The role of acute cellular rejection in the development of HLA antibodies

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Cell mediated and humoral immunity

"There is no doubt that the cell-mediated immune response is the predominant factor in allograft rejection."

"These nonthymus-dependent lymphocytes can become actively sensitized against antigens, but in cell-mediated immunity they participate, if at all, in effector mechanisms only in association with thymus-dependent cells."

"Circulating antibody against donor cells…have been detected, by the use of specially sensitive techniques, while the transplanted organ was still in place, and there seems to be a definite correlation between this finding and the appearance of progressive lesions in the graft, especially vascular lesions."

- Hamburger J, Crosnier J, Dormont J, Bach J-F.
  Renal Transplantation: Theory and Practice, 1972

Cell mediated and humoral immunity

A half century later

- "…lack of association of subclinical TCMR with allograft survival, thus challenging the historical conclusion … that TCMR increases the risk of future graft loss…confirms the findings of recent clinical trials showing that indolent TCMR can be adequately treated and is not associated *per se* with graft loss…"

  - Loupy A et al, *JASN* 26: 1721, 2015

- "We conclude that the main cause of kidney transplant failure is ABMR, which can present even decades after transplantation. In contrast, TCMR disappears by 10 years post-transplant..."

  - Halloran PF et al, *JASN* 26: 1711, 2015

- "However, B cell depletion inhibited alloantibody generation and significantly extended allograft survival, indicating that donor-specific alloantibodies (not T cells) were the critical effector mechanism of renal allograft rejection induced by memory CD4 T cells."

  - Gorbacheva V et al, *JASN* 27: 3299, 2016

ABMR and TCMR

A case of TRANSPLANTESE?

ISO means equal

HOMO means same

"If two individuals are genetically identical, grafts exchanged between them are *equal* but *not* the same. On the other hand, if they are genetically different, their grafts *are* the *same*, but *not* equal. It is here that TRANSPLANTESE ceases to be homologous with English or indeed with common sense."

Gorer PA. *Annals NY Acad Sciences* 87: 604-7, 1960

TCMR and chronic rejection

Table 2. Relationship between acute rejection and chronic rejection[a]

Time after transplantation *months*	% Of transplants with acute rejection		Relative risk of acute rejection for CR (95% confidence interval)
	CR	No CR	
<3	57	44[b]	NS
3–6	25	7[b]	3.25 (2.08–5.09)[c]
6–12	22	8[b]	2.97 (1.88–4.68)[c]
12–24	40	13[b]	3.48 (2.32–5.22)[c]
>24	64	20[b]	10.47 (6.65–16.48)[c]

Abbreviation is: CR, chronic rejection.

[a] The percent of patients with acute rejection episodes, severe acute rejection (greater than 50% reduction in renal failure) and multivariate Cox relative risk (no risk = 1.00).

[b] $P < 0.01$

[c] $P \leq 0.000$

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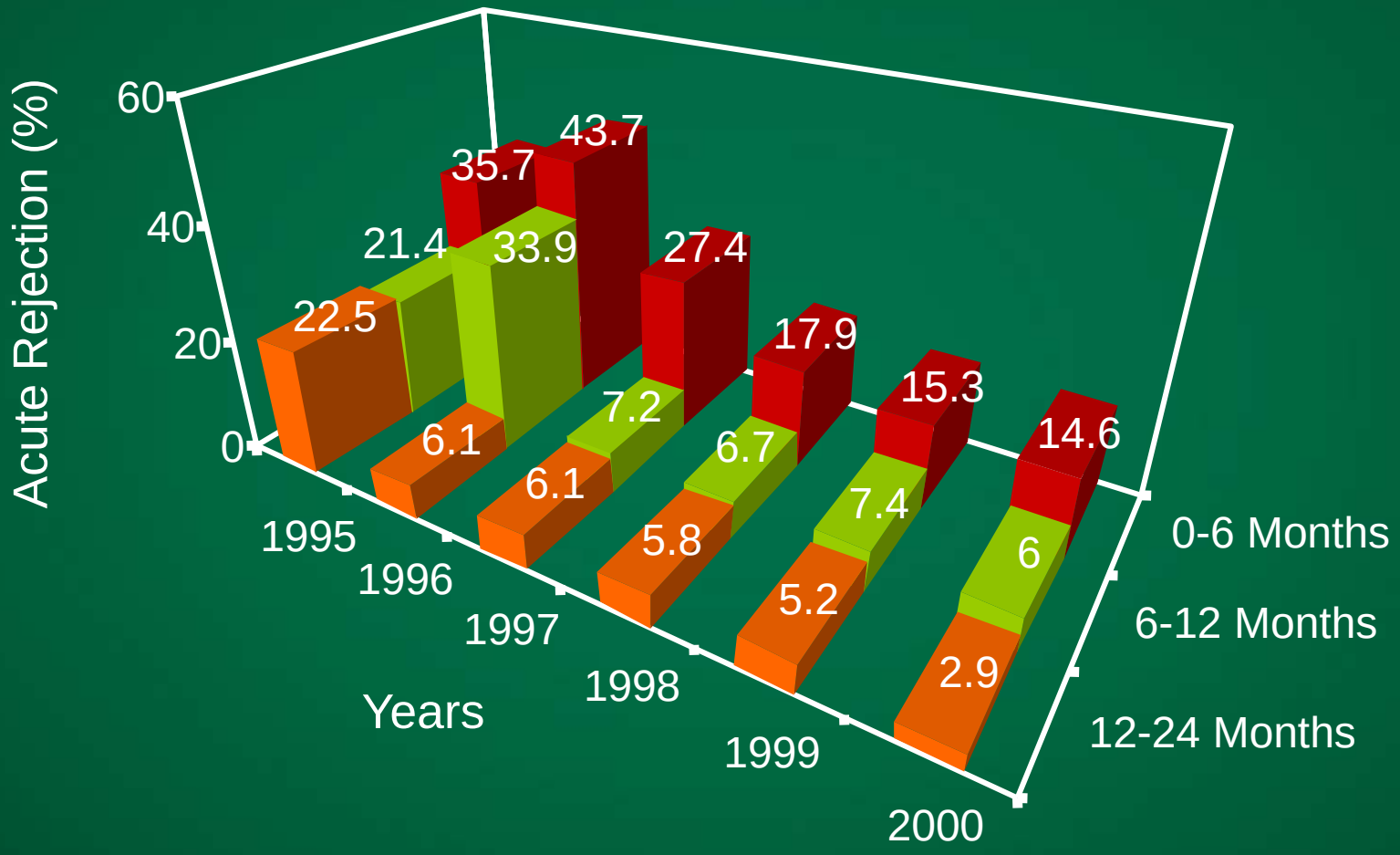
Massy Z et al.

