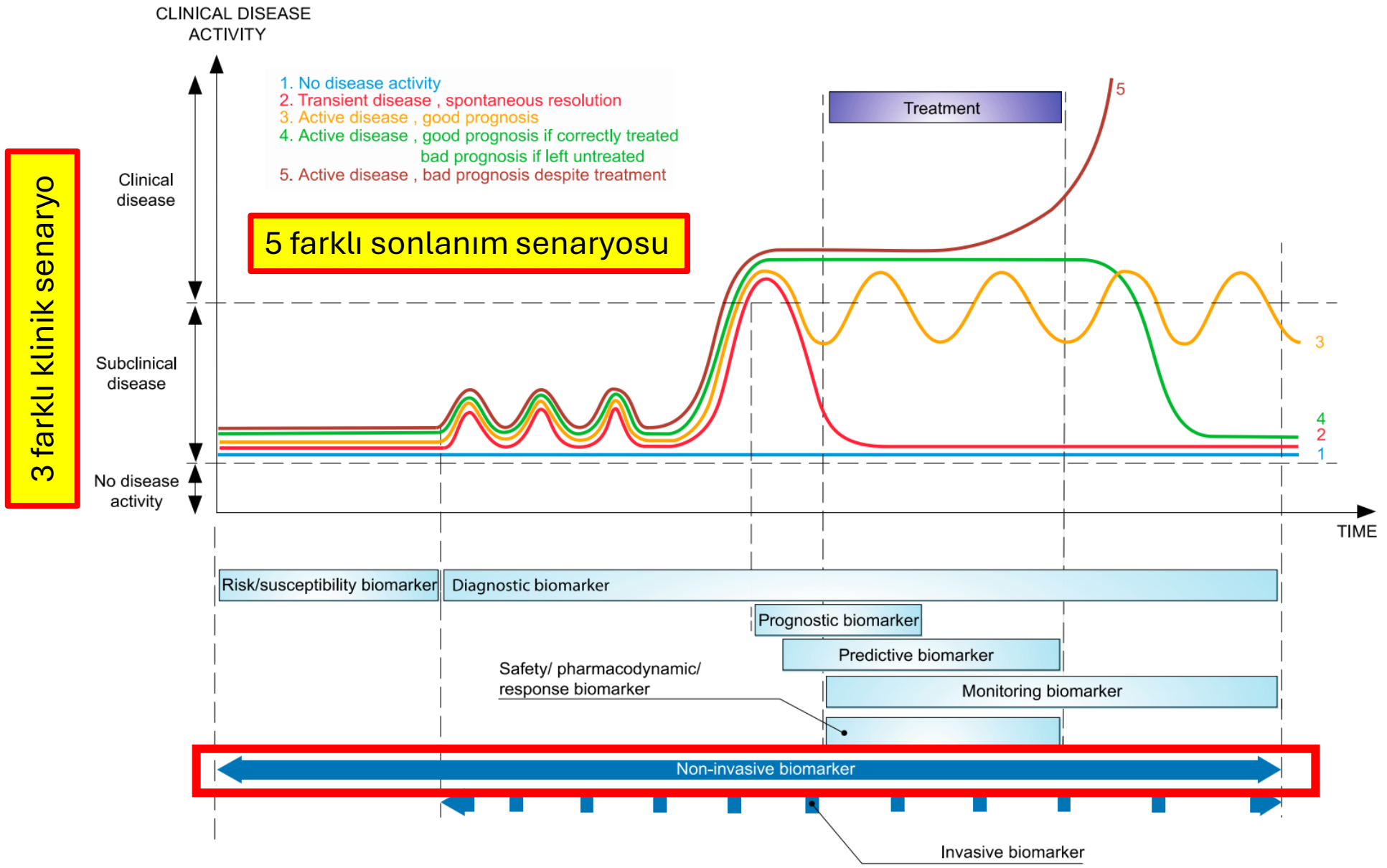
Transplantasyonda Yeni Biyobelirteçler

Dr. Özgür Akın Oto
İstanbul Tıp Fakültesi Nefroloji BD

TİGED-2024

- Risk tayini
- Tanı
- Tarama
- Prognoz
- Tedaviye yanıt



J Am Soc Nephrol. 2018 Jan;29(1):24-34.

Geleneksel Tarama Yöntemleri

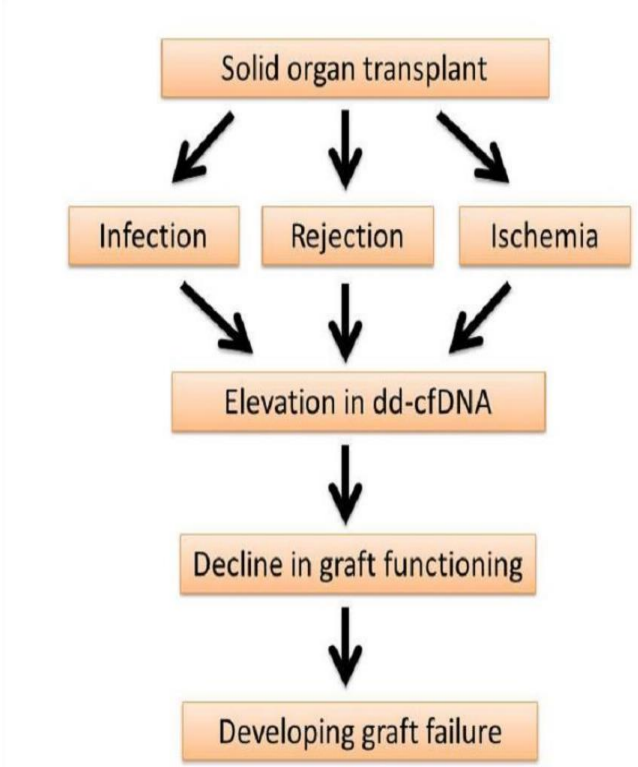
- Kreatinin artışı / Proteinüri
  - Hasarla eş zamanlı yükselmez
- DSA
  - Tüm DSA'lar patojenik değildir
  - Non-HLA antikorlar da rejeksiyona neden olabilir.
- Biyopsi→ Altın standart
  - İnvaziv
  - Komplikasyonlu
  - Pahallı
  - Örnekleme ve yorumlama hataları

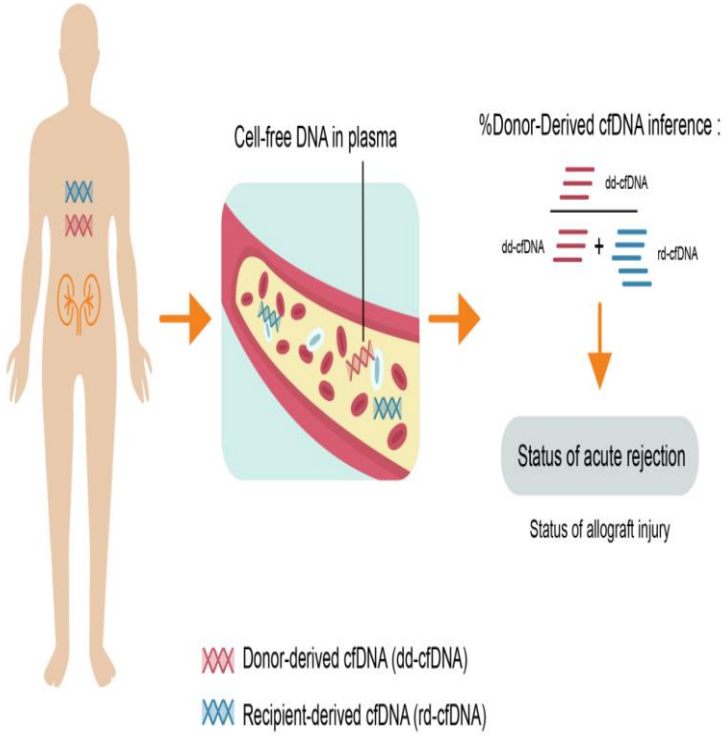
- İmmünolojik biyobelirteçler
  - Cell-free DNA
  - Gen ekspresyon profilleri
  - İdrar kemokinleri
  - İdrar mRNA

- Non-immünolojik biyobelirteçler
  - Graft kalitesi
  - Gecikmiş graft fonksiyonu
  - Kardiyovasküler olaylar/mortalite
  - İnfeksiyonlar
  - Malignite
  - Posttransplant DM

Allograft hasarı → dd-cfDNA artışı

- Büyük oranda endotelyal hücre hasarını yansıtır
- Yarı ömrü çok kısa (<1 saat)
- Rejeksiyon, infeksiyon, ilaç toksitesi
- % → Dd-cfDNA/Total cfDNA
- 3 farklı ticari kit mevcut
  - Allosure (CareDx)
  - Prospera (Natera)
  - TRAC (Viracor Eurofins)





Transplantology 2021, 2(3), 348-361

J Clin Med. 2020 May 14;9(5):1480.

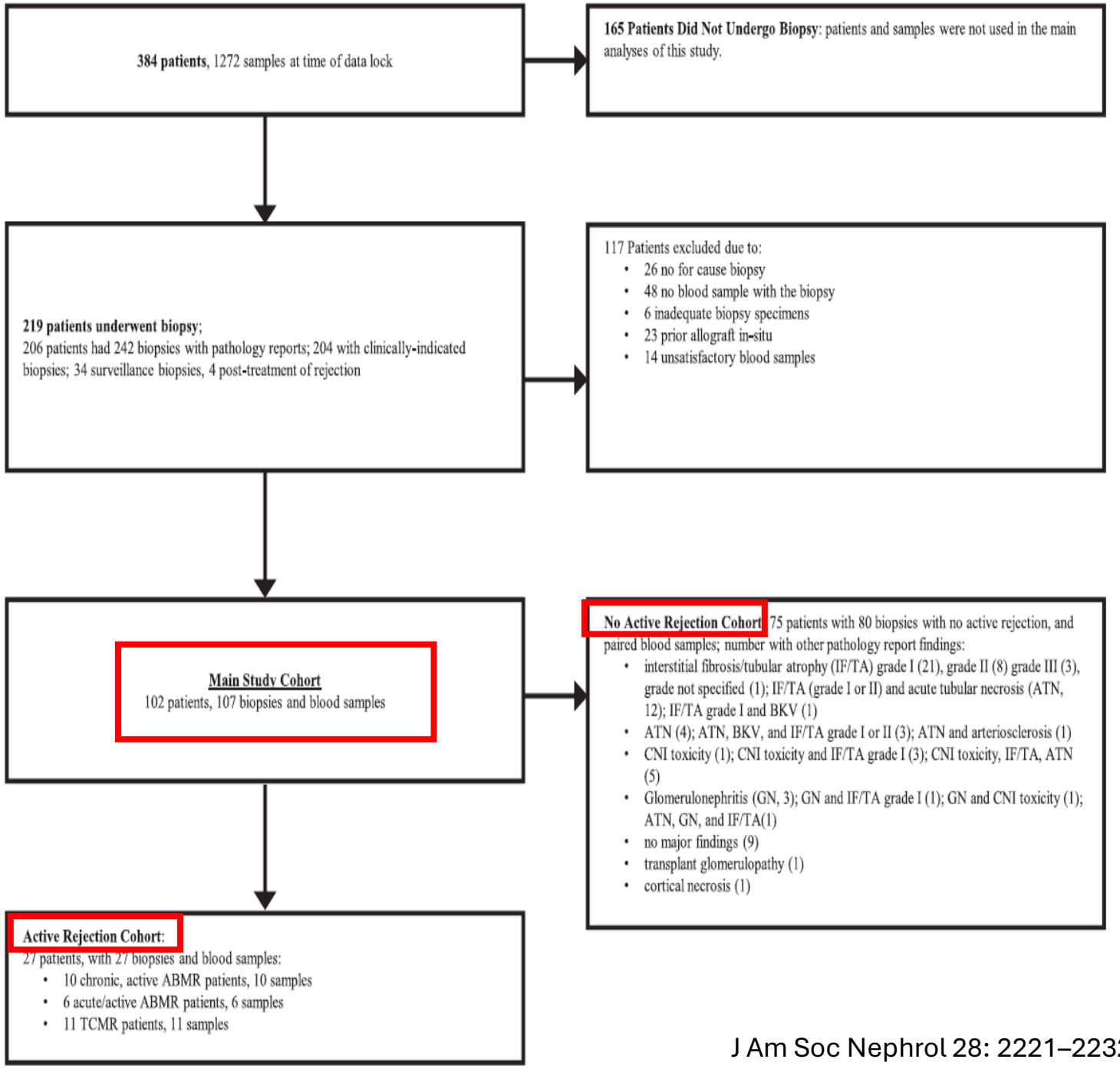
CLINICAL RESEARCH www.jasn.org

Cell-Free DNA and Active Rejection in Kidney Allografts

Roy D. Bloom,* Jonathan S. Bromberg,† Emilio D. Poggio,‡ Suphamai Bunnapradist,§ Anthony J. Langone,‖ Puneet Sood,¶ Arthur J. Matas,** Shikha Mehta,†† Roslyn B. Mannon,††‡‡ Asif Sharfuddin,§§ Bernard Fischbach,‖‖ Mohanram Narayanan,¶¶ Stanley C. Jordan,§*** David Cohen,††† Matthew R. Weir,‡‡‡ David Hiller,§§§ Preethi Prasad,‖‖‖ Robert N. Woodward,¶¶¶ Marica Grskovic,¶¶¶ John J. Sninsky,¶¶¶ James P. Yee,‖‖‖ and Daniel C. Brennan,**** for the Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Active Rejection in Kidney Transplant Recipients (DART) Study Investigators

