

Frailty, ESRD, and Kidney Transplantation

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Funding Road

- AGS Jahnigen Award (07-09)
- NKF of Maryland Mini-grant (07-09)
- Doris Duke Clinical Scientist Development Award (08-12)
- K23AG032885 Paul Beeson Career Development Award (09-12)
- R21DK085409 (10-13)
- R01AG042504 (13-18, if NIH still exists then)

Secondary Data

- USRDS
 - all patients with ESRD
- SRTR
 - transplant waiting list
 - transplant recipients and outcomes
- N=hundreds of thousands or millions
- 8 minutes to download

Primary Data

- Prevalent HD (dialysis center): 146
- Prevalent HD (transplant waitlist): 2194
- KT recipients: 845

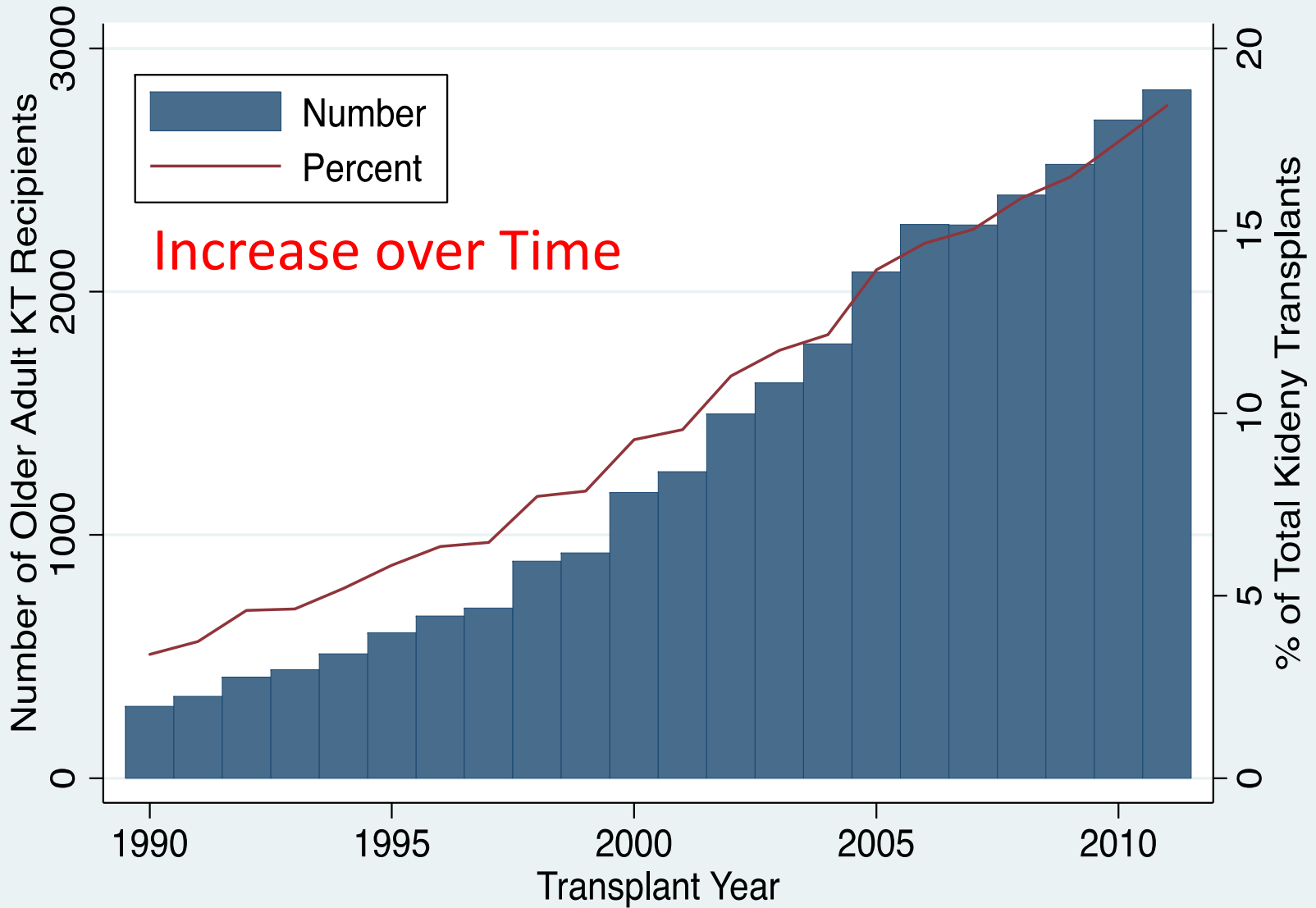
- N~3000
- 8 years to collect

Why Frailty and Transplantation?

