
Expanded Criteria Kidney Donors

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Outline

- **Definition of ECD kidney**
- **Benefits of ECD kidney transplantation**
- **Who should receive an ECD kidney and why**
- **Donor Selection**
- **Donor Management**
- **Conclusions**

Criteria for RR Graft Loss > 1.7 – UNOS

Rosengard et al, AJT, 2002

-important to have evidence based definition

Donor condition	Donor age categories				
	< 10	10-39	40-49	50-59	≥ 60
CVA + HTN + Creat > 1.5				X	X
CVA + HTN				X	X
CVA + Creat > 1.5				X	X
HTN + Creat > 1.5				X	X
CVA					X
HTN					X
Creatinine > 1.5					X
None of the above					X

CVA = CVA was cause of death.
HTN = history of hypertension.
Creat > 1.5 = creatinine > 1.5 mg/dL.

Relative Risk of Graft Loss Based on Donor Characteristics

Port et al Transplantation 74;1281, 2002

TABLE 3. Relative risk^a of graft loss by four donor characteristics

Age (yr)	Relative risk			
	Normal creatinine		High creatinine ^b	
	No HTN	HTN	No HTN	HTN
Cause of death was not CVA				
0-9	1.40**	1.59**	1.52**	—
10-39	1.00 (ref)	1.14**	1.09*	1.24**
40-49	1.17**	1.33**	1.28**	1.45**
50-59	1.41**	1.60**	1.53**	1.74**
60+	1.90**	2.16**	2.07**	2.36**
Cause of death was CVA				
0-9	1.60**	1.82**	1.74**	1.98**
10-39	1.14**	1.30**	1.24**	1.41**
40-49	1.34**	1.52**	1.46**	1.66**
50-59	1.61**	1.83**	1.75**	1.99**
60+	2.17**	2.47**	2.37**	2.69**

^a Risk of graft loss, relative to donors aged 10-39 years with a terminal serum creatinine <1.5 mg/dL but without HTN and CVA; other factors held constant. Adjusted for variables in Table 1, plus year of transplantation. Bolded numbers highlight RR >1.7.

^b Terminal creatinine >1.5 mg/dL.

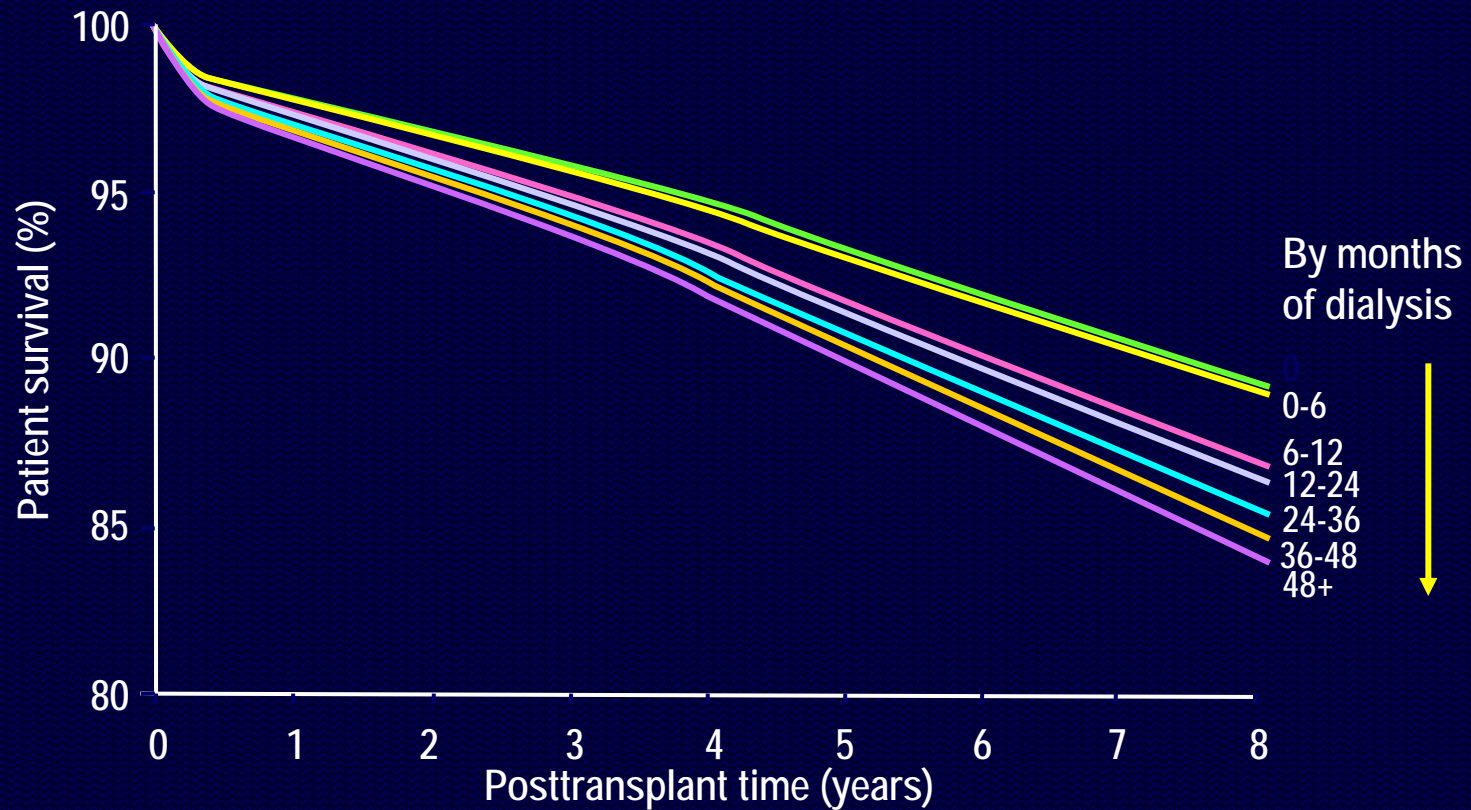
* P<0.05; ** P<0.0005.

Benefits of Expanded Criteria Donor Kidney Transplantation

Why Use ECDs?

- **Risks of waiting time**
- **Benefits of ECDs on patient survival**

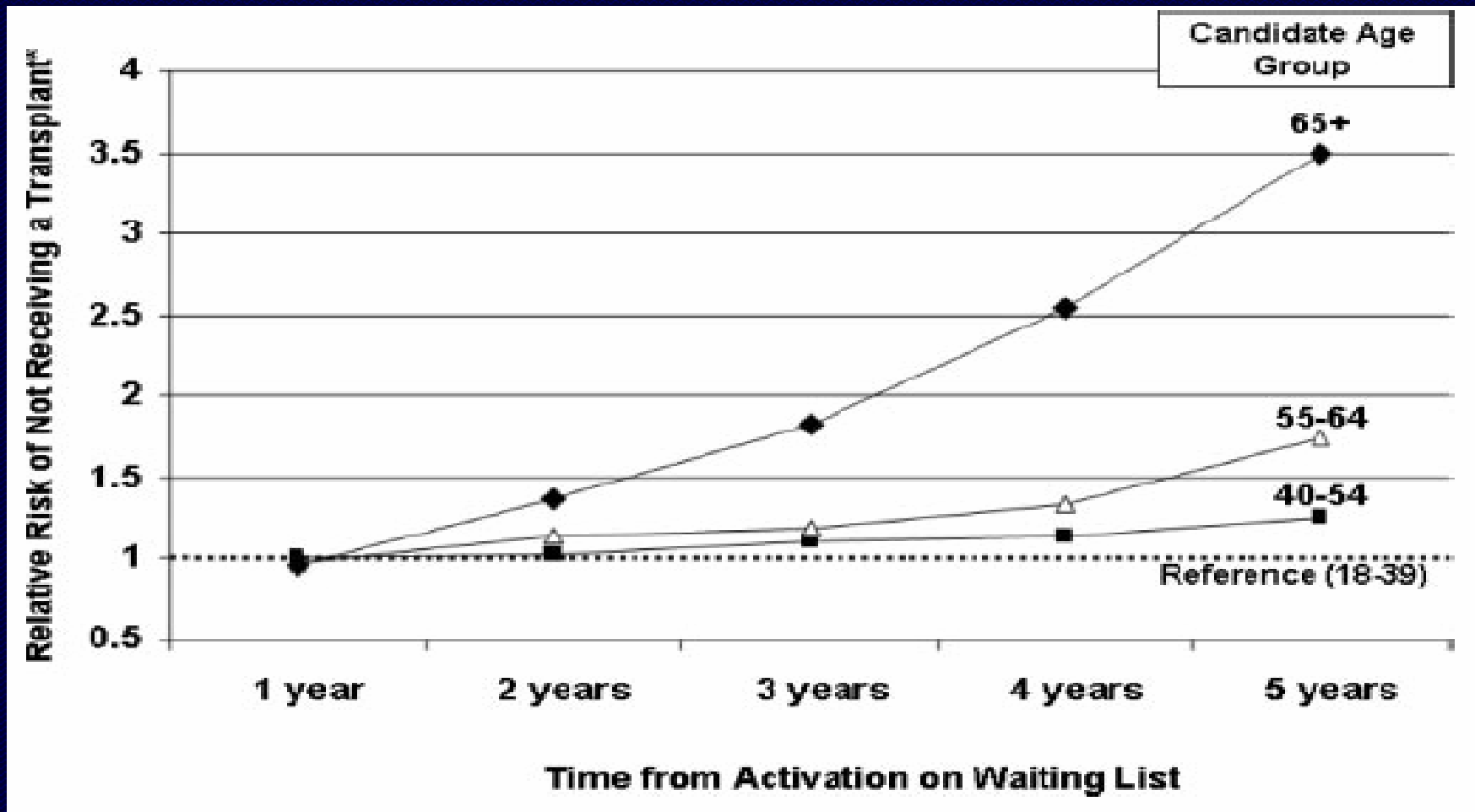
Waiting time Reduces Posttransplant Patient Survival



Retrospective study; n = 73 103 adult primary RTRs from USRDS registry (10/88-06/97)