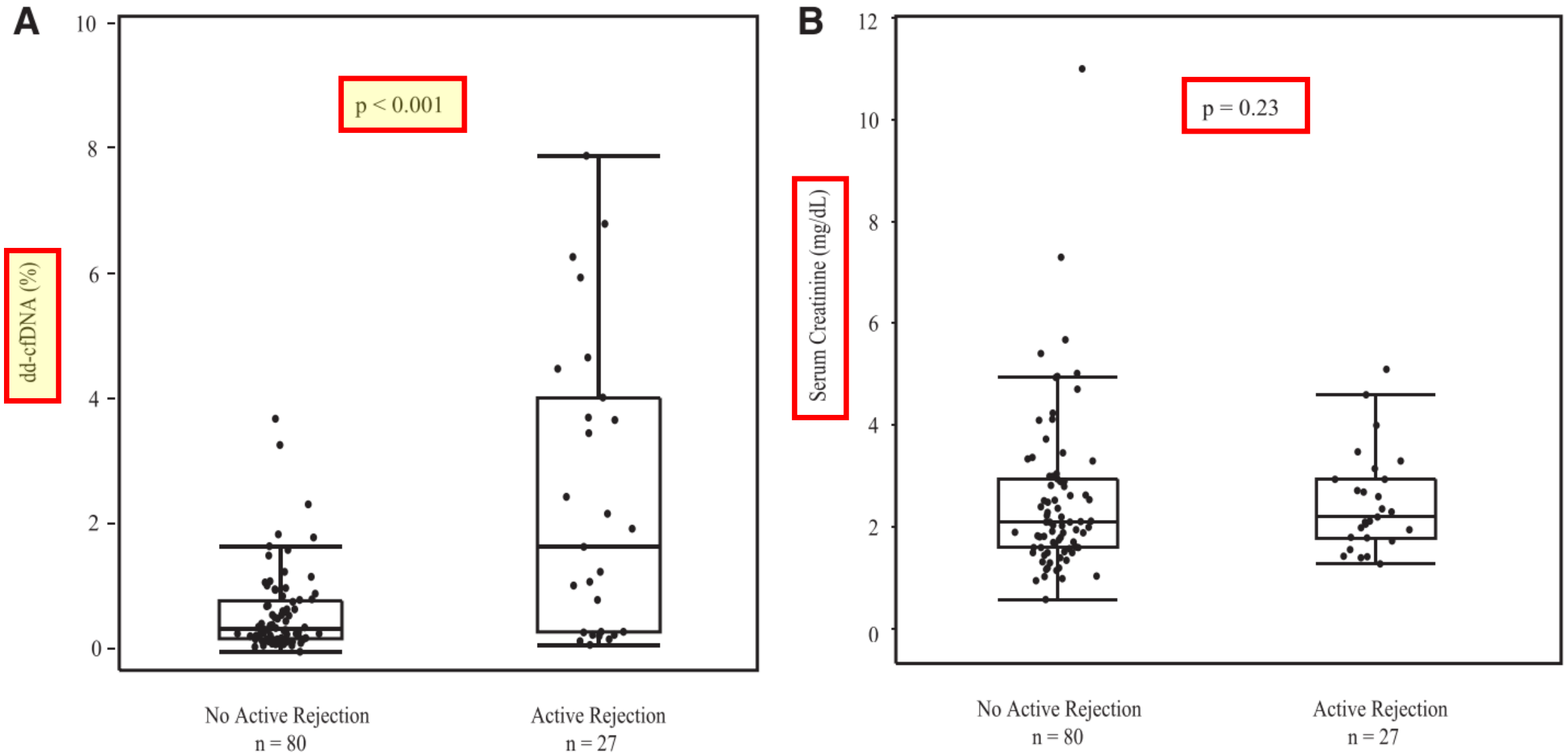
- 14 merkez, 384 hasta
- Prospektif gözlemsel çalışma
- 2 yıl takip

TANISAL



J Am Soc Nephrol 28: 2221–2232, 2017.

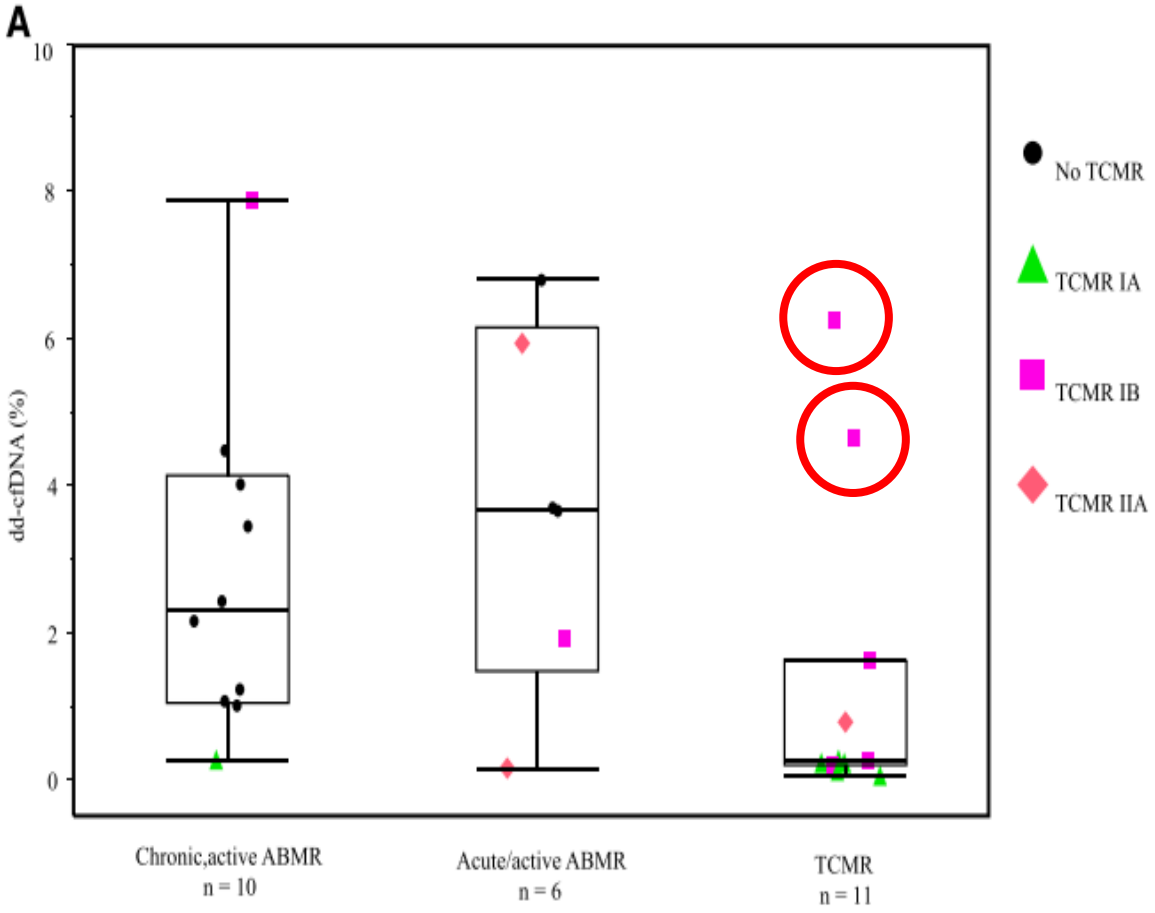
Dd-cfDNA rejeksiyon tanısı koymakta kreatininden daha hassas

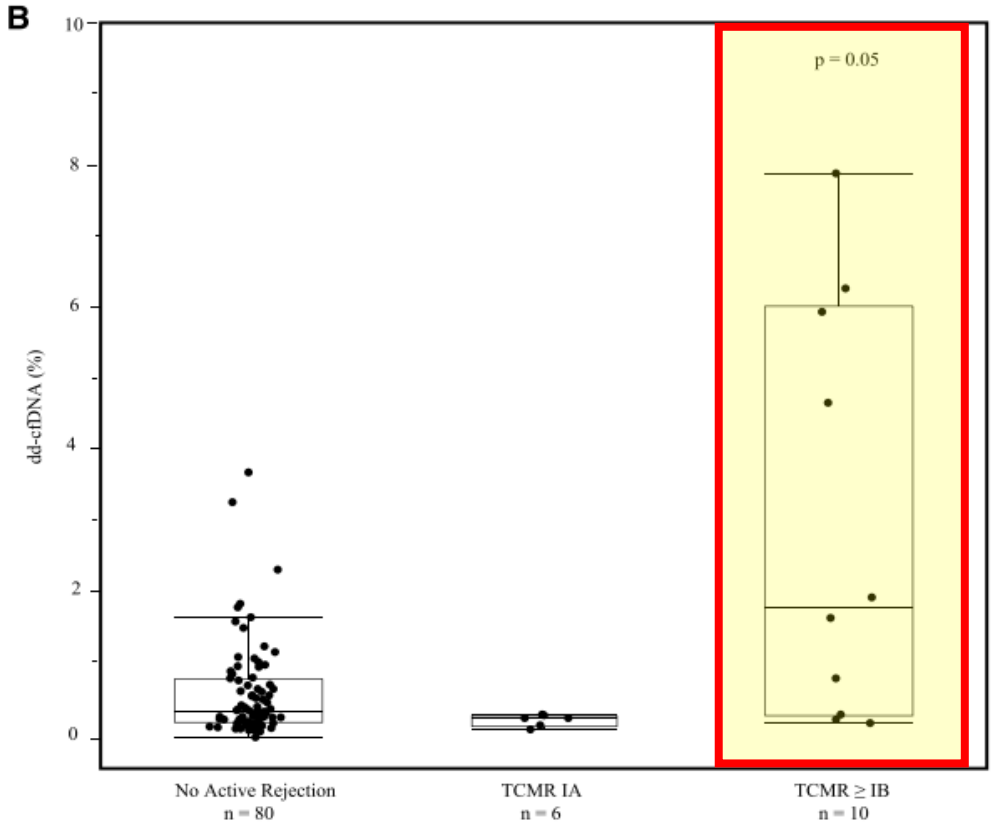


J Am Soc Nephrol 28: 2221–2232, 2017.

- Dd-cfDNA AMR'yi saptayabiliyor
- TCMR için aynı şey geçerli değil

TCMR >1B ise tanısal potansiyele sahip





Cut-off %1

J Am Soc Nephrol 28: 2221–2232, 2017.

Clinical outcomes from the *A*ssessing *D*onor-derived cell-free DNA *M*onitoring *I*nsights of kidney *A*llografts with *L*ongitudinal surveillance (ADMIRAL) study.

PREDİKTİF

Cohort

1094 patients

7 transplant centers

Single Kidney Adult Recipients

90% deceased donor

Multiorgan and pregnancy excluded

3 yrs. post transplant dd-cfDNA surveillance

Median of 6 results per patient

Methods

Post transplant events

Centralized biopsy reporting

Center Standard of Care protocols

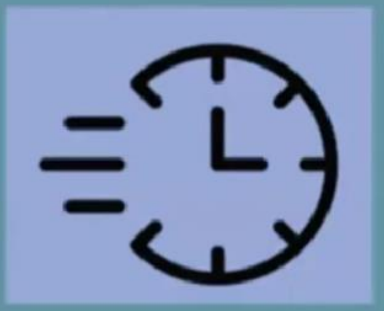
3 years of Outcomes Surveillance

Analysis of
- De-Novo DSA
- eGFR trajectories
- Allograft rejection

Outcomes

eGFR Decline

Persistently elevated dd-cfDNA (>1 result above 0.5%) predicted a > 25% decline in eGFR over 3 years



Temporal Relationship

dd-cfDNA values ≥ 0.5% were associated with a nearly 3-fold increase in the risk of development of de novo donor specific antibody (DSA)