Kidney Int 49: 518, 1996

TCMR and graft survival



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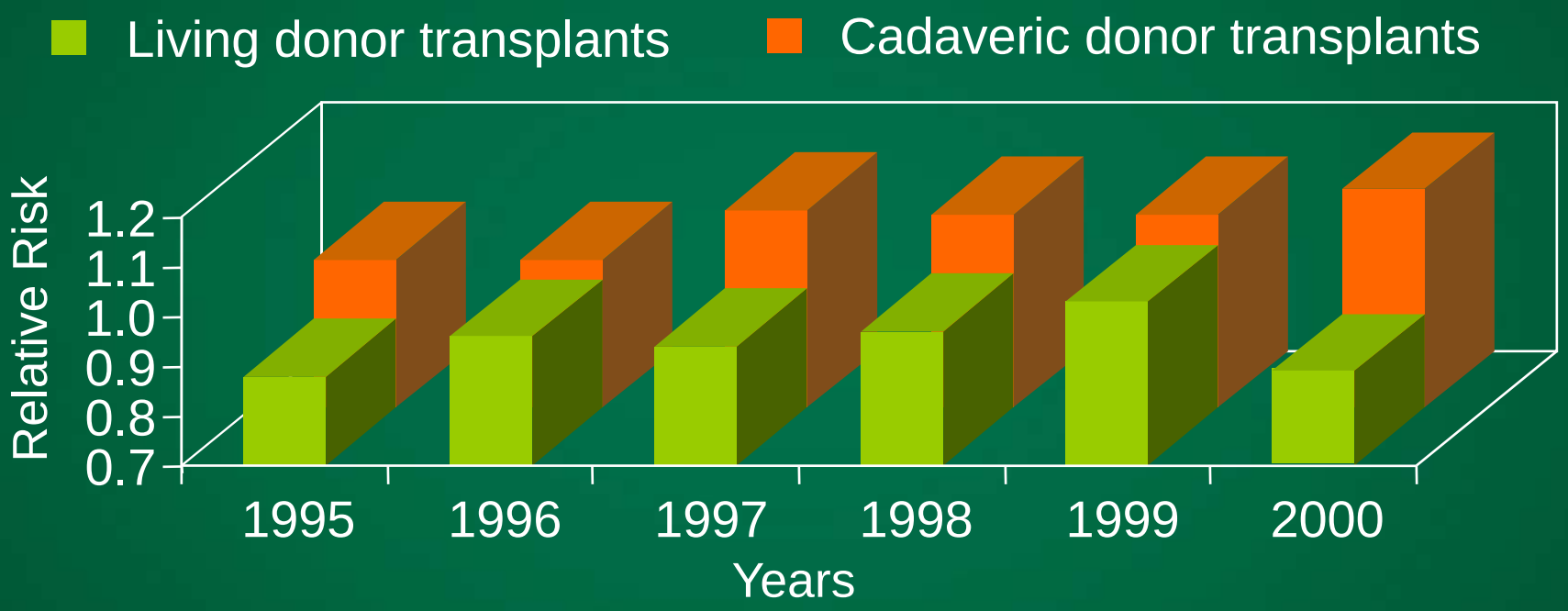
Meier-Kriesche H-U, et al.
Am J Transplant. 2004;4:378-383.

CMR and graft survival



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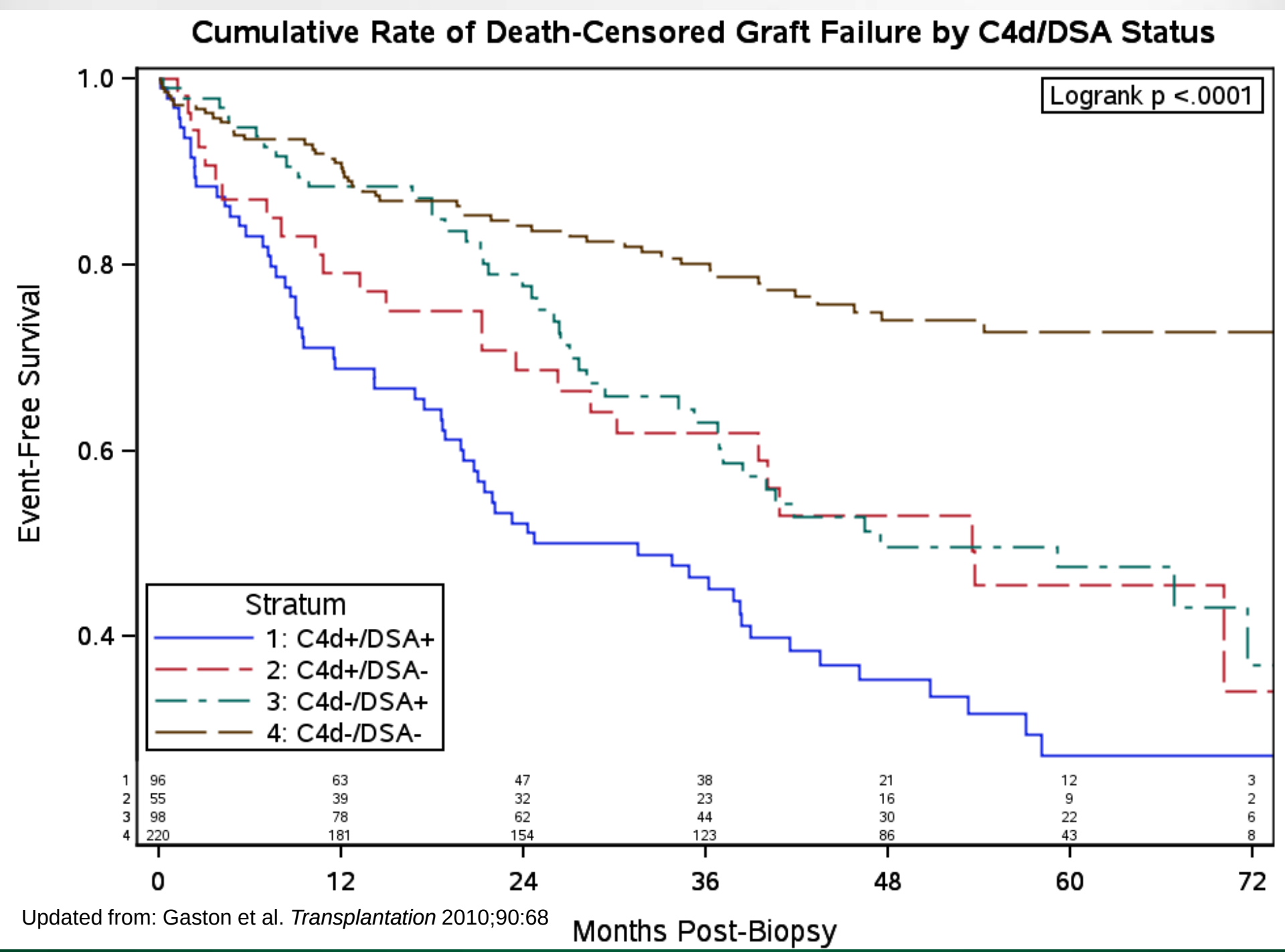
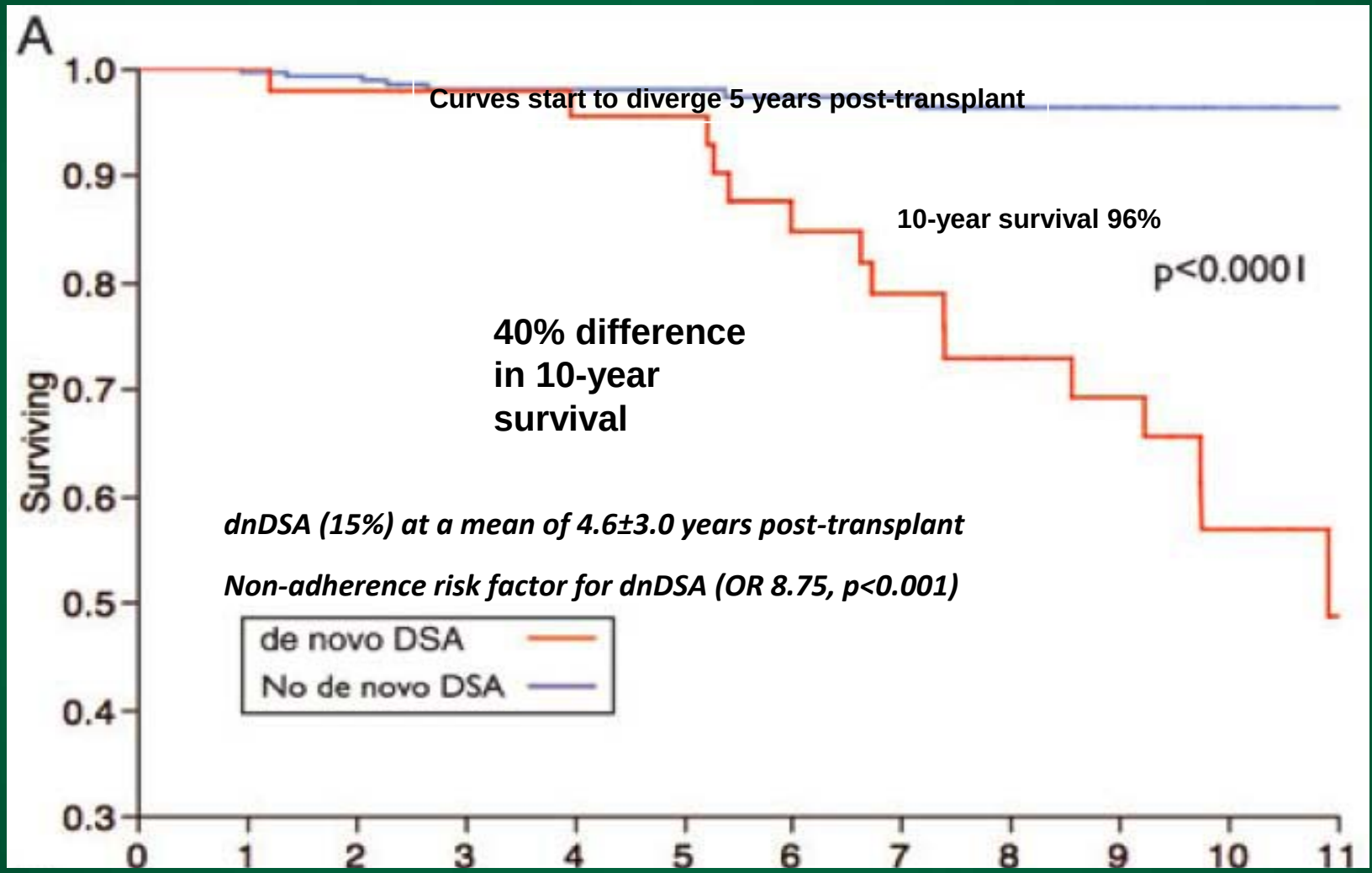


