Chronic renal histological changes at implantation and subsequent deceased donor kidney transplant outcomes: a single-centre analysis

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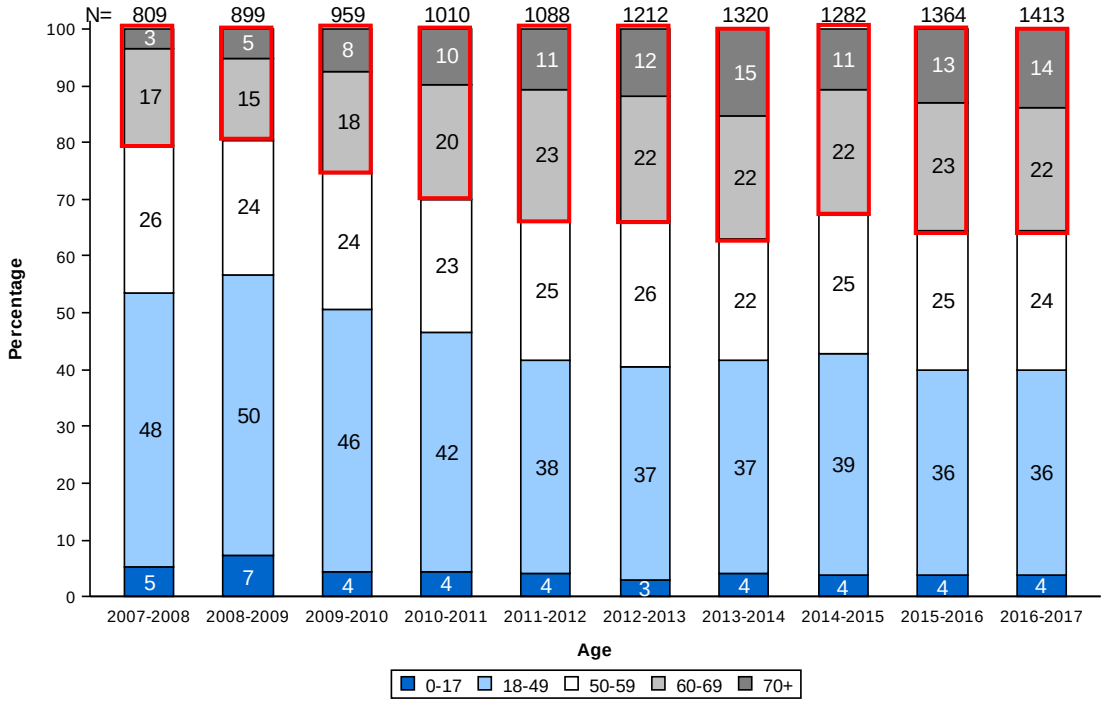
Introduction

- UK deceased kidney donors have changed significantly over the last decade

- Increasing utilisation of older donors

- More kidneys from 'high risk' donors

Age of deceased kidney donors in the UK



Annual report on kidney transplantation 2016/2017, NHSBT

Introduction

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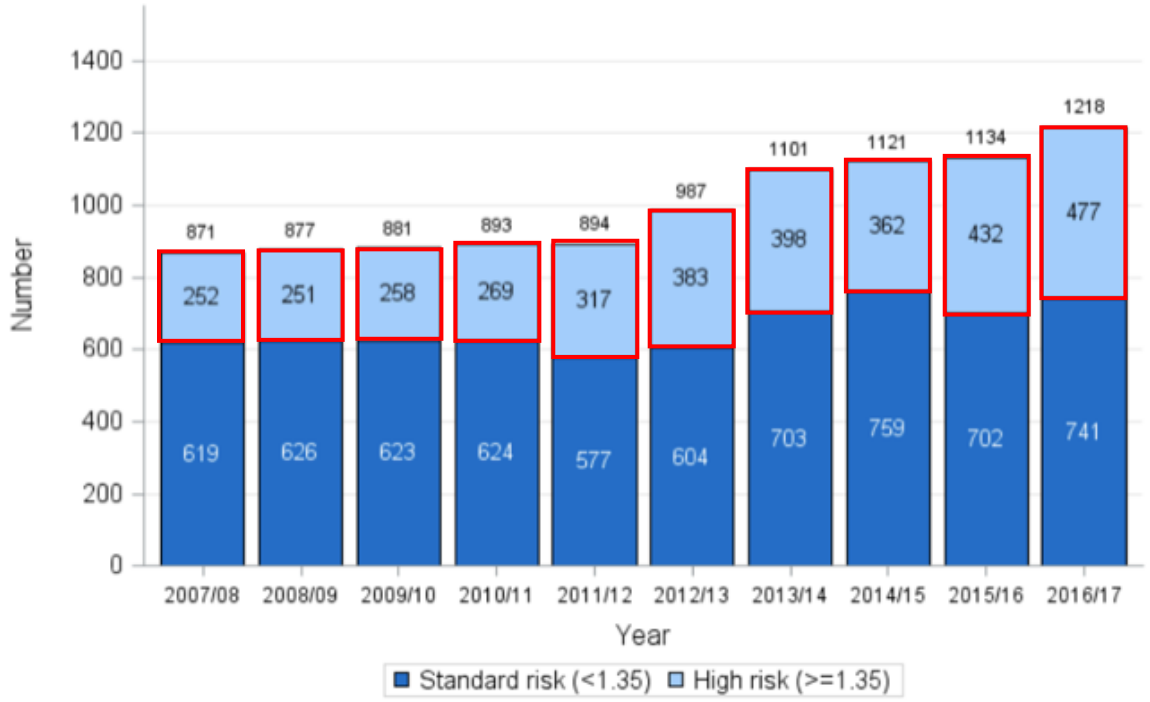
- Increasing utilisation of older donors

- More kidneys from 'high risk' donors

UK Kidney Donor Risk Index of DBD donor kidney transplants



Annual report on kidney transplantation 2016/2017, NHSBT

Introduction

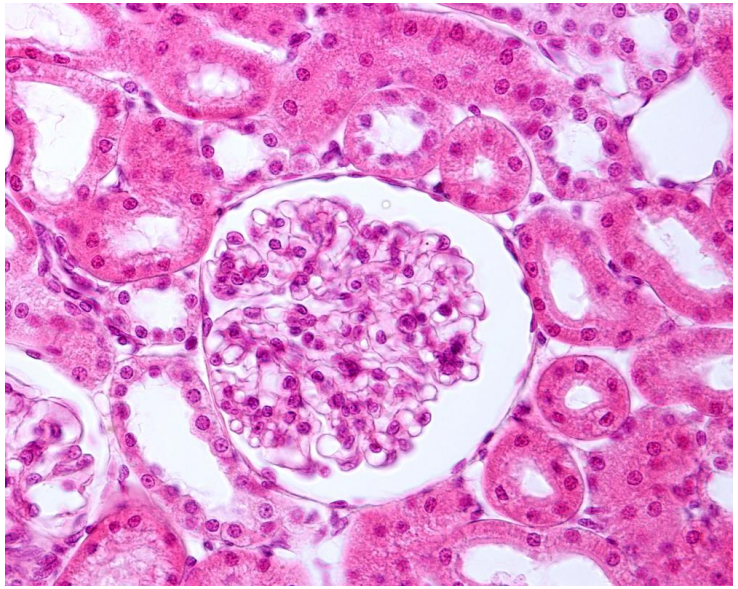
- More accurate donor risk assessment tools are needed to inform utilisation decisions and to enable appropriate recipient selection

Registry-based donor risk indices

- KDRI – Rao et al, *Transplantation* 2009
- UKKDRI – Watson et al, *Transplantation* 2012
- New UKKDRI – Mumford et al, *unpublished*

Introduction

- More accurate donor risk assessment tools are needed to inform utilisation decisions and to enable appropriate recipient selection



Chronic changes on kidney biopsy

- Karpinski – Karpinski et al, *Transplantation* 1999
- Remuzzi – Remuzzi et al, *J Am Soc Nephrol* 1999
- CADI – Nyberg et al, *Transplant* 2001
- Banff – Liapis et al, *Am J Transplant* 2017

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Utility of pre-implantation kidney biopsy?

Baseline Donor Chronic Renal Injury Confers the Same Transplant Survival Disadvantage for DCD and DBD Kidneys

V. Kosmoliaptsis[1], M. Salji[1], V. Bardsley[2], Y. Chen[3], S. Thiru[2], M. H. Griffiths[2], H. C. Copley[1], K. Saeb-Parsy[1], J. A. Bradley[1], N. Torpey[4] and G. J. Pettigrew[1,*]

The Predictive Value of Kidney Allograft Baseline Biopsies for Long-Term Graft Survival

Katrien De Vusser,*† Evelyne Lerut,‡§ Dirk Kuypers,*† Yves Vanrenterghem,*† Ina Jochmans,‖¶ Diethard Monbaliu,‖¶ Jacques Pirenne,‖¶ and Maarten Naesens*†

Evaluation of pre-implantation kidney biopsies: Comparison of Banff criteria to a morphometric approach

José António Lopes, Francesc Moreso, Luis Riera, Marta Carrera, Meritxell Ibernon, Xavier Fulladosa, Josep Maria Grinyó, and Daniel Serón

Nephrol Dial Transplant. 2013 Oct;28(10):2637-44. doi: 10.1093/ndt/gft292. Epub 2013 Jul 30.

Impact of the pre-transplant histological score on 3-year graft outcomes of kidneys from marginal donors: a single-centre study.

Carta P[1], Zanazzi M, Caroti L, Buti E, Mjeshtri A, Di Maria L, Raspollini MR, Minetti EE.

Chronic Histological Damage in Early Indication Biopsies Is an Independent Risk Factor for Late Renal Allograft Failure

M. Naesens[a,b,*], D. R. J. Kuypers[a,b], K. De Vusser[a,b], Y. Vanrenterghem[a,b], P. Evenepoel[a,b], K. Claes[a,b], B. Bammens[a,b], B. Meijers[a,b] and E. Lerut[c]

Received 15 May 2012, revised 15 August 2012 and accepted for publication 30 August 2012

Aims

1. **Determine whether chronic donor histological changes at transplantation were predictive of graft outcomes at our centre**

   If so, what histological score thresholds can be used to determine optimal organ selection?

2. **Determine whether systematic pre-implantation kidney biopsies would have increased organ utilisation**

Methods

- DATA
- INCLUSION CRITERIA
- HISTOPATHOLOGY
- GROUPS
- OUTCOMES
- STATISTICS
- UTILISATION ANALYSIS

- ✓ 10-year period (2005-2015)
- ✓ Retrospective analysis
- ✓ Single-centre
- ✓ Follow-up period:

  5 years *or* 20 January 2018

Methods

- DATA
- INCLUSION CRITERIA
- HISTOPATHOLOGY
- GROUPS
- OUTCOMES
- STATISTICS
- UTILISATION ANALYSIS

- ✓ Deceased donor: DBD & DCD
- ✓ Single kidney-only transplants
- ✓ Adult recipients

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Methods

- DATA
- INCLUSION CRITERIA
- HISTOPATHOLOGY
- GROUPS
- OUTCOMES
- STATISTICS
- UTILISATION ANALYSIS

- **Biopsies taken on the day of transplantation**
- **16G core biopsy:** formalin fixed, paraffin embedded
- **Staining:** H&E, PAS, PAMS and Masson trichrome
- **Karpinski (K) score** by renal histopathologists
  - Scored **0-12** (≥20 glomeruli)
  - Based on glomerular, tubular, interstitial and vascular components (each 0-3)
- **K score <u>not</u> known at the time of transplantation**

Methods

- DATA
- INCLUSION CRITERIA
- HISTOPATHOLOGY
- GROUPS
- OUTCOMES
- STATISTICS
- UTILISATION ANALYSIS

Compare low vs high K score at two thresholds

- K score 0-3 vs 4-12
- K score 0-4 vs 5-12

Methods

- DATA
- INCLUSION CRITERIA
- HISTOPATHOLOGY
- GROUPS
- OUTCOMES
- STATISTICS
- UTILISATION ANALYSIS

- ✓ Graft function (4-variable MDRD eGFR)
- ✓ Death-censored graft survival (DCGS)
- ✓ Patient survival