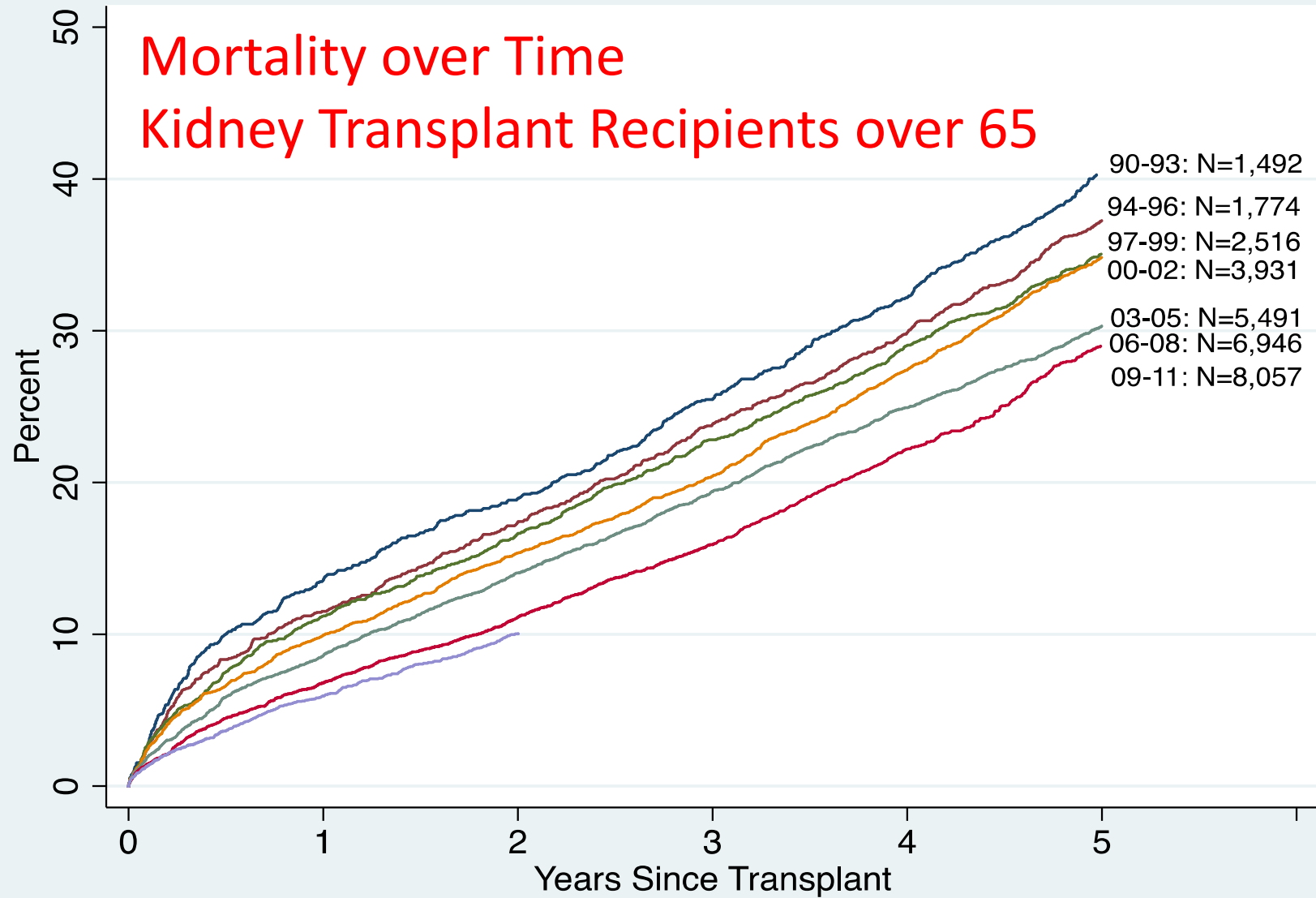
- Older adults comprising higher proportion of:
 - Those considering transplantation
 - Those undergoing transplantation
- Even the younger adults look like older adults
 - End-stage kidney disease
 - Multimorbidity
- Risk prediction is challenging in everyone

Clinical Decision-Making