Updated from: Gaston et al. *Transplantation* 2010;90:68

*dn*DSA and graft survival



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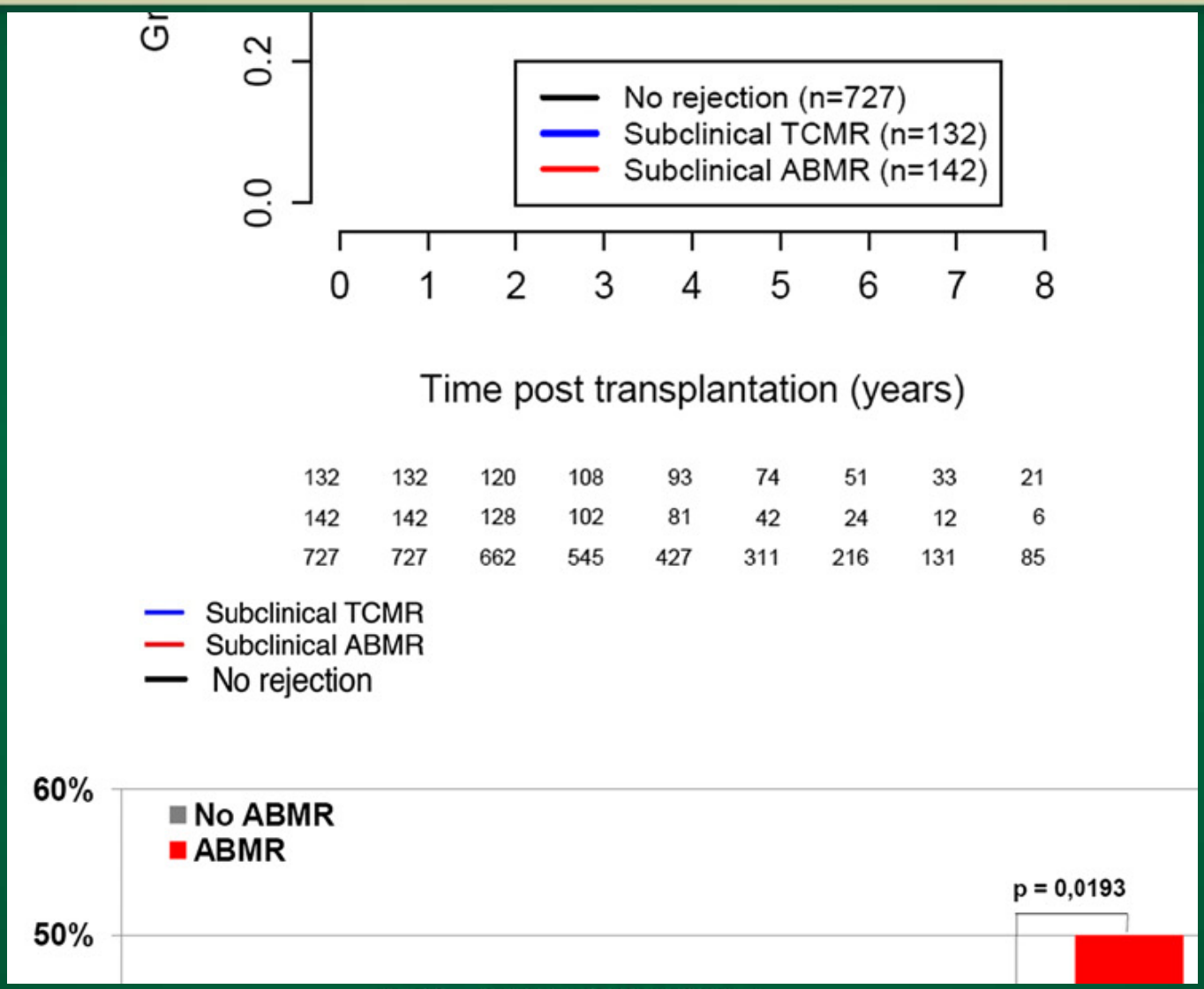
Wiebe C et al. *Am J Transplant* 2012;12:1157

Subclinical rejection and allograft failure



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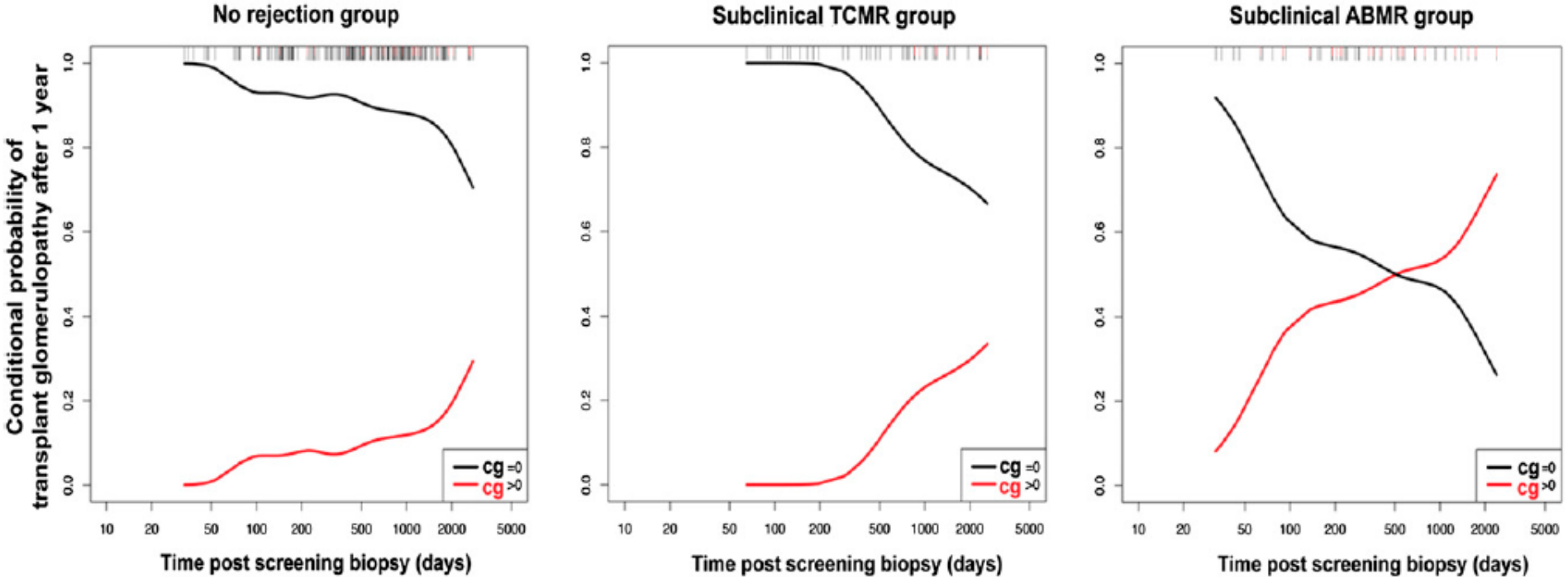
Loupy A et al,
JASN 26: 1721, 2015

Subclinical rejection and TG



In TCMR group, development of TG presaged by *dn*DSA

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Loupy A et al,
JASN 26: 1721, 2015