RR of Not Receiving Kidney Once Placed on List vs Age

Schold and Meier-Kriesche CJASN, 2006



From Ojo et al JASN, 2001

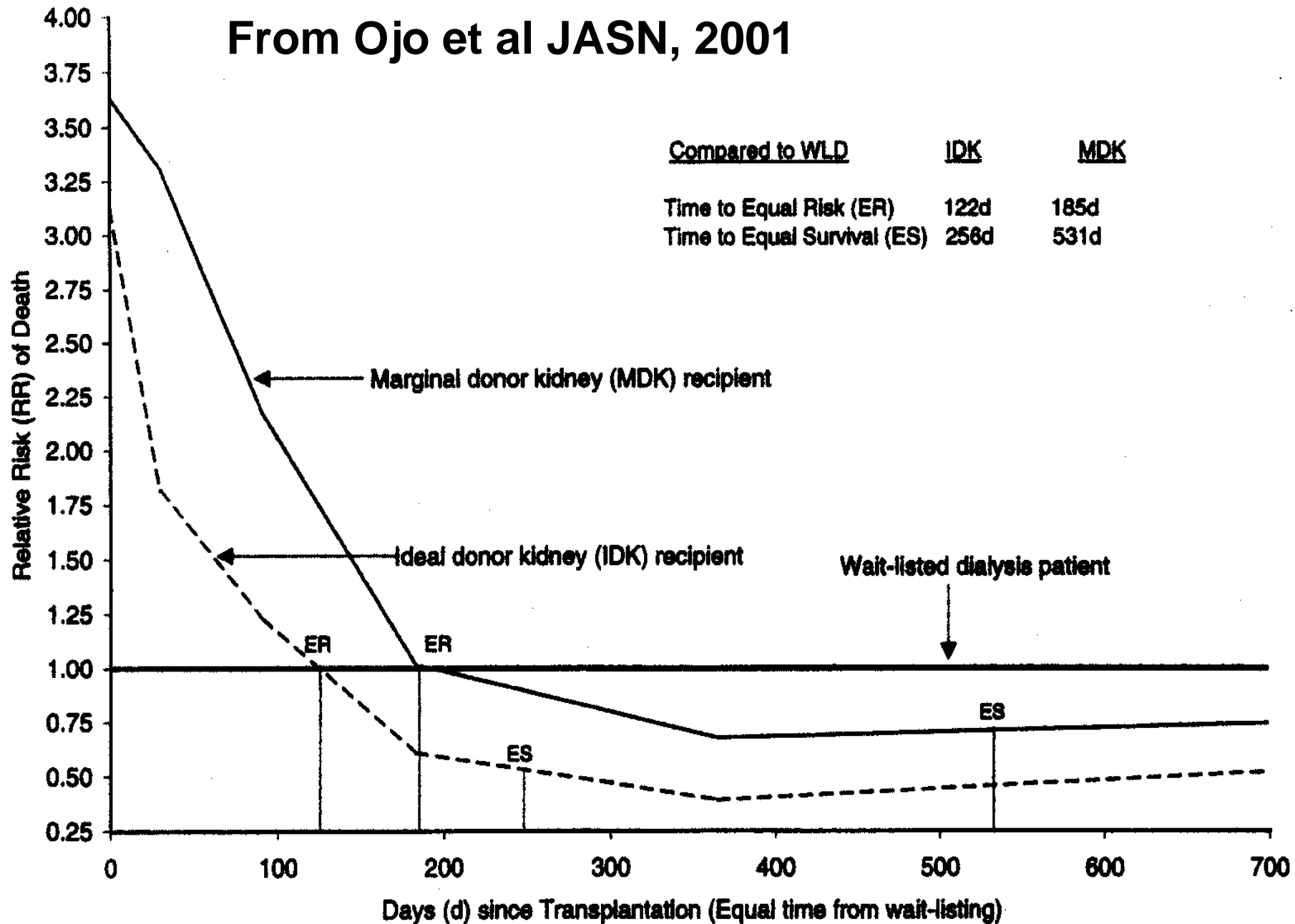
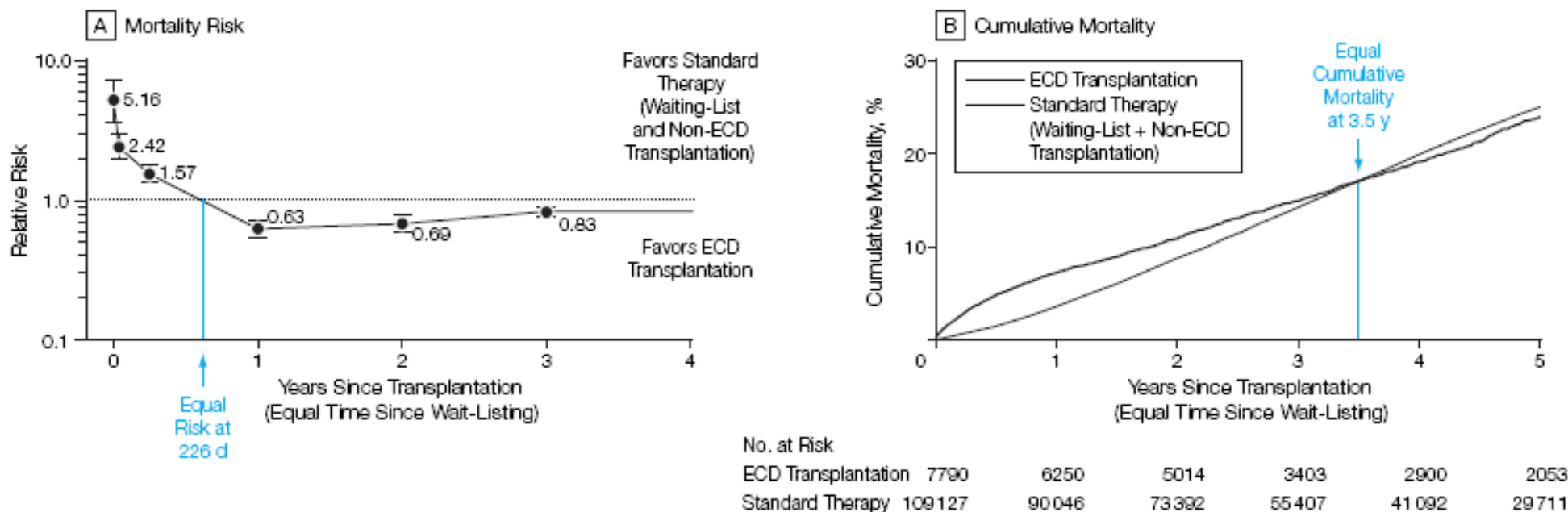


Figure 2. Mortality risks in two groups of cadaveric renal transplant recipients relative to wait-listed dialysis patients.

ECD Transplantation vs Standard Therapy

Merion et al JAMA, 2005

Figure 1. Times to Equal Risk of Mortality and Equal Cumulative Mortality for Expanded Criteria Donor (ECD) Kidney Recipients vs Patients Receiving Standard Therapy



Goals of an ECD Policy

- **Use ECD to increase access to renal transplantation without disadvantaging individual recipients**
- **Use only those kidneys that will give acceptable outcome and develop protocols to optimize**
- **Give ECD kidneys to those who will benefit**
- **Do not offer ECD kidneys to those who will not benefit**

Who Should Receive an ECD Kidney?

**Those who have the most to lose by
waiting**

Table 3. Long-term (3-Year) Relative Risk of Mortality for ECD Transplantation vs Standard Therapy (Waiting-List Candidates and Non-ECD Transplant Recipients)

Group	RR (95% CI)	P Value
All	0.83 (0.77-0.90)	<.001
Age, y		
0-17	0.77 (0.13-4.46)	.77
18-39	0.95 (0.73-1.24)	.72
40-59	0.81 (0.72-0.91)	<.001
≥60	0.78 (0.68-0.90)	<.001
Sex		
Male	0.81 (0.73-0.90)	<.001
Female	0.87 (0.76-1.00)	.04
Race		
White	0.90 (0.82-1.00)	.047
African American	0.79 (0.68-0.93)	.006
Asian	0.44 (0.26-0.74)	.002
Other	0.40 (0.18-0.90)	.03
Ethnicity		
Hispanic	0.81 (0.62-1.06)	.13
Non-Hispanic	0.84 (0.77-0.91)	<.001
ESRD cause		
Glomerulonephritis	0.84 (0.68-1.04)	.10
Diabetes	0.77 (0.67-0.88)	<.001
Hypertension	0.82 (0.69-0.97)	.02
Other	0.89 (0.74-1.05)	.17
Panel reactive antibody, %		
0-9	0.85 (0.78-0.94)	<.001
≥10	0.80 (0.60-1.07)	.14
OPO waiting time, d		
<700	0.97 (0.82-1.16)	.76
700-1350	0.89 (0.78-1.03)	.11
>1350	0.73 (0.64-0.83)	<.001

Merion et al
JAMA, 2005

NO Benefit of ECD in Retransplantation

Miles et al AJT, 2007

Table 3: ECD and non-ECD retransplantation versus conventional therapy (CT)

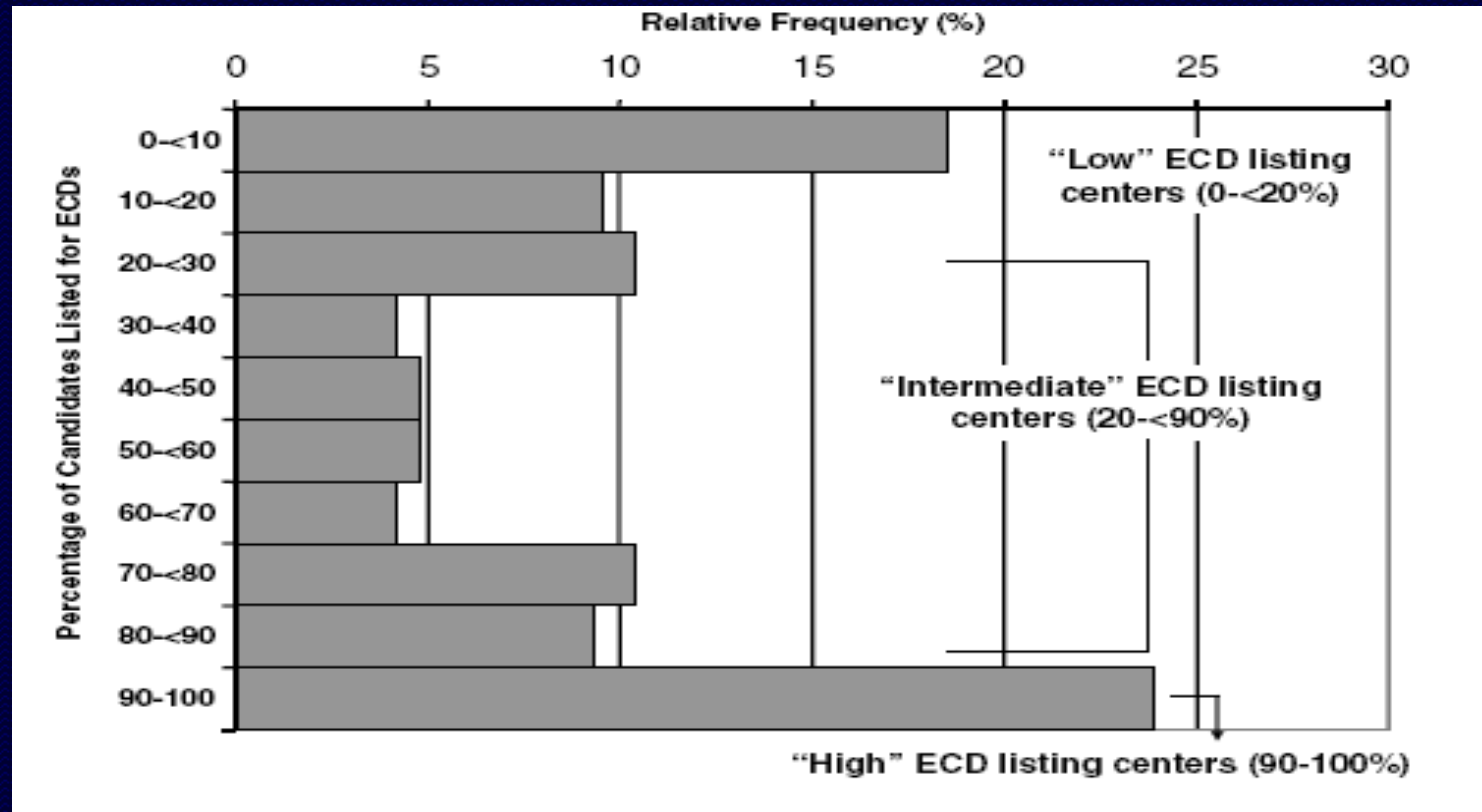
Comparison	Covariate-adjusted hazard ratio (HR)*	95% CI	<i>P</i>
ECD vs. CT	0.98	0.76, 1.26	0.88
Non-ECD vs. CT	0.44	0.39, 0.51	<0.0001

*Adjusted for age, sex, race, primary renal diagnosis, calendar period, time on dialysis before transplant, donor source, region, PRA, time between primary transplantation and graft failure, time between graft failure and relisting.

List Size and Waiting Time

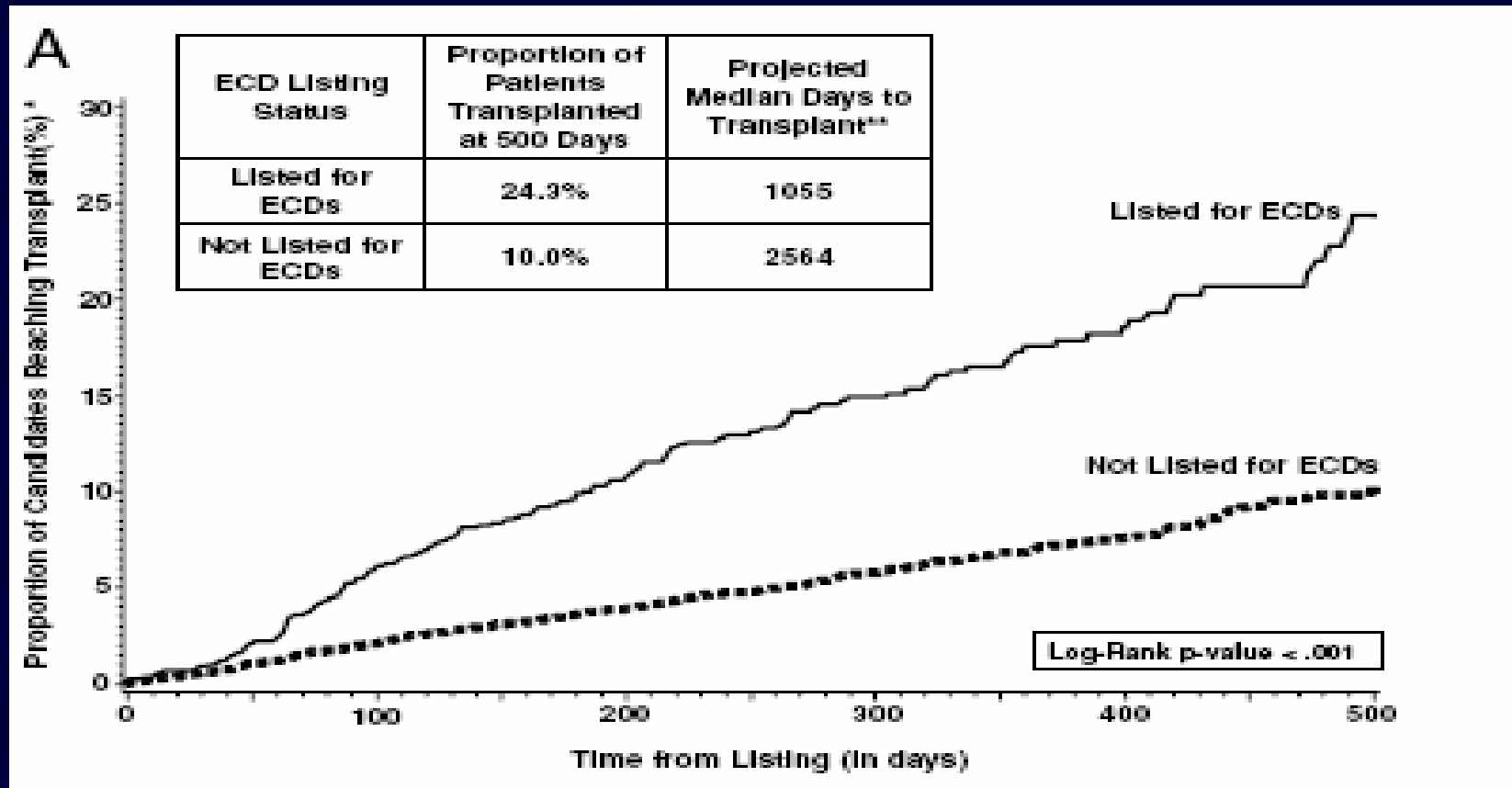
US Centres List Different Proportions of Patients for ECDs