Subclinical Rejection

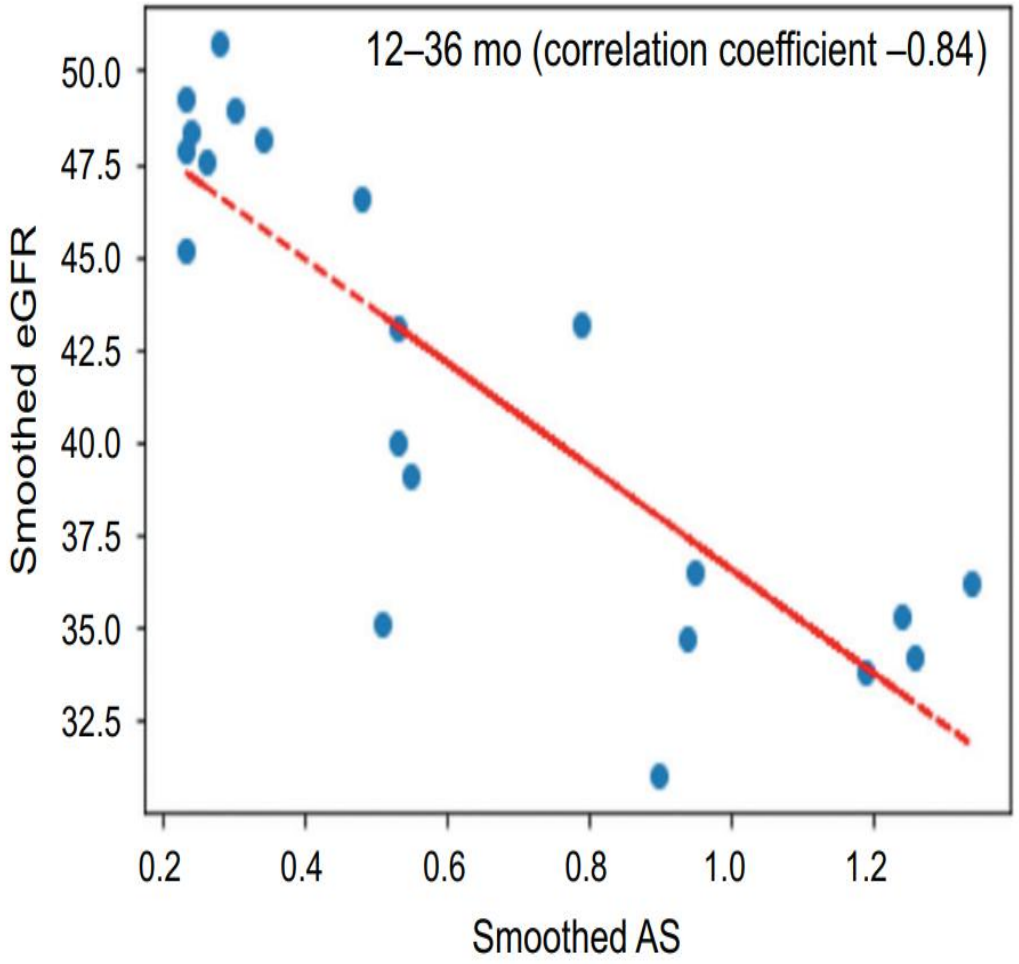
Significant elevations in dd-cfDNA during rejection ahead of changes in serum creatinine

Bu et al 2021

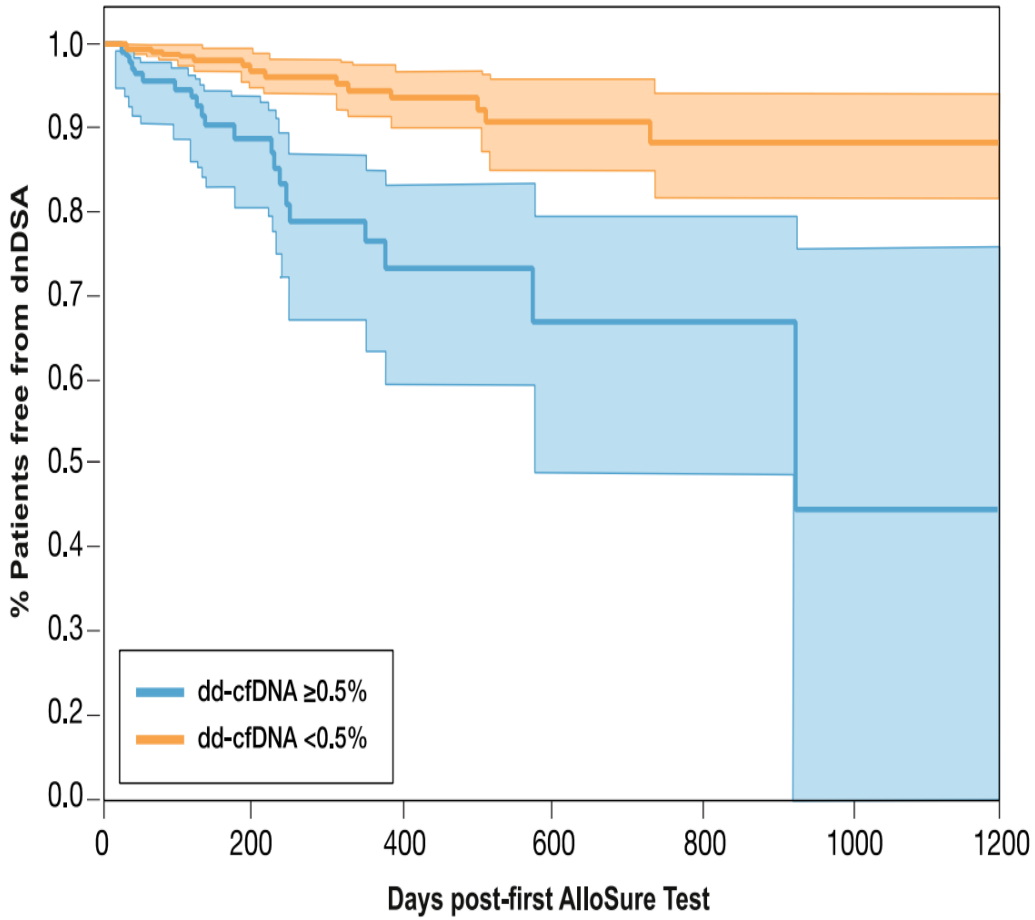
ClinicalTrials.gov Identifier: NCT04566055

CONCLUSION: *The ADMIRAL study demonstrates a broad utility of dd-cfDNA as a leading indicator ahead of clinical presentations of allograft injury, formation of dnDSA, eGFR decline and subclinical rejection.*

dd-cfDNA düzeyleri arttıkça GFR düşüyor

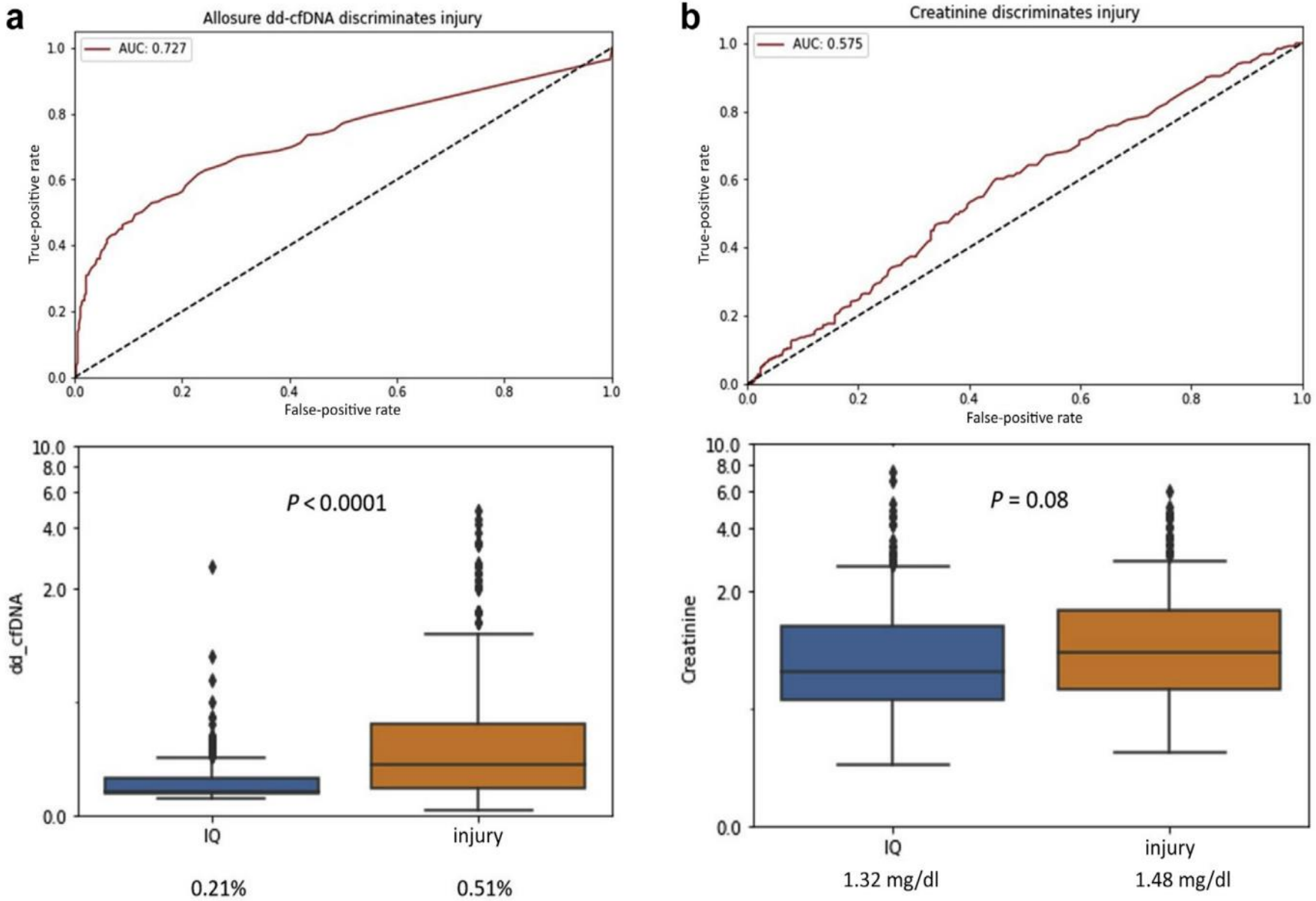


dd-cfDNA >%0.5 olanlarda DSA riski 3 kat daha fazla



Persistan dd-cfDNA yüksekliği (en az 1 ölçümü >%0.5'ten fazla) olanlarda GFR'de %25 azalma riski 2 kat daha fazla

dd-cfDNA allograft hasarını saptamada kreatinine göre daha hassas.



Received: 14 September 2019 | Revised: 30 January 2020 | Accepted: 2 February 2020
DOI: 10.1111/ajt.15822

ORIGINAL ARTICLE

AJT

High levels of dd-cfDNA identify patients with TCMR 1A and borderline allograft rejection at elevated risk of graft injury

Erik Stites[1] | Dhiren Kumar[2] | Oyedolamu Olaitan[3] | Sidney John Swanson[4] | Nicolae Leca[5] | Matthew Weir[6] | Jonathan Bromberg[7] | Joseph Melancon[8] | Irfan Agha[9] | Hasan Fattah[10] | Tarek Alhamad[11] | Yasir Qazi[12,13] | Alexander Wiseman[1] | Gaurav Gupta[2]

- 11 merkez
- 79 hasta (27 borderline, 52 TCMR 1A)
- Hastalar dd-cfDNA açısında düşük (%0.5) ve yüksek (>%0.5) olarak katmanlandırılmış

Dd-cfDNA>%0.5 ise
- GFR kaybı daha fazla
- DSA gelişim riski yüksek
- Rekürren rejeksiyon riski yüksek

TABLE 2 Summary statistics for high vs low donor-derived cell-free DNA (dd-cfDNA)

Measurement	Statistics	All patients	Low (dd-cfDNA < 0.5%)	High (dd-cfDNA ≥ 0.5%)	*P* value
dd-cfDNA measurements[a] (%)	N	79	37	42	-
	Mean (SD)	1.05 (1.267)	0.25 (0.087)	1.76 (1.40)	
	Median (Q1, Q3)	0.64 (0.21, 1.40)	0.21 (0.19, 0.29)	1.40 (0.87, 2.02)	
	Min, Max	0.19, 6.70	0.19, 0.49	0.52, 6.70	
Change in estimated glomerular filtration rate (eGFR; 3-6 mo)	N	79	37	42	.019[b]
	Mean (SD)	−2.85 (7.526)	−0.74 (7.369)	−4.74 (7.247)	
	Median (Q1, Q3)	−2.00 (−5.00, 1.00)	0.00 (−3.00, 2.00)	−3.50 (−8.00, −1.00)	
	Min, Max	−29.00, 16.00	−29.00, 12.00	−20.00, 16.00	
% Change in eGFR (3-6 mo)	N	79	37	42	.004[b]
	Mean (SD)	−4.70 (16.937)	−0.40 (18.149)	−8.54 (14.98)	
	Median (Q1, Q3)	−3.89 (−9.89, 2.33)	0.00 (−4.92, 4.76)	−8.50 (−16.22, −1.39)	
	Min, Max	−70.73, 33.33	−70.73, 33.33	−37.50, 32.65	
Presence of donor-specific antibodies (3-6 mo)	Percentage	18/79 (22.9%)	1/37 (2.7%)	17/42 (40.5%)	<.001[c]
Recurrent rejection	Percentage	9/79 (11.4%)	0/37 (0.0%)	9/42 (21.4%)	.003[c]