Methods

- DATA
- INCLUSION CRITERIA
- HISTOPATHOLOGY
- GROUPS
- OUTCOMES
- STATISTICS
- UTILISATION ANALYSIS

Normality
- Shapiro-Wilk
- Q-Q plots

Demographic comparisons
- Student T test
- Mann-Whitney test
- χ^2 test

Correlation analysis
- Spearman's rho

Kaplan Meier survival
- Log rank

Multivariate analysis
- Linear regression
- Cox regression

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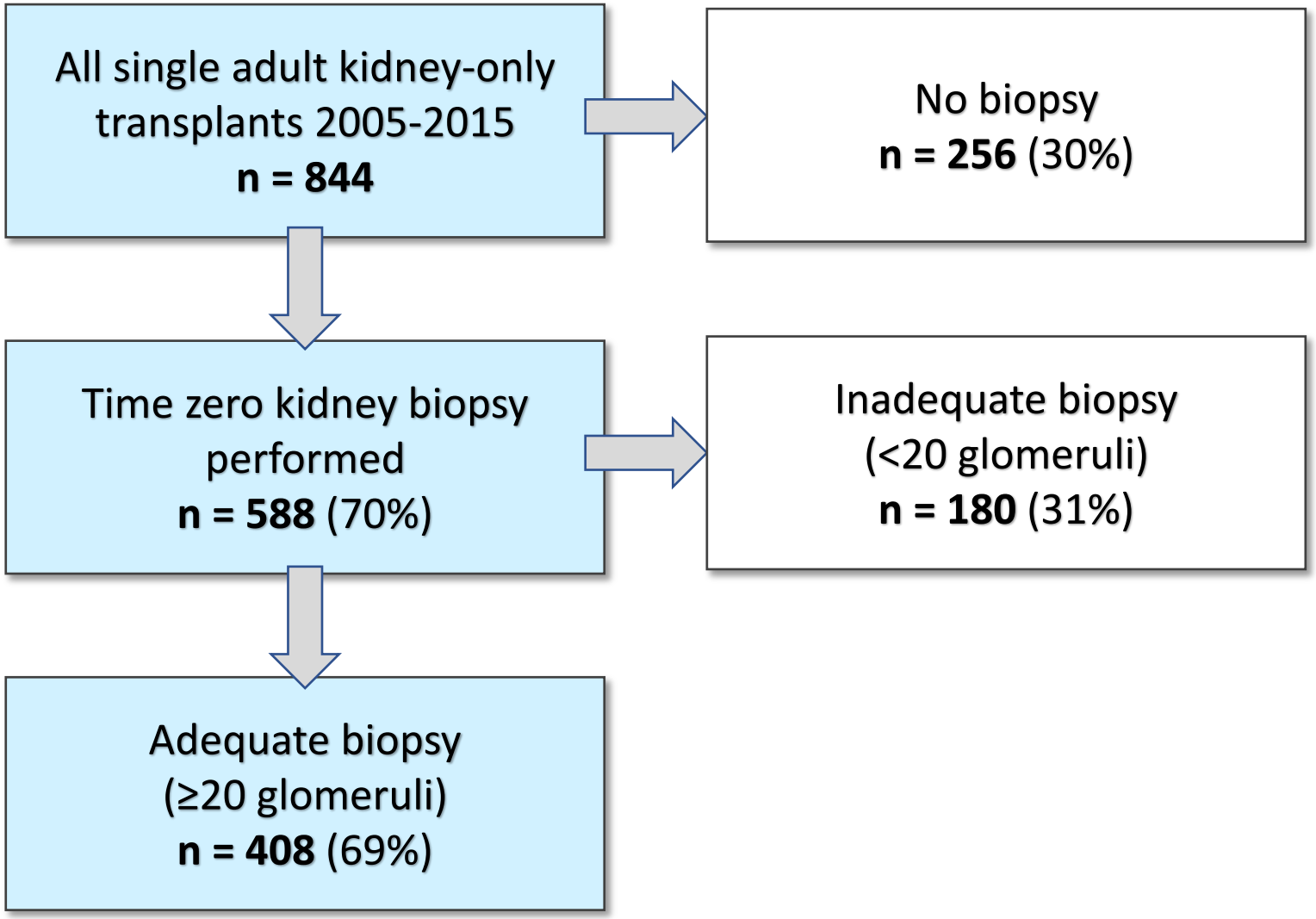
Methods

- DATA
- INCLUSION CRITERIA
- HISTOPATHOLOGY
- GROUPS
- OUTCOMES
- STATISTICS
- UTILISATION ANALYSIS

- **Examine organ utilisation at our centre**
  - 2012-2015, DBD and DCD, donors 60+ years
  - Single and dual transplants, adult recipients
- Retrospectively determine organ utilisation **<u>had we known</u>** the kidney biopsy result pre-operatively, using 0-4 / 5-6 / 7+ thresholds

Results


All single adult kidney-only transplants 2005-2015
n = 844
No biopsy
n = 256 (30%)
Time zero kidney biopsy performed
n = 588 (70%)
Inadequate biopsy
(<20 glomeruli)
n = 180 (31%)
Adequate biopsy
(≥20 glomeruli)
n = 408 (69%)

Results: donor / recipient groups

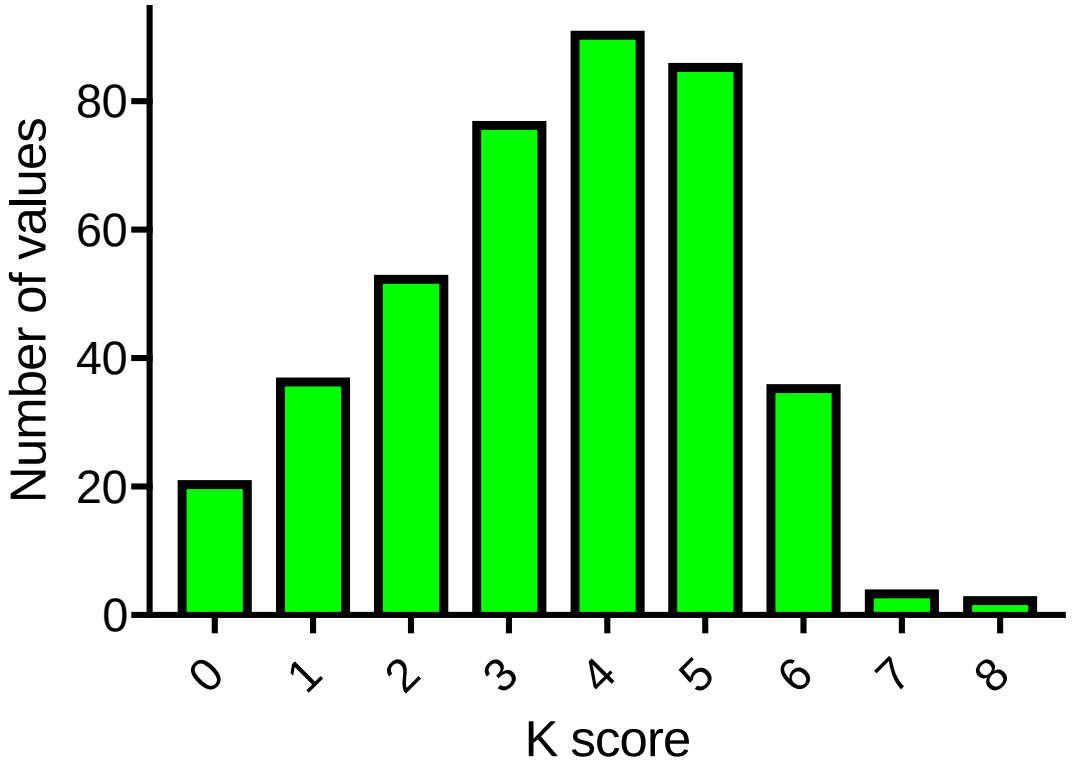
DONOR characteristics	Adequate biopsy (n=408)	No or inadequate biopsy (n=436)	p value
Donor age (years)	51 (41-60)	50 (43-64)	0.38
Donor gender			
Male	210 (51.5%)	222 (50.9%)	0.87
Female	198 (48.5%)	214 (49.1%)	
Donor type			
DBD	274 (67.2%)	292 (67.0%)	0.96
DCD	134 (32.8%)	144 (33.0%)	
Cause of death			
Stroke	241 (59.1%)	241 (55.3%)	0.32
Trauma	40 (9.8%)	38 (8.7%)	
Other	127 (31.1%)	157 (36%)	
UKKDRI	1.04 (0.97-1.46)	1.04 (0.98-1.49)	0.22
≤1.35	261 (65.6%)	227 (62.4%)	0.36
>1.35 (high risk)	137 (34.4%)	137 (37.6%)	
Cold ischaemia time (mins)	840 (660-1027)	900 (690-1050)	0.46

Data are expressed as number (%), median (IQR)

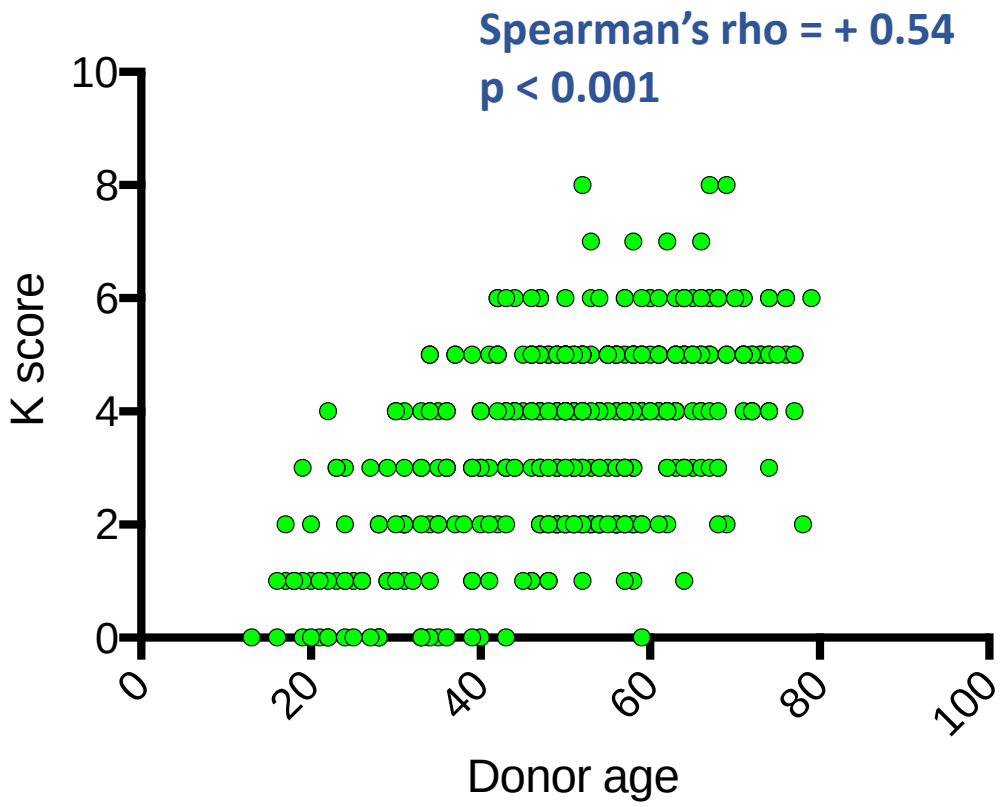
RECIPIENT characteristics	Adequate biopsy (n=408)
Recipient age (years)	50 (42-59)
Recipient gender	
Male	258 (63.2%)
Female	150 (36.8%)
Recipient ethnicity	
White	232 (56.9%)
Black	124 (30.4%)
Other	52 (12.7%)
Primary renal disease	
Diabetes mellitus	41 (10.0%)
Hypertension	73 (17.9%)
Other	294 (72.1%)
Graft number	
1	344 (84.3%)
>1	64 (15.7%)
HLA mismatch level	
1	55 (14%)
2	130 (33%)
3	188 (47%)
4	26 (6%)