Schold et al CJASN, 2006



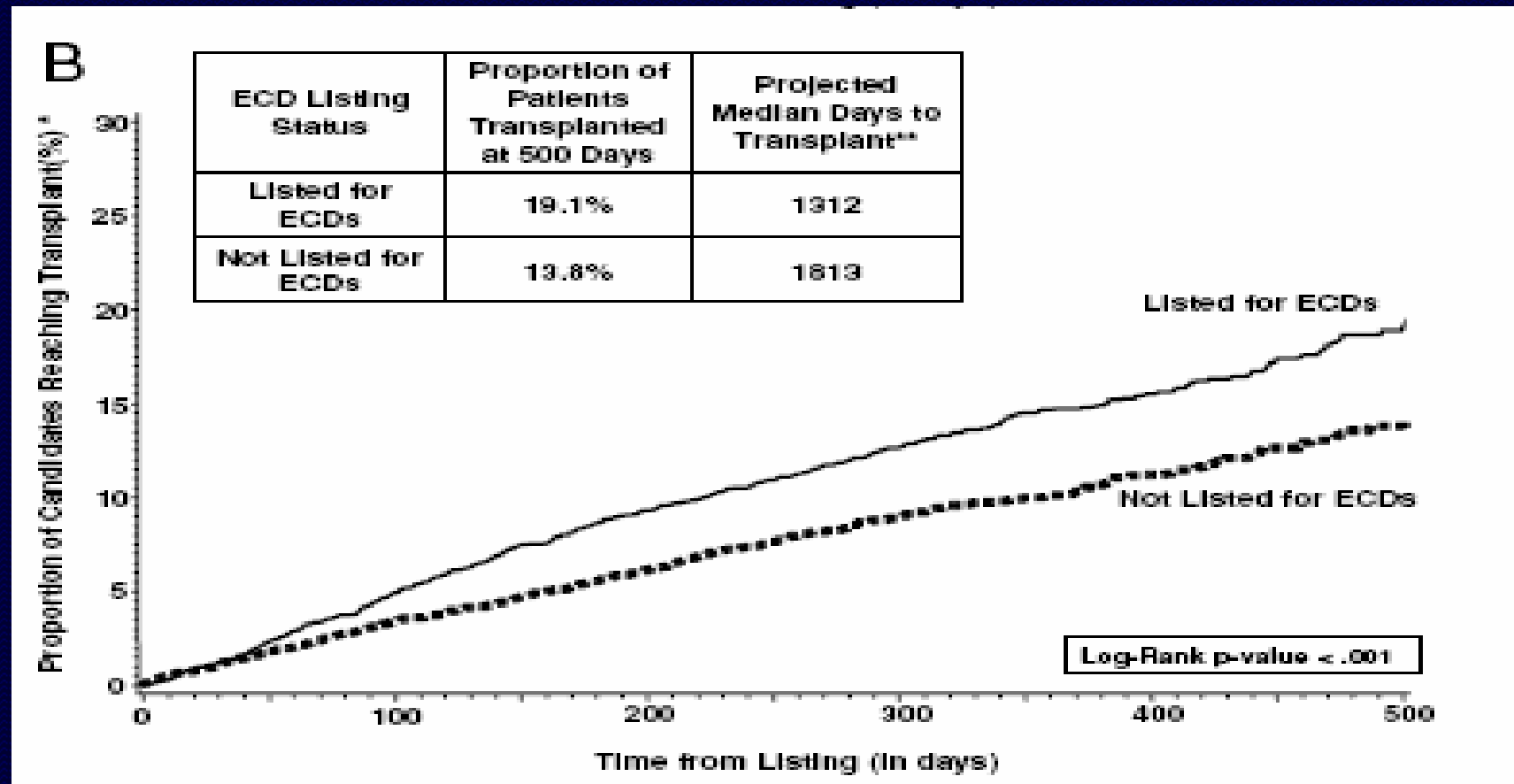
Time to Transplant For Centres Listing Small No for ECD

Schold et al AJT, 2006



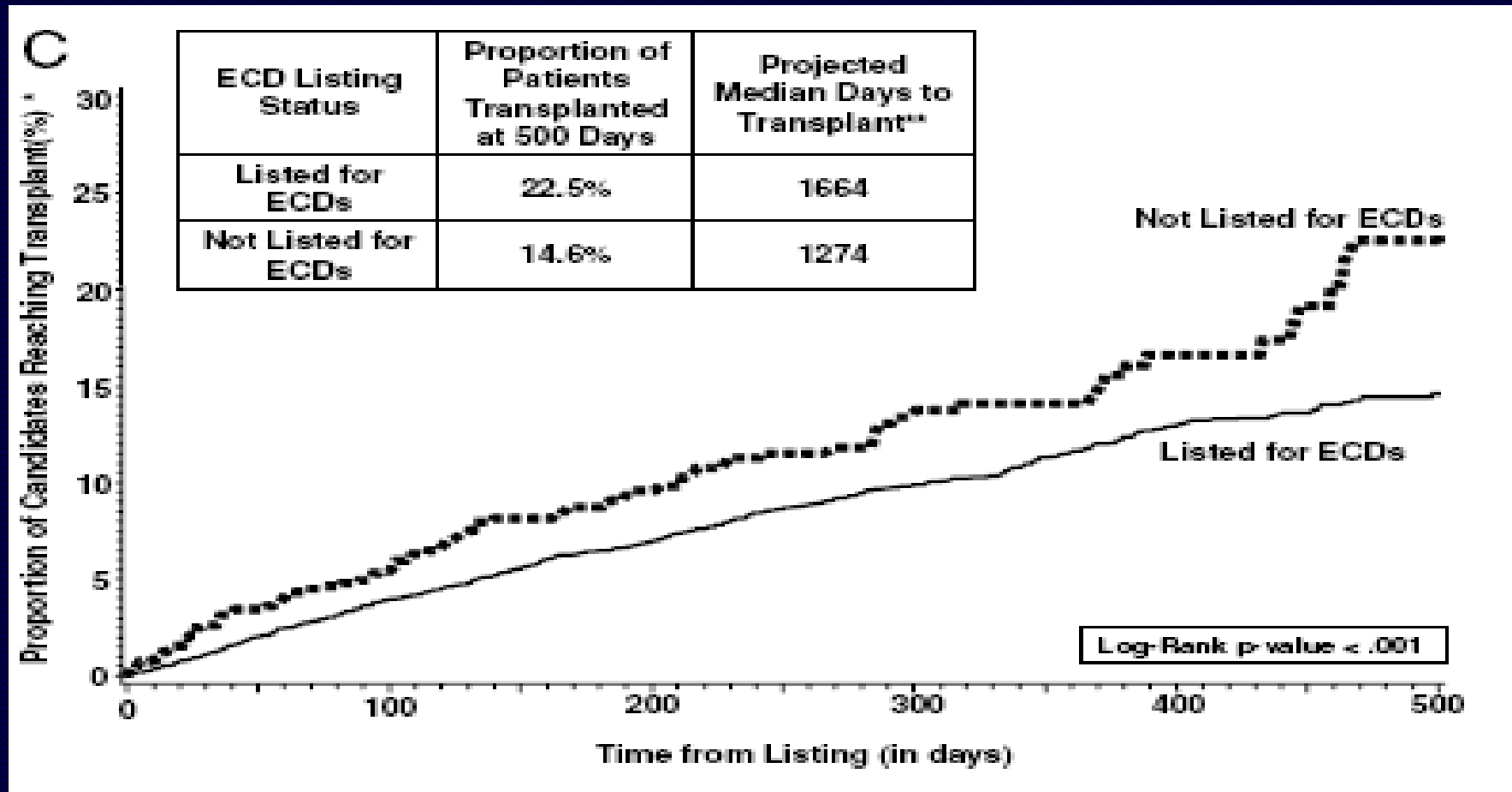
Time To Transplant For Intermediate Listing Centres

Schold et al AJT, 2006



Time To Transplant For High ECD Listing Centres

Schold et al AJT, 2006



Summary

- **Older patients and those with significant morbidity (limited lifespan) have the most to lose by waiting**
- **Thus they should be listed for ECD**
- **Important for centres to keep ECD List size small compared to list for standard donors to ensure less waiting time in order for this benefit to be associated with receipt of ECD**
- **Centres with short waiting time should not have/do not need an ECD List**

Age Matching

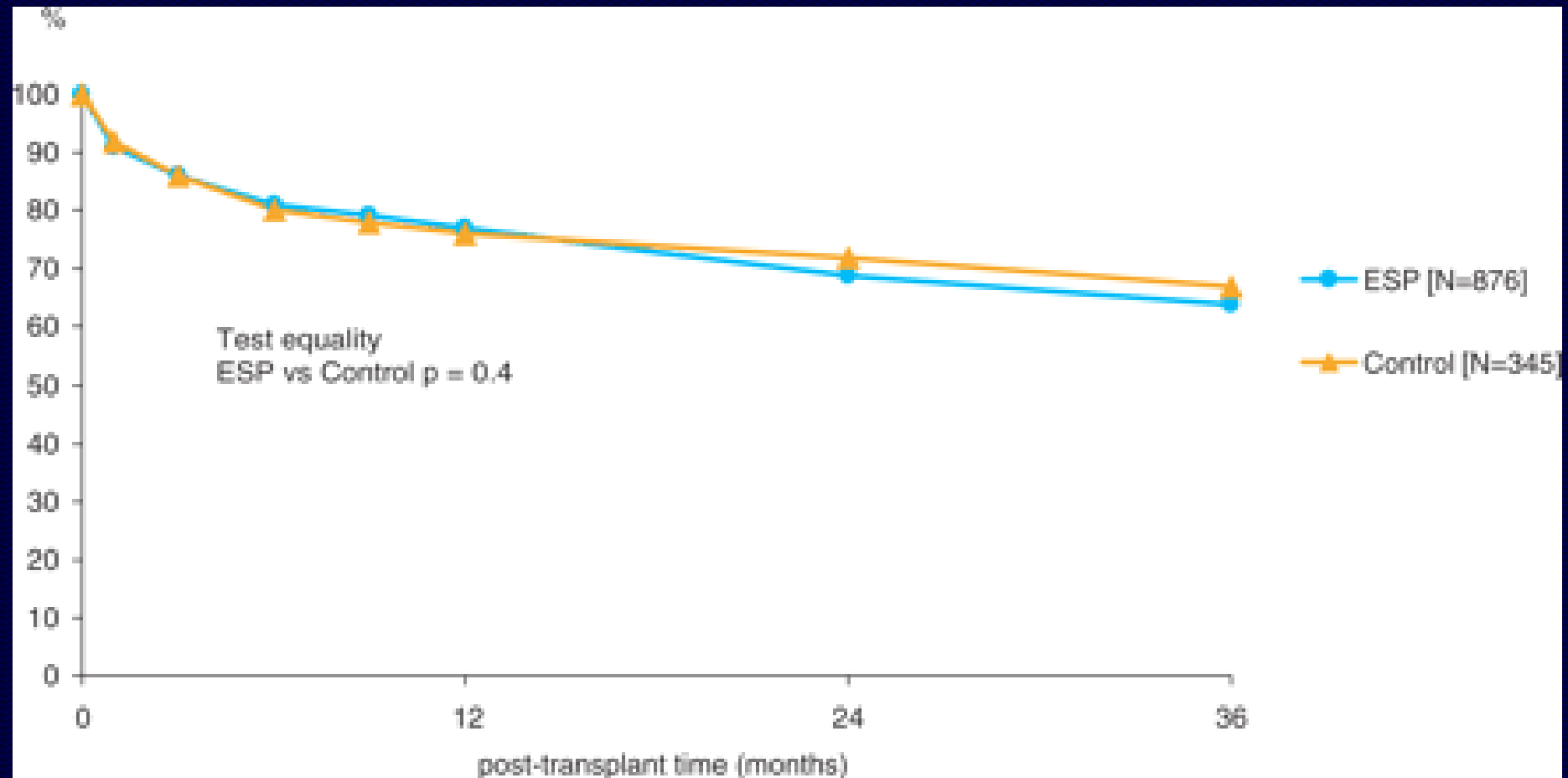
Eurotransplant Senior Programme

Cohen et al Nephrol, Dial And Trans, 2005

- Donor kidneys from those > 65 allocated to recipients >65
- Includes only PRA $< 5\%$ and first transplants
- Double kidney transplant done if donor CrCl < 70 ml/min
- Compared to older donor kidneys allocated by HLA matching to younger recipients