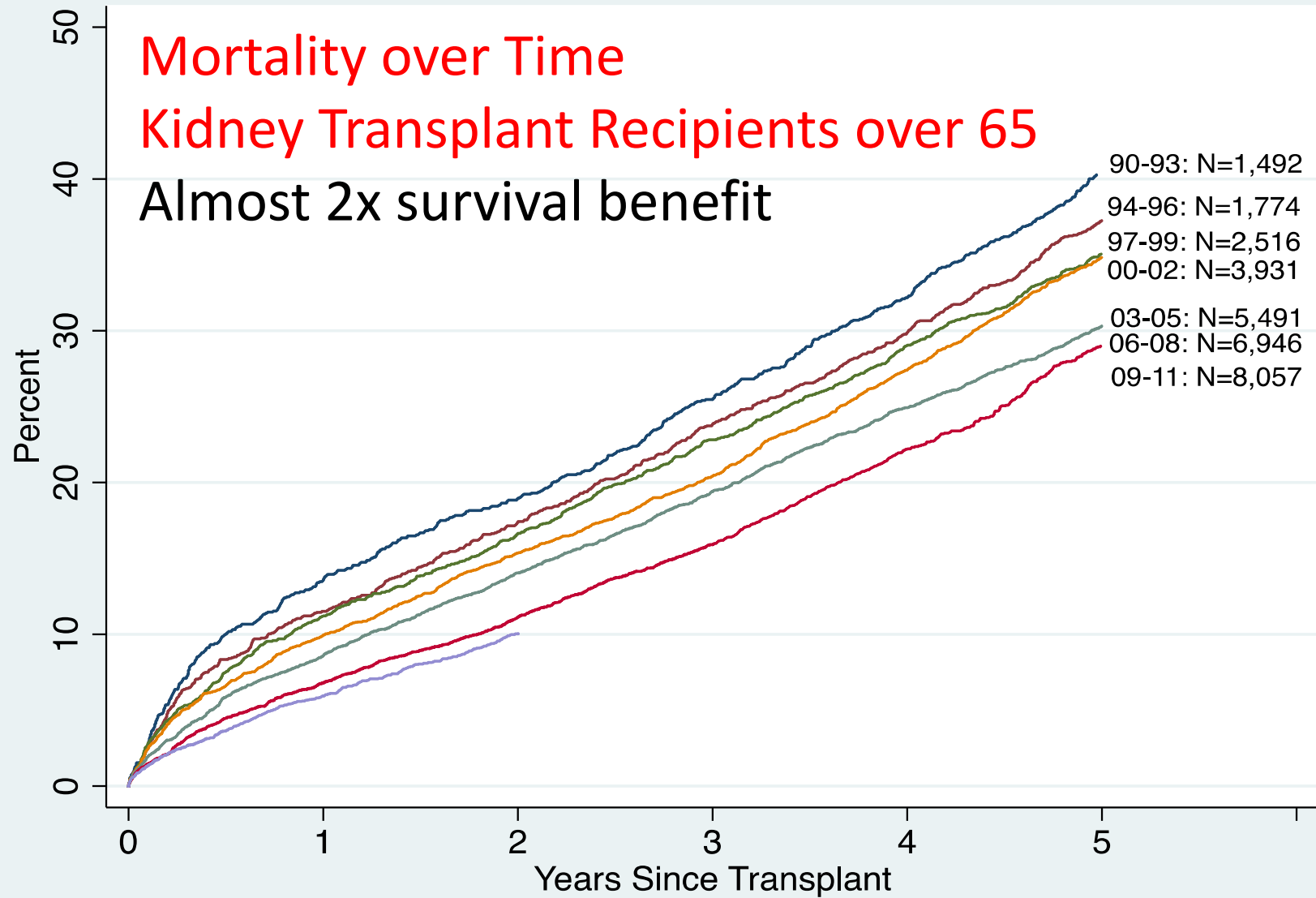
- **Risks:**
 - Up-front risk of surgery (DM, PVD, CAD, frailty, etc)
 - Immunosuppression (infections, side effects)
 - Work (drug levels, labs, clinic, hospitalizations)
- **Benefits:**
 - Longer survival (less so for older adults)
 - Quality of life / energy / etc