Results: K score distribution

Histogram of K score distribution



Donor age versus K score

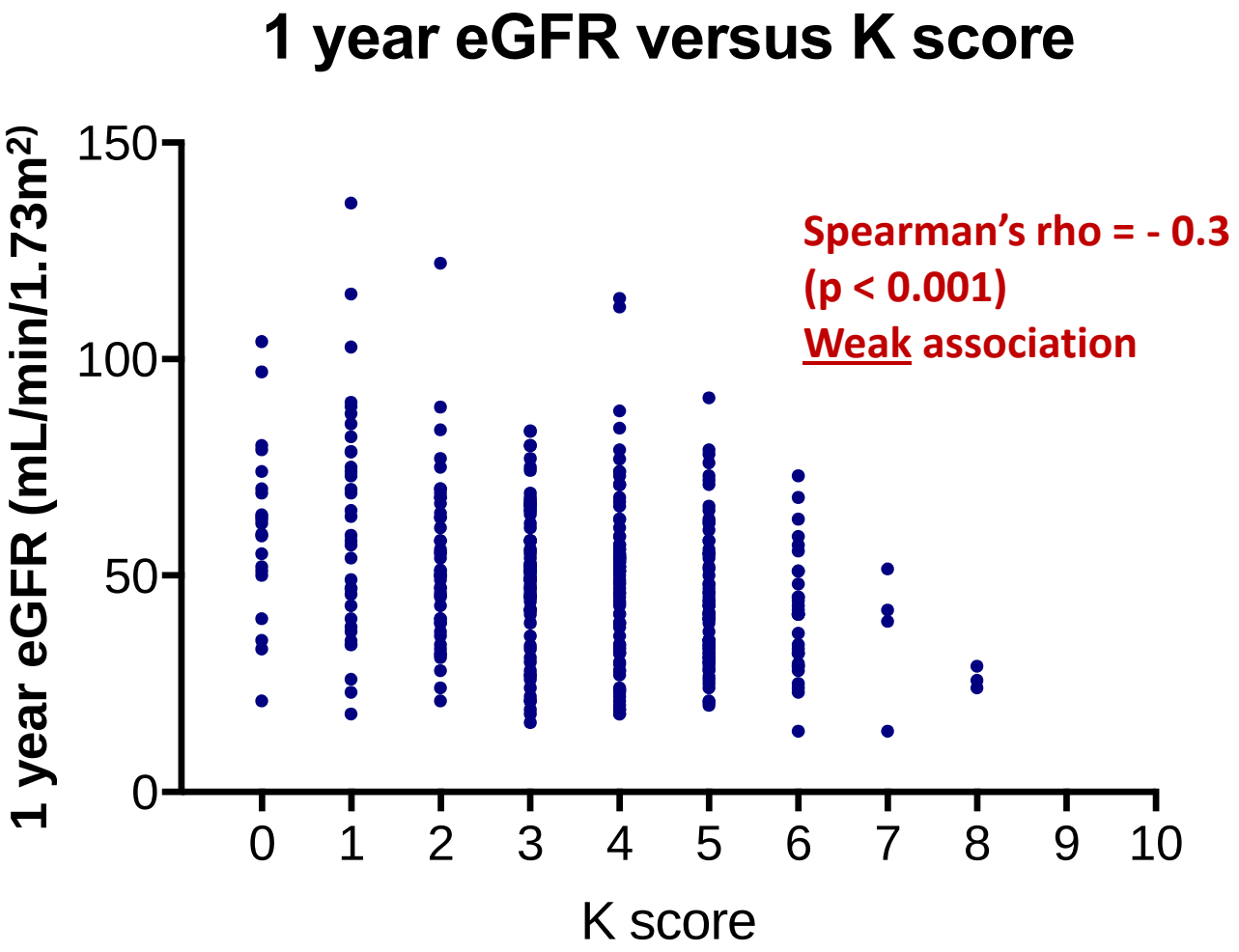


Results: K score and graft function (1)

	K score ≤ 4	K score ≥ 5	p value
1 year eGFR (n=370)	52 (38-66)	41 (32-54)	<0.001
3 year eGFR (n=256)	53 (45-67)	46 (33-58)	<0.001
5 year eGFR (n=141)	51 (37-63)	45 (34-66)	0.35

Data are expressed as median (IQR), mL/min/1.73m^2

Graft failures excluded



Results: K score and graft function (2)

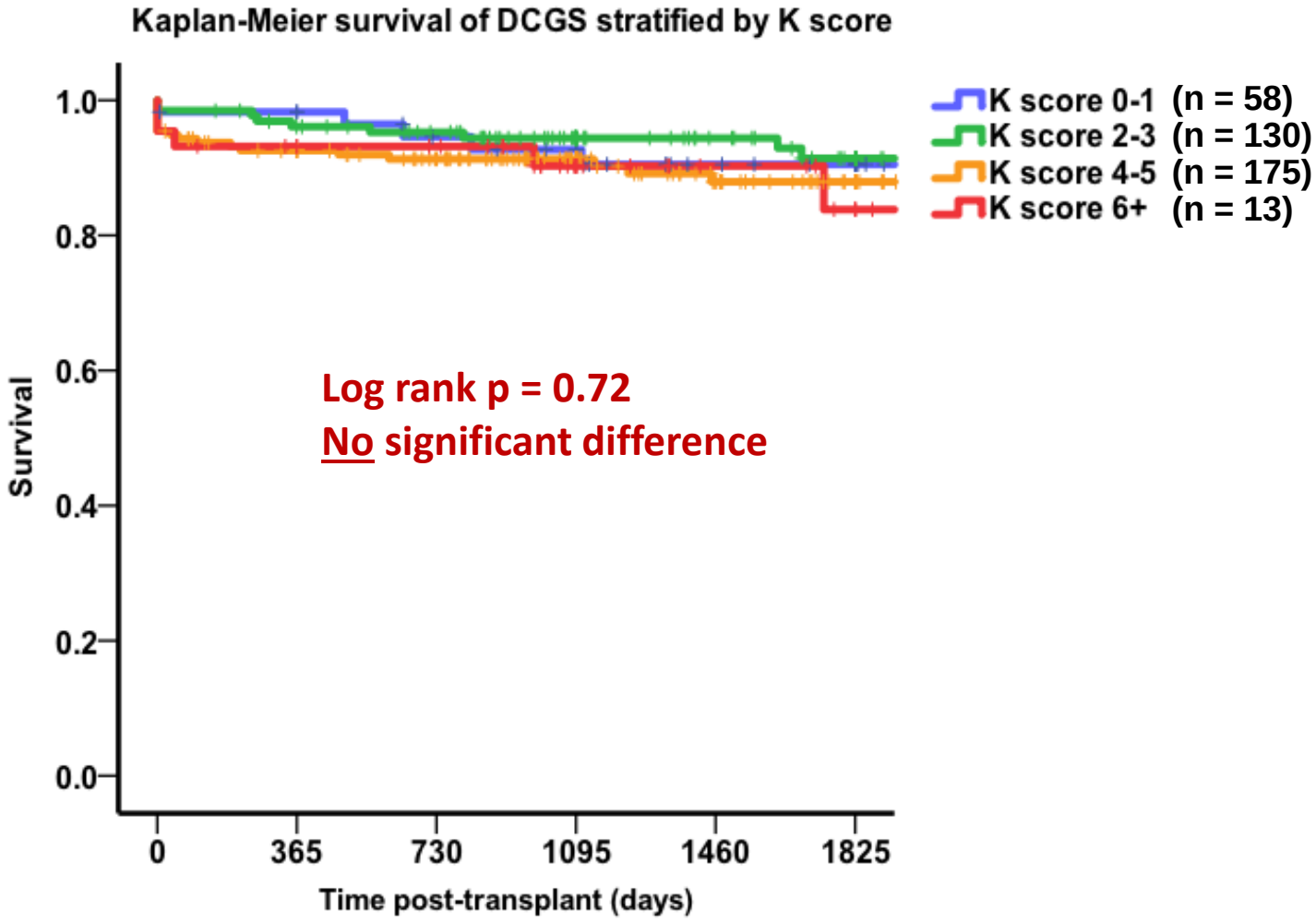
Linear regression analysis

Covariates in the equation
K score ~~Donor age~~ UKKDRI Recipient age Graft number Transplant type (DBD/DCD) Cold ischaemia time HLA mismatch level

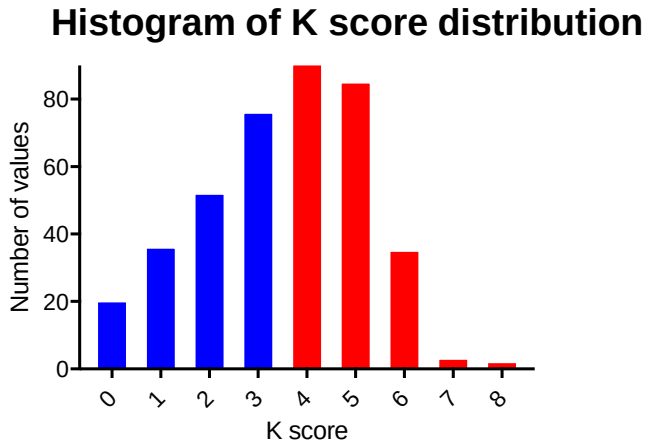
→

Predictors of lower graft function at 1 year
• For each K score increment → eGFR drops by **3** mL/min/1.73m^2 ($p = 0.02$) • For each UKKDRI increase by 0.1 → eGFR drops by **1.5** mL/min/1.73m^2 ($p < 0.001$) *These effects were replicated at 3 years*

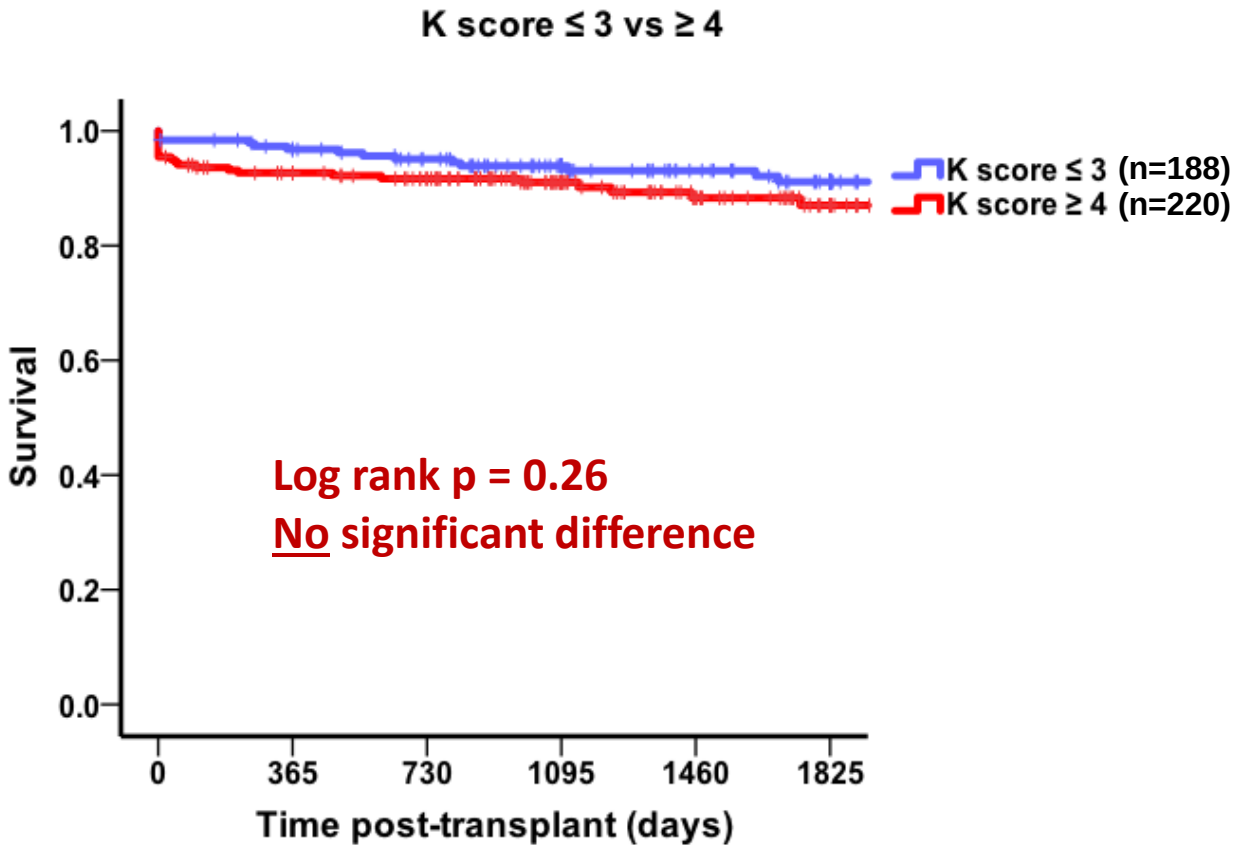
Results: K score and graft survival (1)



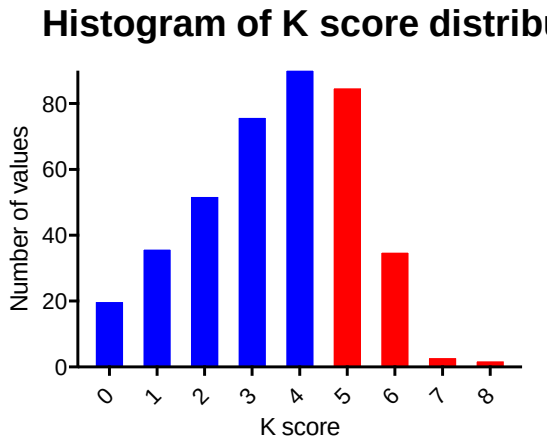
Results: K score and graft survival (2)