Dd-cfDNA riskli borderline rejeksiyonları ayırt edici potansiyele sahip

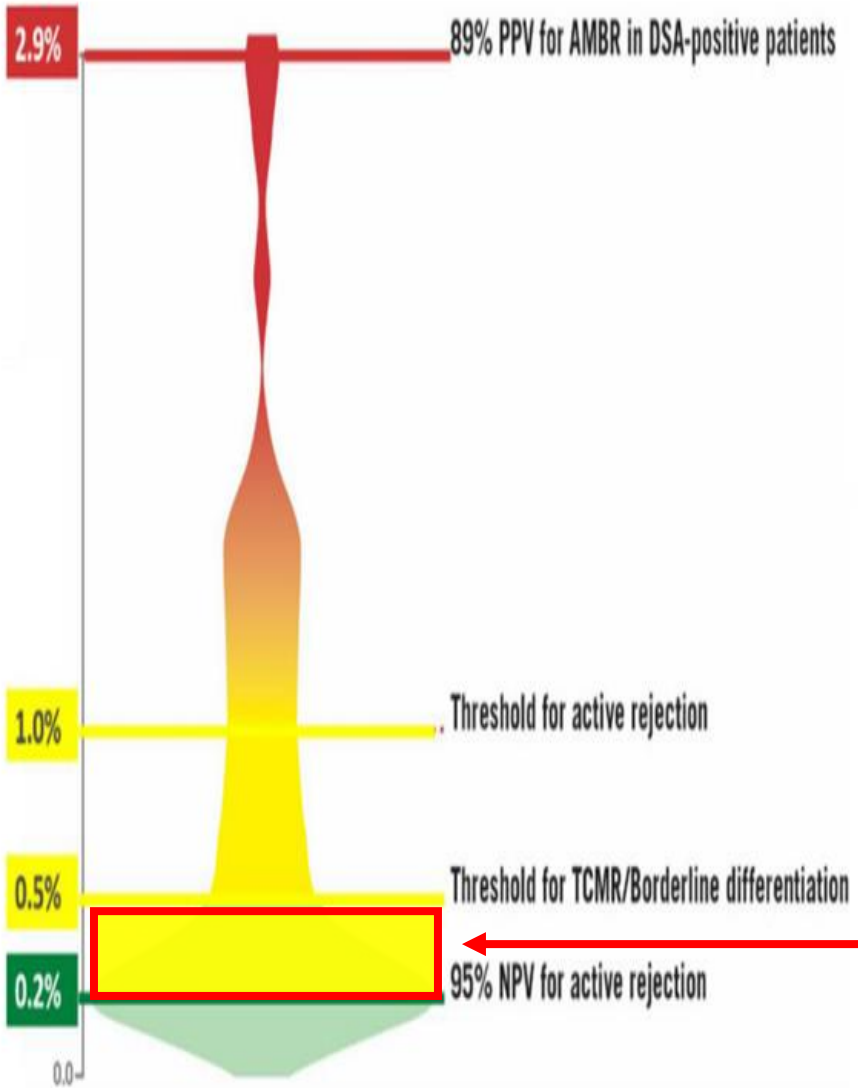


Table 2. Biological variation for dd-cfDNA, cardiac injury biomarkers, and other commonly measured analytes.

Biomarker, typical value[a]	CV_A, %	CV_I, %	CV_G, %	II	RCV, %	RCV, absolute[a]
dd-cfDNA, 1%	6.8	21	37	0.57	61	0.61%

- dd-cfDNA >%1 ise ABMR veya TCMR 1B riski yüksek
- dd-cfDNA >%0.5 <%1 ise DSA gelişme, GFR kaybı ve rejeksiyon riski riski yüksek

dd-cfDNA <%0.5 olan hastalarda seri ölçümlerde %61'den fazla olan artışlar anlamlı

Biophys Rev (2020) 12:917–924

J Appl Lab Med. 2017 Nov 1;2(3):309-321.

Genel olarak her 3 testin de performansları benzer

	TRAC Kidney	AlloSure Kidney	Prospera
# of SNPs	>100,000 (whole genome sequencing)	405 SNPs	13,392 SNPs
Sensitivity	64%	59.3%	88.7%
Specificity	85.1%	84.7%	72.6%
PPV†	39.7%	40.9%	36.6%
NPV†	91.9%	92.1%	97.3%

Dezavantajlar:

- PPV düşük: BK nefropati, piyelonefrit vb diğer hasar nedenleri ile rejeksiyonu ayırt edemiyor
- Pahallı

J Am Soc Nephrol 2017; 28:2221.

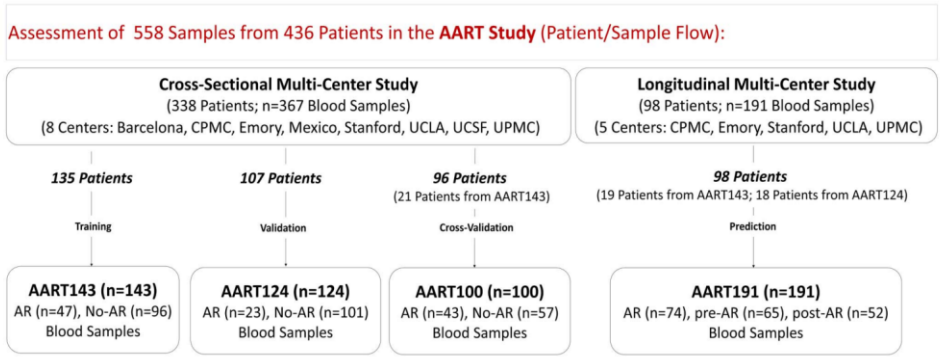
J Clin Med 2018; 8:19.

TRAC White Paper.

The kSORT Assay to Detect Renal Transplant Patients at High Risk for Acute Rejection: Results of the Multicenter AART Study

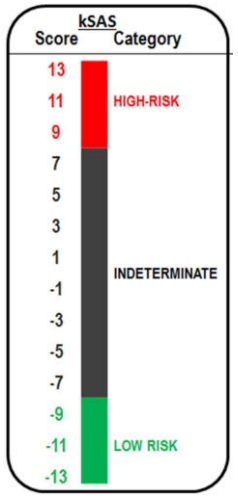
Silke Roedder[1☯], Tara Sigdel[1☯], Nathan Salomonis[2☯], Sue Hsieh[1], Hong Dai[3¤a], Oriol Bestard[4], Diana Metes[5], Andrea Zeevi[5], Albin Gritsch[6], Jennifer Cheeseman[7], Camila Macedo[5], Ram Peddy[3], Mara Medeiros[8], Flavio Vincenti[1], Nancy Asher[1], Oscar Salvatierra[9], Ron Shapiro[5], Allan Kirk[7¤b], Elaine Reed[6], Minnie M. Sarwal[1*]

KSORT akut rejeksiyonu tespit edebiliyor



AR için anlamlı 17 genin ekspresyonu için tarama (PCR)

- Apotozis
- Lökosit trafiği
- Monosit aktivasyonu
- Hücre sağkalımı



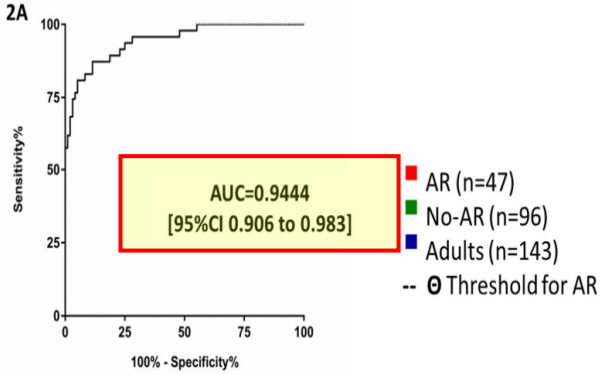


Table 2. Performance of kSORT in the AART143, AART124, and AART100 cohorts.

Statistics	kSORT Predictions					
	AART143 (Training Set)		AART124 (Validation Set)		AART100 (Cross-Validation Set)	
	AR	No-AR	AR	No-AR	AR	No-AR
Real Results						
AR	39	8	21	2	36	3
No-AR	9	87	1	100	3	43
Sensitivity (95% CI)	82.98% (69.19%–92.35%)		91.30% (71.96%–98.93%)		92.31% (79.13%–98.38%)	
Specificity (95% CI)	90.63% (82.95%–95.62%)		99.01% (94.61%–99.97%)		93.48% (82.1%–98.63%)	
PPV (95% CI)	81.25% (68.06%–89.81%)		95.46% (78.20%–99.19%)		93.21% (79.68%–97.35%)	
NPV (95% CI)	91.58% (84.25%–95.67%)		98.04% (93.13%–99.46%)		93.48% (82.45%–97.76)	
AUC (95% CI)	0.94 (0.91–0.98)		0.95 (0.88–1.00)		0.92* (0.86–0.98)	

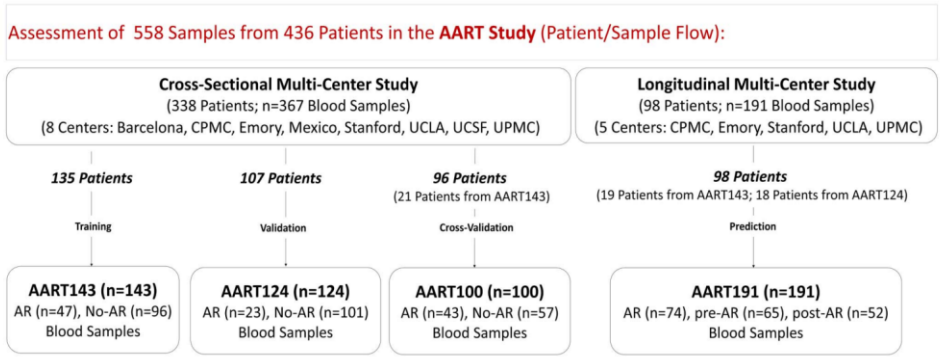
*AUC was calculated based on kSORT scores for $n = 100$ patients including high risk for AR ($n = 39$), low risk for AR ($n = 46$), and indeterminate ($n = 15$).
NPV, negative predictive value.
doi:10.1371/journal.pmed.1001759.t002

PLoS Med. 2014 Nov; 11(11): e1001759.

The kSORT Assay to Detect Renal Transplant Patients at High Risk for Acute Rejection: Results of the Multicenter AART Study

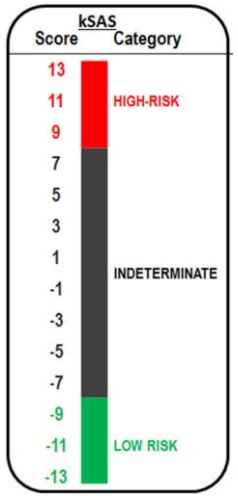
Silke Roedder[1☯], Tara Sigdel[1☯], Nathan Salomonis[2☯], Sue Hsieh[1], Hong Dai[3¤a], Oriol Bestard[4], Diana Metes[5], Andrea Zeevi[5], Albin Gritsch[6], Jennifer Cheeseman[7], Camila Macedo[5], Ram Peddy[3], Mara Medeiros[8], Flavio Vincenti[1], Nancy Asher[1], Oscar Salvatierra[9], Ron Shapiro[5], Allan Kirk[7¤b], Elaine Reed[6], Minnie M. Sarwal[1*]

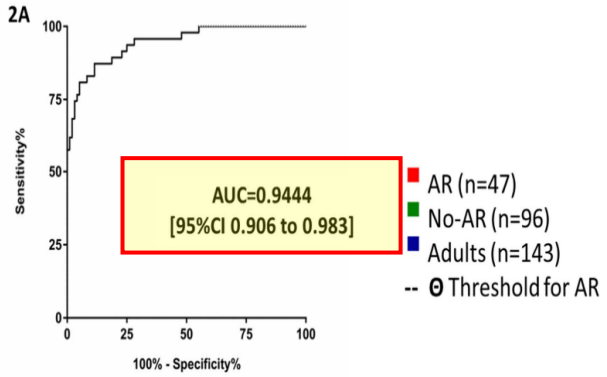
KSORT akut rejeksiyonu tespit edebiliyor



AR için anlamlı 17 genin ekspresyonu için tarama (PCR)

- Apotozis
- Lökosit trafiği
- Monosit aktivasyonu
- Hücre sağkalımı





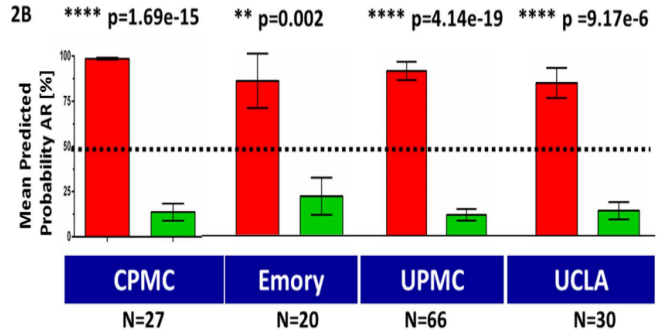


Table 2. Performance of kSORT in the AART143, AART124, and AART100 cohorts.

