

## **Supplementary Digital Content 1 (SDC 1)**

Comparing recipients at 1-year with versus without peritubular capillaritis respectively, graft function was similar at both 1-year (1.4 md/dL versus 1.3 mg/dL,  $p=0.568$ ) and latest median follow up time (2.0 mg/dL versus 1.5 mg/dL,  $p=0.142$ ). There was no difference in the presence of proteinuria between recipients with or without capillaritis (47.6% versus 31.8%,  $p=0.101$ ). However, patients with peritubular capillaritis were more likely to have donor-specific antibody at 1-year (with versus without, 62.9% versus 39.4% respectively,  $p=0.045$ ).

## **SDC 2**

### ***Proteinuria and 1-year histology and outcomes***

46.4% of HLA-incompatible recipients had proteinuria (detected by dipstick analysis) at 1-year post-transplantation, although no direct relationship was observed with presence of concomitant DSA ( $p=0.375$ ). Recipients with any degree of proteinuria, versus recipients with none, at 1-year post-transplantation were more likely to have transplant glomerulopathy (41.1% versus 12.3% respectively  $p<0.001$ ) and glomerulitis (73.2% versus 39.4% respectively,  $p<0.001$ ). No significant difference was observed in peritubular capillaritis (58.8% versus 42.3% respectively,  $p=0.101$ ) or C4d deposition (23.6% versus 12.1%,  $p=0.077$ ). Graft survival was significantly worse amongst HLA-incompatible recipients based upon presence or absence of detectable proteinuria at 1-year respectively (77.2% versus 98.5%,  $p<0.001$ ). Of note we did not have the data to ascertain whether proteinuria was of new-onset or existed pre-transplant.

### SDC 3

#### ***Comparative analysis of biopsies at 1-year post HLA-incompatible kidney transplantation***

Supplementary Table 1 compares 23.6% of biopsies performed in the context of transplant dysfunction (indication-based) versus 76.2% planned protocol biopsies. Not surprisingly, indication biopsies performed in the context of transplant dysfunction at 1-year post transplant had worse graft survival versus protocol biopsies (73.3% versus 93.6%,  $p=0.002$ ).

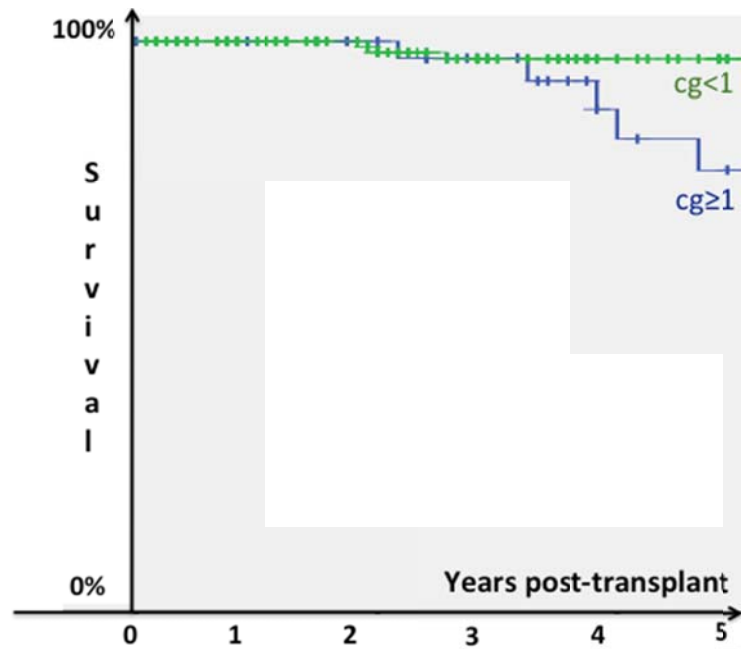
We also explored difference in outcome comparing 1-year biopsies to what we have termed the 'clean' biopsy (no evidence of any C4d deposition, transplant glomerulopathy or microcirculation inflammation). At 1-year post-transplantation 32.0% of HLA-incompatible recipients had 'clean' biopsies and had 100.0% long-term death-censored graft survival (versus 84.3% without a clean biopsy,  $p=0.005$ ). 84.6% of 'clean' biopsies were derived from protocol biopsies, with 15.4% from indication biopsies. Clean biopsies were less likely than other biopsies to have had any preceding AMR-alone (20.5% versus 40.5%,  $p=0.023$ ) or mixed AMR/cellular (33.3% versus 51.2%,  $p=0.048$ ) rejection, and were also less likely to have concomitant DSA present at 1-year (clean versus other, 46.8% versus 78.3%  $p=0.004$ ).