Disappearance of T Cell-Mediated Rejection Despite Continued Antibody-Mediated Rejection in Late Kidney Transplant Recipients

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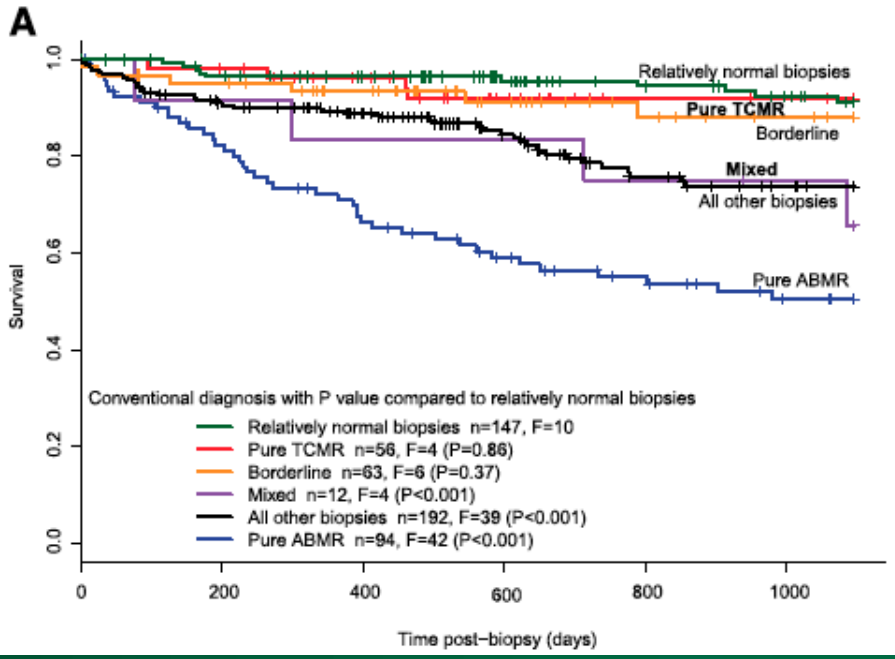
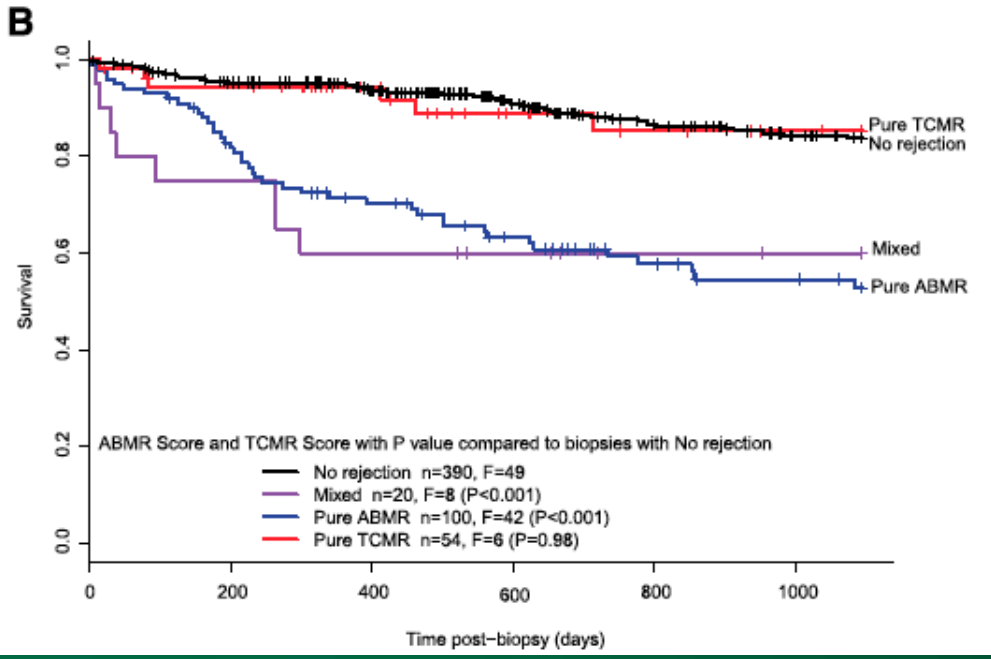
Halloran P et al.
J Am Soc Nephrol 26: 1711, 2015

Impact of processes on graft survival





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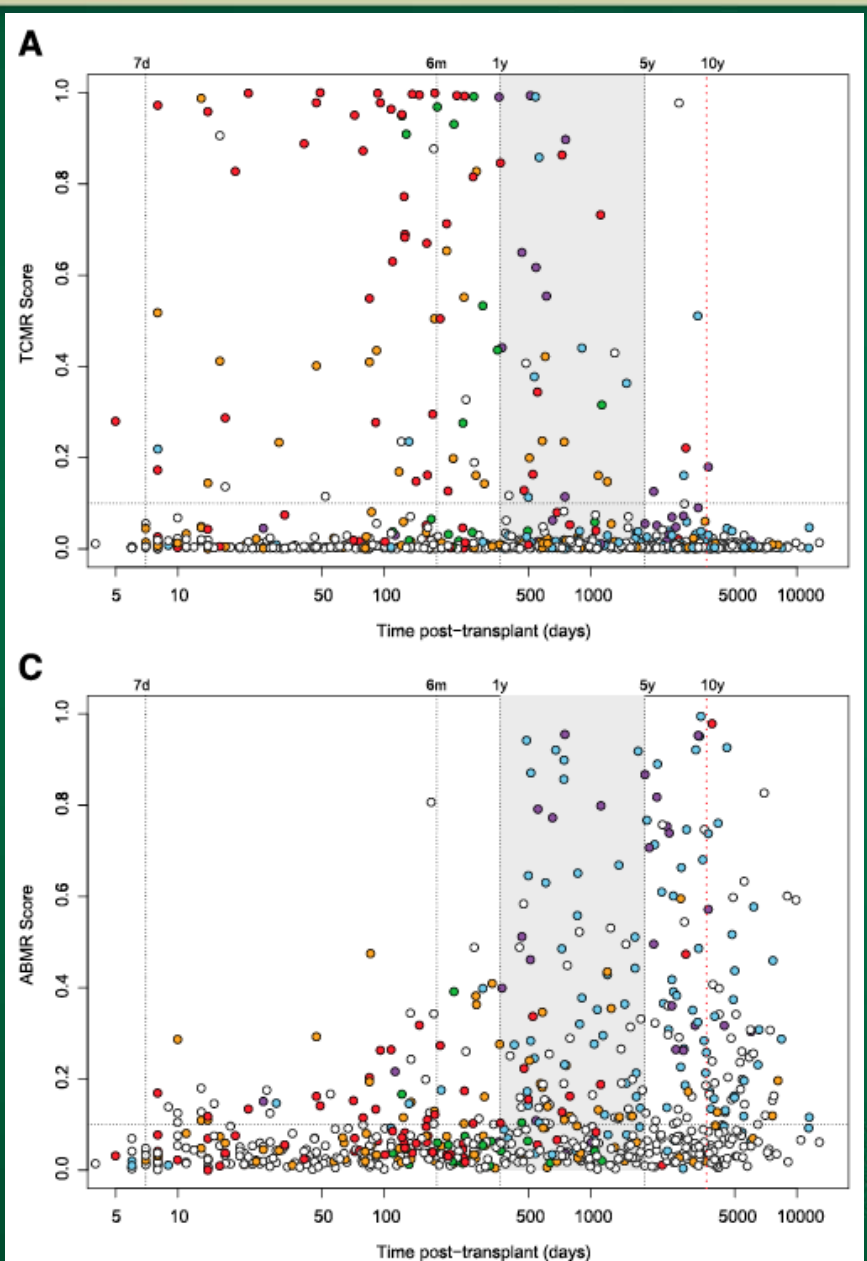
Halloran P et al.
J Am Soc Nephrol 26: 1711, 2015