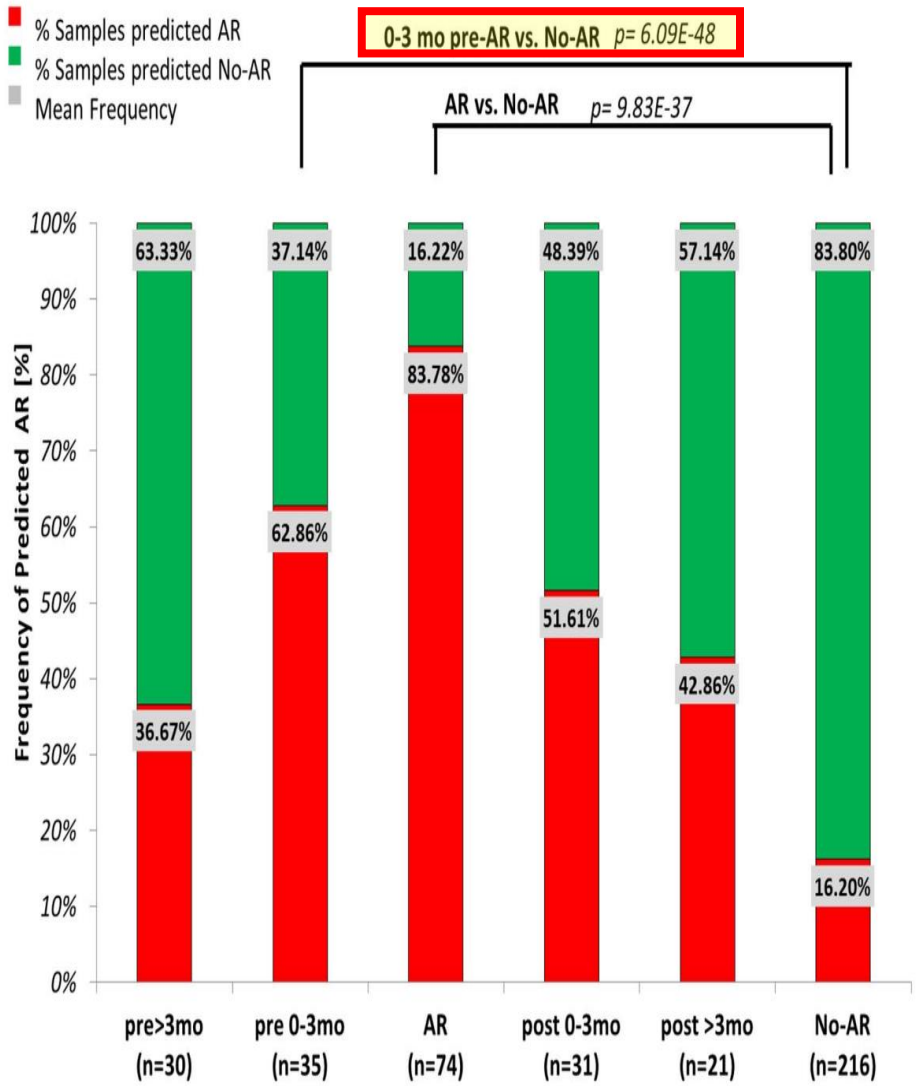
Statistics	kSORT Predictions					
	AART143 (Training Set)		AART124 (Validation Set)		AART100 (Cross-Validation Set)	
	AR	No-AR	AR	No-AR	AR	No-AR
Real Results						
AR	39	8	21	2	36	3
No-AR	9	87	1	100	3	43
Sensitivity (95% CI)	82.98% (69.19%–92.35%)		91.30% (71.96%–98.93%)		92.31% (79.13%–98.38%)	
Specificity (95% CI)	90.63% (82.95%–95.62%)		99.01% (94.61%–99.97%)		93.48% (82.1%–98.63%)	
PPV (95% CI)	81.25% (68.06%–89.81%)		95.46% (78.20%–99.19%)		93.21% (79.68%–97.35%)	
NPV (95% CI)	91.58% (84.25%–95.67%)		98.04% (93.13%–99.46%)		93.48% (82.45%–97.76)	
AUC (95% CI)	0.94 (0.91–0.98)		0.95 (0.88–1.00)		0.92* (0.86–0.98)	

*AUC was calculated based on kSORT scores for $n = 100$ patients including high risk for AR ($n = 39$), low risk for AR ($n = 46$), and indeterminate ($n = 15$).
NPV, negative predictive value.
doi:10.1371/journal.pmed.1001759.t002

Validasyon kohortları da benzer

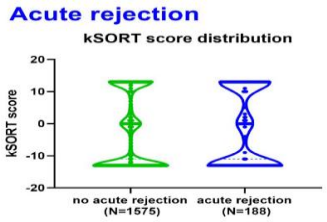
PLoS Med. 2014 Nov; 11(11): e1001759.

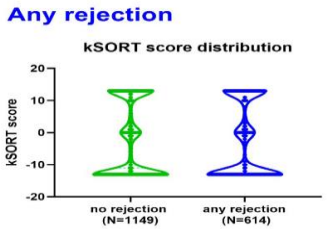
KSORT akut rejeksiyon gelişebileceğini 3 ay öncesinden öngörebiliyor



PLoS Med. 2014 Nov; 11(11): e1001759.

Performansı hakkında negatif sonuçlar da mevcut





Presence vs absence of acute rejection (TCMR and/or ABMR)				
Sample Characteristic	No acute rejection (N = 1575)	Acute rejection (N = 188)	Total (N = 1763)	*P* value
Donor-specific HLA antibodies	349/1548 (22.55%)	95/185 (51.35%)	444/1733 (25.62%)	<.0001
eGFR (mL/min/1.73m^2)*	46.0 ± 19.7	36.4 ± 21.3	45.0 ± 20.1	<.0001
Proteinuria (g/24h)*	0.17 (0.10;0.30)	0.30 (0.17;0.64)	0.18 (0.10;0.38)	.009
Biopsy timing after transplant	361 (91;370)	148.0 (30;365)	358.0 (90;370)	<.0001
Biopsy quality				
Adequate	1346/1572 (85.62%)	174/188 (92.55%)	1520/1760 (86.36%)	.01
Marginal	226/1572 (14.38%)	14/188 (7.45%)	240/1760 (13.64%)	
Type of biopsy				
Protocol biopsy	1194/1575 (75.81%)	82/188 (43.62%)	1276/1763 (72.38%)	<.0001
Indication biopsy	381/1575 (24.19%)	106/188 (56.38%)	487/1763 (27.62%)	
kSORT score	−11.0 (−13;13)	−11.0 (−13;13)	−11.0 (−13;13)	.46
kSORT Rejection Risk Category				
Low risk (LR)	803/1575 (50.98%)	95/188 (50.53%)	898/1763 (50.94%)	.53
Indeterminate risk (IND)	294/1575 (18.67%)	26/188 (13.83%)	320/1763 (18.15%)	
High risk (HR)	478/1575 (30.35%)	67/188 (35.64%)	545/1763 (30.91%)	

Am J Transplant. 2021 Feb;21(2):740-750.

Application of TruGraf v1: A Novel Molecular Biomarker for Managing Kidney Transplant Recipients With Stable Renal Function

C.L. Marsh[a,b,*], S.M. Kurian[b], J.C. Rice[a], T.C. Whisenant[c], J. David[d], S. Rose[d], C. Schieve[d], D. Lee[d], J. Case[b], B. Barrick[b], V.R. Peddi[e], R.B. Mannon[f], R. Knight[g], D. Maluf[h], D. Mandelbrot[i], A. Patel[j], J.J. Friedewald[k], M.M. Abecassis[k], and M.R. First[d,k]

[a]Scripps Center for Organ Transplantation, La Jolla, California, United States; [b]Scripps Clinic Bio-Repository and Transplantation Research, La Jolla, California, United States; [c]University of California, San Diego, School of Medicine, Center for Computational Biology and Bioinformatics, La Jolla, California, United States; [d]Transplant Genomics Inc, Mansfield, Massachusetts, United States; [e]California Pacific Medical Center, San Francisco, California, United States; [f]University of Alabama School of Medicine, Birmingham, Alabama, United States; [g]Houston Methodist Hospital, Houston, Texas, United States; [h]University of Virginia, Charlottesville, Virginia, United States; [i]University of Wisconsin, Madison, Wisconsin, United States; [j]Henry Ford Hospital, Detroit, Michigan, United States; and [k]Comprehensive Transplant Center, Northwestern University, Chicago, Illionis, United States

- 192 hasta
- 7 merkez
- 120 farklı genin ekspresyonu
  - TX (Transplant eXcellence)
  - Not-TX (renal disfonksiyon/rejeksiyon)

Table 1A. Results of TruGraf Blood Test and Comparison With Clinical Phenotype in All 192 Kidney Transplant Recipients with Stable Renal Function

	Clinical Phenotype not-TX	Clinical Phenotype TX
TruGraf Blood Test not-TX	26	42
TruGraf Blood Test TX	8	116

Accuracy = 142/192 (74%).
Accuracy of TruGraf TX result 116/124 (94%).
NPV = 91%.
PPV = 48%.
Sensitivity = 76%.
Specificity = 73%.

Table 1B. Results of TruGraf Blood Test and Comparison With Clinical Phenotype in 99 Kidney Transplant Recipients With Stable Renal Function and Biopsy-Confirmed Phenotypes

	Clinical Phenotype Not-TX	Clinical Phenotype TX
TruGraf Blood Test not-TX	17	19
TruGraf Blood Test TX	7	56

Accuracy = 73/99 (74%).
Accuracy of TruGraf TX result 56/63 (89%).
NPV = 89%.
PPV = 48%.
Sensitivity = 71%.
Specificity = 75%.

Transplant Proc. 2019 Apr;51(3):722-728.

Validation of a Blood Gene Expression Classifier to Differentiate Immune Quiescence from Rejection

Kidney360

DCAF12
MARCH8
FLT3
IL1R2
PDCD1

5 gene classifier (Developed on 56 peripheral blood samples)

AlloMap Kidney

PRIMARY Validation set

Q samples 98
R samples 18
7 TCMR
10 ABMR
1 Mixed

SECONDARY Validation set

Q samples 8
R samples 11
7 TCMR
2 ABMR
2 Mixed

Q, quiescence; R, rejection

AlloMap Kidney Classifier Scores

	PRIMARY Validation	SECONDARY Validation
Quiescence	**9.49** (7.68-11.53) *Median*	The cohorts were statistically different and the medians were similar to the primary validation set
Rejection	**13.09** (11.25-15.28) *Median*	
	p<0.001	*p=0.028*
AUC for discriminating rejection	**0.786**	**0.800**

0.894 AUC

The ability to discriminate rejection from quiescence was improved when AlloSure and AlloMap Kidney were used together

Conclusions Validation of AlloMap Kidney demonstrated the ability to differentiate between rejection and immune quiescence using a range of scores. The diagnostic performance suggests that assessment of the mechanisms of immunological activity is complementary to allograft injury information derived from AlloSure dd-cfDNA.

Enver Akalin, Matthew R. Weir, Suphamai Bunnapradist, et al. ***Clinical Validation of an Immune Quiescence Gene Expression Signature in Kidney Transplantation.*** *Kidney360*. DOI: 10.34067/KID.0005062021
Visual Abstract by Edgar Lerma, MD, FASN

AlloMap Kidney Skor 11.5 → maksimum spesifite, sensitivite

A peripheral blood gene expression signature to diagnose subclinical acute rejection

METHODS

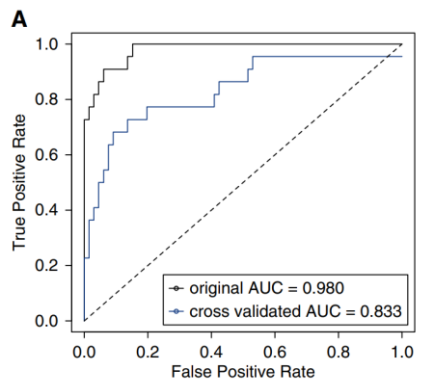
Discovery of 17 gene set for Acute Cellular Rejection (ACR) diagnosis

- Transcriptomic Analysis (N=127)
  - Discovery Cohort (RNA-seq, N=88)
  - Validation Cohort (Microarray, N=65)

Development of Targeted Expression (TREx) Assay

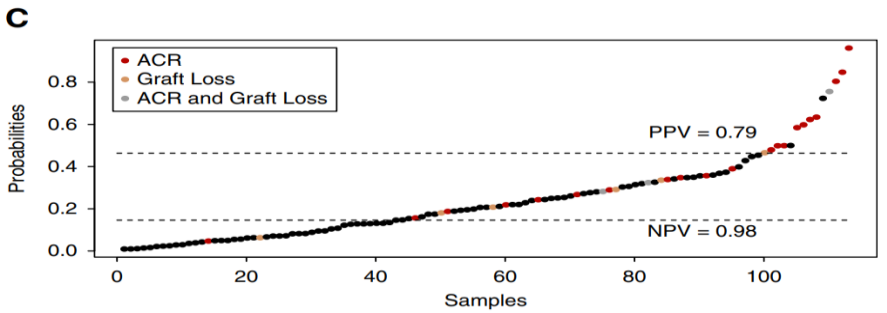
- GoCAR* Training (N=113)
  - Logistic Regression Model
    - GoCAR Testing (N=64)
    - Belgian Testing (N=46)

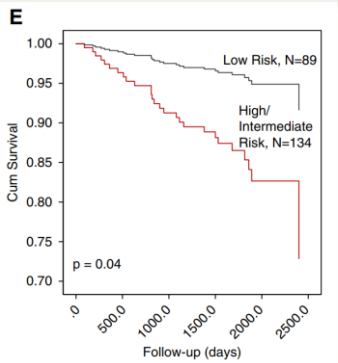
*GoCAR: Genomics of Chronic Allograft Rejection study



OUTCOMES

1. RNA sequencing identified a 17 gene set for accurate diagnosis of subclinical acute rejection
2. TREx assay based on the 17 gene set achieved PPV=0.79 and NPV=0.98 for subclinical ACR diagnosis
3. The patients with high or intermediate risk sores had high risk of graft loss





CONCLUSION: The TREx assay allows the noninvasive diagnose of subclinical acute rejection in the graft and may represent a useful tool to risk-stratify kidney transplant recipients.

doi: 10.1681/ASN.2018111098

TREx: Subklinik TCMR için Tanısal ve prognostik

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Can blood gene expression assays and donor-derived cellfree DNA be used to diagnose subclinical rejection?

