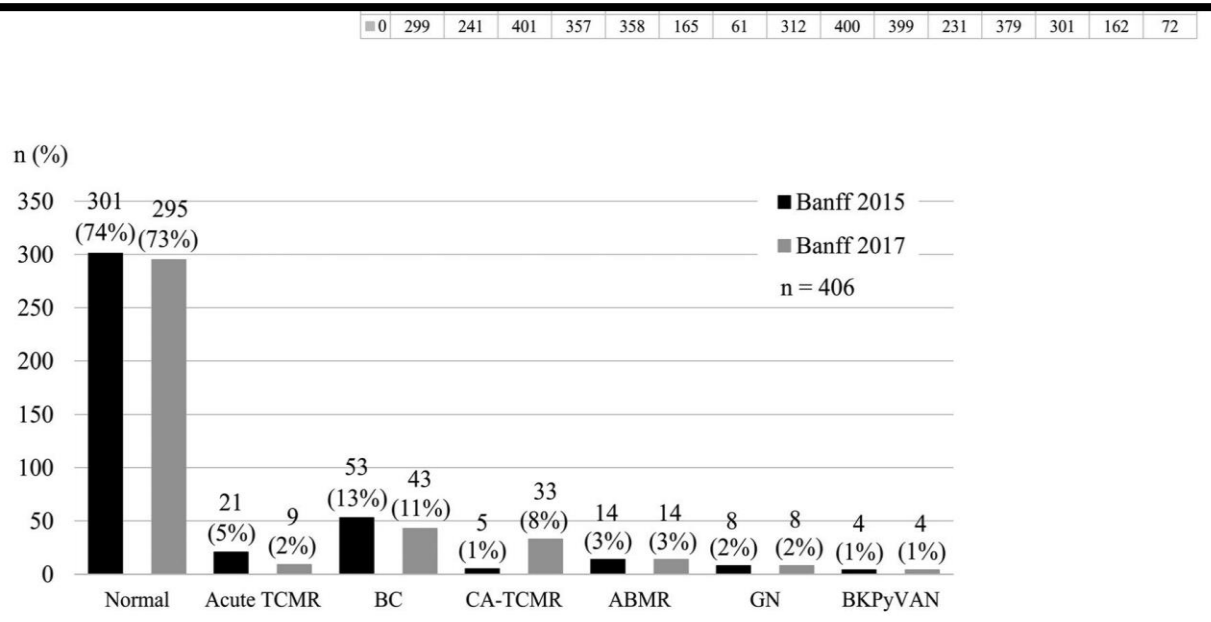

FIGURE 3 Numbers and proportions of the diagnoses provided by the criteria of Banff 2015 or 2017. Of the 28 patients diagnosed with CA-TCMR grade I, moderate or severe renal tubulitis was observed in scarred areas only (n = 11) or both scarred and nonscarred areas (n = 17). ABMR, antibody-mediated rejection; BC, borderline changes; GN, glomerulonephritis; BKPyVAN, BK polyomavirus-associated nephropathy; CA-TCMR, chronic active T cell–mediated rejection; TCMR, T cell–mediated rejection

*CA-TCMR tanısı Serum Kr: 2 kat artış ve graft kaybı riskinde 5.42 kat artış ile ilişkili

* CA-TCMR graft yaşam süresini belirleyici en kötü 2. prognostik faktör.

Prognoz

*Genelde kötü prognozlu (ABMR sonrası ikinci kötü)

*Uzun dönem graft kaybı ile ilişkili

Kronik ve akut TCMR bir arada olabilir (kriterler birlikte varsa)

Kidney International (2022) 101, 678–691; https://doi.org/10.1016/ j.kint.2021.11.028
*Nakagawa K, Am J Transplant. 2021

Özet

- Kronik aktif TCMR donör antijenlerine karşı gelişen T-hücre aracılı immün reaksiyonun neden olduğu, bir tür kronik aktif graft hasarıdır.
- Tanıda sklerotik kortikal parankimdeki interstisyel inflamasyon skoru (**i-IFTA**), total kortikal parankimdeki interstisyel inflamasyon skoru (**ti)** , interstisyel fibrozis alanlarındaki tübülit skoru (**t-IFTA)** ve kronik allograft arteriopati bulguları **(v, cv)** kullanılır.
- Graft yaşam süresini etkileyen en önemli faktörlerden biridir
- İmmunsupressif tedaviye yanıtı ve steroid duyarlı/dirençli gurubu ayırabilecek gen ekspresyon analizleri ve transkriptomik çalışmalara gereksinim vardır.
- Tanı kriterlerinin yeniden gözden geçirilmesine gereksinim vardır