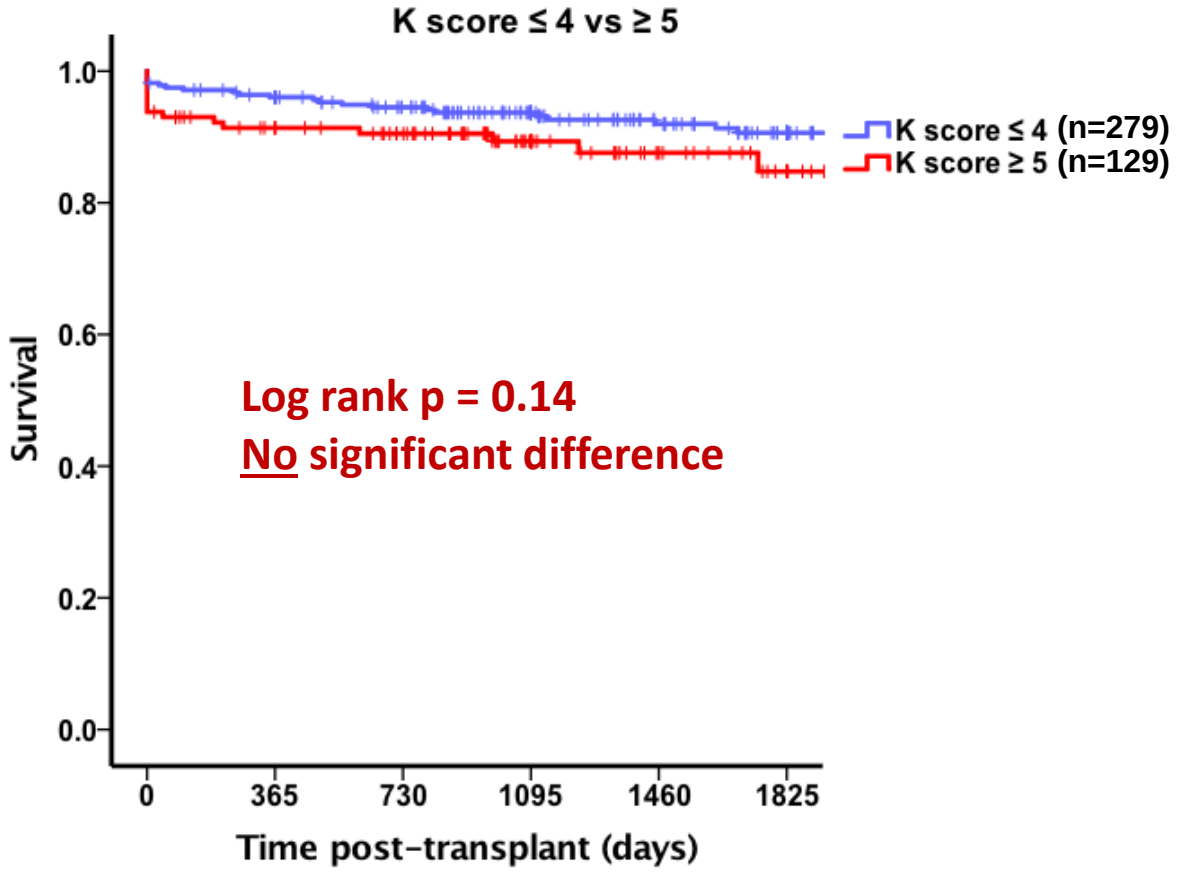
	K score ≤ 3	K score ≥ 4	p value
Donor age (years)	44 (30-53)	57 (49-63)	<0.001
Donor male gender	99 (53%)	111 (53%)	0.70
Donor cause of death			
Stroke	100 (53%)	141 (64%)	0.001
Trauma	29 (15%)	11 (5%)	0.001
UKKDRI	1.01 (0.80-1.09)	1.34 (1.01-1.54)	<0.001
Recipient age (yr)	48 (41-57)	52 (44-62)	0.001
Recipient male gender	116 (62%)	142 (65%)	0.60
Cold ischaemia time (min)	804 (649-1005)	843 (529-1028)	0.28



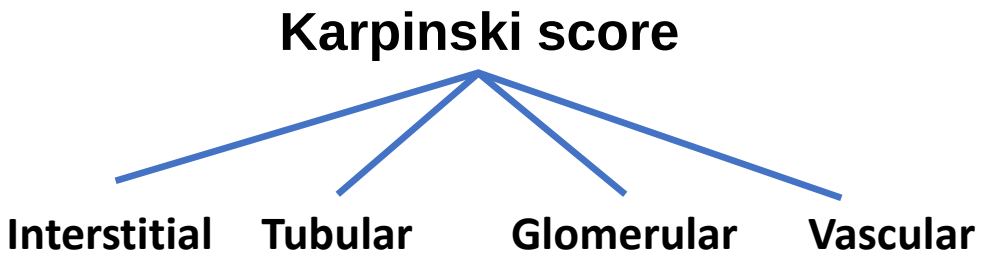
Results: K score and graft survival (3)



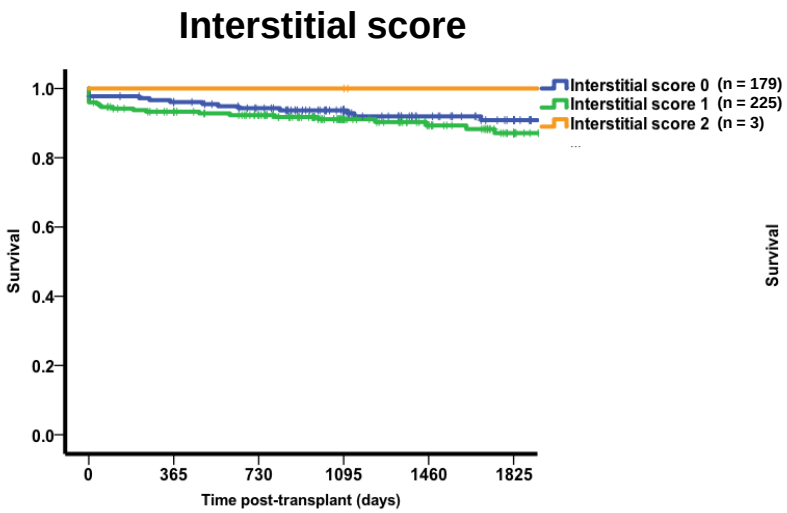
	K score ≤ 4	K score ≥ 5	p value
Donor age (yr)	49 (35-57)	58 (50-66)	<0.001
Donor male gender	143 (51%)	67 (52%)	0.92
Donor cause of death			
Stroke	115 (41%)	86 (67%)	0.73
Trauma	32 (11%)	8 (6%)	0.73
UKKDRI	1.02 (0.83-1.28)	1.39 (1.01-1.85)	<0.001
Recipient age (yr)	49 (40-58)	54 (46-63)	0.005
Recipient male gender	116 (42%)	92 (71%)	0.02
Cold ischaemia time (min)	810 (641-1020)	866 (643-1011)	0.48

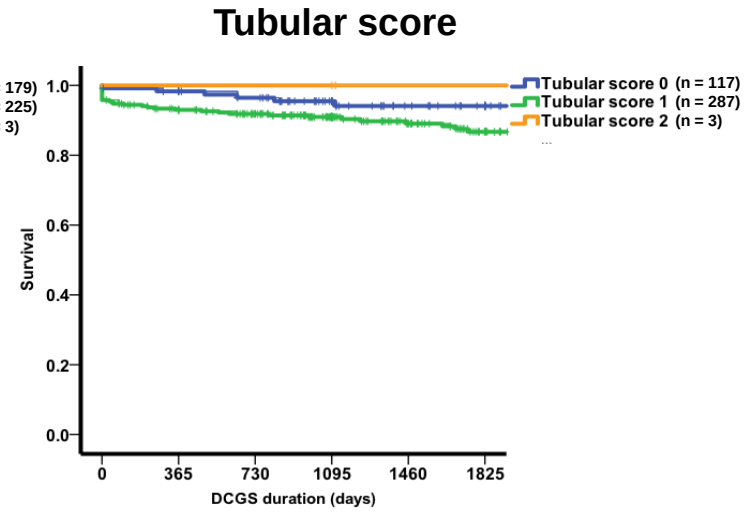


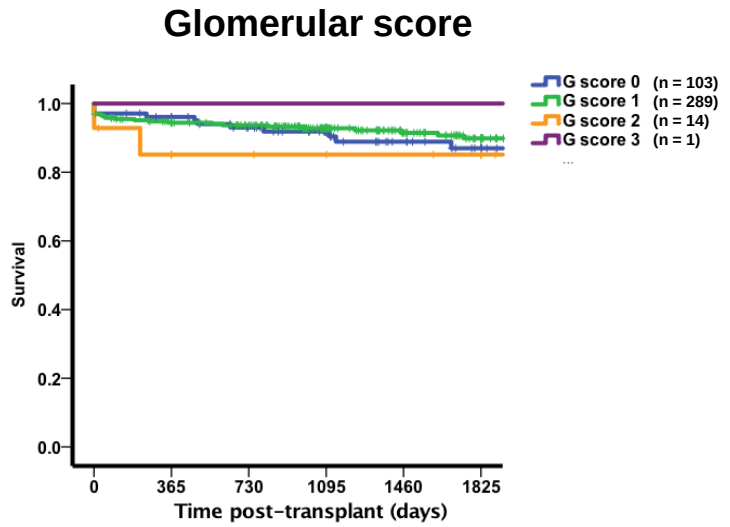
Results: K score and graft survival (4)

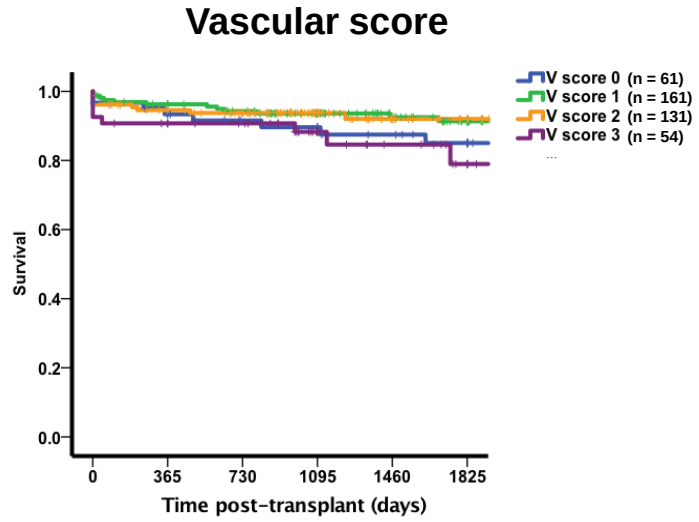


K score component	Association with death censored graft survival?	p value
Interstitial	✘	0.31
Tubular	✘	0.33
Glomerular	✘	0.78
Vascular	✘	0.31



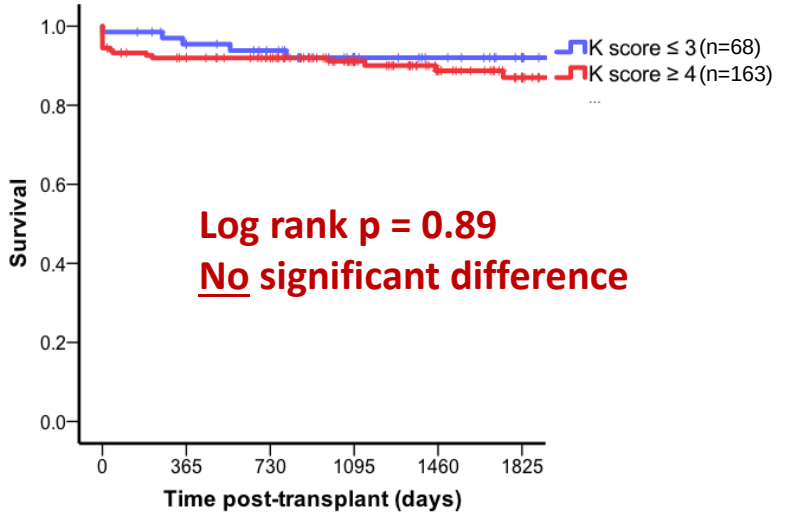




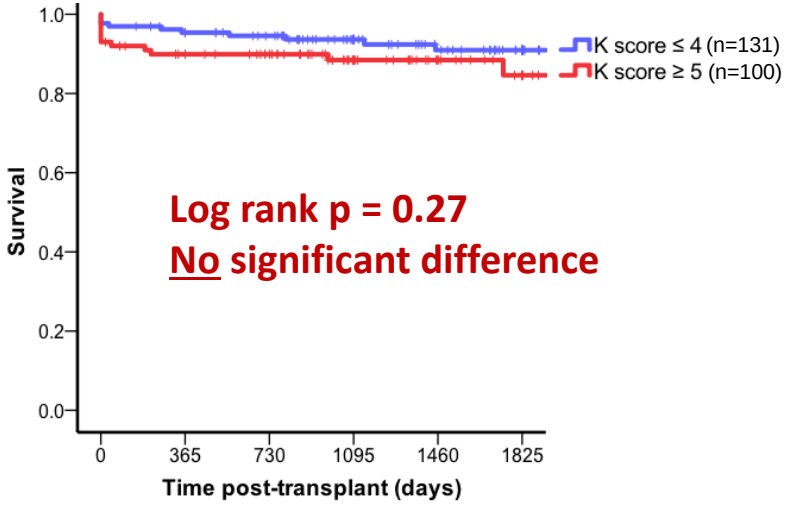


Results: K score and graft survival (5)