CJASN
Clinical Journal of the American Society of Nephrology

Methods

Post hoc analysis
Clinical Trials in Organ Transplantation 08

Surveillance biopsies
2 to 6, 12, and 24 months post-transplant

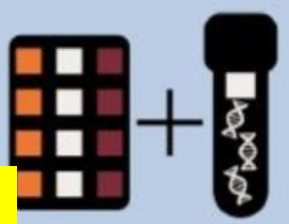
208 subjects
428 biopsy samples

2011 – 2014

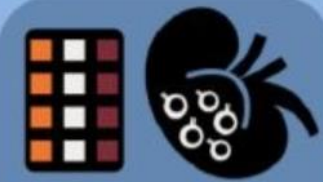
Results

TruGraf

TRAC (Eurofins)



Diagnosis of Subclinical Rejection	Gene Expression Profile Assay (95% CI)	Donor Derived cfDNA (95% CI)	Combined Tests (95% CI)
Positive Predictive Value	47% (0.35- 0.59)	56% (0.44-0.67)	81% (0.63-0.95)
Negative Predictive Value	82% (0.78-0.86)	84% (0.80-0.88)	88% (0.84-0.92)
AUROC	0.75	0.72	0.81



Gene expression profile better at detecting cellular rejection

AUROC 0.80 vs. 0.62, P=0.001

Donor Derived cfDNA better at detecting antibody rejection

AUROC 0.84 vs. 0.71, P=0.003

Conclusions Donor-derived cellfree DNA and gene expression profiles provide a less invasive monitoring strategy for subclinical rejection, with different detection of antibody- and cell-mediated rejection.

Sookhyeon Park, Kexin Guo, Raymond L. Heilman, et al. ***Combining Blood Gene Expression and Cell-Free DNA to Diagnose Subclinical Rejection in Kidney Transplant Recipients***. CJASN doi: 10.2215/CJN.05530421. **Visual Abstract by Sinead Stoneman, MB BCh BAO, MRCPI**

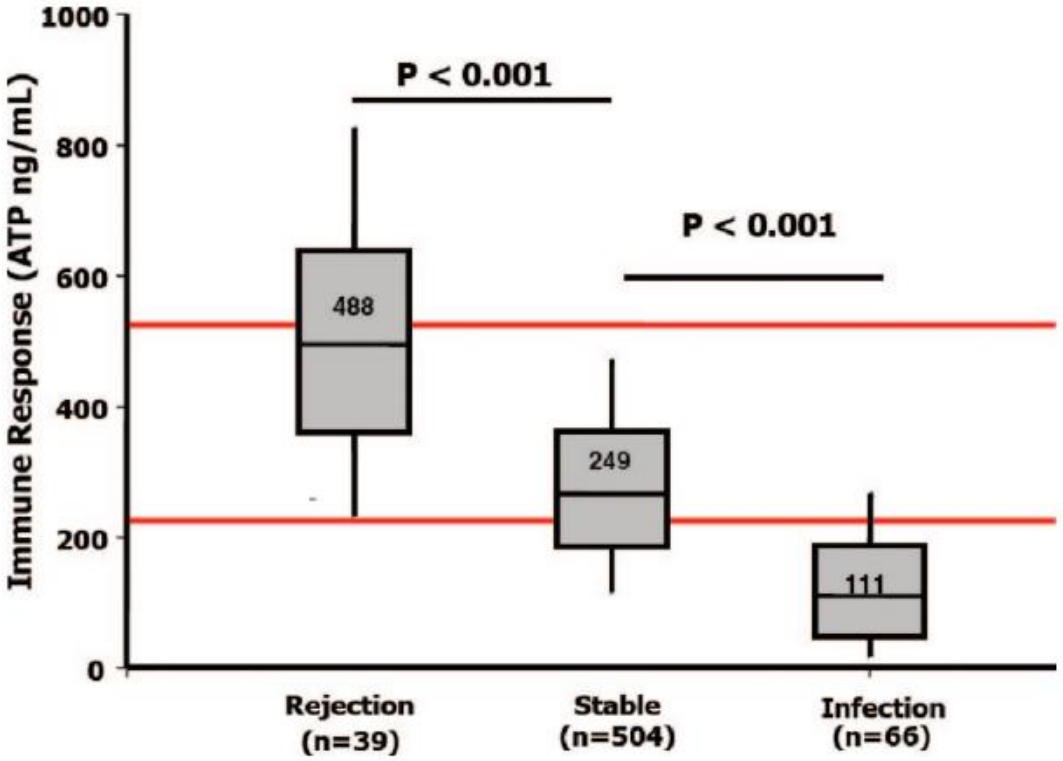
Clin J Am Soc Nephrol. 2021 Oct;16(10):1539-1551.

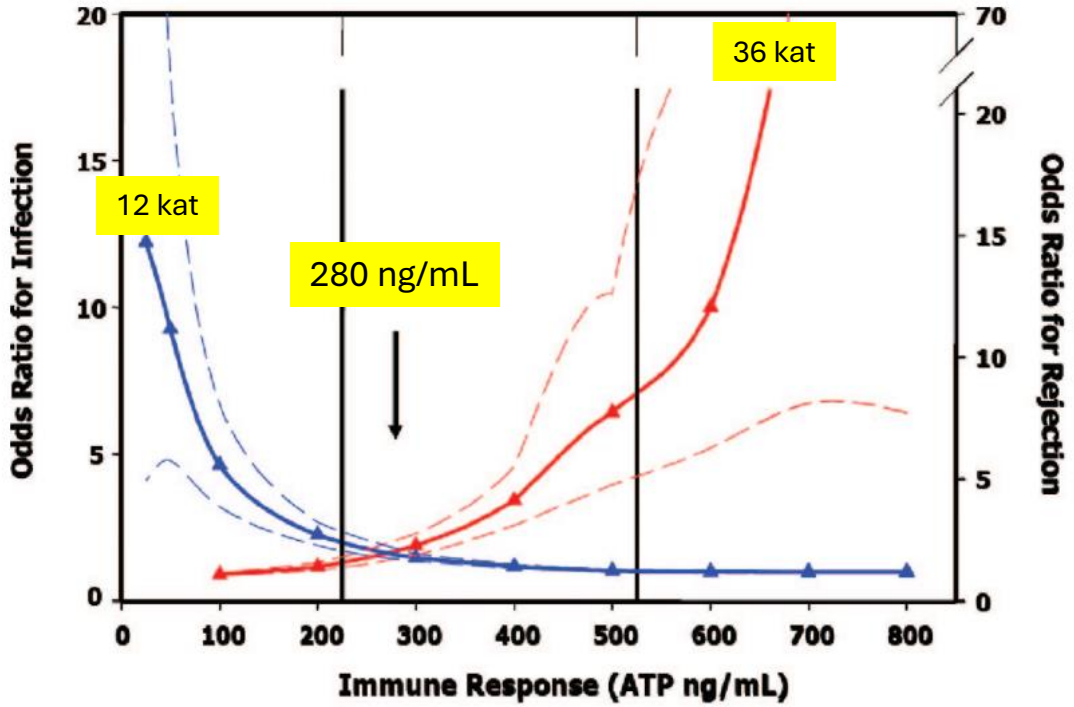
Assessing Relative Risks of Infection and Rejection: A Meta-analysis using an Immune Function Assay

Richard J. Kowalski,[1,11] Diane R. Post,[1] Roslyn B. Mannon,[2] Anthony Sebastian,[3] Harlan I. Wright,[3] Gary Sigle,[3] James Burdick,[4] Kareem Abu Elmagd,[5] Adriana Zeevi,[5] Mayra Lopez-Cepero,[6] John A. Daller,[7] H. Albin Gritsch,[8] Elaine F. Reed,[8] Johann Jonsson,[9] Douglas Hawkins,[10] and Judith A. Britz[1]

ImmuKnow

- Mitogen ile stimüle edilmiş CD4+T-hücrelerini intraselüler ATPdüzeylerini ölçer
- Yüksek ise rejeksiyon, düşük ise infeksiyon





ImmuKnow → Tanısal gücü tartışmalı

Table 4. Distribution of T cell assay (TCA, ImmuKnow) values in the setting of subsequent opportunistic infection (OI) *versus* controls without OI

TCA Result	OI (n = 94)	No OI (n = 94)
Low (≤225 ng/ml)	20 (21%)	16 (17%)
Moderate (226 to 524 ng/ml)	53 (57%)	52 (55%)
Strong (≥525 ng/ml)	21 (22%)	26 (28%)

The values are the percentages of tests.

Clin J Am Soc Nephrol. 2011 Feb;6(2):423-9.

Table 8. Sensitivity, specificity of a TCA ≥525, and acute rejection

	Versus Controls	*Versus* All Samples
Sensitivity	23.4	25.0
Specificity	80.9	77.5
Odds ratio	1.87	1.15
95% confidence interval	0.47 to 8.38	0.61 to 2.19

Performance of the ImmuKnow Assay in Differentiating Infection and Acute Rejection After Kidney Transplantation: A Meta-Analysis

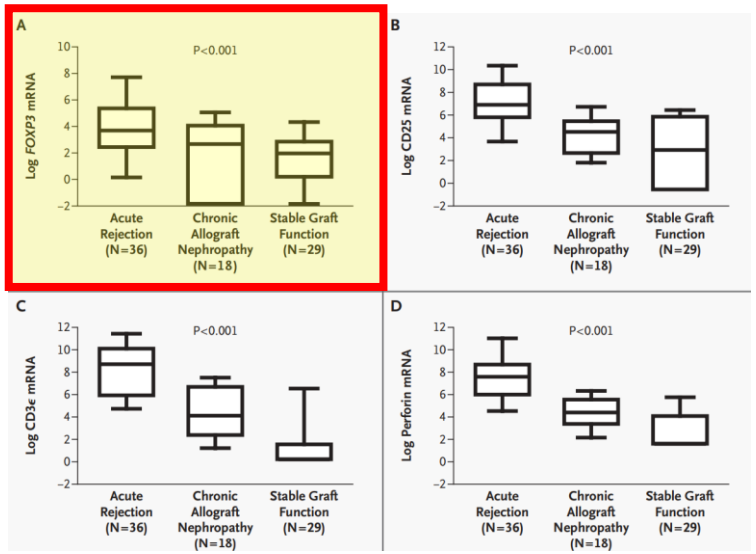
Z. Wang[a], X. Liu[a], P. Lu[a], Z. Han[a], J. Tao[a], J. Wang[b], K. Liu[c], B. Wu[a], C. Yin[a], R. Tan[a], and M. Gu[a,*]

[a]Department of Urology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [b]Department of Urology, Nanjing Children's Hospital, Nanjing, China; and [c]Department of Urology, Huai'an First People's Hospital, Huai'an, China

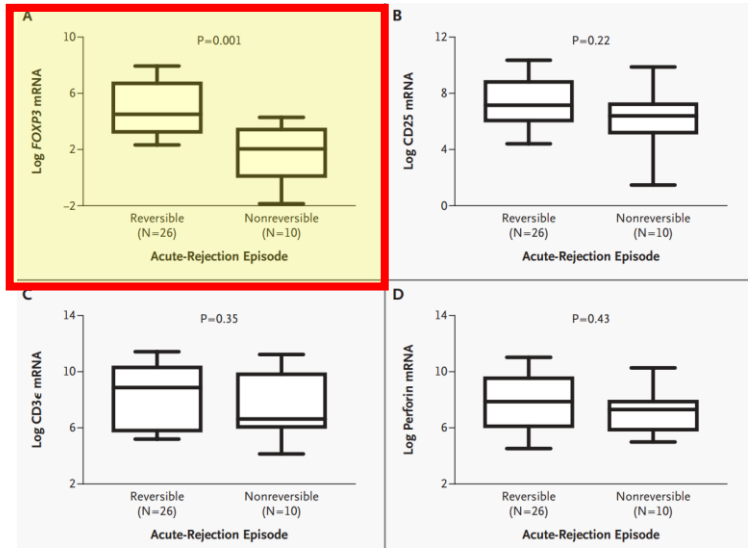
Conclusions. Our analysis did not support the use of the ImmuKnow assay to predict or monitor the risks of infection and acute rejection in renal transplant recipients. Further studies are needed to confirm the relationships between the ImmuKnow assay and infection and acute rejection in kidney transplantation.

Transplant Proc. 2014 Dec;46(10):3343-51.