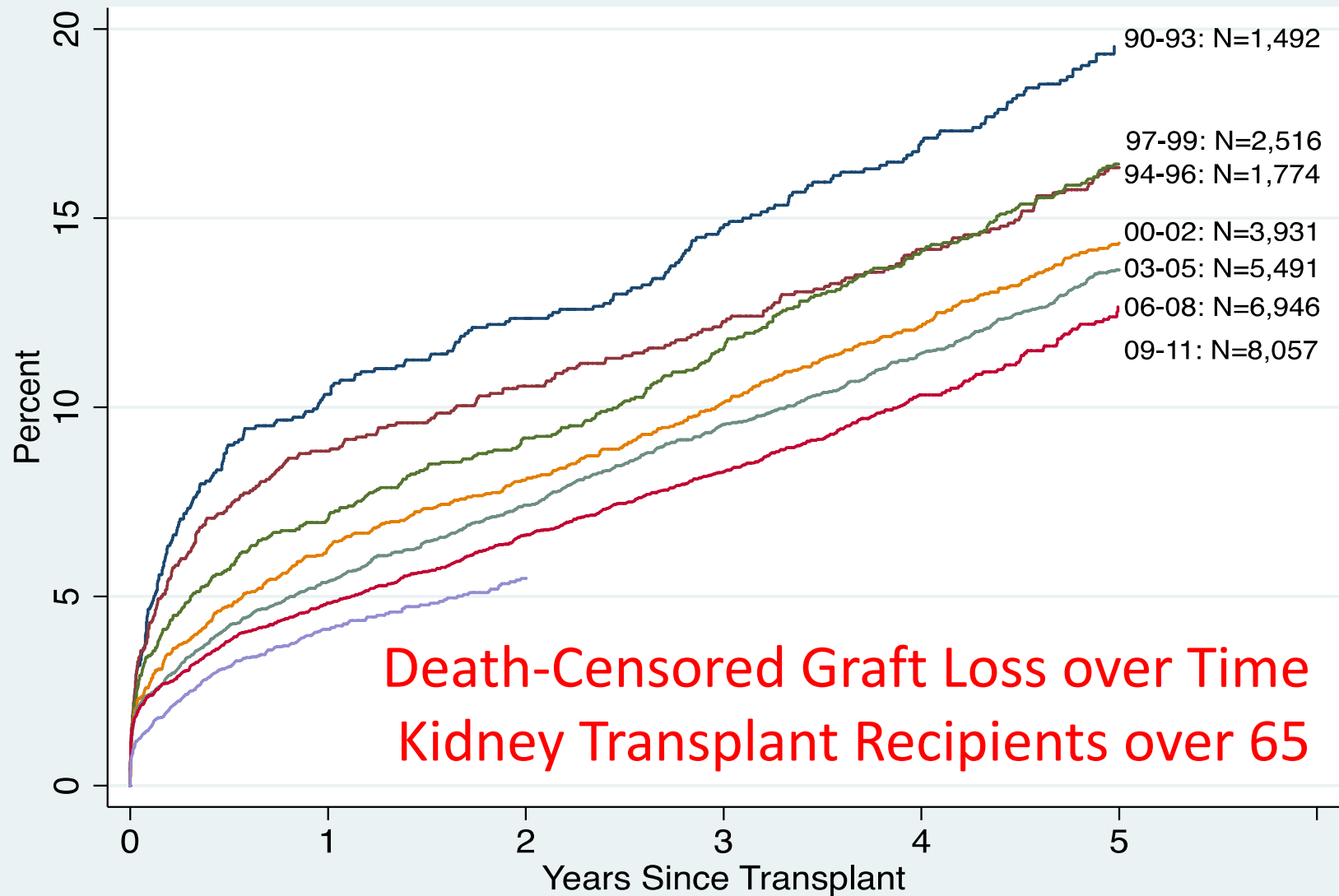
McAdams-DeMarco/Segev, JAGS, 2014



McAdams-DeMarco/Segev, JAGS, 2014

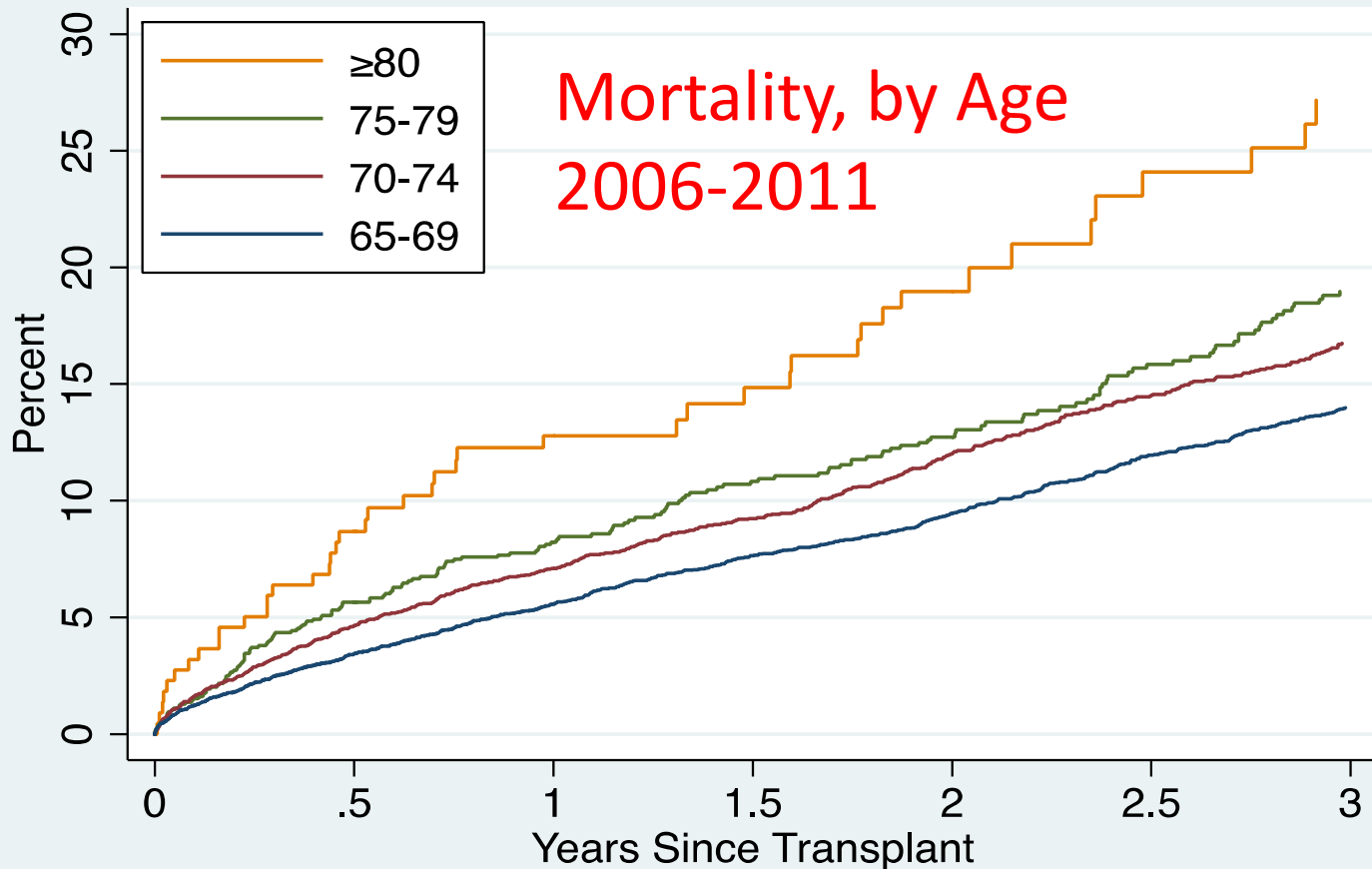


McAdams-DeMarco/Segev, JAGS, 2014



Death-Censored Graft Loss over Time
Kidney Transplant Recipients over 65