Decline in TCMR transcripts over time



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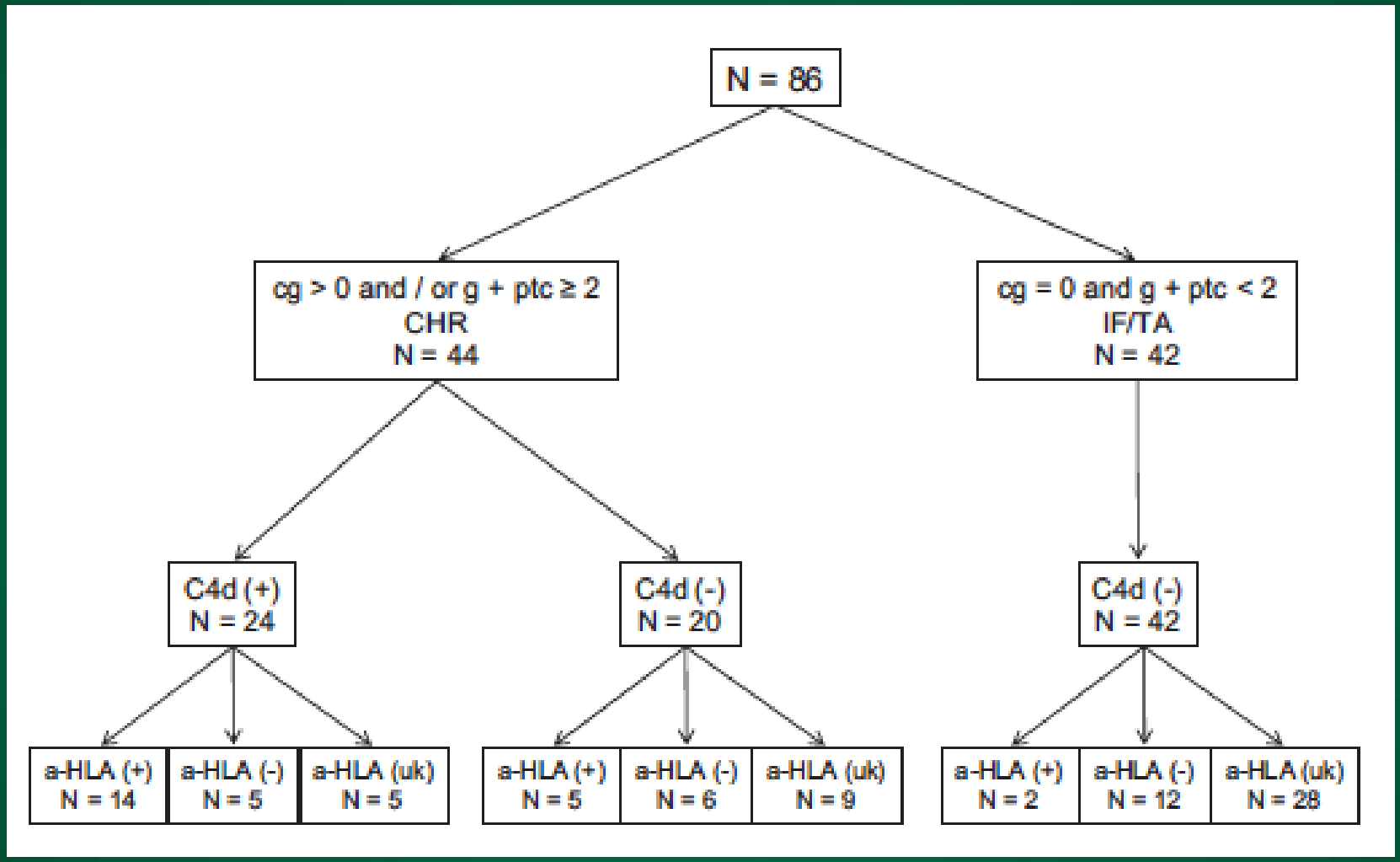
Relationship of TCMR and *dn*DSA



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Moreso F et al.
Transplantation 93: 41, 2012

Relationship of TCMR and *dn*DSA

TABLE 4. Histological findings in the protocol biopsy from patients diagnosed of chronic humoral rejection or IF/TA in the biopsy for cause

Variable (n=44)	CHR (n=42)	IF/TA	*P*
Time of biosy (mo)	4.5±2.4	4.6±3.3	ns
Number of glomeruli	13±7	12±7	ns
Glomerulosclerosis (%)	2±5	3±6	ns
Arterial sections	6±5	4±3	ns
Glomerulitis (g)	0.16±0.57	0.07±0.26	ns
Interstitial infiltrate (i)	0.98±0.66	0.55±0.63	0.0034
Tubulitis (t)	0.59±0.58	0.36±0.62	0.0248
Vasculitis (v)	0.02±0.15	0	ns
Arteriolar hialynosis (ah)	0.20±0.51	0.02±0.15	0.0432
Transplant glomerulopathy (cg)	0.20±0.46	0.14±0.35	ns
Interstitial fibrosis (ci)	0.59±0.69	0.50±0.67	ns
Tubular atrophy (ct)	0.59±0.69	0.45±0.63	ns
Transplant vasculopathy (cv)	0.11±0.39	0.12±0.33	ns
Mesangial matrix expansion (mm)	0.23±0.44	0.21±0.43	ns
Peritubular capillaritis (ptc)	1.00±0.77	0.81±0.62	ns
C4d (negative/focal/diffuse)	3/1/1	3/1/1	ns

Mean±SD of each Banff score is shown.

CHR, chronic humoral rejection; IF/TA, interstitial fibrosis and tubular atrophy.

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Moreso F et al.
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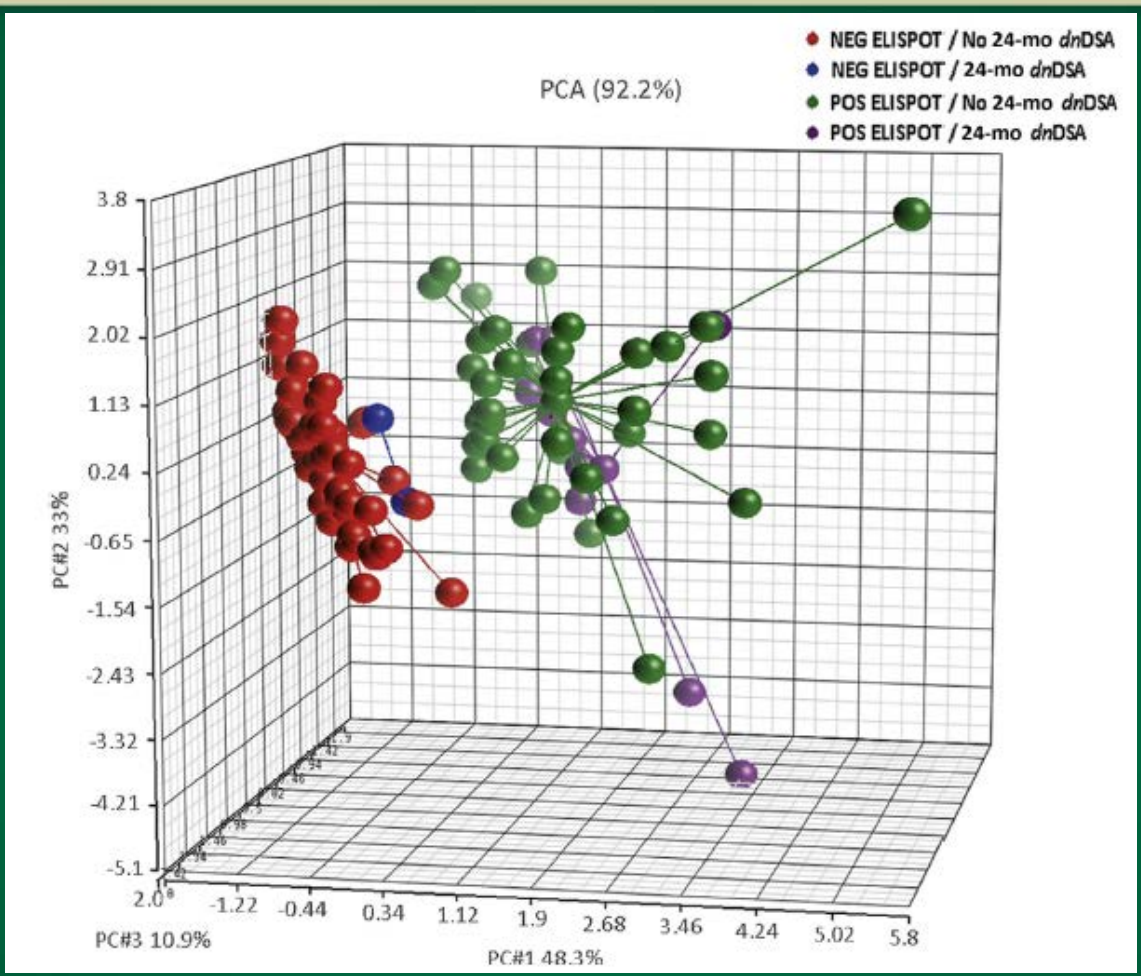
Memory T cells and *dn*DSA