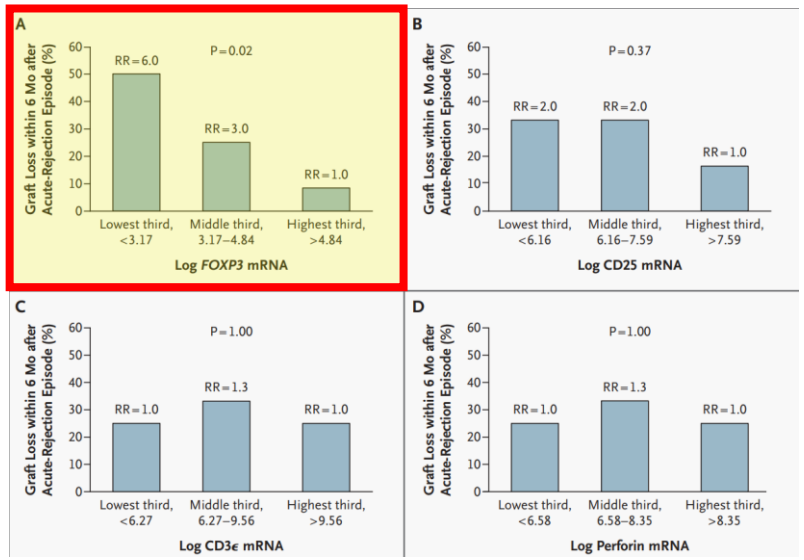
Treg markerı → FOXP3 (üriner mRNA düzeyleri)



Tanısal



Tedavi yanıtını ön gördürücü



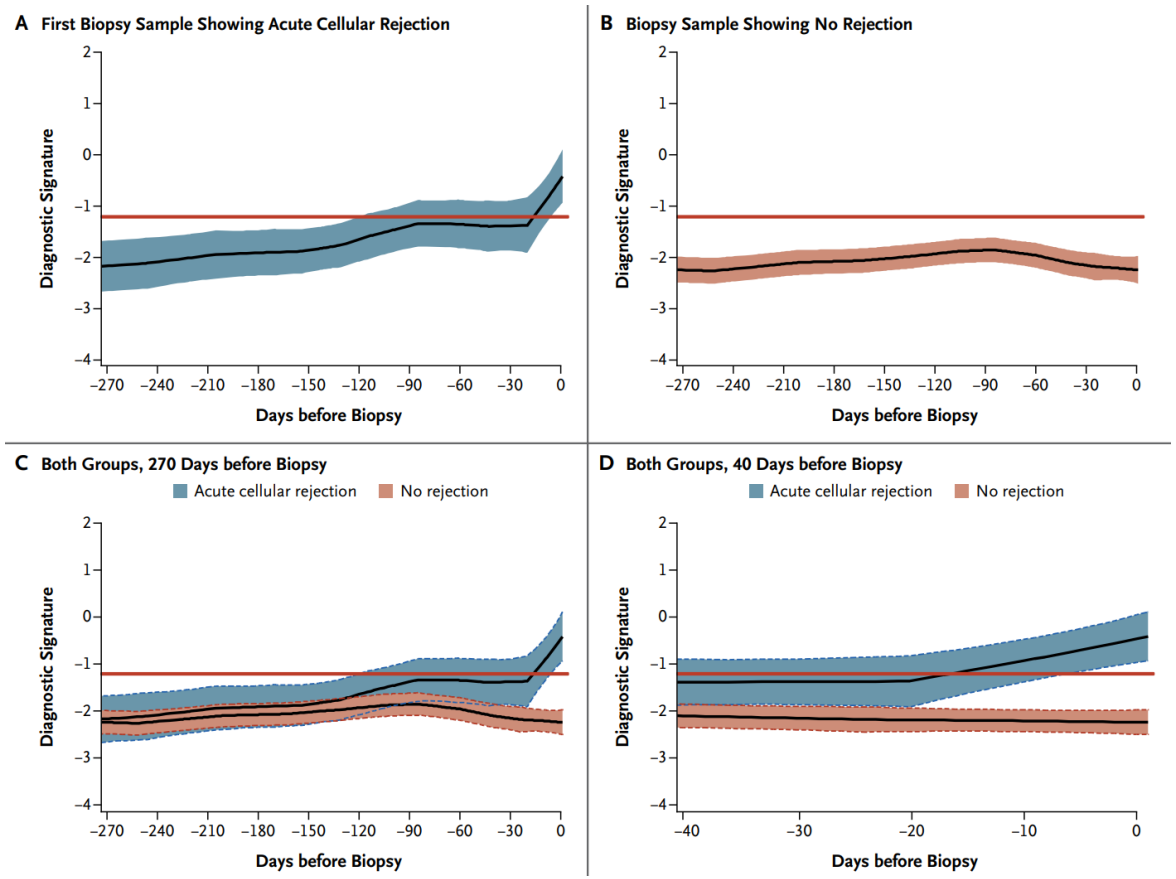
Prognostik

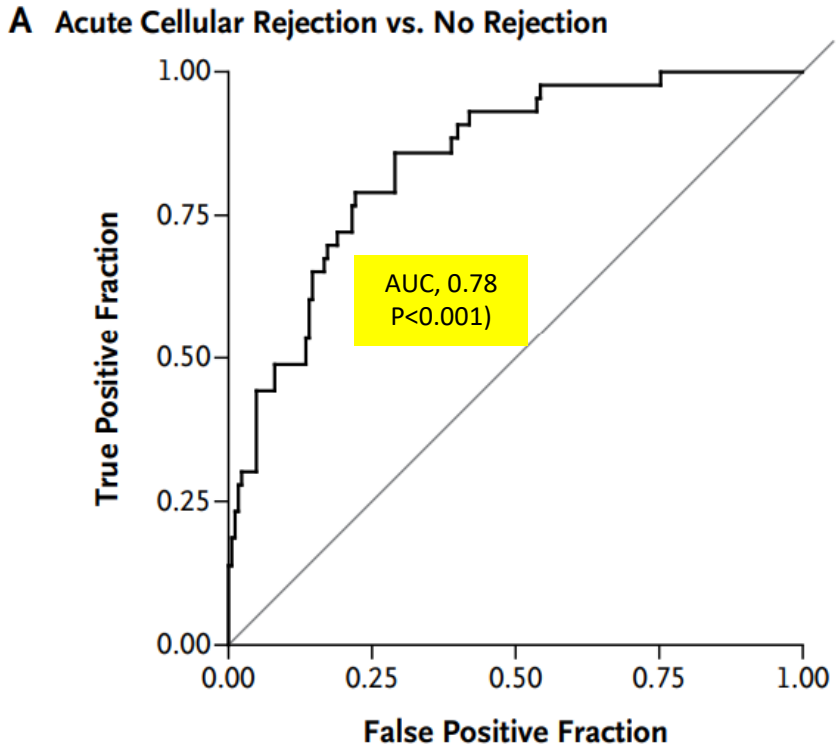
N Engl J Med. 2005 Dec 1;353(22):2342-51.

Urinary-Cell mRNA Profile and Acute Cellular Rejection in Kidney Allografts

485 hasta
4300 idrar örneği
3 gen imzası

- CD3ε mRNA
- İnterferon-inducible protein 10
- 18S rRNA



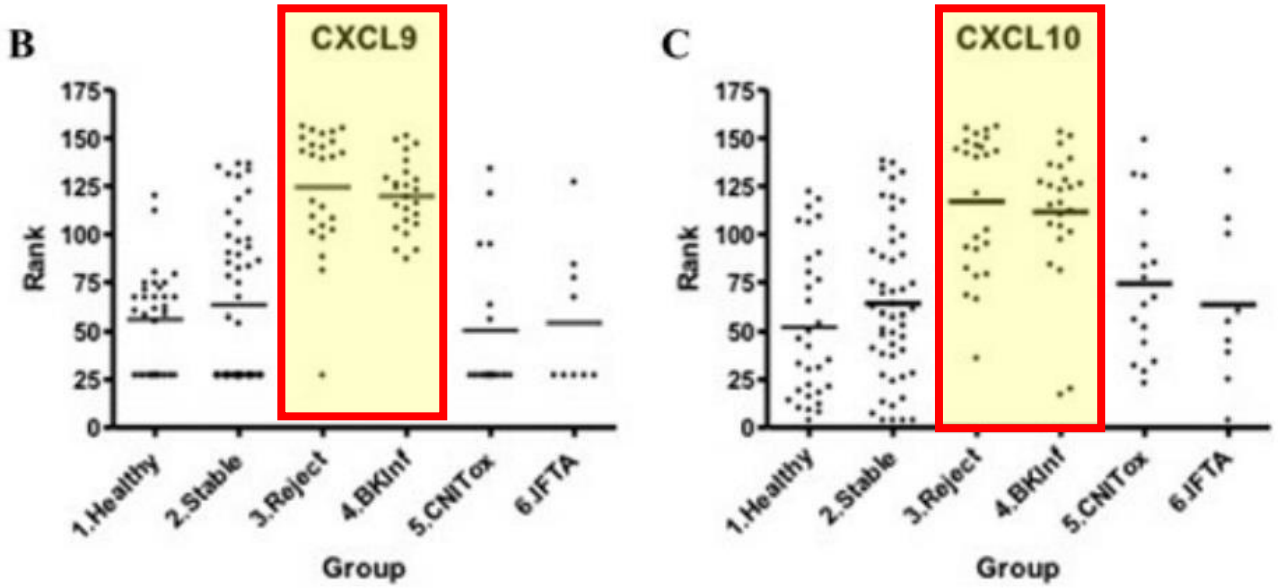


Rejeksiyondan önce m-RNA düzeyleri yükseliyor

N Engl J Med. 2013 Jul 4;369(1):20-31.

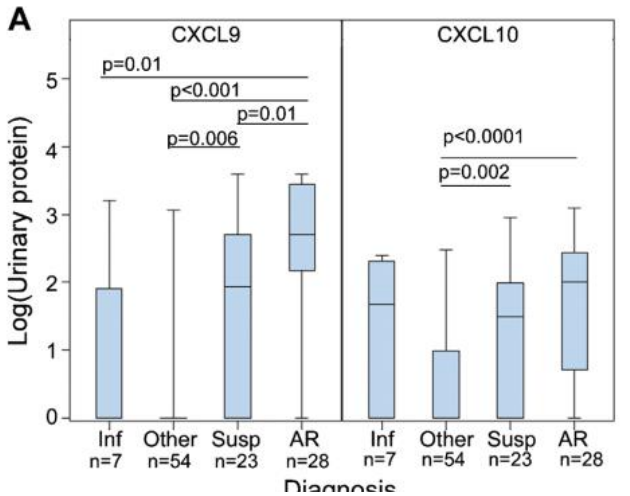
İdrar kemokinleri CXCL9-CXCL10

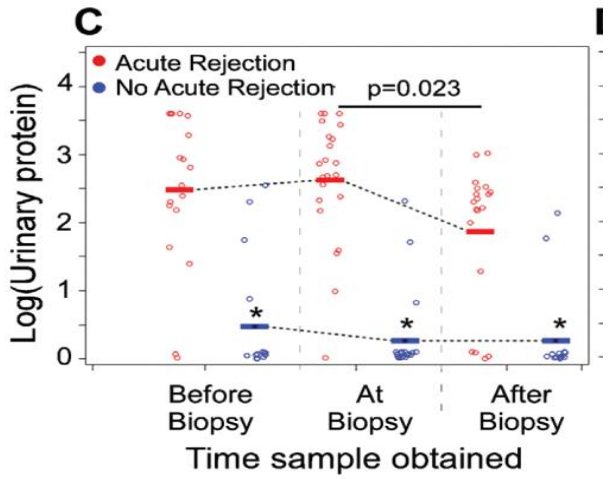
İlk çalışmalarda BK ile rejeksiyonda artıyor
Ancak ikisini birbirinden ayıramıyor



Am J Transplant. 2011 Oct;11(10):2228-34.