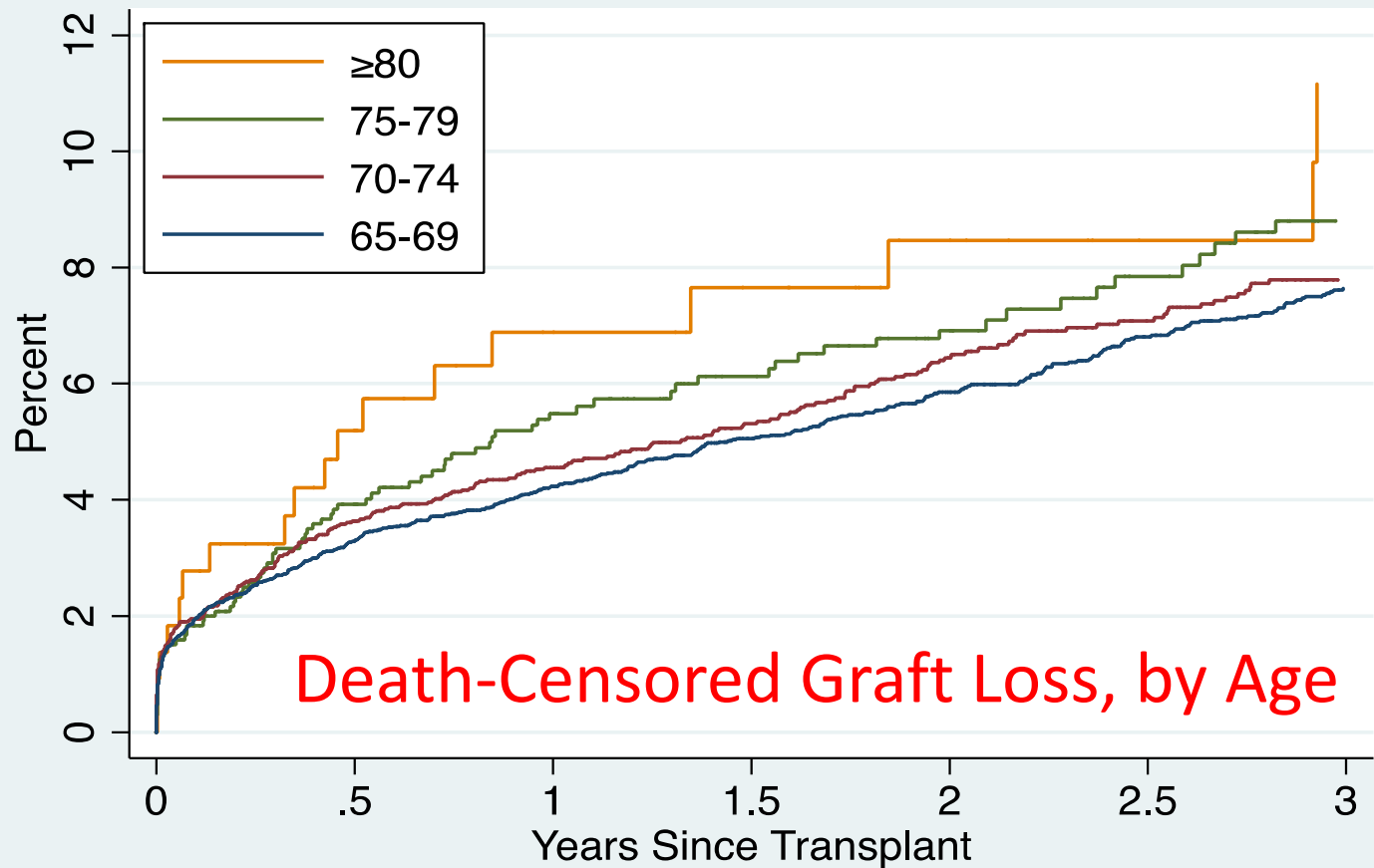
McAdams-DeMarco/Segev, JAGS, 2014



Number at risk

≥80:	240	188	170	124	118	74	71
75-79:	1,389	1,127	997	754	738	512	493
70-74:	4,456	3,652	3,293	2,458	2,383	1,671	1,627
65-69:	8,918	7,370	6,721	5,122	5,021	3,566	3,484