Posttxp IFNγ Elispot at 3 and 6 mos predicted subclinical CMR at 6 mos

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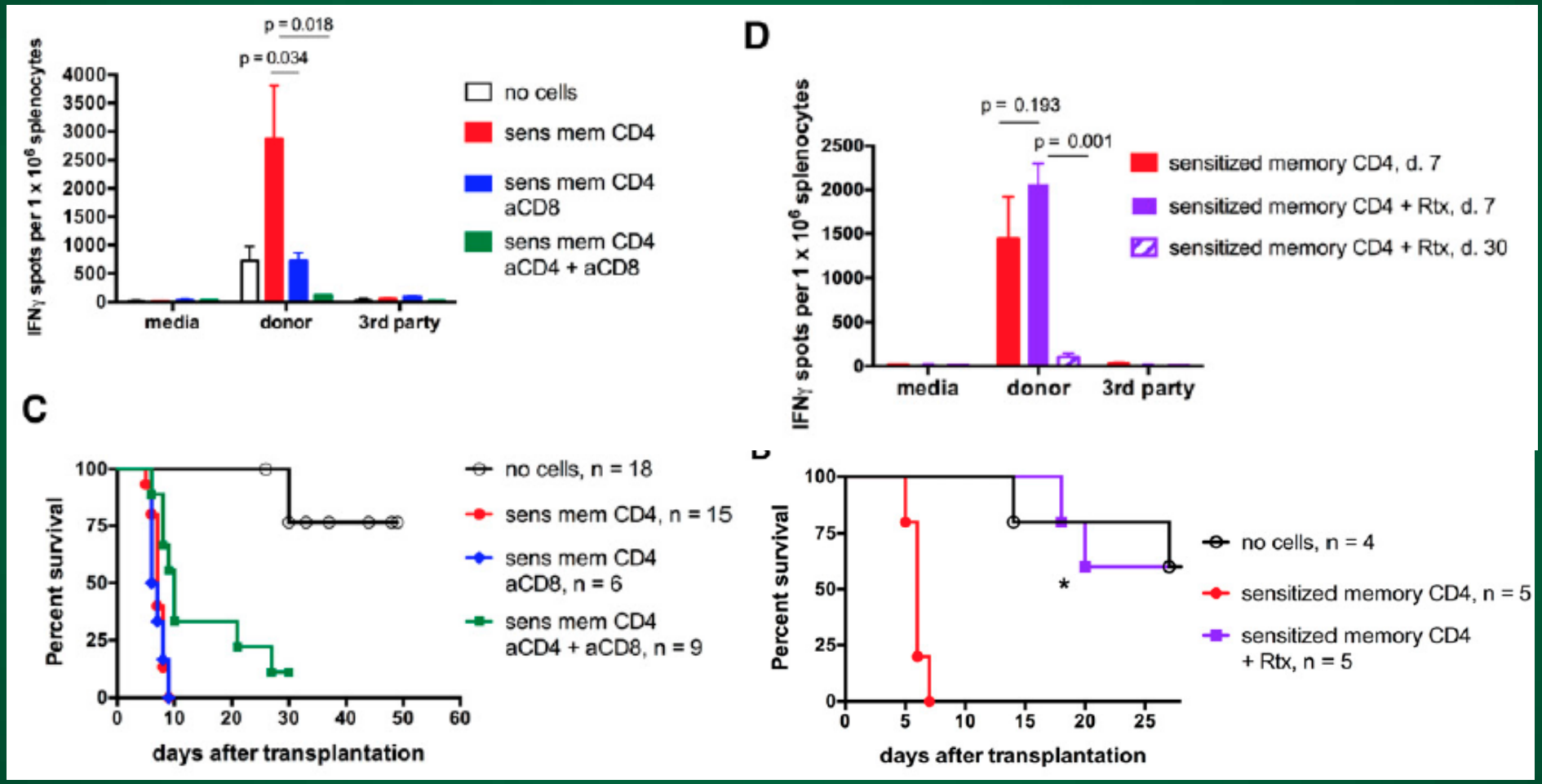
Crespo E et al. *Kidney Int,* 2017

Relationship of TCMR and *dn*DSA



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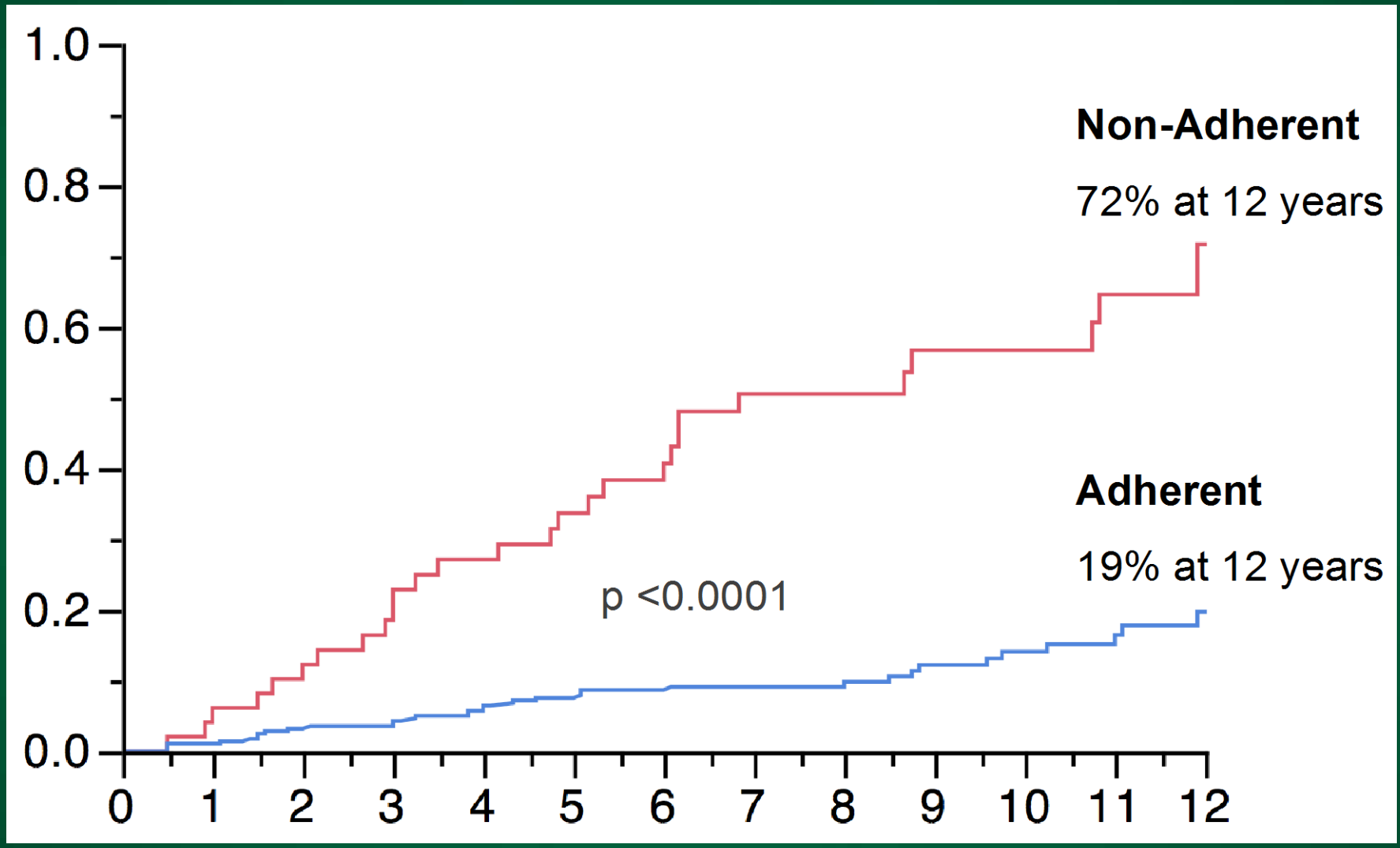
Gorbacheva V et al.
JASN 27: 3299, 2016