Sonraki çalışmalarda CXCL9 rejeksiyonu ayırt ediyor





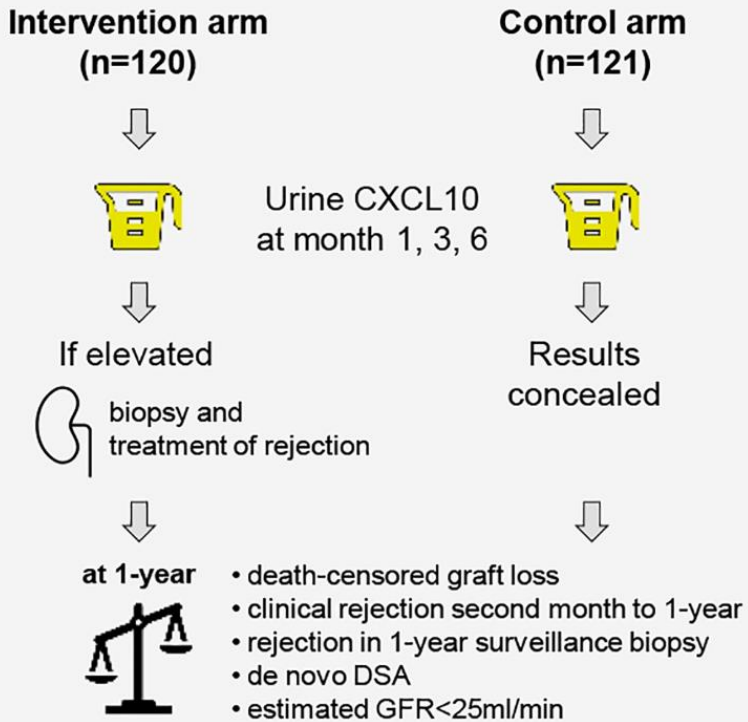
Am J Transplant. 2013; 13: 2634–2644

Randomized Trial to Assess the Clinical Utility of Renal Allograft Monitoring by Urine CXCL10 Chemokine

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

CXCL10 monitörizasyonu sonlanımları değiştirmiyor

METHODS



OUTCOME

	Intervention arm	Control arm	
1 Intention-to-treat analysis (n=241)			
Combined endpoint at 1-year	**51%**	**49%**	=
Individual endpoints at 1-year			
• death-censored graft loss	1%	2%	=
• clinical rejection second month to 1-year	13%	14%	=
• rejection in 1-year surveillance biopsy	45%	38%	=
• de novo DSA	5%	3%	=
• estimated GFR<25ml/min	1%	3%	=
2 Per-protocol analysis (n=175)			
Combined endpoint at 1-year	**55%**	**49%**	=
Individual endpoints at 1-year			=

Conclusion

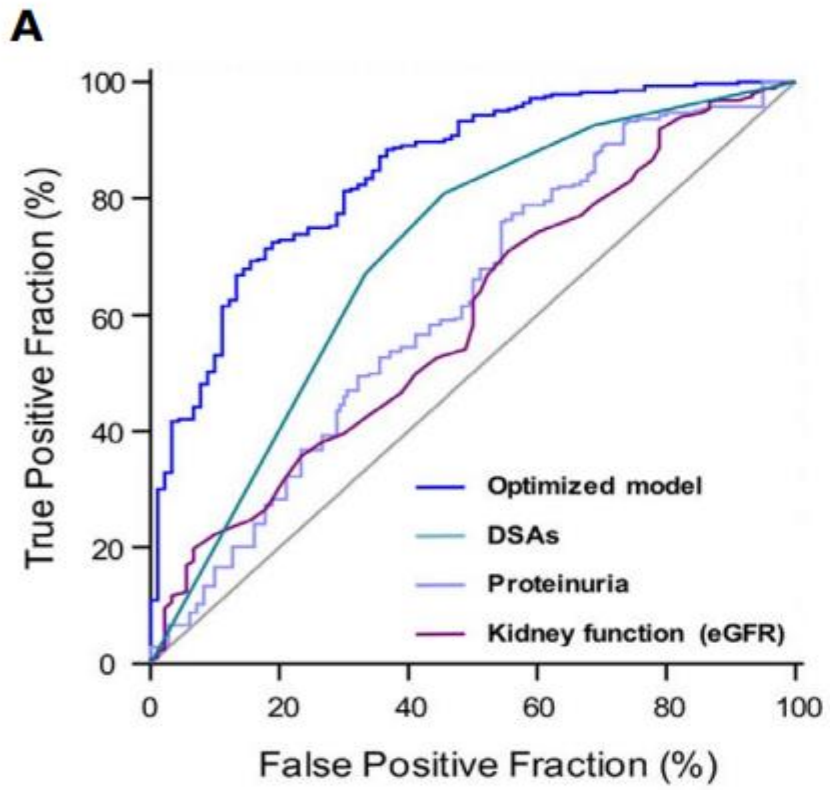
This study could not demonstrate a beneficial effect of urine CXCL10 monitoring on 1-year outcomes

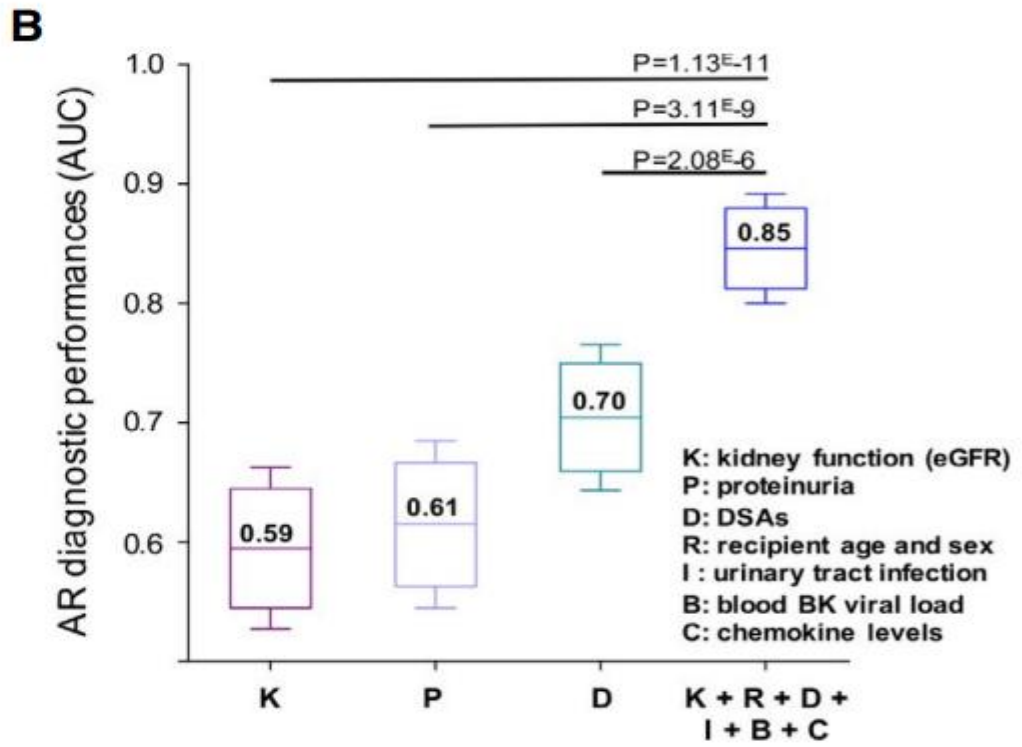
J Am Soc Nephrol. 2023 Aug 1;34(8):1456-1469.

Development and validation of an optimized integrative model using urinary chemokines for noninvasive diagnosis of acute allograft rejection

Claire Tinel[1,2,3,4] | Arnaud Devresse[1,5,6] | Agathe Vermorel[1] | Virginia Sauvaget[2] | David Marx[7] | Véronique Avettand-Fenoel[4,8] | Lucile Amrouche[1,2,4] | Marc-Olivier Timsit[4,9] | Renaud Snanoudj[10] | Sophie Caillard[7] | Bruno Moulin[7] | Jérome Olagne[7] | Marie Essig[11,12] | Wilfried Gwinner[13] | Maarten Naesens[14,15] | Pierre Marquet[12] | Christophe Legendre[1,2,3,4] | Fabiola Terzi[2] | Marion Rabant[2,4,16] | Dany Anglicheau[1,2,3,4]

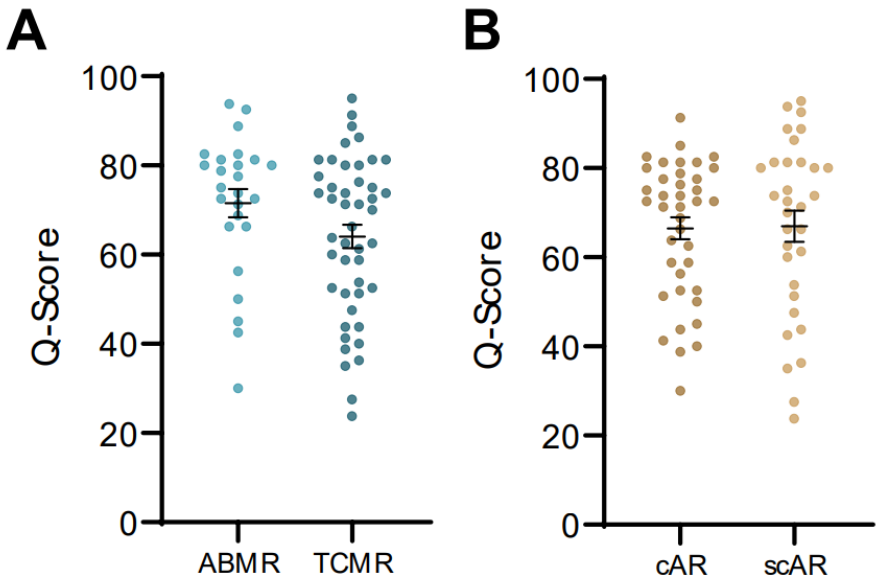
Kemokinler ile diğer değişkenlerin kombinasyonunun tanısal gücü daha yüksek



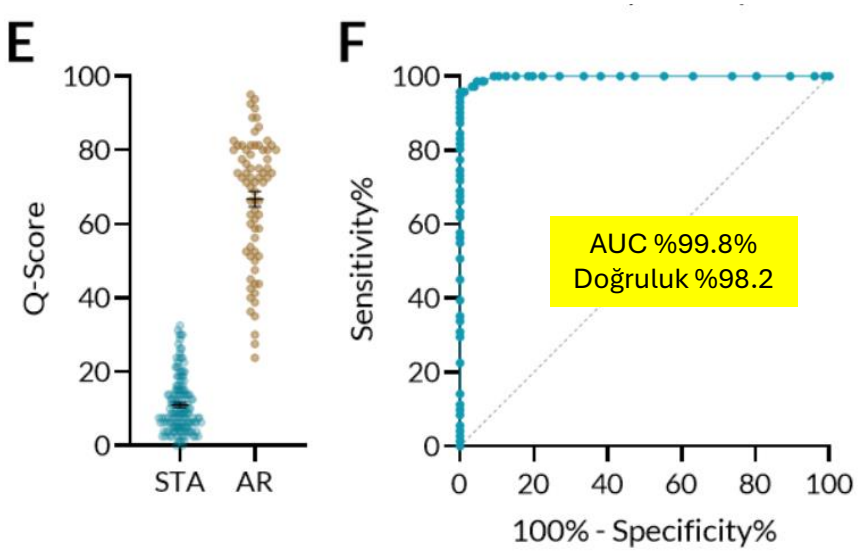


Am J Transplant. 2020 Dec;20(12):3462-3476.

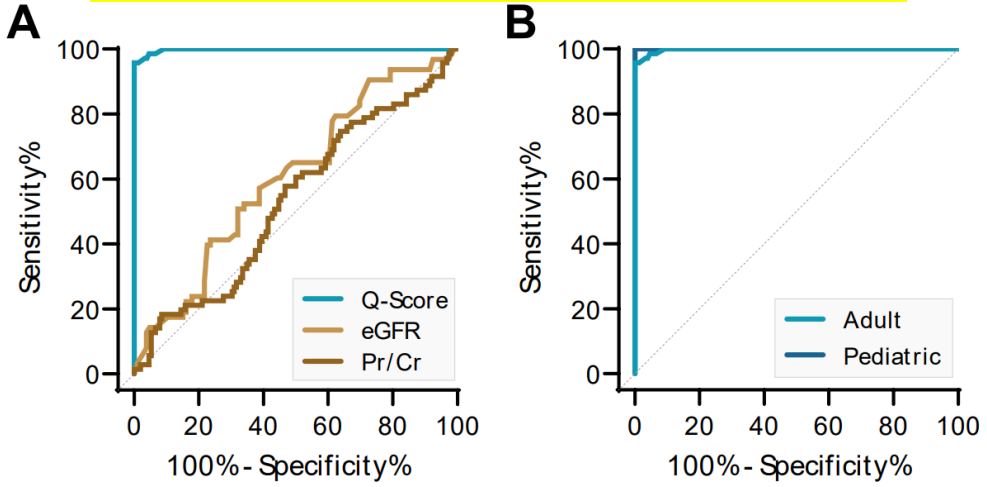
Qsant test: cell-free DNA, methylated-cell-free DNA, clusterin, CXCL10, kreatinin, proteinüri

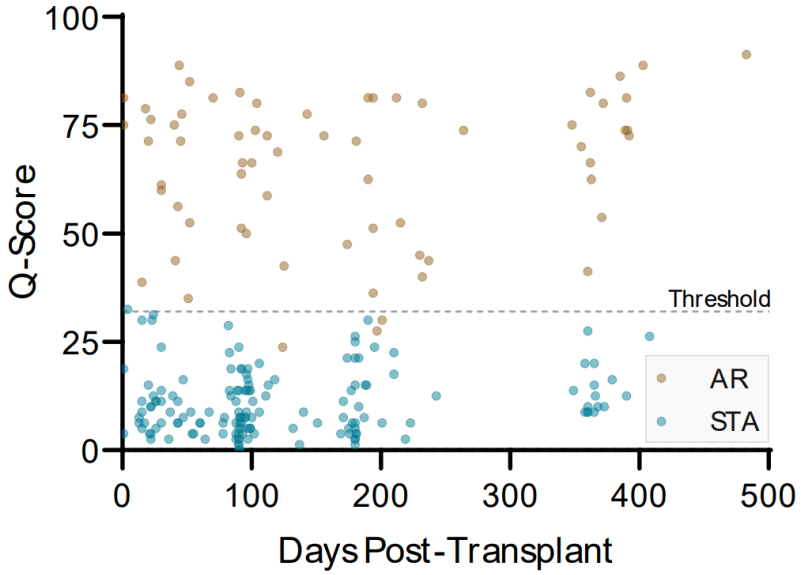


Q Score		
	<32	>=32
AR	1.95%	98.55%
No AR	98.05%	1.44%



Klinik/subklinik rejeksiyonları ayırt edebiliyor





Tüm yaş gruplarında konvansiyonel belirteçlerden daha üstün

J Clin Med. 2020 Jul 22;9(8):2325.