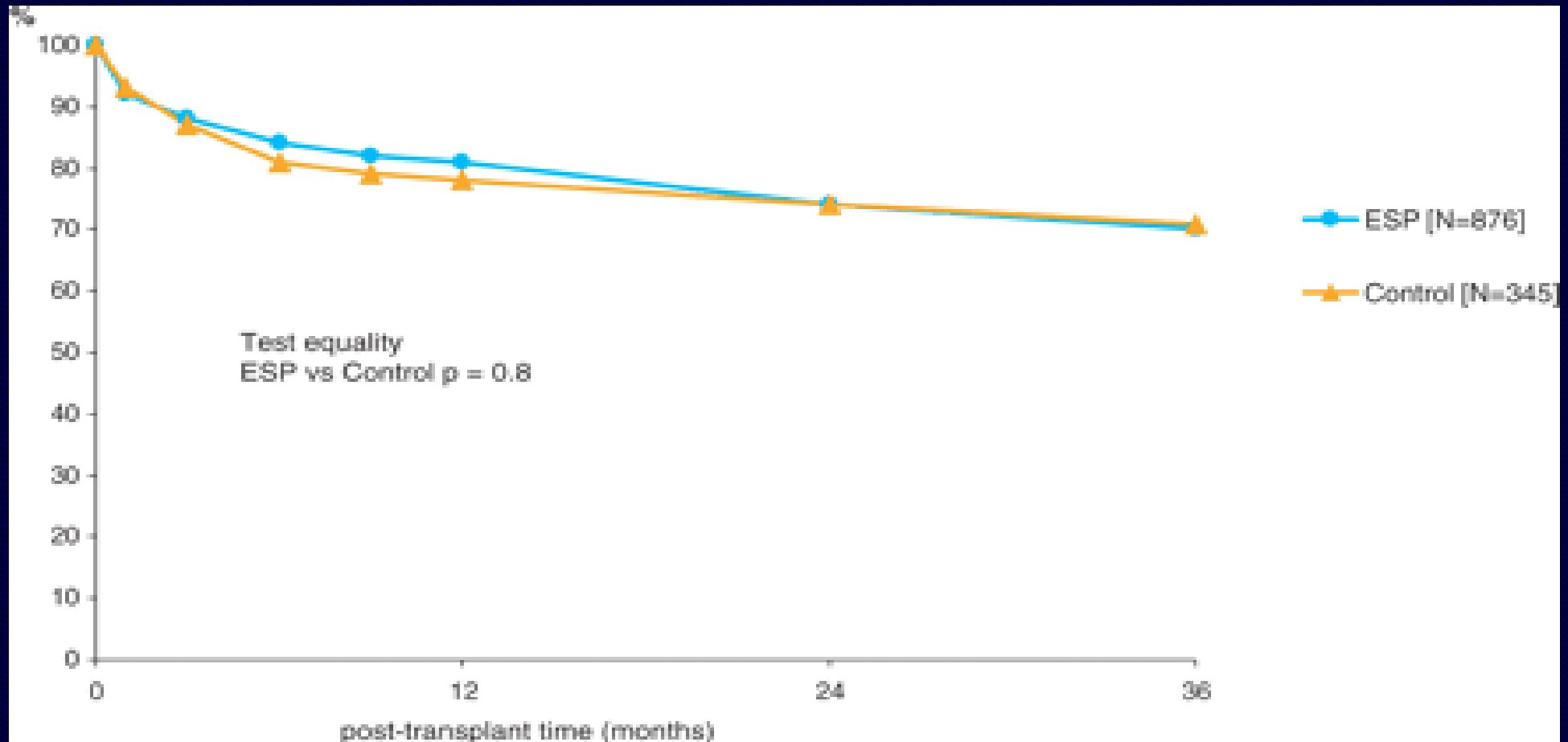
Graft Survival in Eurotransplant Seniors' Programme

Cohen et al, 2005



Death Censored Graft Survival in Eurotransplant Seniors' Programme

Cohen et al, 2005



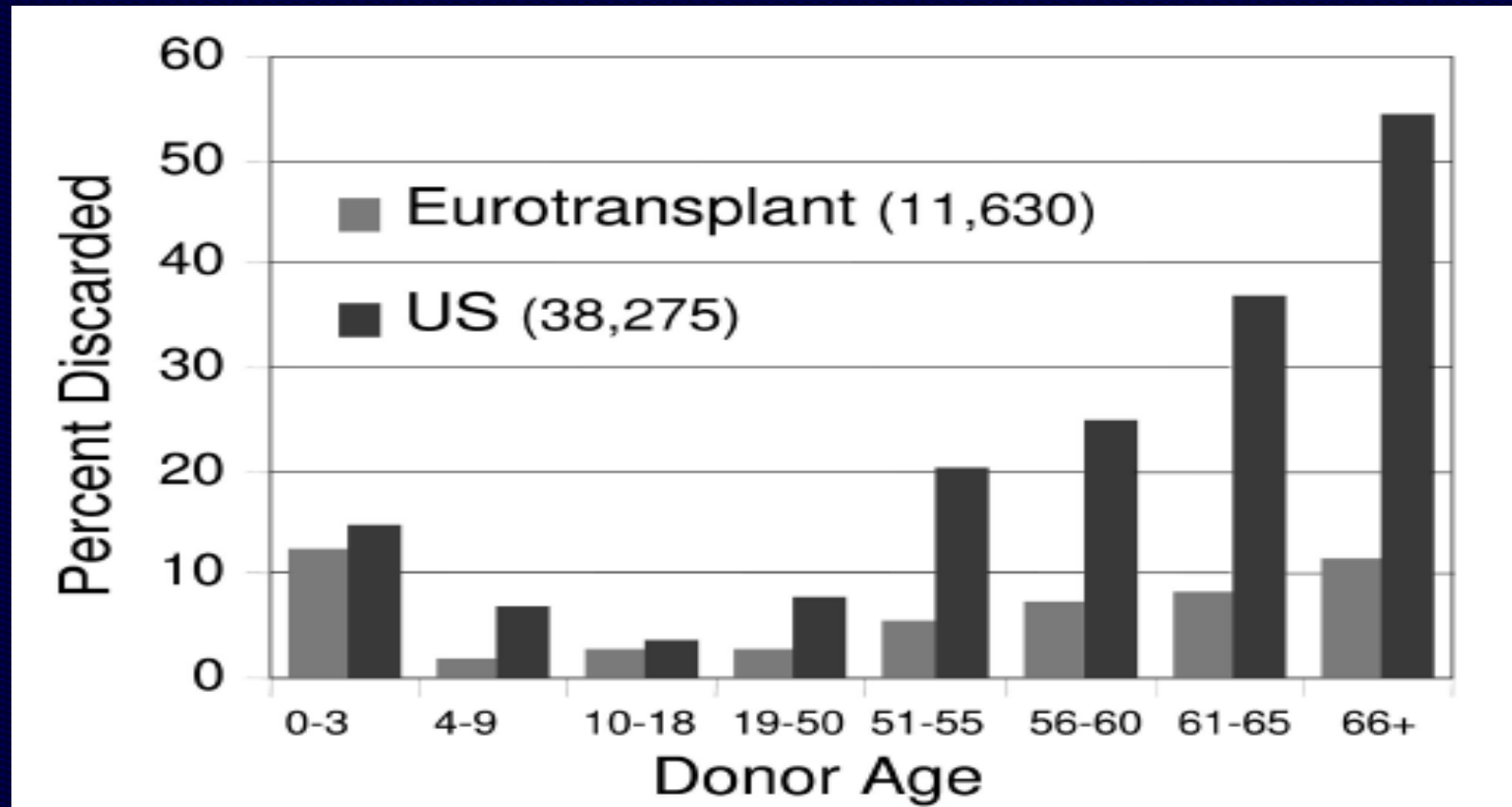
Donor Selection

LIMITATIONS OF PATHOLOGY

- **No validated prospective data showing benefit**
- **Processing increases Cold Ischemia Time and requires Renal Pathologist on call 24/7**
- **Substantial Cost**
- **In US vs Europe many more discarded kidneys (50 vs 10%) from older donors**
- **No difference in results**

Kidney Discard Rates Eurotransplant vs US

Cecka et al, Transplantation, 2006



Reasons For Kidney Discard in The US 2000-2003

Cecka et al Transplantation, 2006

TABLE 1. Major reasons for kidney discard in the United States stratified by donor age

Reason	0-3 years	4-5 years	6-18 years	19-50 years	51-55 years	56-60 years	61-65 years	66+ years
Biopsy	8 (4.8)	2 (8.3)	15 (7.8)	442 (27.8)	285 (38.6)	305 (43.0)	326 (43.1)	570 (44.3)
No Report	107 (64.1)	7 (29.2)	30 (15.5)	224 (14.1)	89 (12.0)	121 (17.0)	101 (13.4)	187 (14.5)
Function	4 (2.4)	0 (0.0)	24 (12.4)	149 (9.4)	98 (13.3)	62 (8.7)	79 (10.4)	132 (10.3)
Anatomic	14 (8.4)	1 (4.2)	19 (9.8)	106 (6.7)	37 (5.0)	41 (5.8)	42 (5.6)	77 (6.0)
No Recipient	15 (9.0)	6 (25.0)	7 (3.6)	119 (7.5)	38 (5.1)	16 (2.3)	50 (6.6)	75 (5.8)
History	2 (1.2)	2 (8.3)	8 (4.1)	86 (5.4)	20 (2.7)	20 (2.8)	31 (4.1)	35 (2.7)
Others	17 (10.2)	6 (25.0)	90 (46.6)	465 (29.2)	172 (23.3)	145 (20.4)	127 (16.8)	210 (16.3)
Total	167	24	193	1,591	739	710	756	1,286

Data are numbers of kidneys discarded (%).

Factors Predictive of Discard of ECD Kidneys vs Outcomes

Leichtman et al WTC, 2006

- 458 ECD kidneys were removed and perfused by 3 OPOs and 20 transplant centres
- 277 were transplanted
- Adjusted odds ratios for discard showed significance for older age, final serum creatinine 90-135 and >135 uM, high resistance, peripheral vascular disease, urine protein, Hepatitis B Core Ab, cysts, days in hospital, surgical injury, glomerulosclerosis
- Only significant factor for graft loss was final serum creatinine > 135 uM

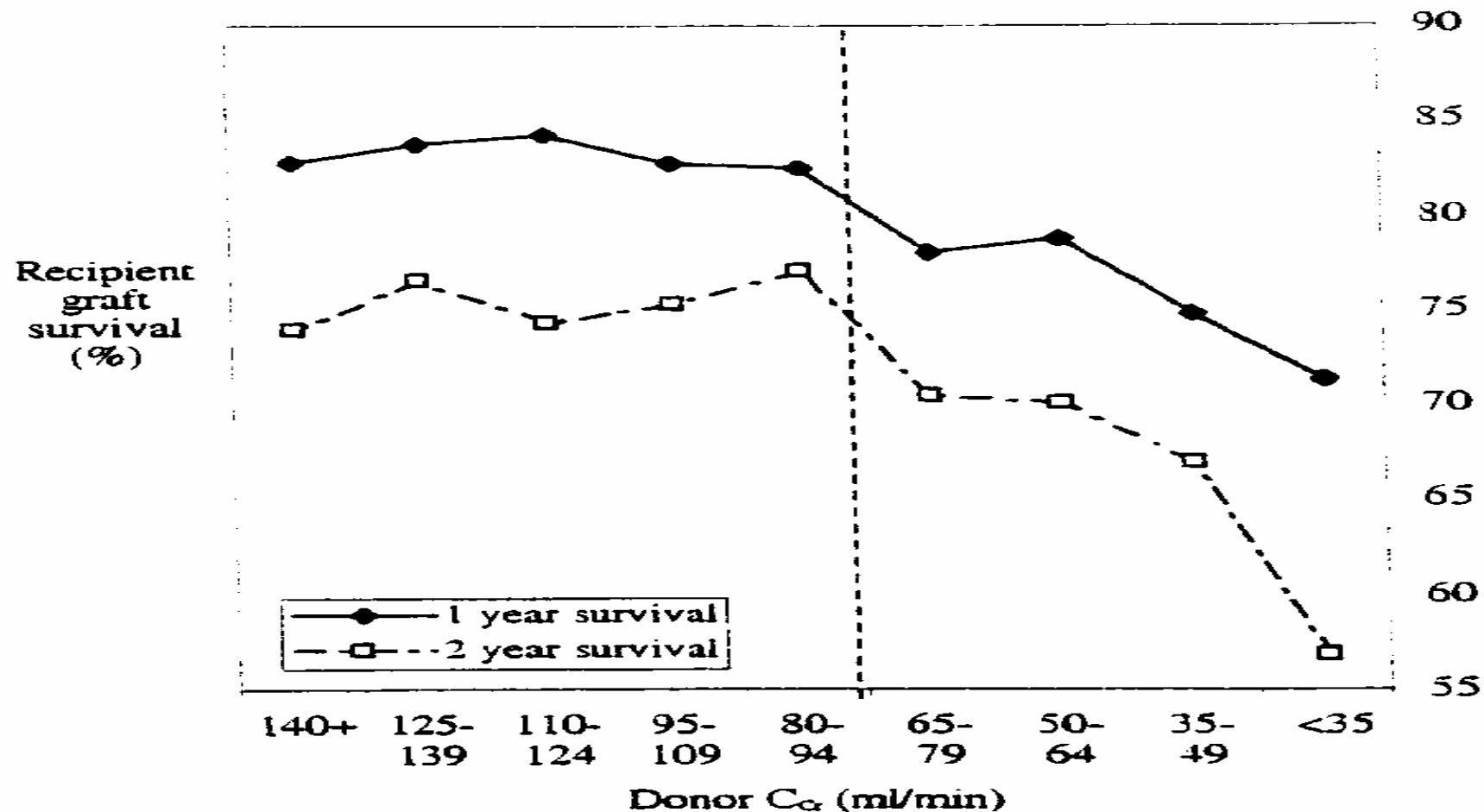


FIGURE 3. Actuarial 1- and 2-year recipient graft survival from donors aged ≥ 55 years of age as a function of Cockcroft-Gault estimated donor creatinine clearance (Donor- C_{Cr}), $n=4732$. As creatinine clearance falls lower than 80 ml/min, there is a progressive decline in graft survival at 1 and 2 years.