Nonadherence and DSA



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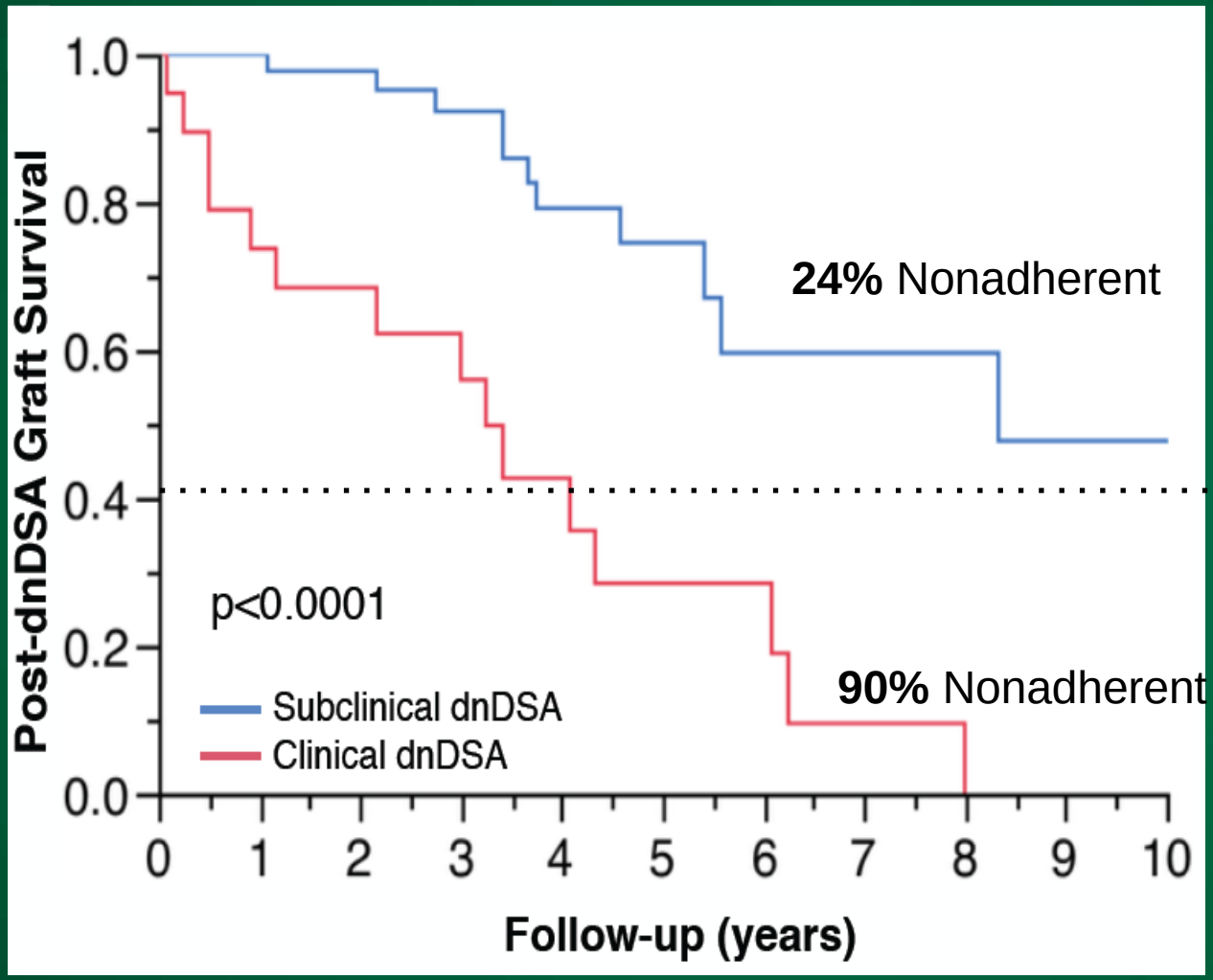
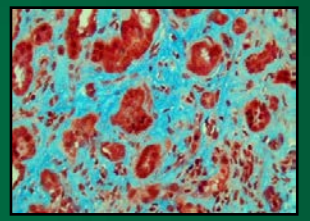
Wiebe et al.

Am J Transplant 15: 2921, 2015

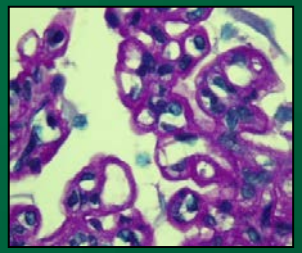
Nonadherence, DSA, and graft failure



IFTA
ci3,ct3



TG
cg3



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Wiebe C et al.
Am J Transplant 15: 2921, 2015

Nonadherence, DSA, and graft dysfunction

	No DSA No GDF (n=388)	No DSA GDF (n=56)	dnDSA Subclin (n=45)	dnDSA Clinical (n=19)	P
DGF (%)	12	25	9	26	0.03
Nonadherence (%)	5	18	24	90	<0.001
TCMR (0-12 mos) (per pt)	0.1±0.3	0.4±0.8	0.3±0.6	0.6±0.7	<0.001
eGFR (6m)(ml/min)	60±20	53±17	60±17	57±20	0.11
eGFR (3y post DSA)	-	-	48±18	18±13	<0.001
eGFR (5y post txp)	55±23	42±21	-	-	<0.001

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Am J Transplant 15: 2921, 2015

TCMR, *dn*DSA, and histology

Banff score		Cellular rejection ≤12 months	*dn*DSA development
n (% with score)		OR per rejection (95%CI)	OR of yes vs. no (95%CI)
cg ≥1	89 (8%)	1.16 (0.8–1.6)	4.42 (2.5–8.1)***
cg ≥2	30 (3%)	0.70 (0.3–1.3)	10.36 (3.6–37.8)***
cg = 3	13 (1%)	0.82 (0.3–2.1)	18.50 (3.2–350.9)***
ci ≥1	558 (51%)	1.55 (1.3–1.9)***	1.00 (0.7–1.4)
ci ≥2	177 (16%)	1.73 (1.4–2.1)***	1.28 (0.8–1.9)
ci = 3	39 (4%)	1.30 (0.9–1.9)	0.63 (0.3–1.4)
ct ≥1	671 (62%)	1.30 (1.1–1.6)**	0.70 (0.5–1.0)
ct ≥2	168 (15%)	1.58 (1.3–2.0)***	1.10 (0.7–1.7)
ct = 3	53 (5%)	1.31 (0.9–1.8)	0.99 (0.5–2.0)
cv ≥1	392 (38%)	1.26 (1.1–1.5)**	0.86 (0.6–1.2)
cv ≥2	88 (8%)	1.40 (1.1–1.8)**	1.15 (0.7–2.0)
cv = 3	13 (1%)	1.19 (0.5–2.2)	1.07 (0.3–4.5)

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Wiebe C et al.
Am J Transplant 15: 2921, 2015

Long term deterioration of kidney allograft function (DeKAF): Prospective Cohort

- 3358 patients at 6 centers transplanted 2006-11
  - Functioning grafts at 90 days
  - Baseline status established @ 90d
  - Mean f/u of 32 months
- 568 had "index biopsy" - first for cause biopsy >90d
  - >25% increase in serum creatinine (92%)
  - New onset proteinuria (8%)
- Index biopsy v. no index biopsy
  - Death: 6.0 v. 4.8% (p=0.24)
  - DCGF: 21.7% v. 1.8% (p<0.0001)

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Gaston RS et al, ATC 2011 and submitted for publication

Risk factors for index biopsy

Parameter	No IndexBx	Index Bx	P
N	2287	460	
Recipient Age (y)	50±14	46±16	0.001
Gender (% male)	63	59	0.13
Race (% black)	17	21	0.02
PRA ≥ 10%	41	40	0.84
Serum Cr @ 90d (mg/dl)	1.43±0.5	1.46±0.5	0.27
DGF (%)	9	14	0.002
AR before 90d (%)	8.1	14.4	0.001