Donors aged 50+ years

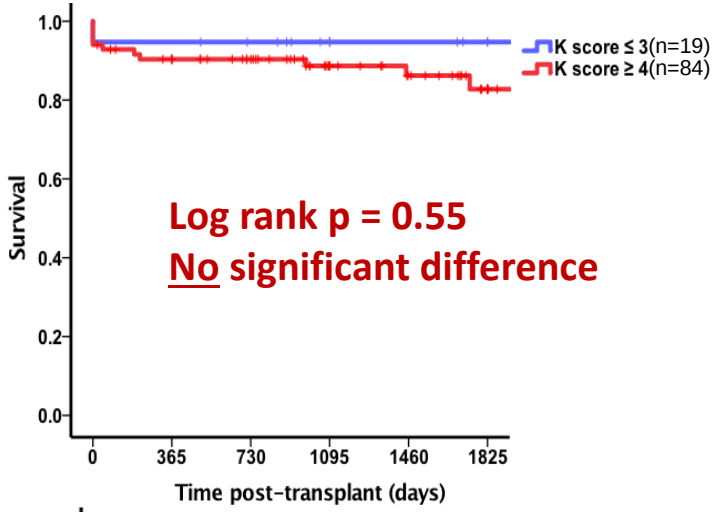


Log rank p = 0.89
No significant difference

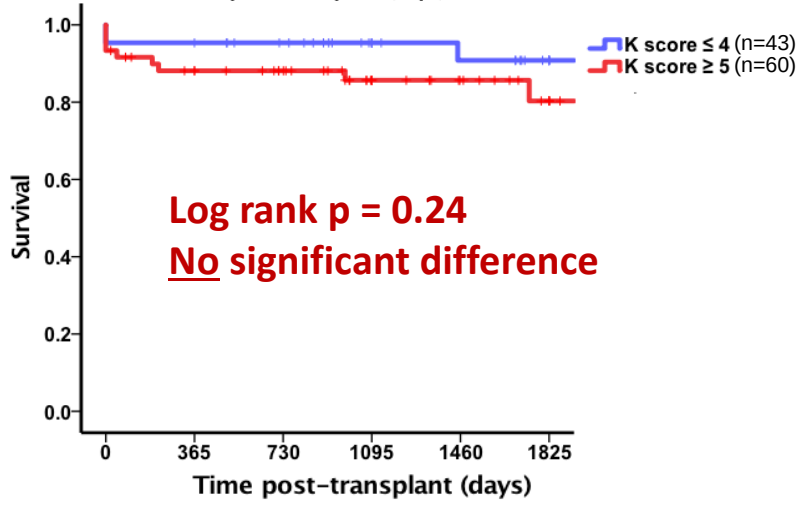


Log rank p = 0.27
No significant difference

Donors aged 60+ years



Log rank p = 0.55
No significant difference



Log rank p = 0.24
No significant difference

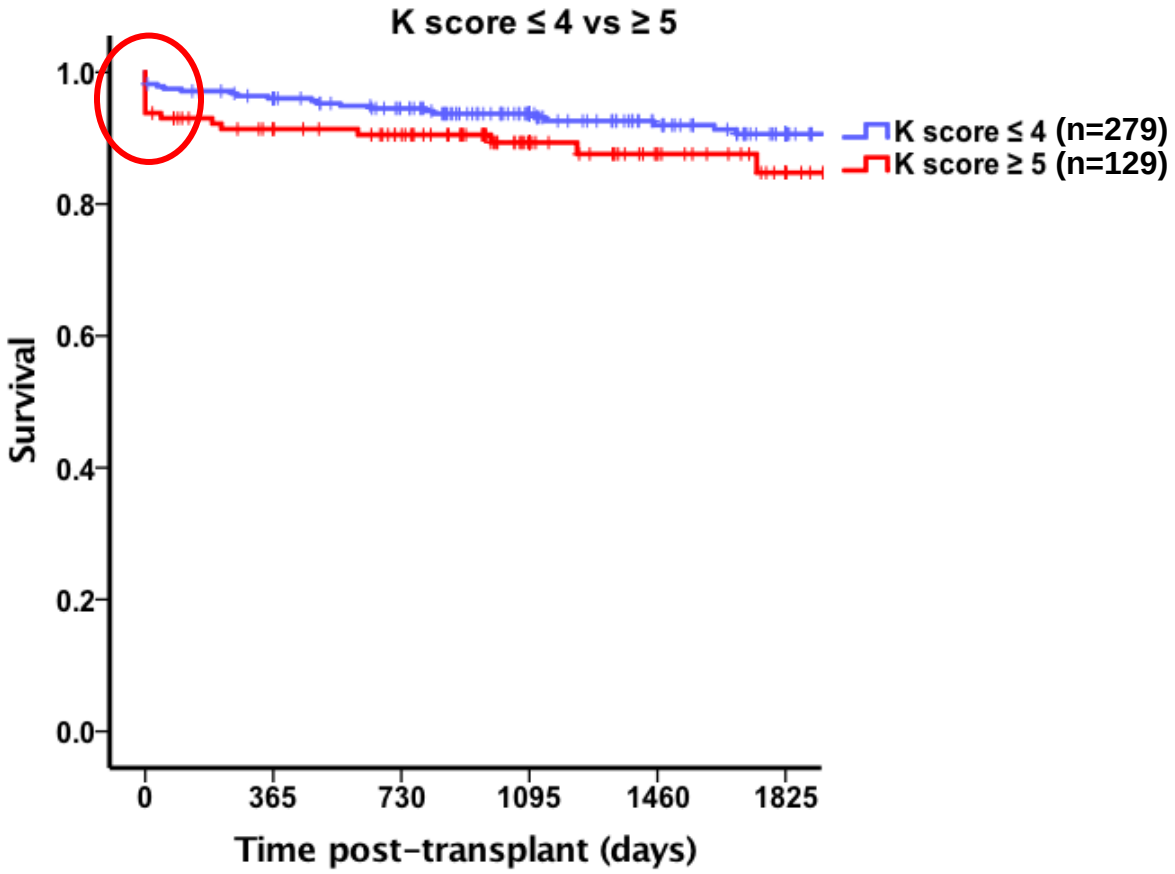
Results: predictors of DCGS

Cox regression analysis

Covariates in the equation	→	Independent predictors of DCGS
K score ~~Donor age~~ UKKDRI Recipient age Graft number Transplant type (DBD/DCD) Cold ischaemia time HLA mismatch level		K score does not predict DCGS (p = 0.60) Graft number >1 only predictor of DCGS (p < 0.001)

Results: primary non-function (PNF)

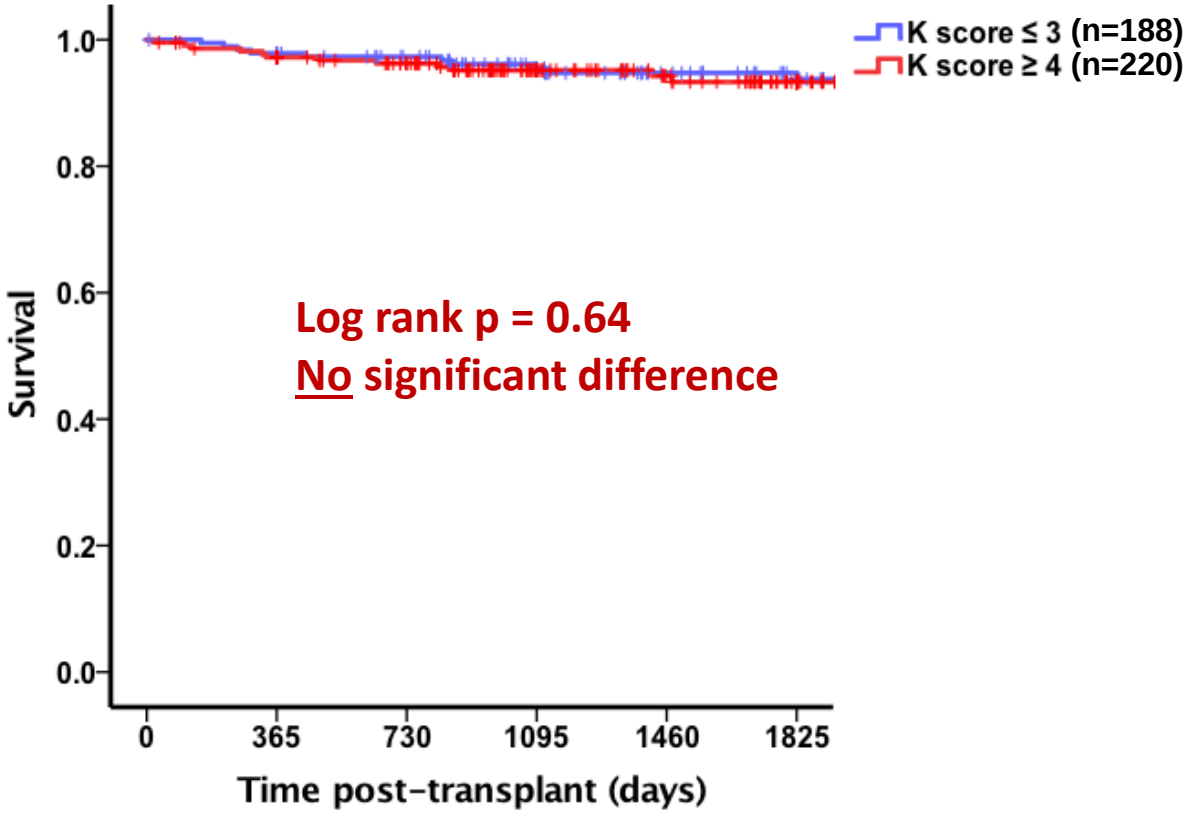
Death-censored graft survival



- **Does K score predict 'PNF'?**
  - 'PNF' defined as graft survival of zero days, regardless of cause
- **Multivariate analysis:**
  - K score ≥ 5 is an independent predictor of 'PNF' (HR 3.5, p = 0.04)

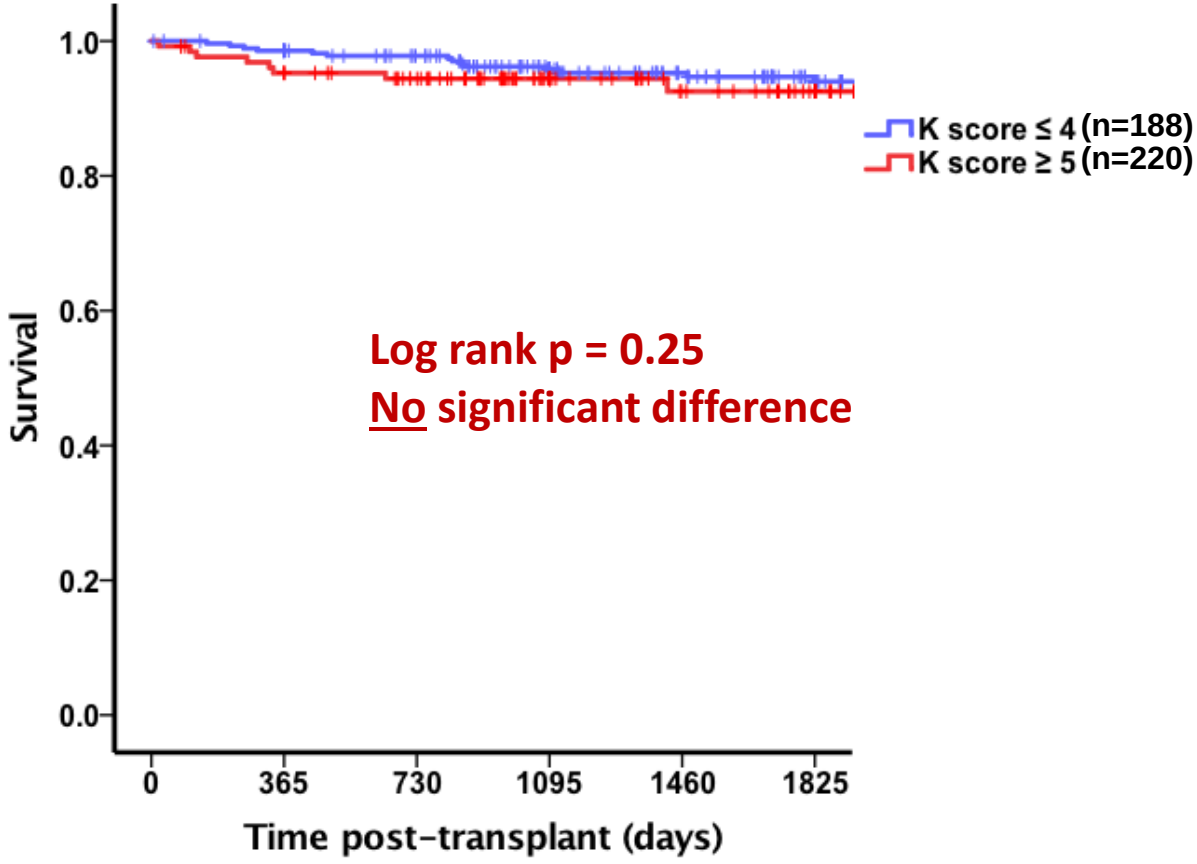
Results: patient survival

Patient survival stratified by K score ≤ 3 vs ≥ 4



Log rank p = 0.64
No significant difference

Patient survival stratified by K score ≤ 4 vs ≥ 5



Log rank p = 0.25
No significant difference

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Results: impact on organ utilisation