Double Kidney Transplantation

Hypothesis

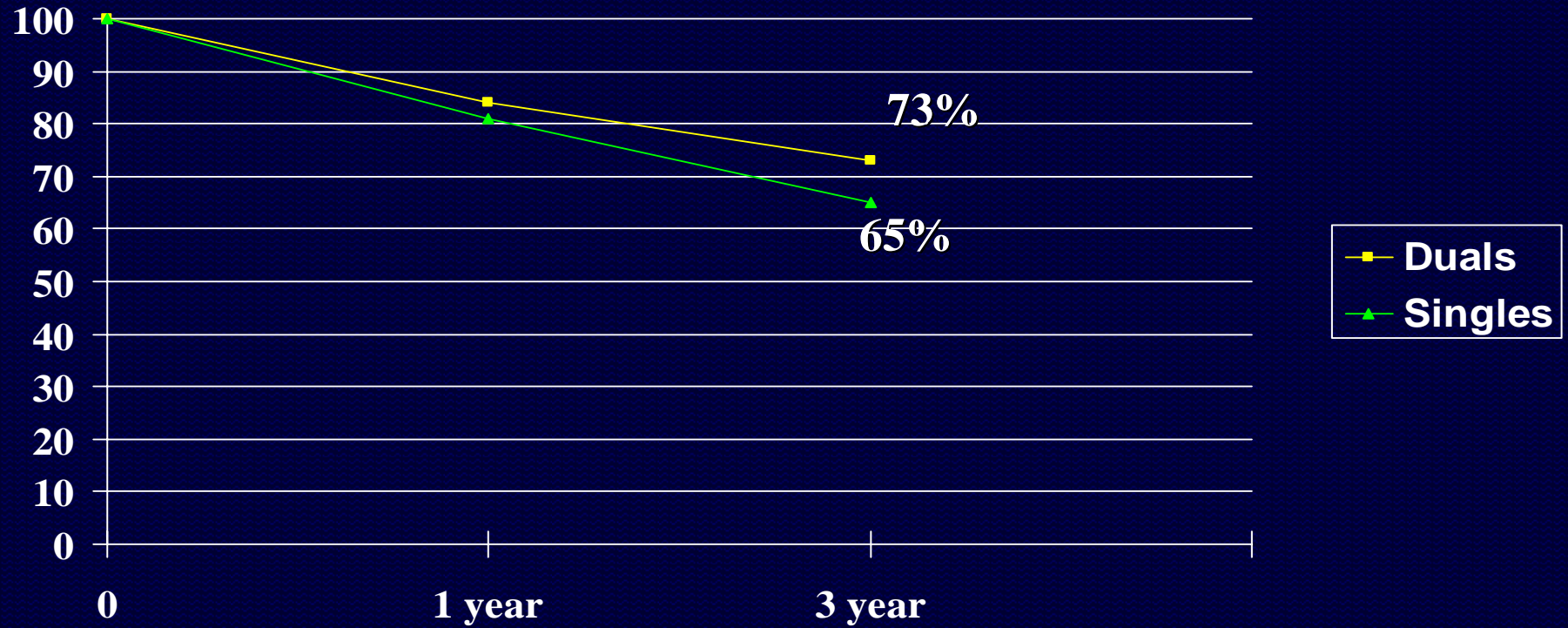
- **Reduced allograft survival of kidneys from older donors relates to reduced functional nephron mass**
- **The use of 2 kidneys from an ECD into a single recipient will compensate for reduced nephron mass and improve longterm graft survival**

The Dual Kidney Registry

Alfrey et al, Transplant Proceedings, 2003

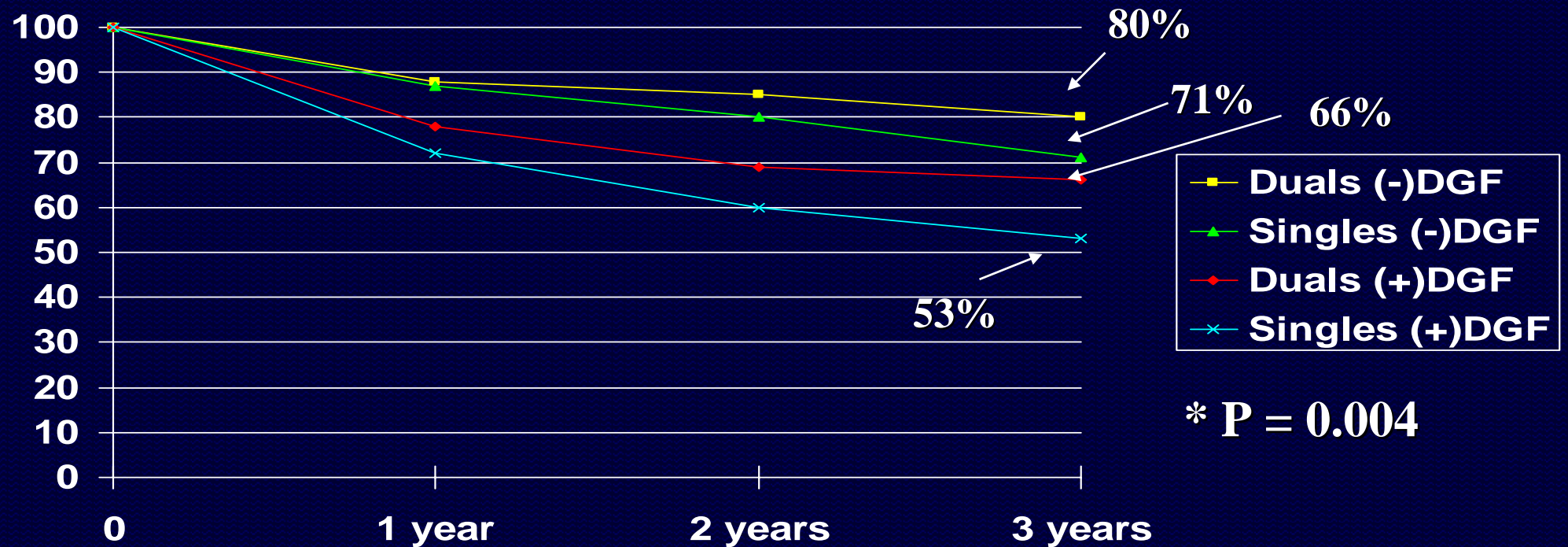
- 239 Dual recipients from 9 centers
- 4746 recipients of single aged donor kidneys from UNOS database

Actuarial Graft Survival



Actuarial Graft Survival Dual Kidney Registry and UNOS

Alfrey et al



Single vs Double Transplants Based on Biopsy

Remuzzi et al NEJM, 2006

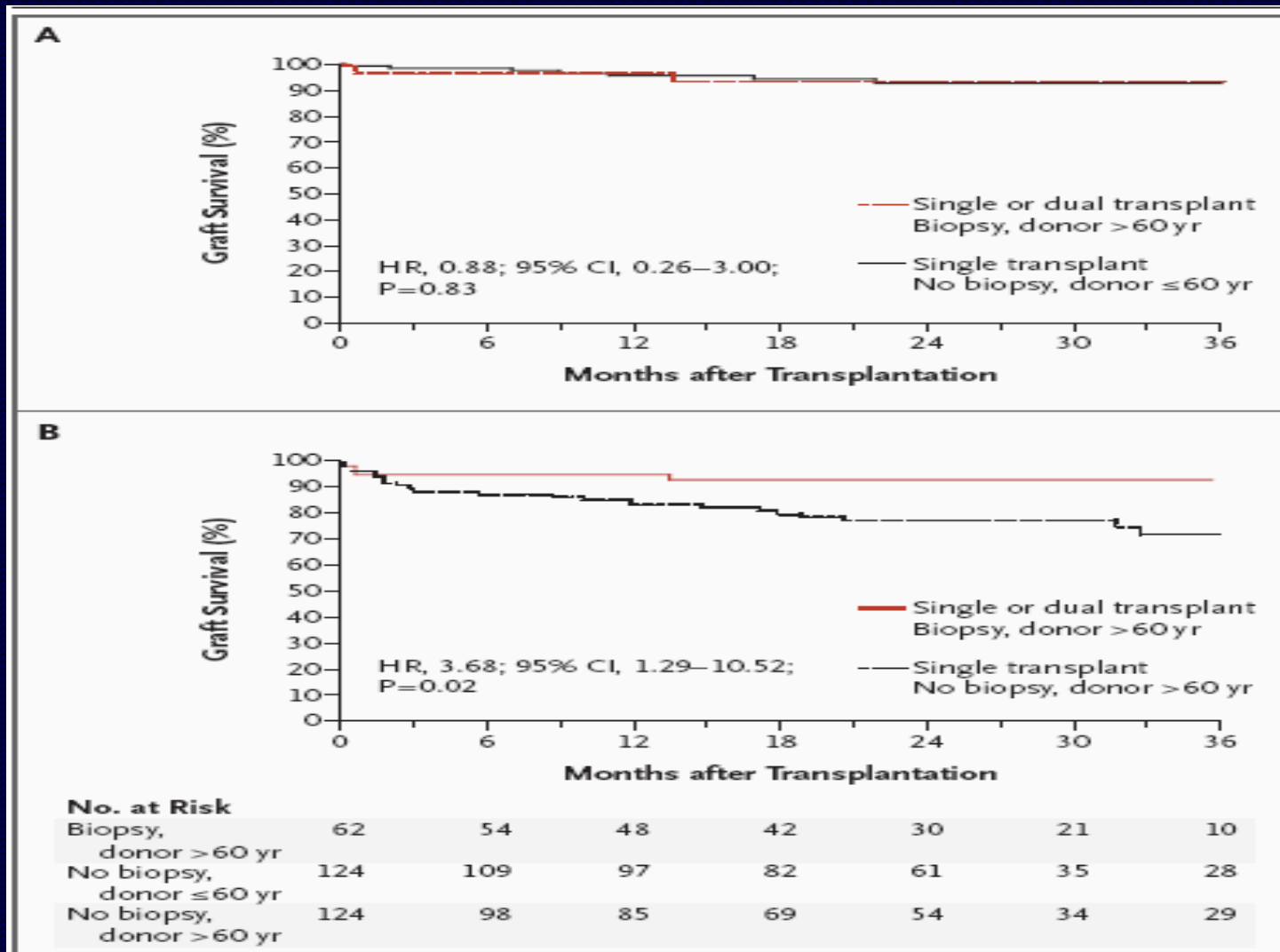


Figure 2. Kaplan–Meier Estimates of Graft Survival.