**Figure S1.** Kaplan-Meier estimates of death-censored graft survival are shown for HLA-incompatible kidney transplant recipients on the basis of presence or absence at 1-year

biopsy of; transplant glomerulopathy (1a), concomitant C4d deposition and transplant glomerulopathy (1b), glomerulitis (1c) and peritubular capillaritis (1d). Data is right-censored to account for sample losses before final outcome is observed. Death-censored graft survival data was analyzed with censoring at 5-years post-biopsy.

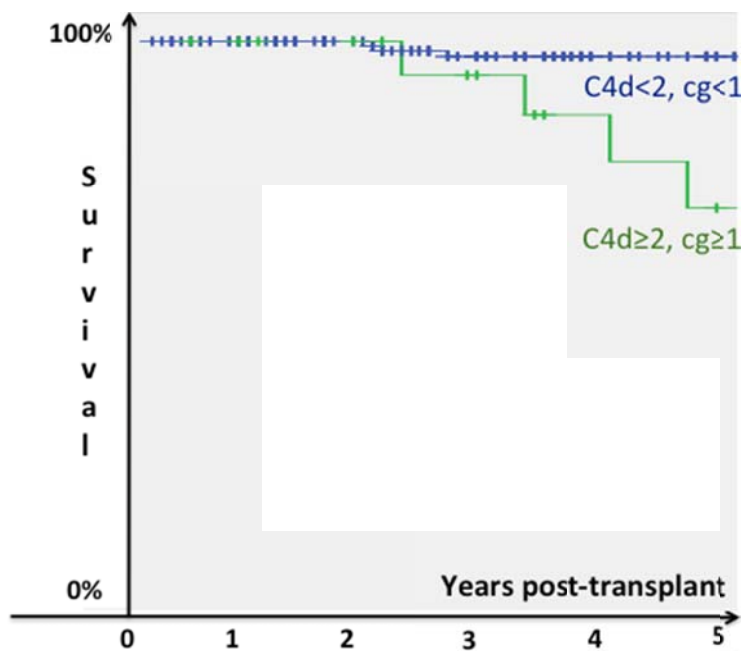
**Supplementary  
Figure 1a.**

Kaplan-Meier  
death-censored  
graft survival  
curve for  
transplant  
glomerulopathy  
(cg)



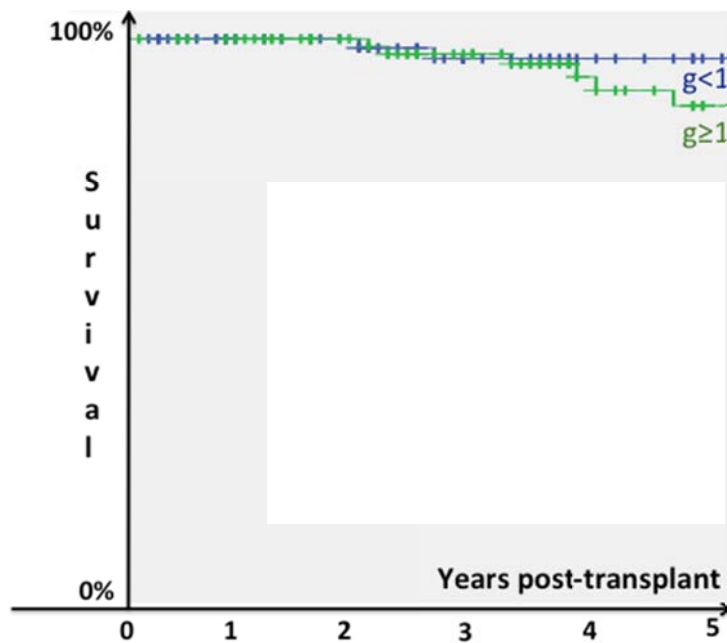
Numbers at risk						
Time (years)	0	1	2	3	4	5
$cg \geq 1$	30	28	26	20	13	10
$cg < 1$	90	73	58	45	30	22

**Supplementary  
Figure 1b.** Kaplan-  
Meier death-  
censored graft  
survival curve for  
C4d/transplant  
glomerulopathy  
(C4d/TG)