Clinically acceptable kidneys

- 2012 to 2015
- Donors ≥ 60 years
- Adequate 'time zero' biopsy

Single
73 kidneys
73 recipients

Median 1 year eGFR 38
1 year DCGS 90%

Dual
40 kidneys
20 recipients

Median 1 year eGFR 51
1 year DCGS 88%

TOTAL
113 kidneys
93 recipients

Utilisation algorithm

- **Single kidney transplant(s)?**
  - One kidney at our centre?
    - K score 0-4 → SINGLE
    - K score 5+ → DECLINE
  - Both kidneys at our centre?
    - Both K scores 0-4 → SINGLE
    - Highest K score 5-6 → DUAL
    - Highest K score 7-12 → DECLINE
- **Dual kidney transplant?**
  - Both K scores 0-4 → SINGLE x 2
  - Highest K score 5-6 → DUAL
  - Highest K score 7-12 → DECLINE

Single
54 kidneys
54 recipients

Dual
30 kidneys
15 recipients

Decline
29 kidneys

TOTAL
84 kidneys
69 recipients

Conclusions

- Kidneys with K scores 0 to 8 have been implanted as single grafts with good results
- For every increment in K score, there is a 3 mL/min/1.73m^2 drop in eGFR at 1- and 3-years
- There is no association between K score and medium-term DCGS
  - Independent predictor of primary non-function
- Retrospective application of a clinico-pathological tool to our programme suggests that organ utilisation would have decreased
- These data do not support the widespread use of PIKB in our deceased donor kidney programme, given our current donor risk profile

Acknowledgments

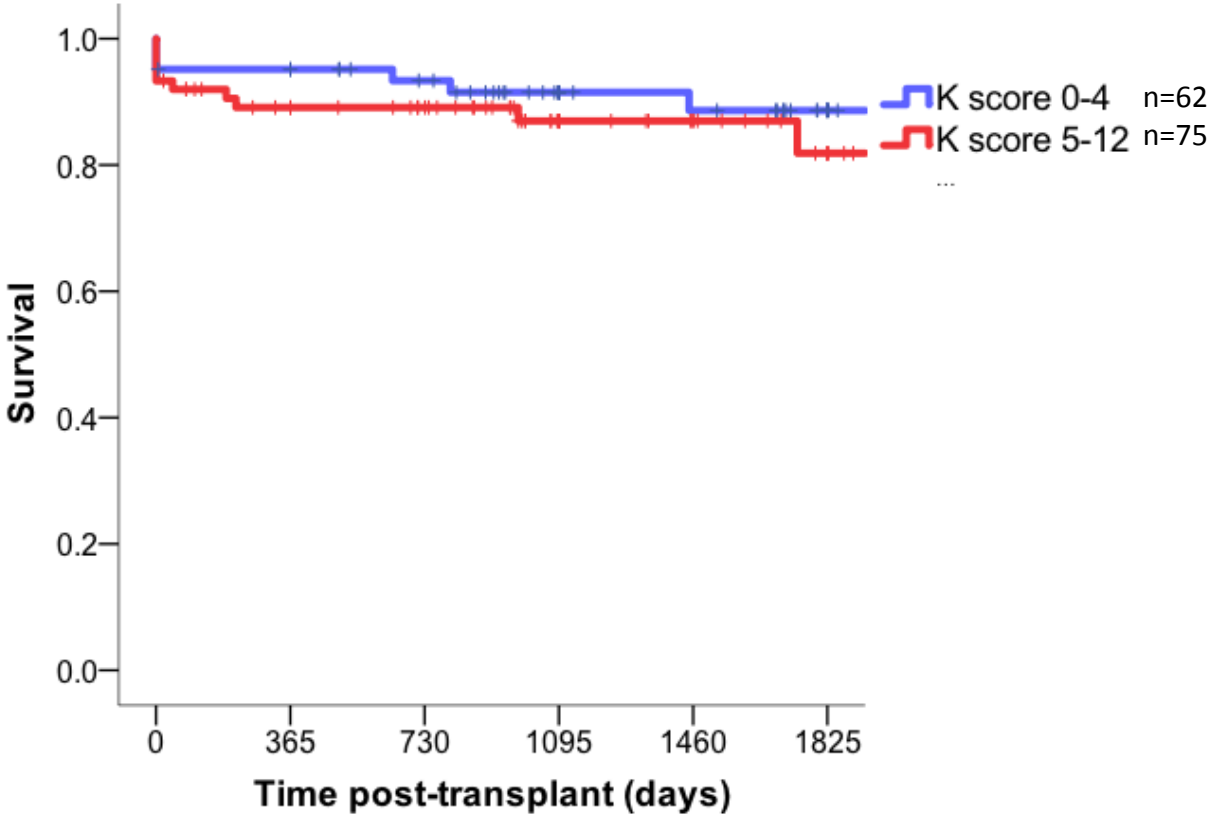
Yes I donate
ORGAN DONATION

- **Surgical colleagues**
    - Geoff Koffman, John Taylor, Francis Calder, Nizam Mamode, Jonathon Olsburgh, Martin Drage, Ioannis Loukopoulos, Nikolaos Karydis
- **Histopathology colleagues**
    - Patrick O'Donnell, Fahim Tungekar, Robert Hangartner, Ran Perera
- Patrick Trotter, NHS Blood and Transplant
- Donors, recipients, and their families