Allocation of Extended Criteria Donor Kidneys Toronto General Hospital Series 1999-2007

Single kidney transplants (n=69)if:

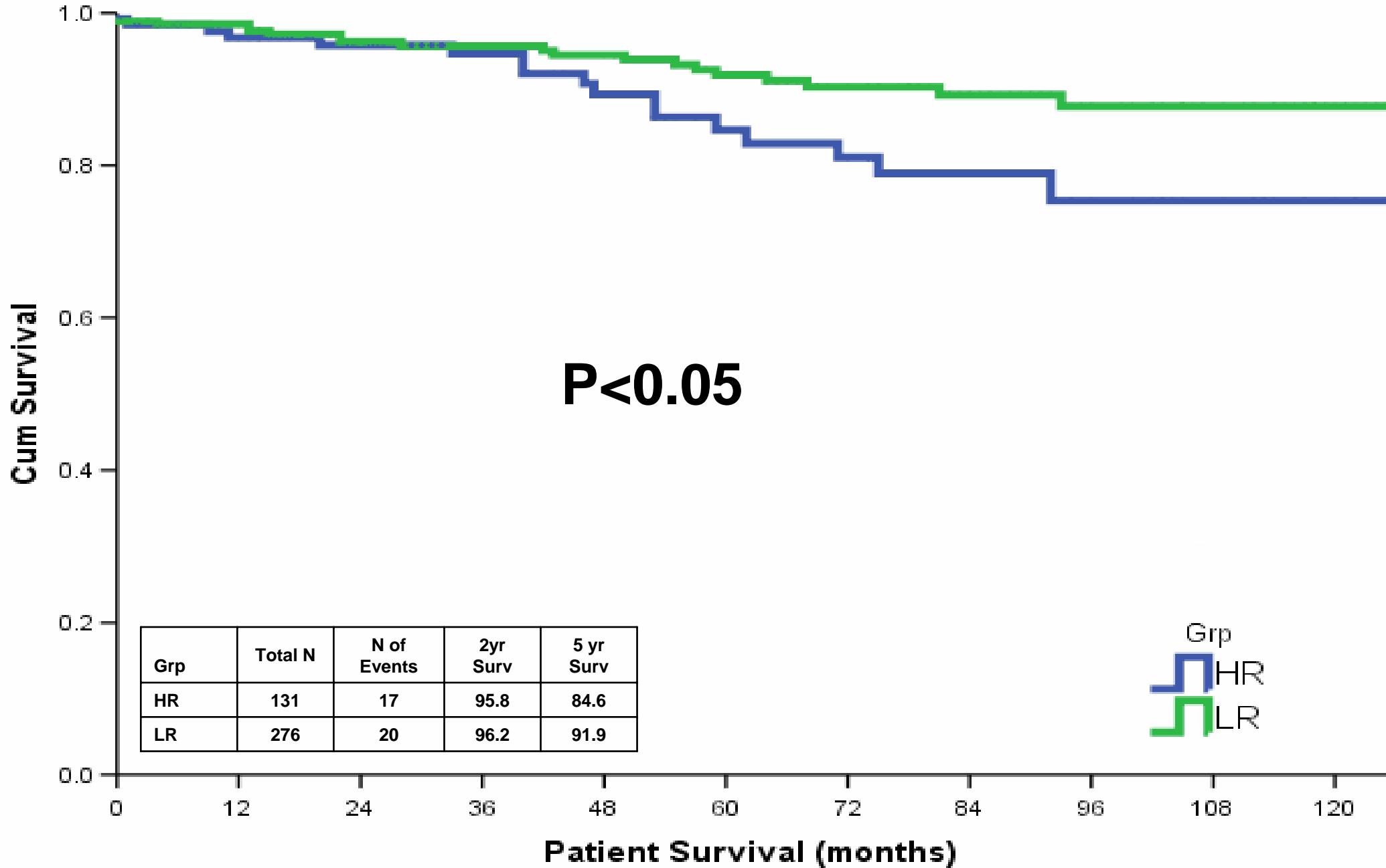
- donor biopsy score ≤ 3 and/or
- calculated creatinine clearance ≥ 80 ml/min

Double transplants (n=62) if :

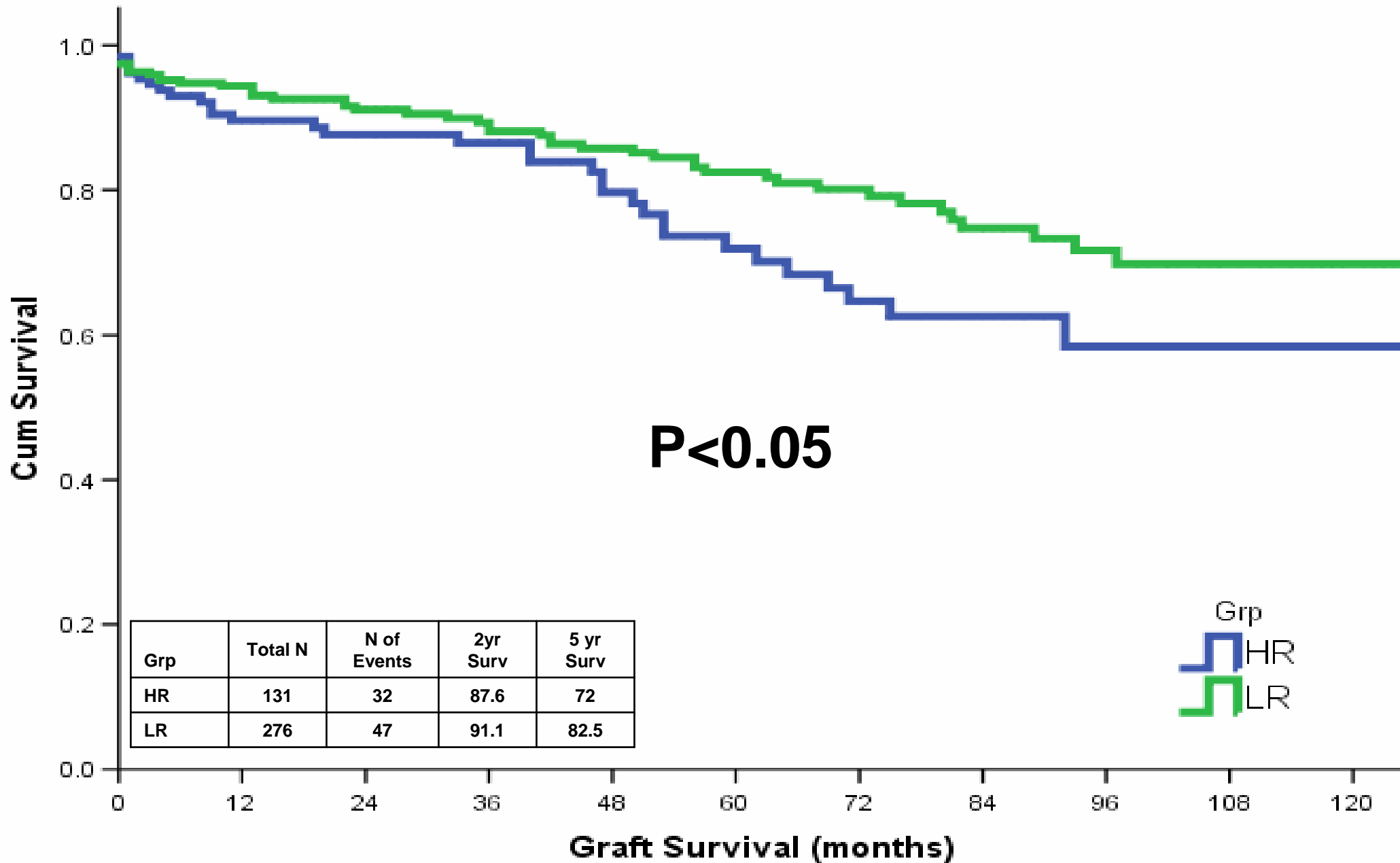
- donor biopsy score 4-6 and/or
- calculated creatinine clearance 60-79 ml/min