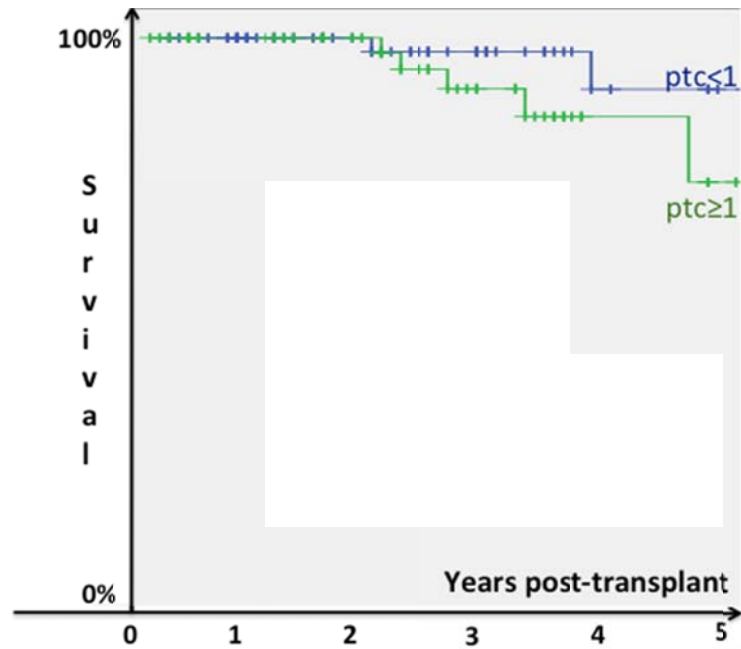
Numbers at risk						
Time (years)	0	1	2	3	4	5
C4d≥2, cg≥1	12	12	12	11	8	6
C4d<2, cg<1	109	88	71	53	35	25

**Supplementary  
Figure 1c.** Kaplan-  
Meier death-  
censored graft  
survival curve for  
glomerulitis (g)



Numbers at risk						
Time (years)	0	1	2	3	4	5
$g \geq 1$	67	62	53	43	29	21
$g < 1$	54	40	32	23	15	11

**Supplementary  
Figure 1d.** Kaplan-  
Meier death-  
censored graft  
survival curve for  
peritubular  
capillaritis (ptc)



Numbers at risk						
Time (years)	0	1	2	3	4	5
ptc $\geq 1$	44	35	27	18	7	4
ptc $< 1$	42	32	23	13	8	6

**Table S1 – Comparison of 1-year biopsies from HLA-incompatible kidney transplant recipients performed in context of transplant dysfunction (indication) or protocol**

<b>Parameter</b>	<b>Protocol (n=93)</b>	<b>Indication (n=31)</b>	<b>P value</b>
Detectable proteinuria (dipstick analysis)	38.3%	71.0%	0.001
eGFR (mL/min)	60.3	45.7	0.002
Donor-specific antibody present	46.2%	82.4%	0.007
C4d deposition	13.8%	29.6%	0.057
Transplant glomerulopathy	17.4%	51.7%	<0.001
Glomerulitis	54.8%	55.2%	0.975
Peritubular capillaritis	44.9%	60.0%	0.289
Death-censored graft survival	93.6%	73.3%	0.002



**Table S2 – Comparison of HLA-incompatible recipients included or excluded in study cohort on basis of 1-year biopsy data availability**

Parameter		Included in study cohort (1-year biopsy performed)	Excluded from study cohort (1-year biopsy not performed)	P value
Age (over median 46)		56.1%	48.6%	0.186
Females		59.5%	62.9%	0.372
Ethnicity	White	78.4%	77.1%	0.550
	Black	18.2%	15.7%	
	Hispanic	2.0%	2.9%	
	Other	1.4%	4.3%	
Follow up (days)		1449	1840	0.006
Cellular rejections		45.3%	28.6%	0.182
Antibody-mediated rejections		25.9%	32.9%	0.282
Mixed rejections		37.8%	31.4%	0.468
Patient survival		90.5%	89.9%	0.531
Death-censored graft survival		93.2%	85.5%	0.073
Lost to follow up*		7.7%	11.9%	0.743

\*Classified as patients with no clinical data within last 18 months and not known to have died or lost kidney allograft.