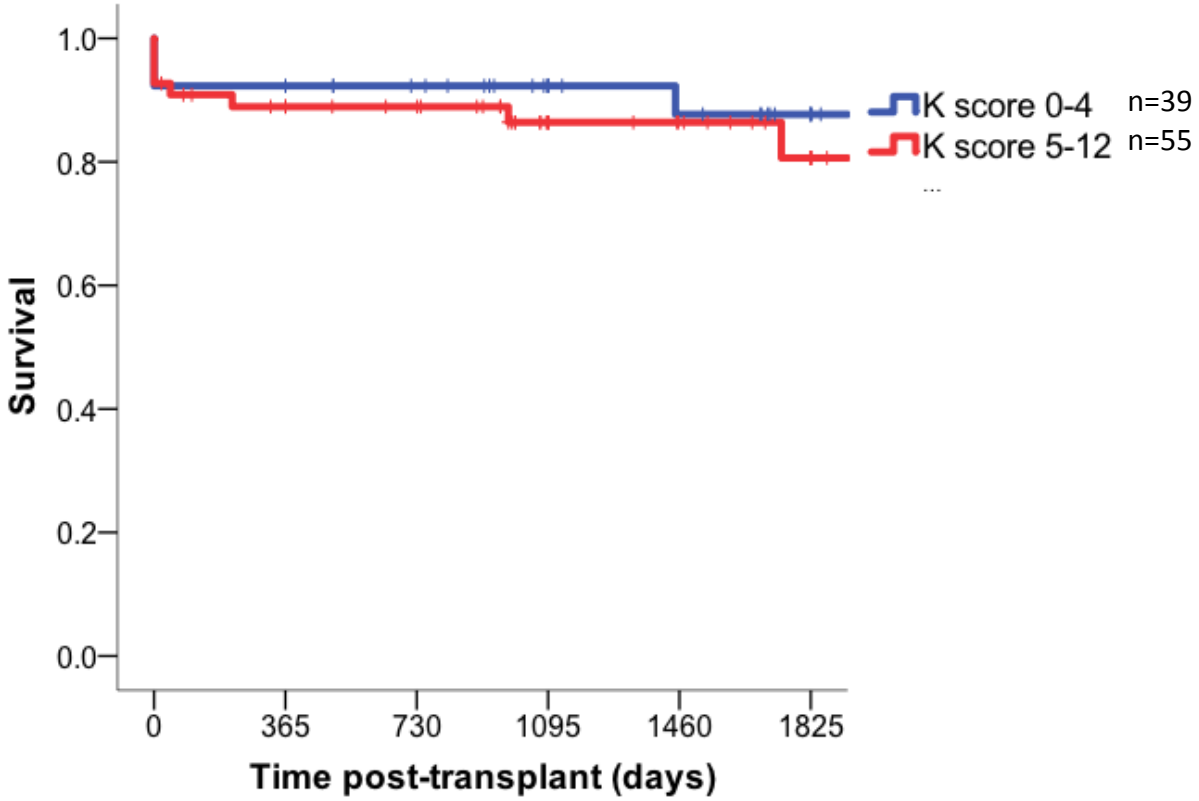
#kidneytransplantbiopsy

Appendix 1: DCGS in high UKKDRI donors

DCGS in patients with UKKDRI ≥ 1.35

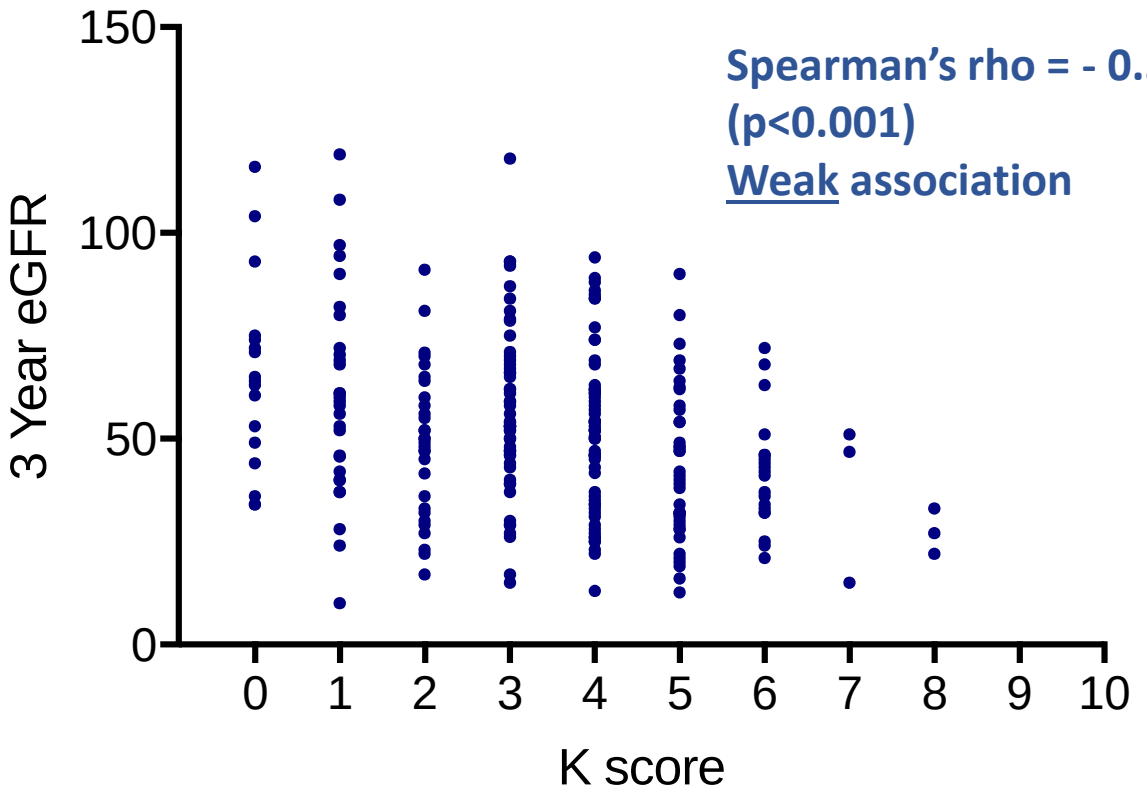


DCGS in patients with UKKDRI ≥ 1.50

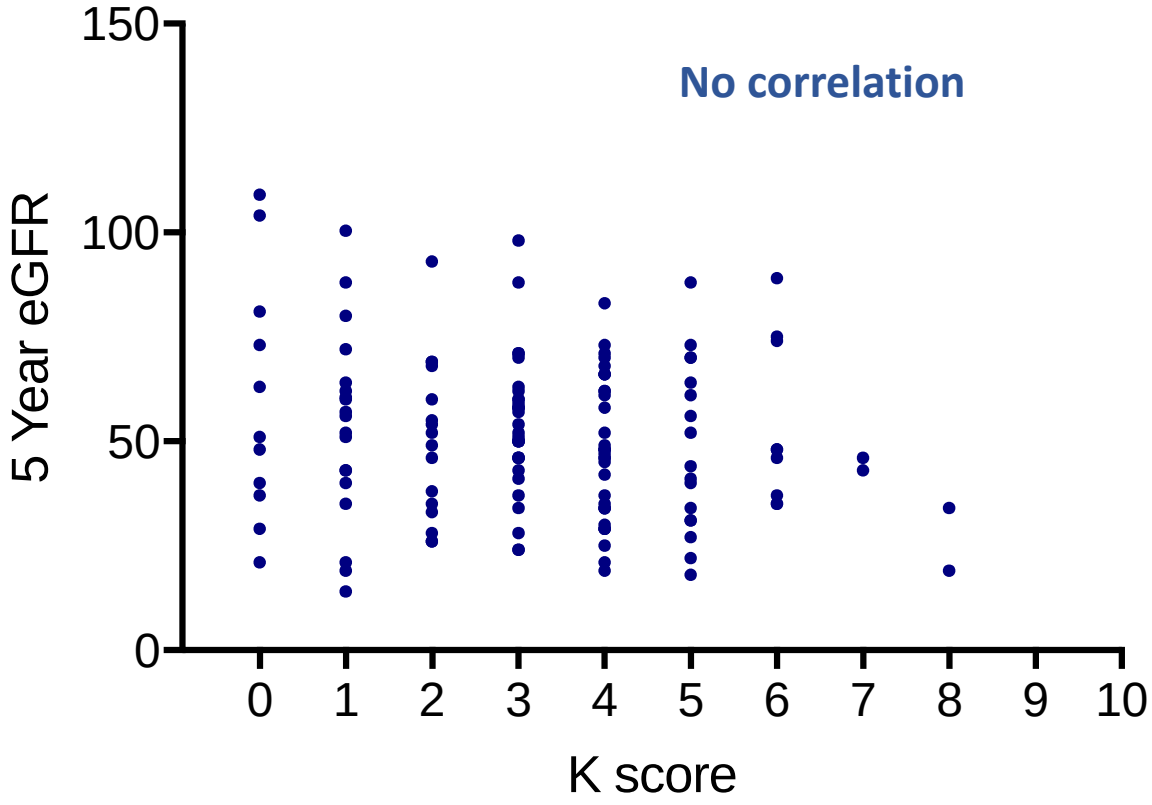


Appendix 2: K score and graft function

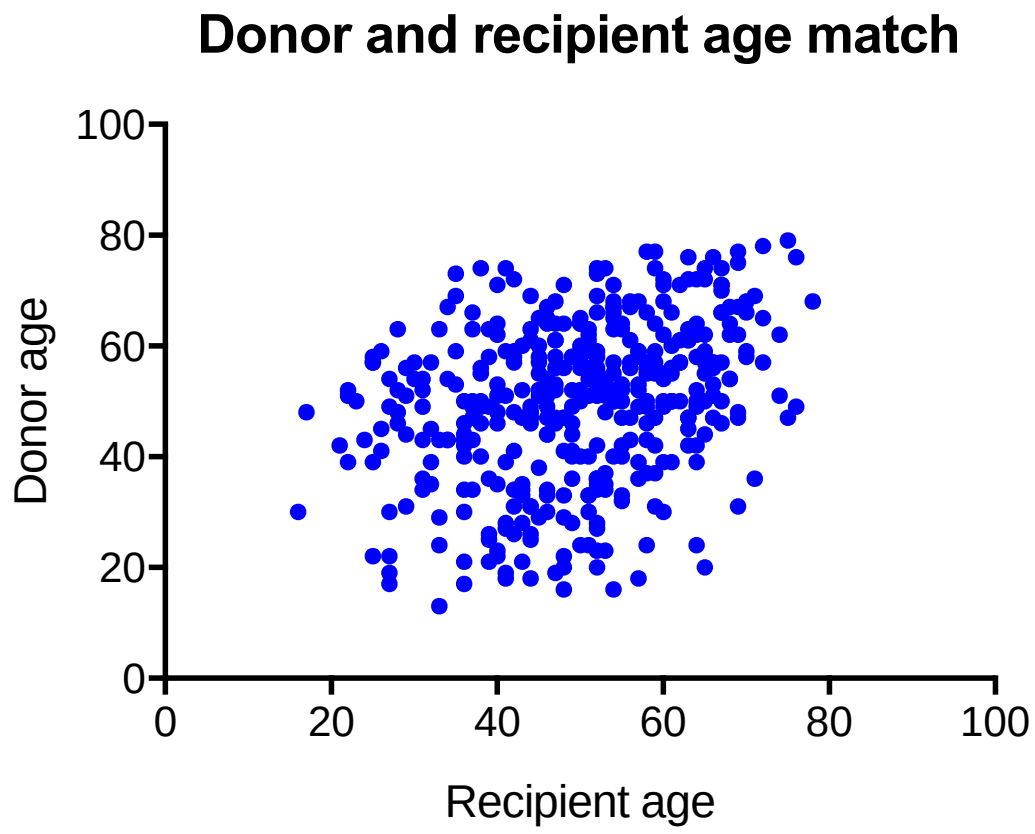
3 year eGFR according to K score



5 year eGFR according to K score

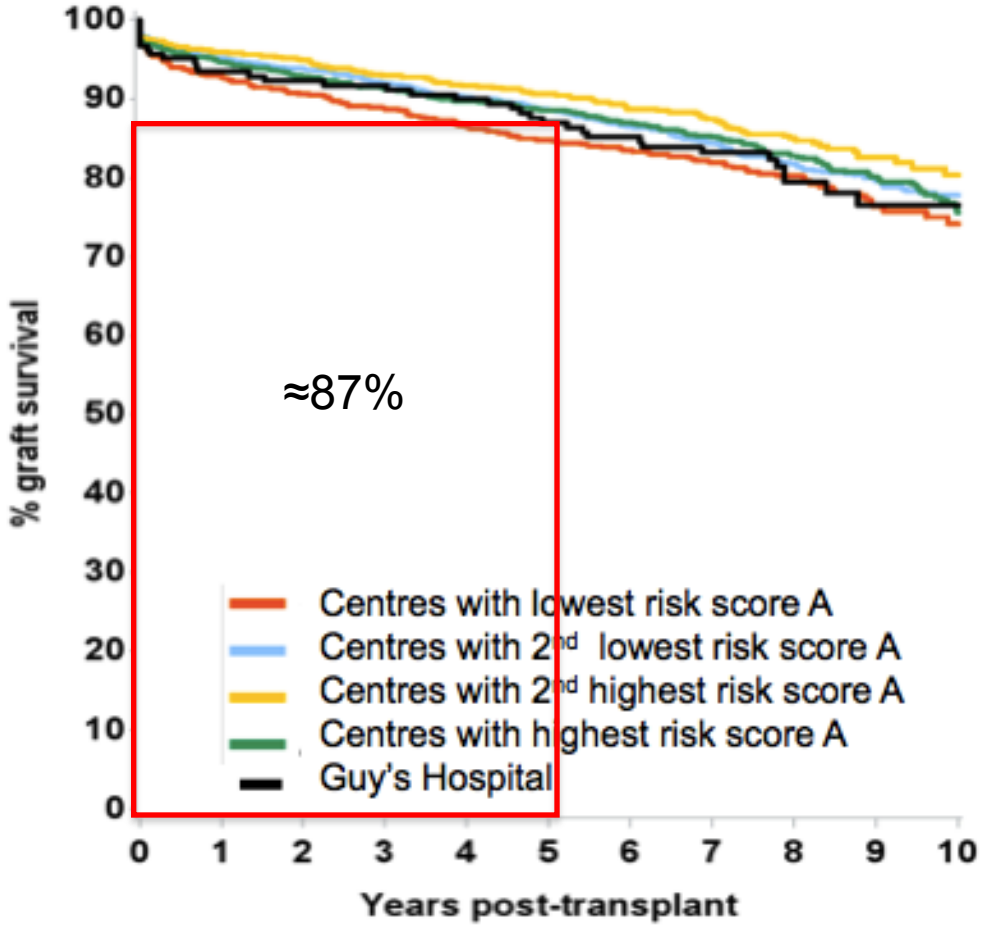


Appendix 3: donor and recipient age

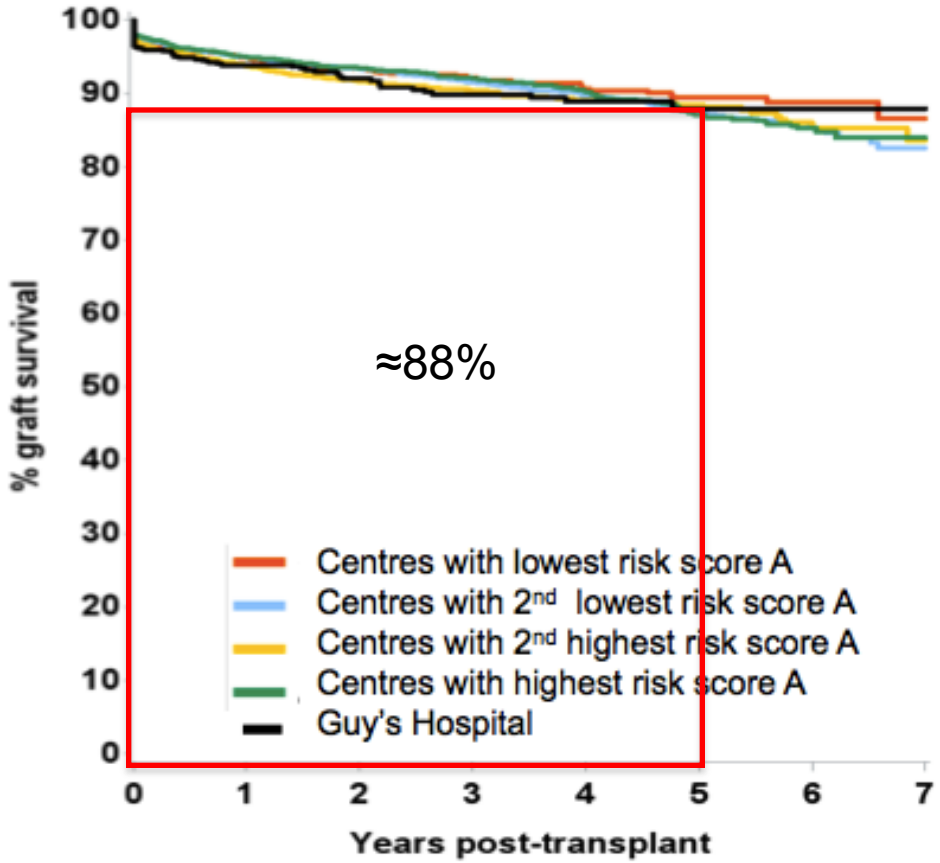


Appendix 4: DSGS at Guy's (registry data)

First graft survival post-transplantation, 2006-2010

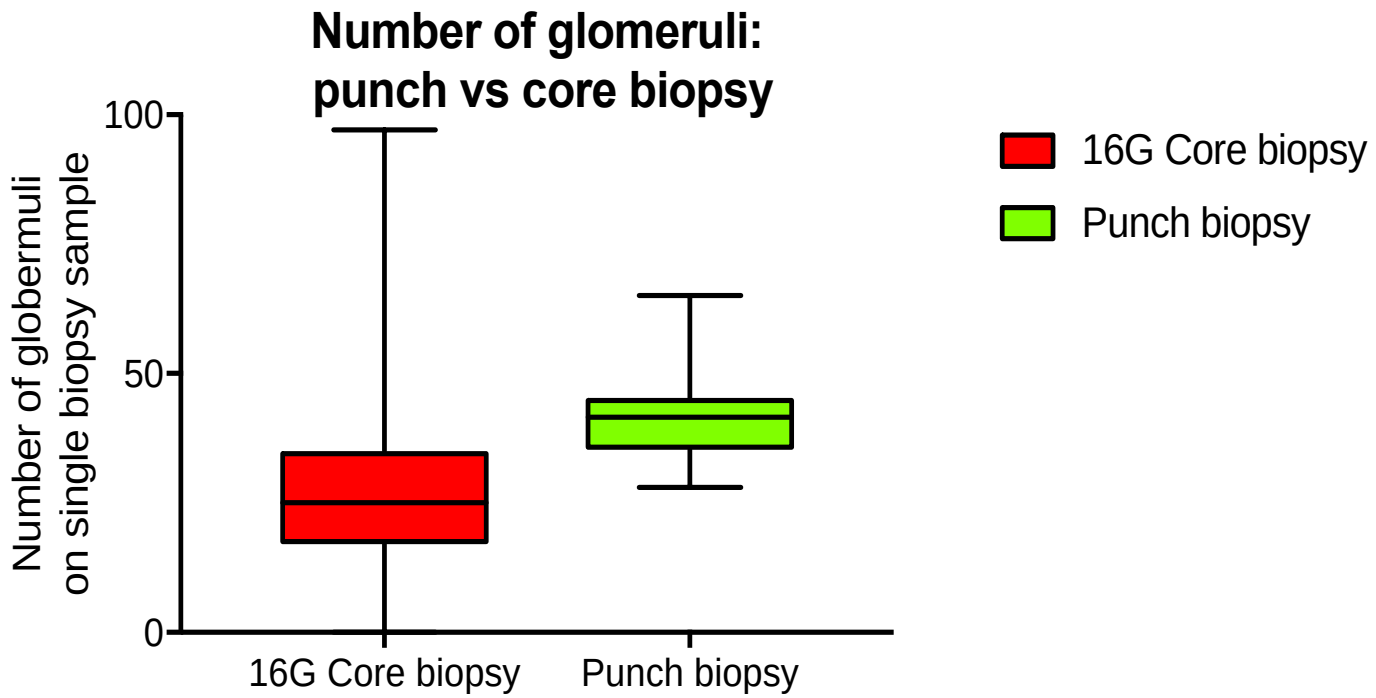


First graft survival post-transplantation, 2011-2016



Appendix 5 – Biopsy adequacy rates

	Punch biopsy	16G Core biopsy
Number of values	16	576
Minimum	28	0
25% Percentile	35.25	17
Median	42	25
75% Percentile	45.25	35
Maximum	65	97
Shipiro-Wilk test of normality	Non-parametric	
Mann-Whitney test comparing both medians	p = <0.001	
Fisher's exact test comparing adequacy	p = 0.005	