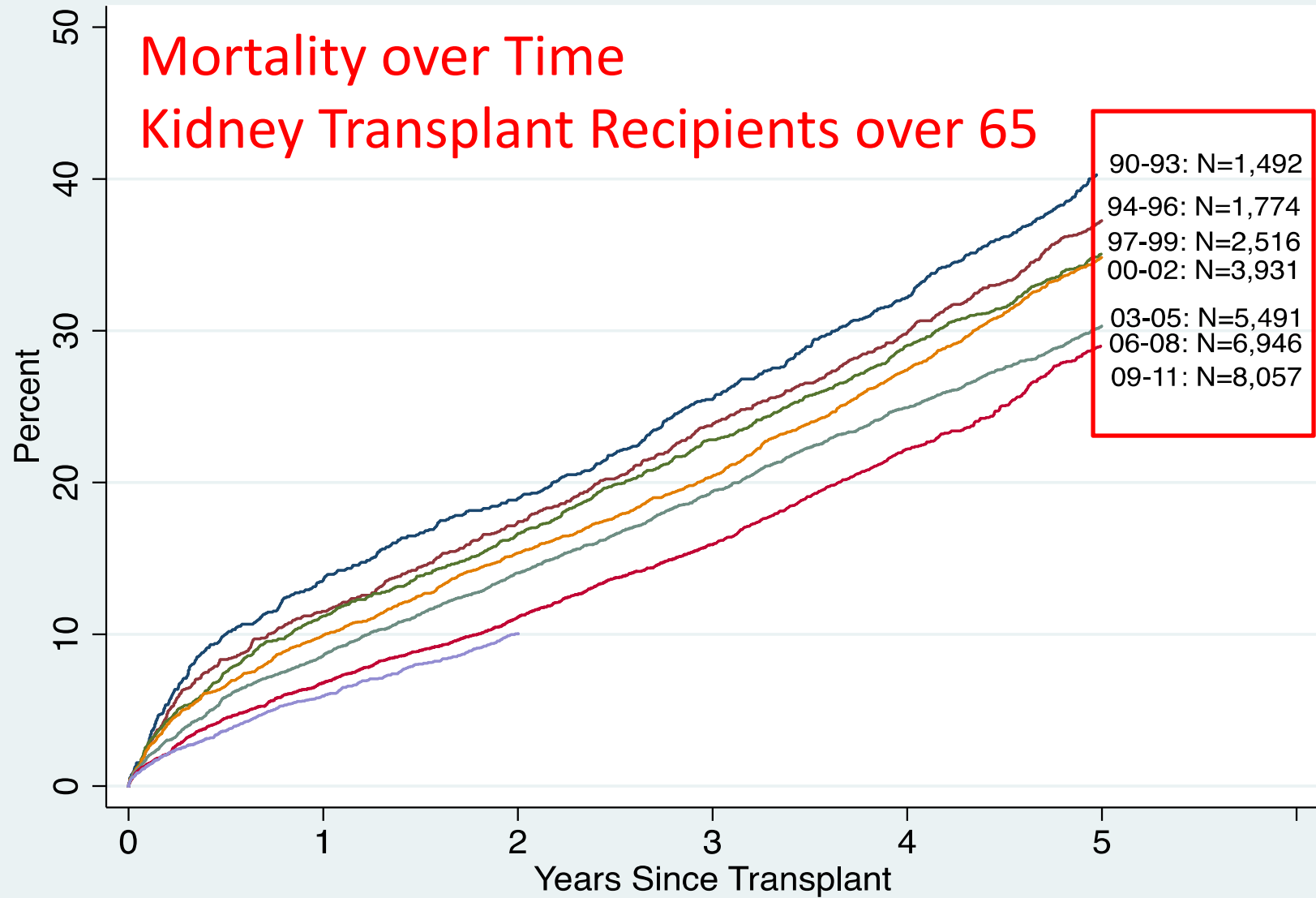
McAdams-DeMarco/Segev, JAGS, 2014



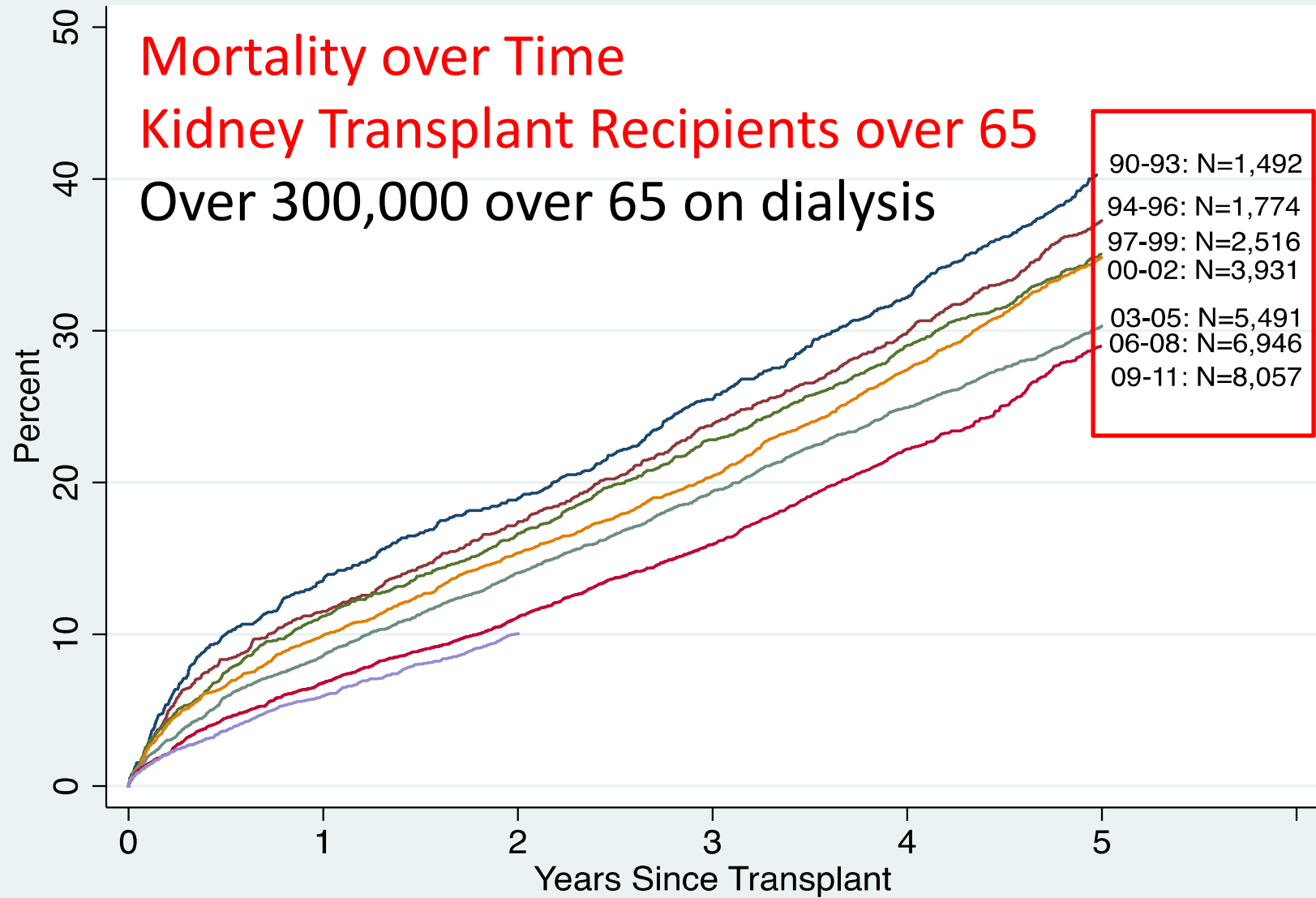
Number at risk

≥80:	240	181	161	119	112	69	66
75-79:	1,389	1,096	960	721	702	486	467
70-74:	4,456	3,545	3,180	2,364	2,283	1,586	1,543
65-69:	8,918	7,163	6,488	4,912	4,792	3,385	3,297