Compared with 276 low risk single transplants done
concurrently

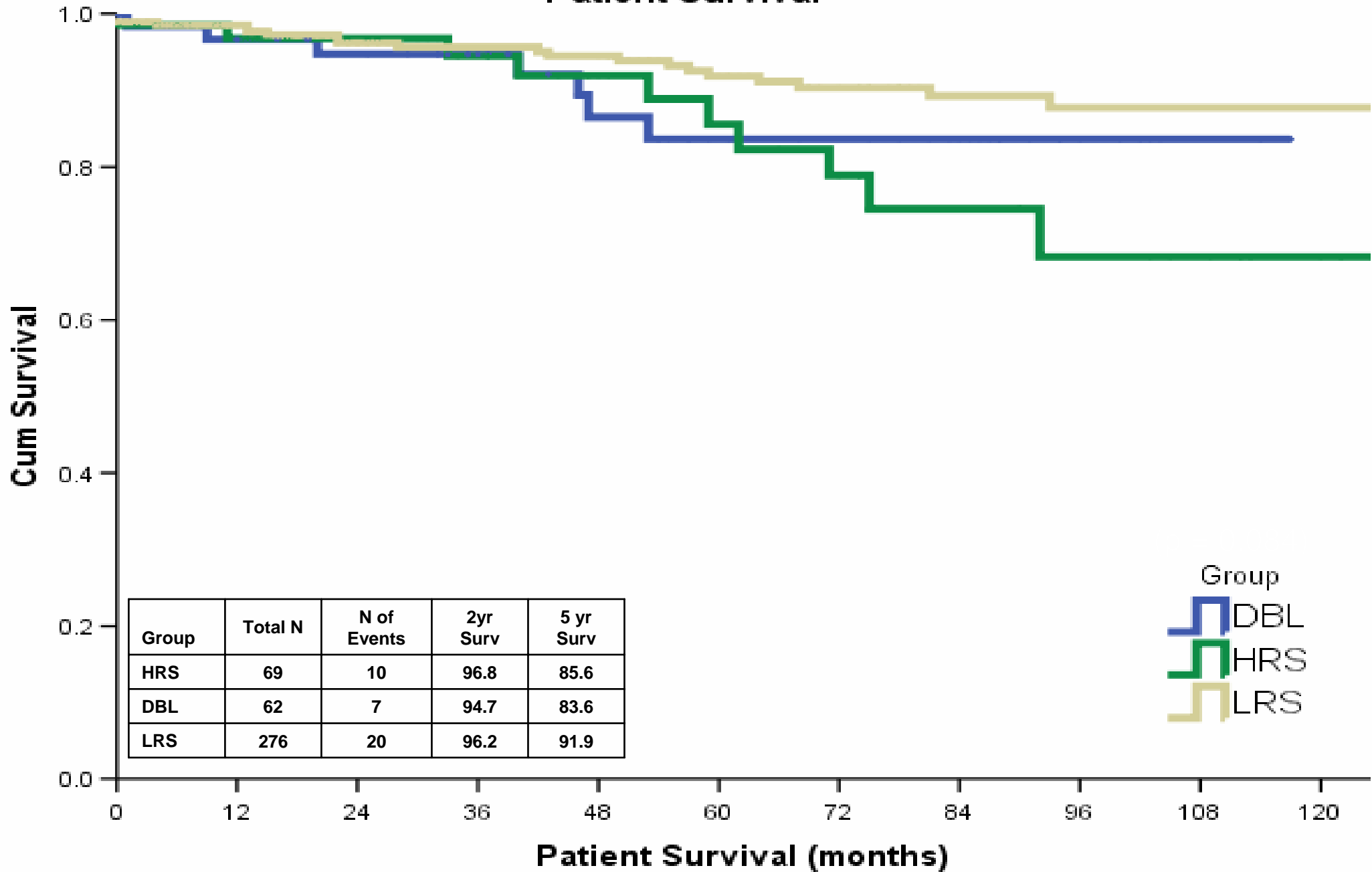
Patient Survival



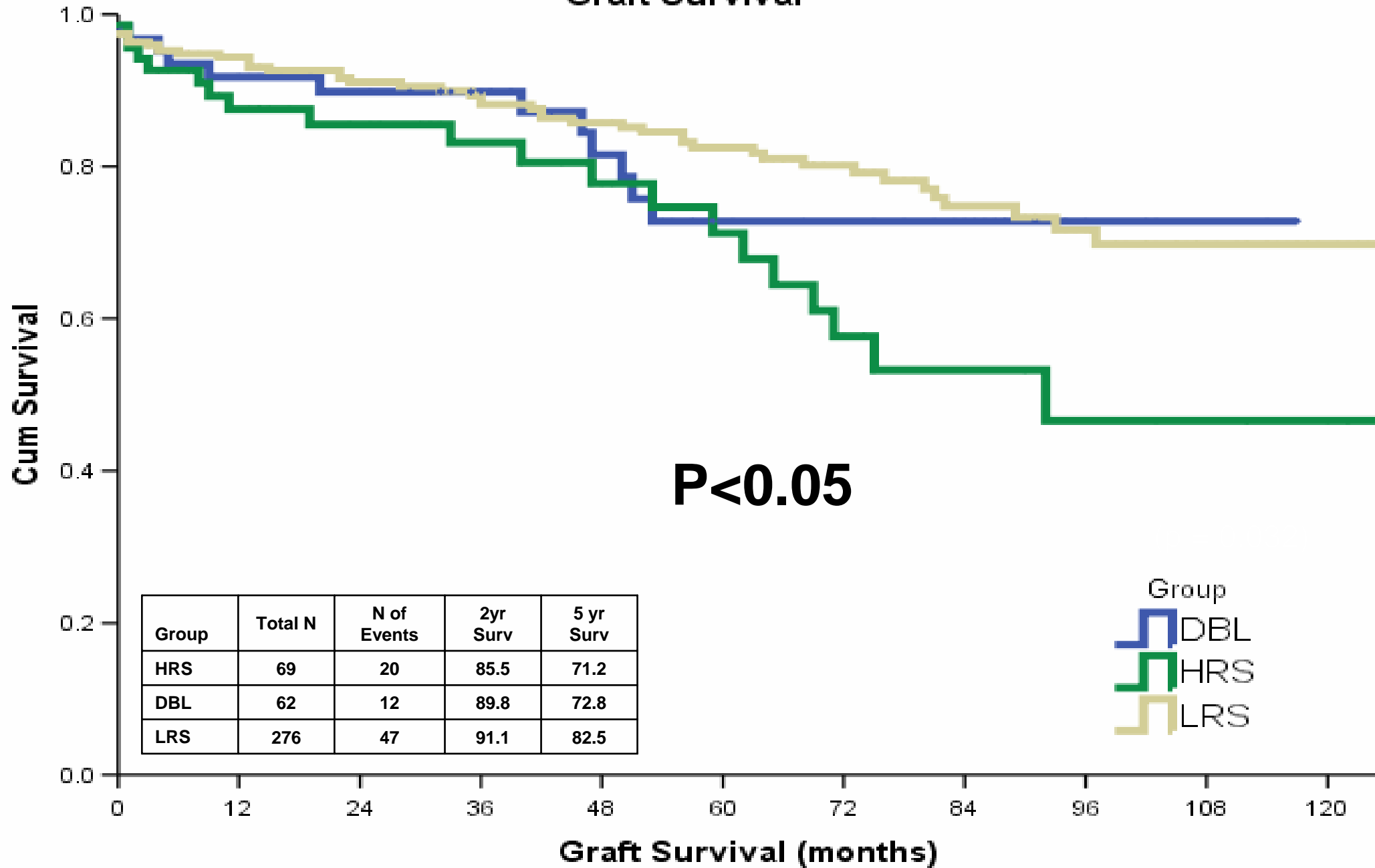
Graft Survival



Patient Survival



Graft Survival



Toronto ECD Rules

- ECD decision based on US criteria
- If CrCl (Cockcroft Gault) ≥ 70 ml/min, use as singles
- If CrCl 50 – 70 ml/min, use as doubles
- If CrCl < 50 ml/min, discard
- Biopsy prior to use only in unusual circumstances

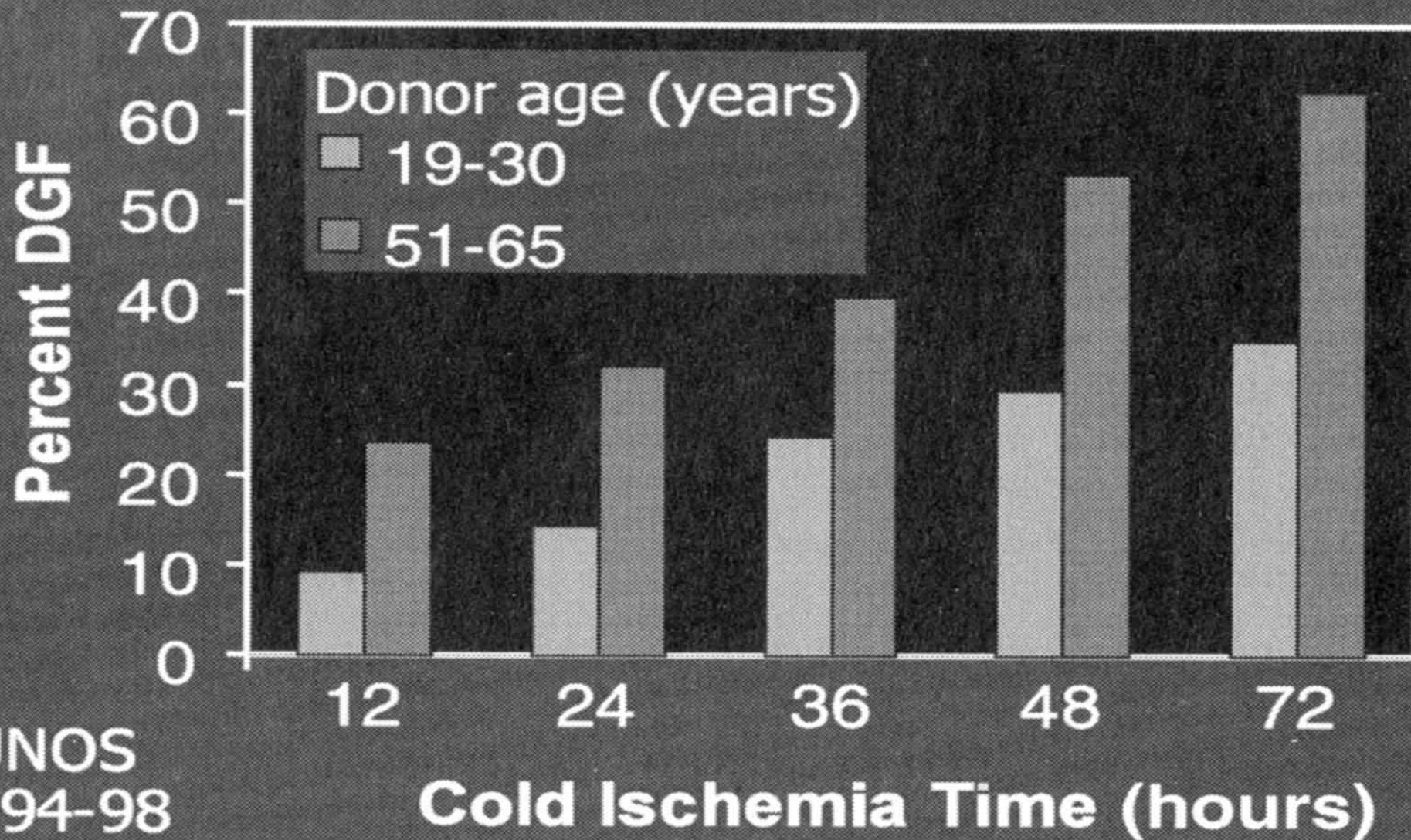
UNOS

ECDs May Be Used as Doubles If No One Will Use as Singles and 2 or More Of:

- (i) Donor age greater than 60 years;
- (ii) Estimated donor creatinine clearance less than 65 ml/min based upon serum creatinine upon admission;
- (iii) Rising serum creatinine (greater than 225 uM) at time of retrieval;
- (iv) History of medical disease in donor (defined as either longstanding hypertension or diabetes mellitus);
- (v) Adverse donor kidney histology (defined as moderate to severe glomerulosclerosis (greater than 15% and less than 50%).