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Appendix 6: Time-zerO Biopsy Investigators (TOBI)

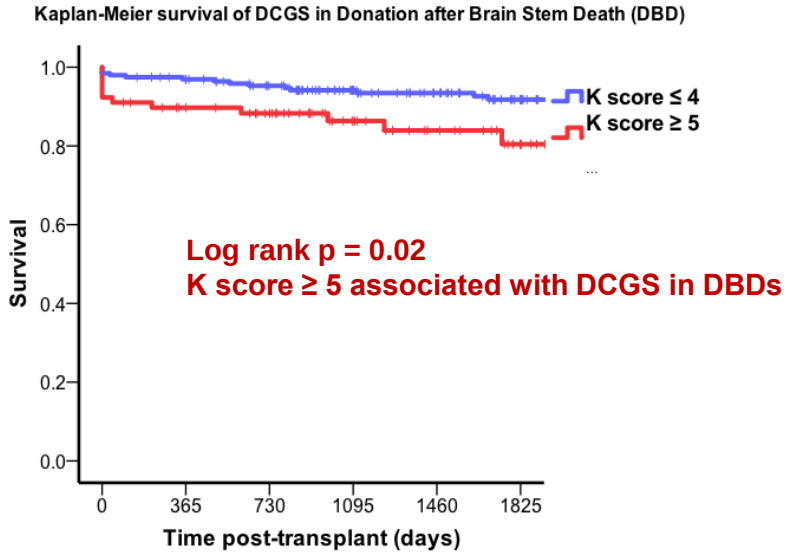
- National, multi-centre, retrospective analysis of biopsies of deceased donor kidneys
  - Re-analysis of time-zero or pre-implantation kidney biopsies 1.1.08-1.1.16 by multiple blinded renal pathologists
  - Linkage to the national transplant registry to capture donor / recipient variables and determine patient outcomes
  - Aims:
    1) determine association between chronic changes at the time of transplantation and subsequent graft and patient outcomes
    2) determine the most accurate histological and/or clinico-histopathological scoring systems
    3) better define inter-observer variability between renal pathologists
- Group

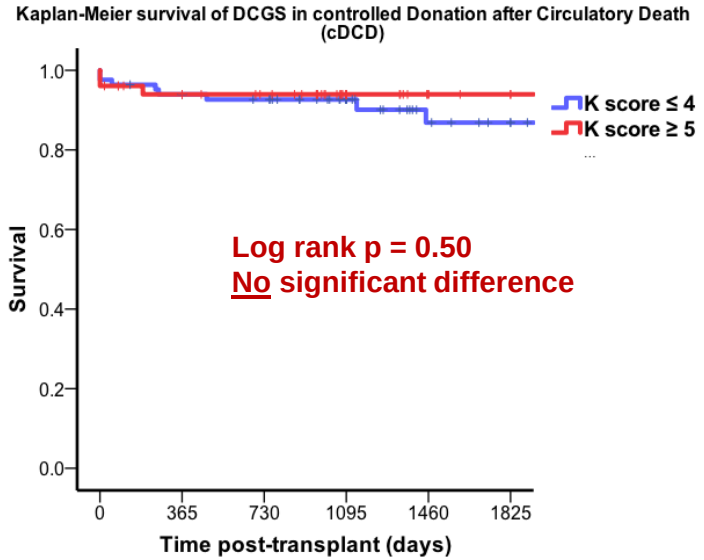
Chris Callaghan, transplant surgeon, London
Candice Roufosse, pathologist, London
Rachel Johnson, statistician, NHSBT
Desley Neil, pathologist, Birmingham
Gavin Pettigrew, transplant surgeon, Cambridge
Rachel Hilton, nephrologist, London

- Next steps
  - Combination of Guy's and Cambridge databases and re-analysis via the national transplant registry
  - Exchange historical slides between Guy's and Cambridge renal histopathologists for blinded scoring
  - Broaden TOBI group and invite interested UK renal transplant centres to join
  - Funding application (NIHR RfPB)

Appendix 7: Graft survival: DBD vs DCD

- 274 DBDs vs.134 DCDs
- Overall, DCGS was the same between DBDs and DCDs (p=0.99)
- No association between K score and DCGS in DCDs (p=0.50)
- Association between K score and DCGS in DBDs (p=0.02)
  - Association lost if PNF patients removed

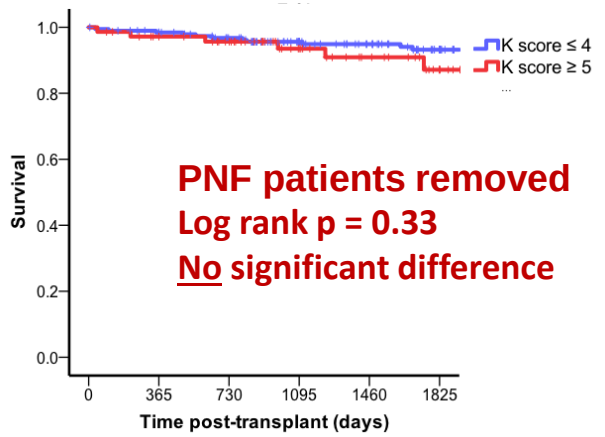




Appendix 8: Graft survival: DBD vs DCD

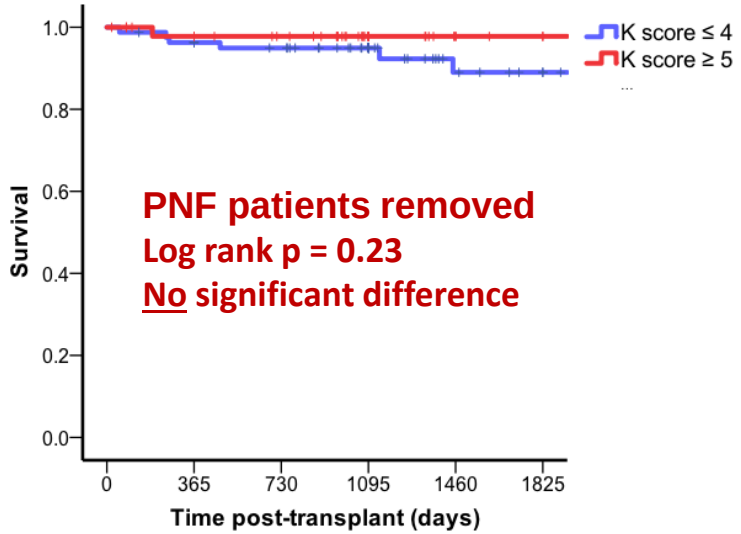
- 274 DBDs vs.134 DCDs
- Overall, DCGS was the same between DBDs and DCDs (p=0.99)
- No association between K score and DCGS in DCDs (p=0.50)
- Association between K score and DCGS in DBDs (p=0.02)
  - Association lost if PNF patients removed

Kaplan-Meier survival of DCGS in Donation after Brain Stem Death (DBD)

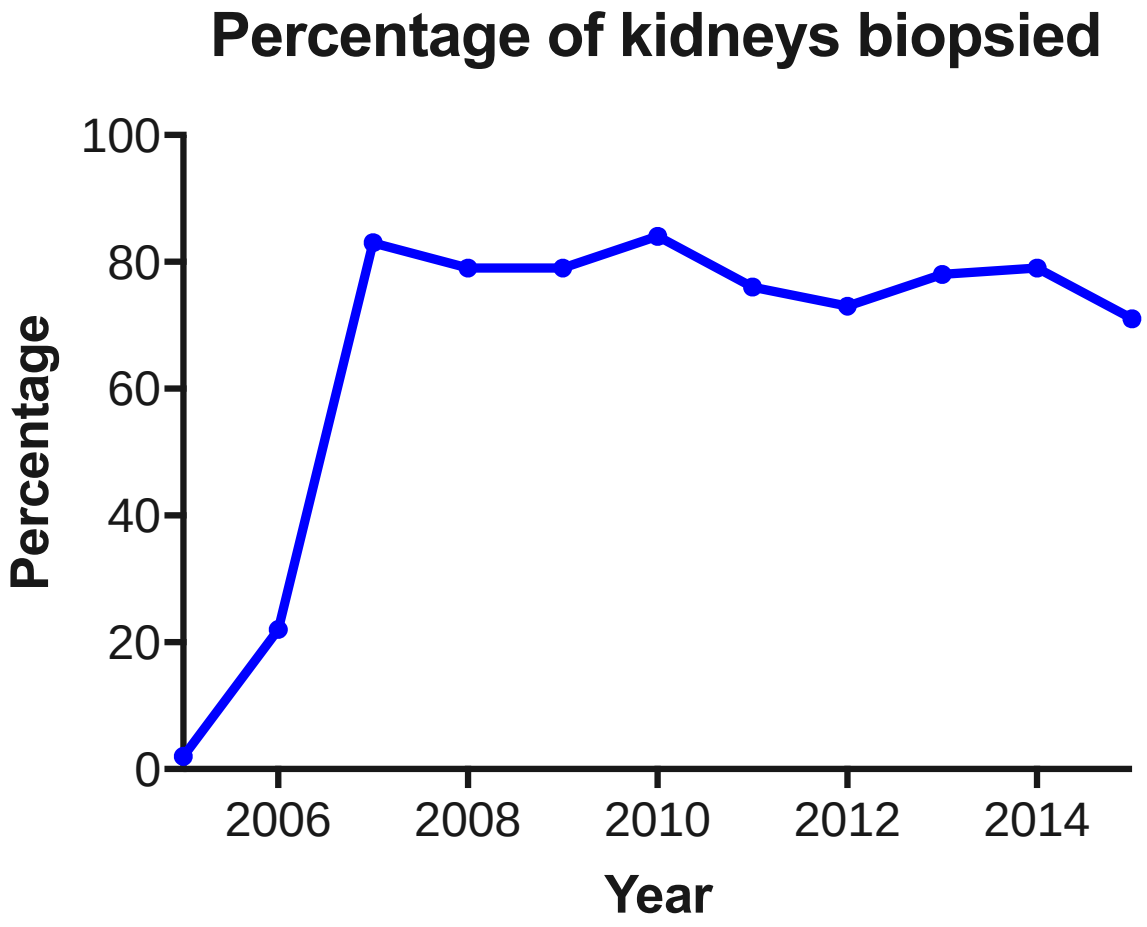


PNF patients removed
Log rank p = 0.33
No significant difference

Kaplan-Meier survival of DCGS in controlled Donation after Circulatory Death (cDCD)



PNF patients removed
Log rank p = 0.23
No significant difference


Percentage of kidneys biopsied
Percentage
100
80
60
40
20
0
2006
2008
2010
2012
2014
Year

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Results: impact on organ utilisation

Clinically acceptable kidneys

- 2012 to 2015
- Donors ≥ 60 years
- Adequate 'time zero' biopsy

Single
73 kidneys
73 recipients

Median 1 year eGFR 38 mL/min/1.73m^2
1 year DCGS 90%

Dual
40 kidneys
20 recipients

Median 1 year eGFR 51 mL/min/1.73m^2
1 year DCGS 88%

TOTAL
113 kidneys
93 recipients

Utilisation algorithm

- **Single kidney transplant(s)?**
  - One kidney at our centre?
    - K score 0-4 → SINGLE
    - K score 5+ → DECLINE
  - Both kidneys at our centre?
    - Both K scores 0-4 → SINGLE
    - Highest K score 5-6 → DUAL
    - Highest K score 7-12 → DECLINE
- **Dual kidney transplant?**
  - Both K scores 0-4 → SINGLE x 2
  - Highest K score 5-6 → DUAL
  - Highest K score 7-12 → DECLINE

Single
54 kidneys
54 recipients

Median 1 year eGFR 43 mL/min/1.73m^2
1 year DCGS 90% (n=30)

Dual
30 kidneys
15 recipients

Median 1 year eGFR 51 mL/min/1.73m^2
1 year DCGS 75% (n=8)

Decline
29 kidneys

TOTAL
84 kidneys
69 recipients