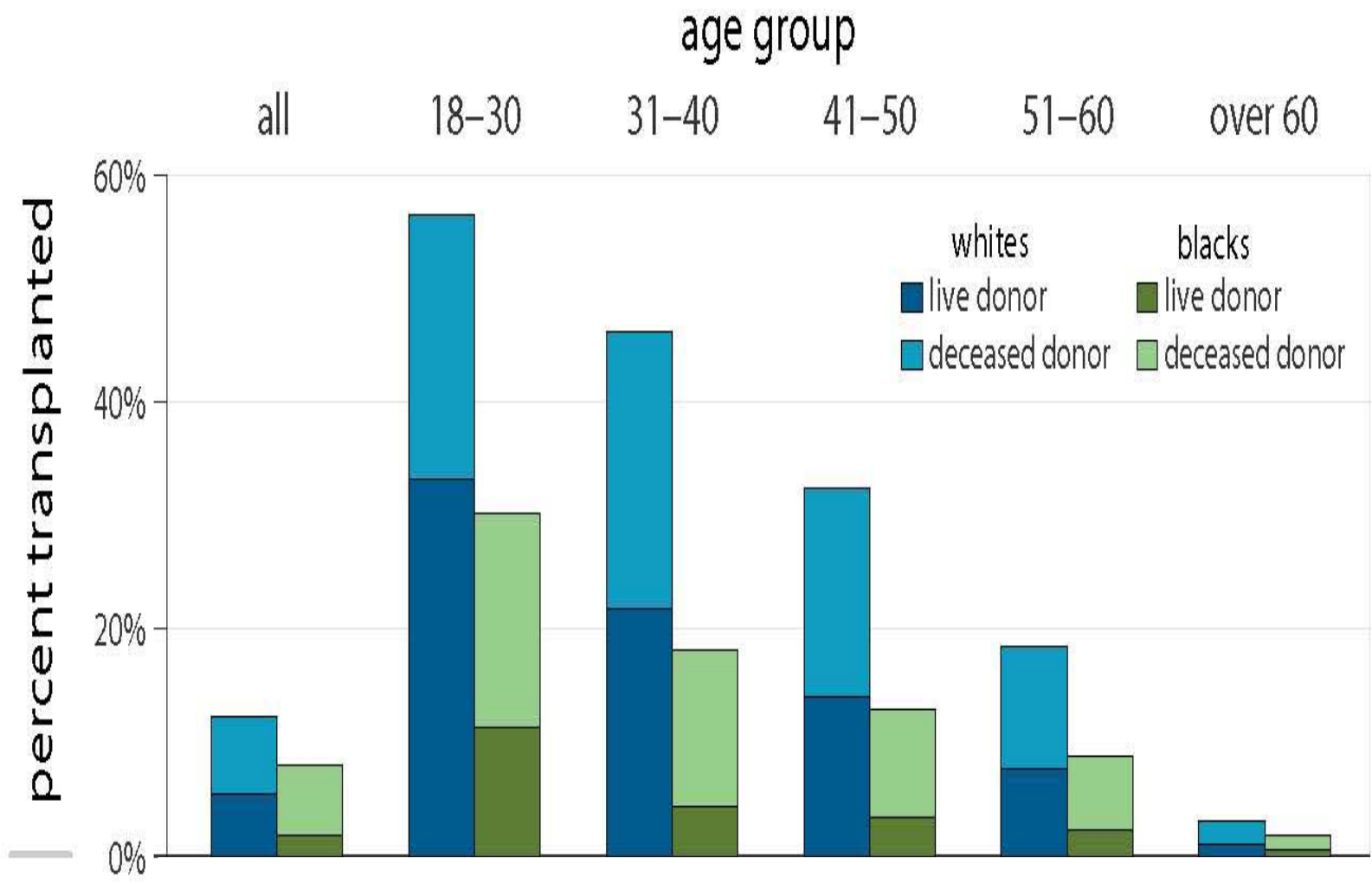
McAdams-DeMarco/Segev, JAGS, 2014



McAdams-DeMarco/Segev, JAGS, 2014

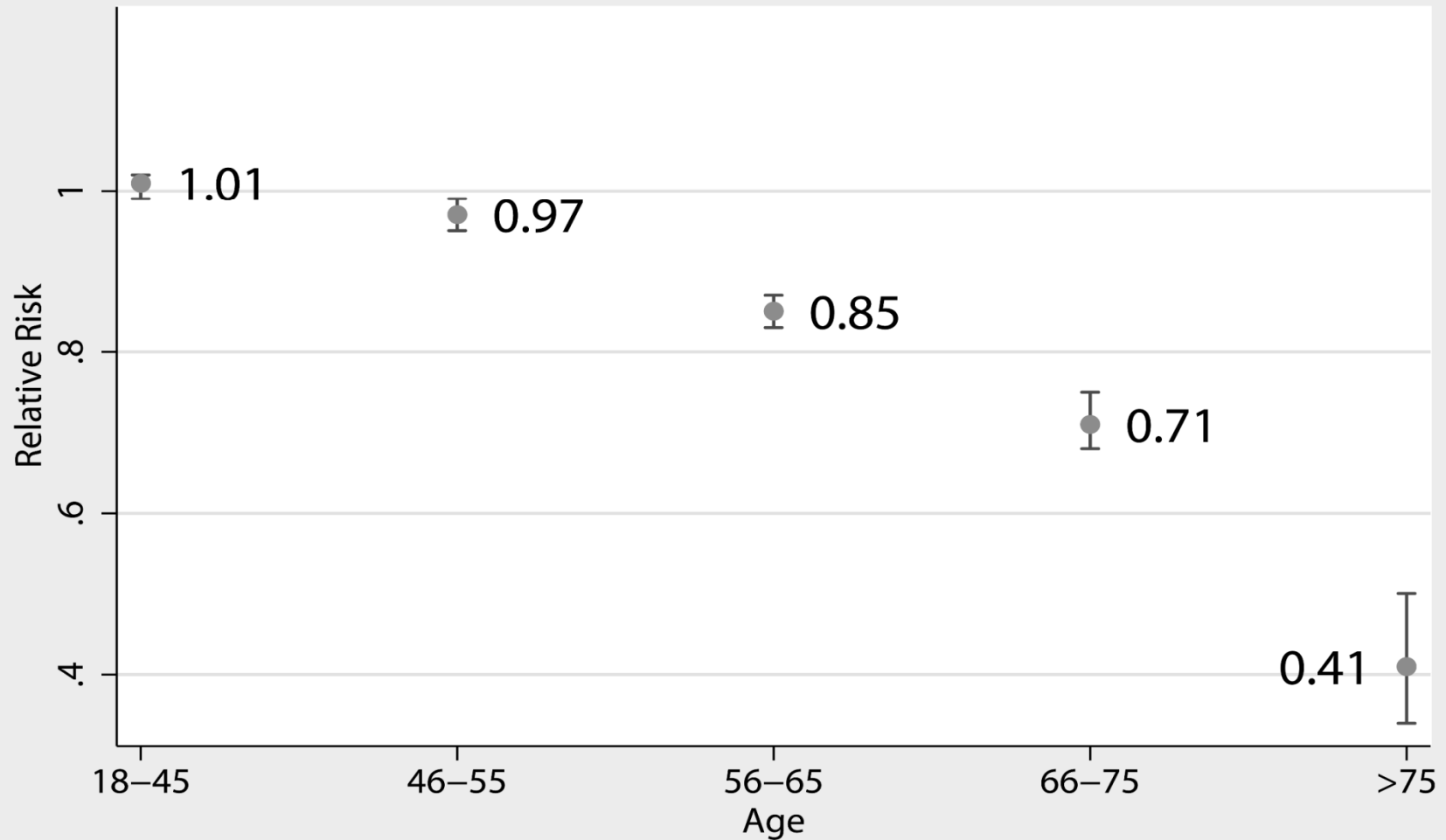


McAdams-DeMarco/Segev, JAGS, 2014



Kucirka/Segev, JAMA 2011

Adjusted Relative Risk of Access to Transplantation By Gender (Female versus Male)



Kucirka/Segev, JASN 2009

Access to Transplantation

- Look at KT recipients over 65 (1999-2006)
- Predict how long they survive after KT
- Quintiles (excellent candidates = top quintile)
- Go back to the ESRD patients, apply model to them (dropping those with absolute contraindications)
- See who from each prediction bin gets listed

KT Outcomes in Older Adults

Age (per year, centered at 70)	0.96 (0.94–0.97)	<.001
Dialysis time before 3 years (spline)*	0.78 (0.73–0.84)	<.001
Dialysis time after 3 years (spline)*	0.93 (0.88–0.99)	.03
Female	1.12 (0.98–1.27)	.09
Congestive heart failure	0.74 (0.65–0.85)	<.001
Cardiac arrhythmia	0.64 (0.55–0.75)	<.001
Complicated diabetes mellitus	0.71 (0.62–0.80)	<.001
Chronic pulmonary disease	0.71 (0.59–0.85)	<.001
Coronary artery disease	0.84 (0.72–0.98)	.03
Hypertension	1.24 (1.03–1.51)	.02