Management of Cold Ischemia

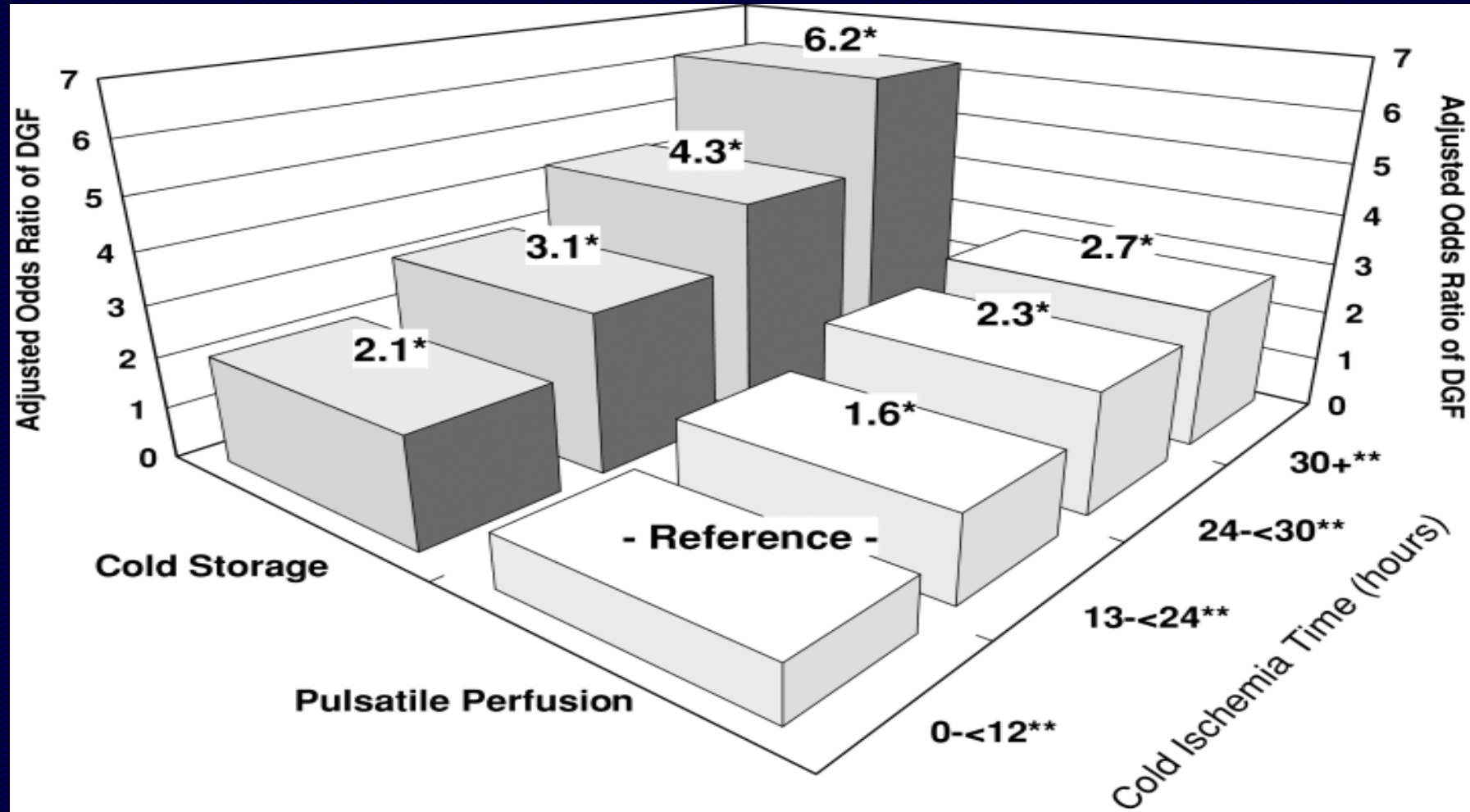
Cold Ischemia Time and Donor Age



UNOS
1994-98

Analysis of Effect of Pulsatile Perfusion on DGF in SRTR

Schold et al Am J Trans, 2005



Effect of Pulsatile Perfusion on Graft Loss in SRTR

Schold et al Am J Trans, 2005

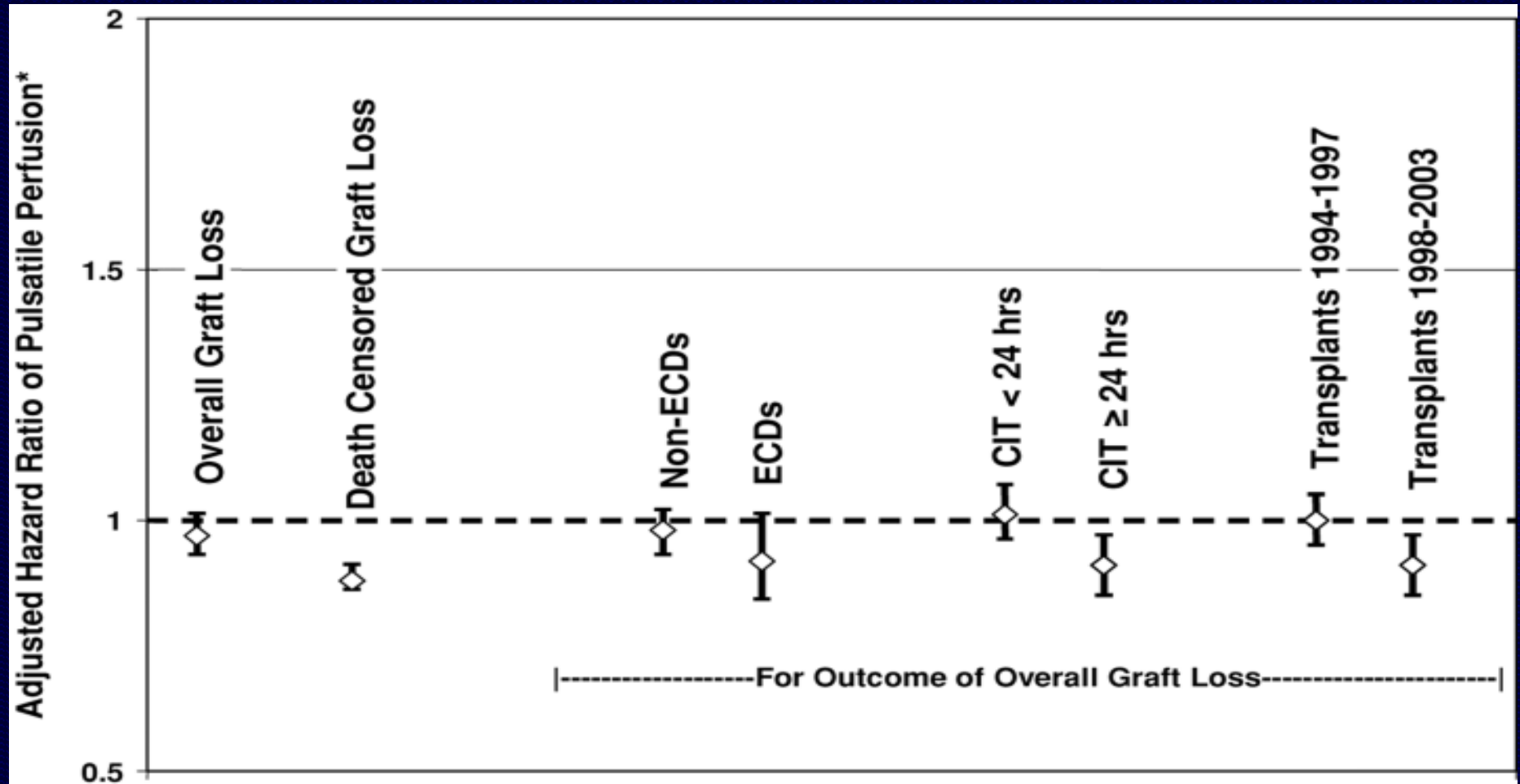


Table 3: Prognostic factors for developing DGF in ECD kidneys

Factors	Unadjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Donor				
DCD vs. DBD	2.26 (1.50–3.40)	<0.001	3.17 (2.05–4.91)	<0.001
Terminal serum Cr >1.5 vs. ≤ 1.5 mg/dL	1.29 (1.09–1.51)	0.002	1.25 (1.05–1.49)	0.01
History of hypertension yes vs. no	1.21 (1.06–1.38)	0.003	1.09 (1.02–1.16)	0.01
Female vs. male	0.83 (0.73–0.93)	0.002	0.85 (0.75–0.97)	0.01
Suboptimal graft* vs. all others	1.46 (1.21–1.75)	<0.001	1.40 (1.16–1.70)	0.001
Cold ischemia time				
13–24 vs. 0–12 h	1.33 (1.15–1.53)	<0.001	1.33 (1.14–1.70)	<0.001
25–30 vs. 0–12 h	1.51 (1.23–1.85)	<0.001	1.48 (1.19–1.82)	<0.001
>30 vs. 0–12 h	2.45 (1.97–3.05)	<0.001	2.15 (1.70–2.74)	<0.001
Recipient				
Peak PRA >50 vs. 0–50%	1.42 (1.16–1.74)	0.001	1.74 (1.40–2.15)	<0.001
Female vs. male	0.78 (0.69–0.89)	<0.001	0.77 (0.67–0.87)	<0.001
African American vs. other races	1.39 (1.22–1.58)	<0.001	1.28 (1.12–1.47)	<0.001
Diabetes vs. others	1.25 (1.09–1.44)	0.001	1.26 (1.10–1.45)	0.001
Dialysis type				
Peritoneal vs. none	1.47 (1.15–1.87)	0.002	1.43 (1.12–1.84)	0.004
Hemodialysis vs. none	2.01 (1.67–2.41)	<0.001	1.90 (1.57–2.30)	<0.001
HLA-A mismatches (range 0–2)	1.10 (1.01–1.20)	0.02	1.02 (0.93–1.13)	0.65
HLA-B mismatches (range 0–2)	1.19 (1.09–1.29)	<0.001	1.08 (0.97–1.20)	0.14
HLA-DR mismatches (range 0–2)	1.18 (1.09–1.28)	<0.001	1.15 (1.04–1.26)	0.005
Transplant location shared vs. local	1.20 (1.05–1.36)	0.007	1.01 (0.87–1.18)	0.85
Storage type PP vs. cold storage	0.59 (0.50–0.69)	<0.001	0.51 (0.43–0.61)	<0.001

DCD = donation after cardiac death; DBD = donation after brain death.

*Graft with at least one of the following biopsy results performed at transplant center: (1) glomerulosclerosis >10%; (2) fibrosis; and (3) arteriosclerosis.

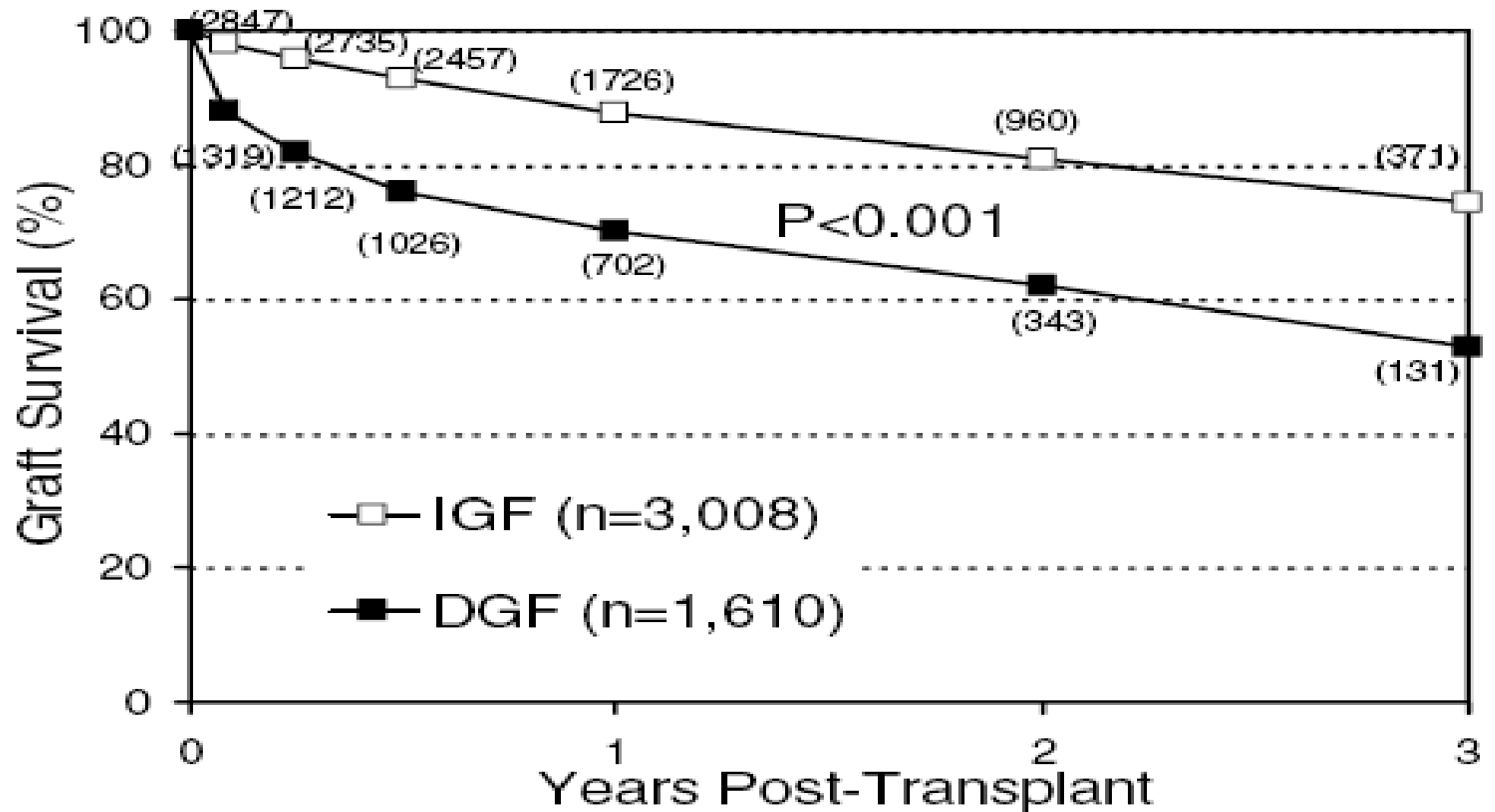


Figure 1: The impact of delayed graft function (DGF) on expanded criteria donors (ECD) kidney transplantation. Numbers

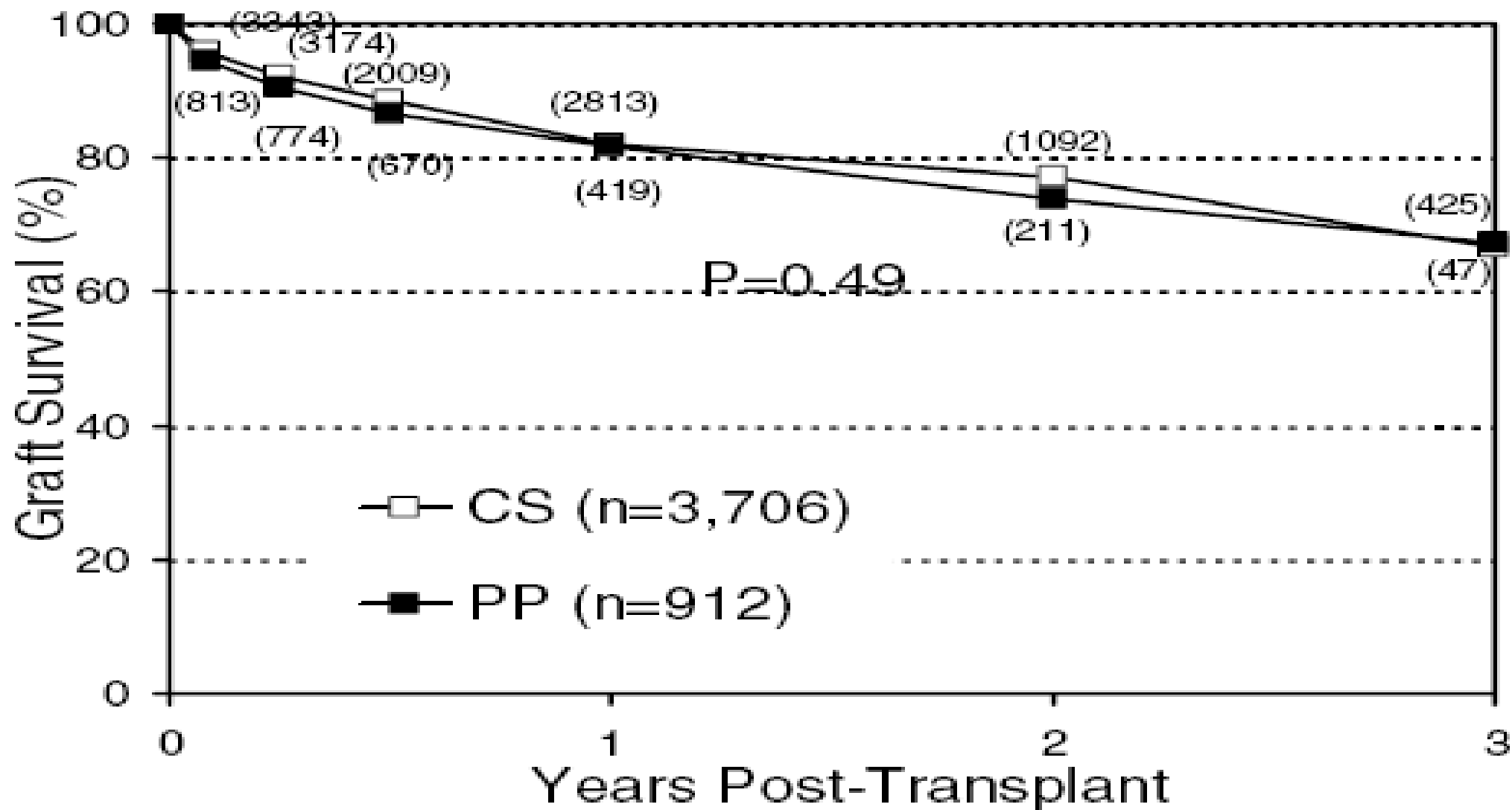


Figure 3: Overall graft survival of ECD kidney transplants according to storage method (ECD-CS vs. ECD-PP).

Conclusions

- **ECD kidneys, as used currently, are associated with reduced graft function and longterm graft survival**
- **However, they provide acceptable function in that they offer a significant survival benefit as compared to dialysis IF THEY REDUCE WAITING TIME**
- **This benefit will be greater for those patients with a shortened lifespan, which increases the adverse effect of waiting**
- **Available data suggest assigning ECD to older/sicker recipients to ensure optimal risk:benefit**
- **Careful individualized explantation/informed consent mandatory**

Conclusions II

- **Clinical and pathologic scoring systems are available to determine which kidneys to use, but none proven to be ideal**
- **Most useful are donor age, renal function and possibly pathology however no proven benefit and increased cost/cold time**
- **Acceptable short term results obtained with dual kidney transplants but, while data suggestive, not clear that they provided an advantage over single transplants or how to determine which kidneys to use as double vs single**
- **Pulsatile perfusion may improve results of transplantation with ECD but prospective RCT needed to be sure in view of extra cost**