Hunsicker L et al, ATC 2011

DeKAF: Risk factors for death-censored graft failure after 90 days

Covariate	Hazard Ratio (95% CI)	P
Recipient age (per 10 yr)	0.73 (0.6-0.9)	<0.001
Days on dialysis (v. none)		<0.001
1d-1yr	1.73 (1.01-3.0)	
1 yr-3yr	2.58 (1.5-4.4)	
PRA ≥ 20%	1.49 (0.9-2.4)	0.09
Induction (v. polyclonal)		0.003
IL2 antagonist	2.75 (1.3-5.6)	
None	6.65 (1.9-23)	
AR before 90 d	1.24 (0.8-1.9)	0.32
Delayed graft function	0.96 (0.6-1.6)	0.86
Serum creat @ 90d	2.69 (2.2-3.2)	<0.001
Index biopsy (v. none)	24.8 (16.8-36)	<0.001

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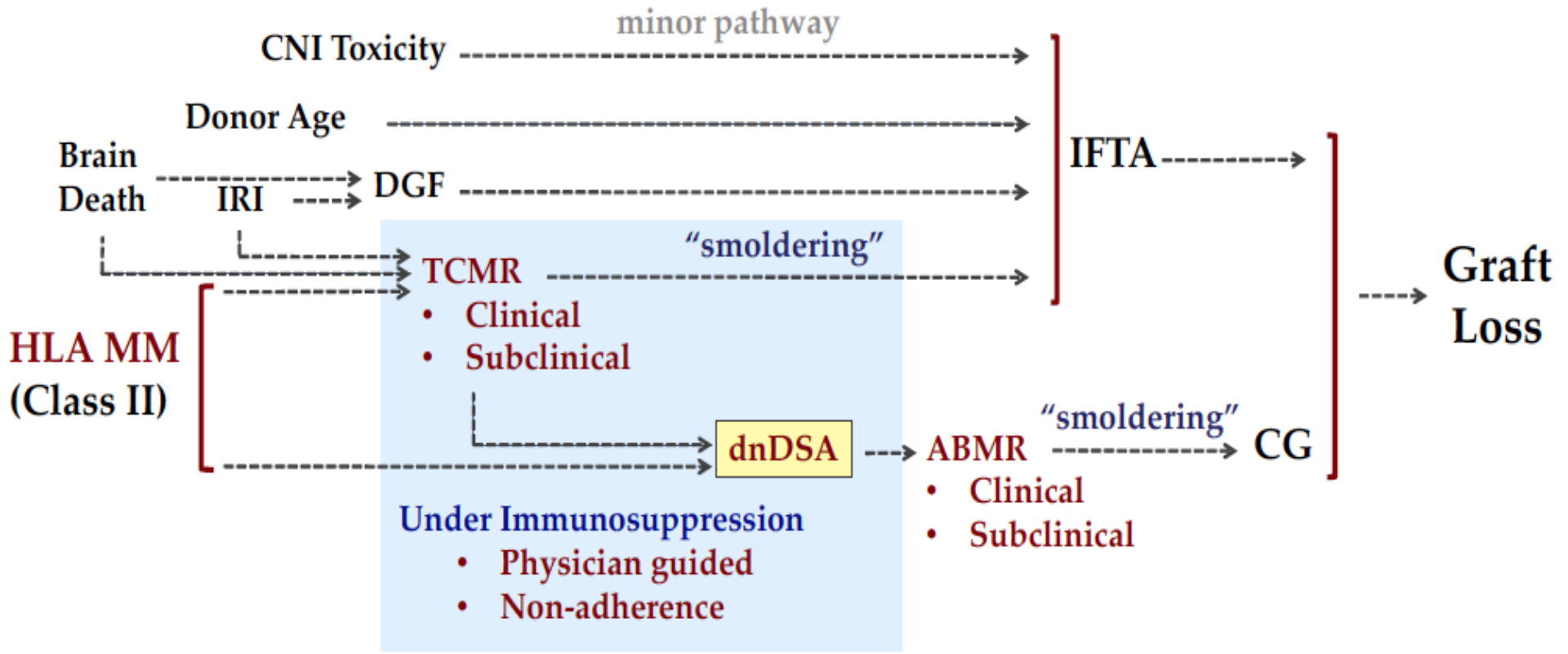
Gaston RS et al, ATC 2011 and submitted for publication

Mechanisms of Alloimmune Mediated Graft Loss



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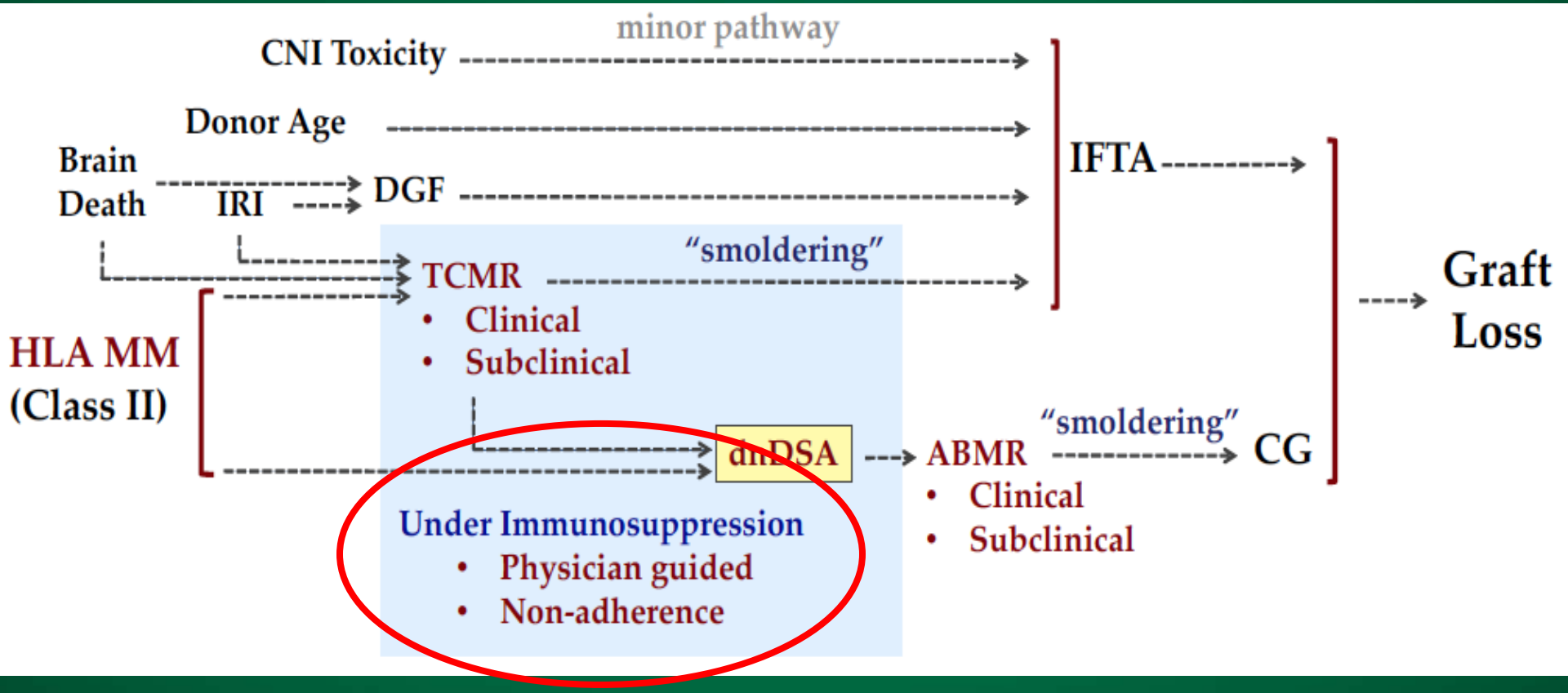
Wiebe et al.,
Transplantation (2016) 100: 2048

Mechanisms of Alloimmune Mediated Graft Loss



Wiebe et al.,
Transplantation (2016) 100: 2048

Conclusions

- The impact of TCMR is less than thought in past
  - Has declined in frequency and is relatively responsive to treatment
  - Pales in comparison to sABMR as predictor of graft dysfunction and failure
- TCMR remains as a risk factor for *dn*DSA
  - Particularly in setting of inadequate immunosuppression (minimization/nonadherence)
- Key question: given role of T cell in promoting B cell responses, can there be effective prevention/control of DSA without effective anti-T cell therapy?