Drug dependence	0.16 (0.03–0.78)	.02
Peripheral vascular disease	0.74 (0.63–0.86)	<.001
Polycystic kidney disease	1.59 (1.20–2.11)	.001
Deficiency anemia	0.85 (0.71–1.02)	.08
Other neurological disorder	0.52 (0.32–0.83)	.007
Liver disease	0.61 (0.46–0.80)	<.001
Depression	0.66 (0.46–0.95)	.02
Peptic ulcer disease	0.66 (0.41–1.06)	.08
Current smoking	0.69 (0.47–1.02)	.06

Grams/Segev, JAGS 2011

Access to Transplantation

	Excellent candidates (3yr>87.6%)	Good candidates (3yr>78.3%)	Remaining candidates (3yr<78.3%)
N	11,756	43,291	72,913
(%)	(9.1%)	(33.6%)	(56.6%)

Grams/Segev, JAGS 2011

Access to Transplantation

	Excellent candidates (3yr>87.6%)	Good candidates (3yr>78.3%)	Remaining candidates (3yr<78.3%)
N	11,756	43,291	72,913
(%)	(9.1%)	(33.6%)	(56.6%)
% with access	23.7	8.7	2.5
% transplanted	13.2	4.2	1.1

Grams/Segev, JAGS 2011

Access to Transplantation

	Excellent candidates (3yr>87.6%)	Good candidates (3yr>78.3%)	Remaining candidates (3yr<78.3%)
N	11,756	43,291	72,913
(%)	(9.1%)	(33.6%)	(56.6%)
% with access	23.7	8.7	2.5
% transplanted	13.2	4.2	1.1

11% would find live donors!

Grams/Segev, JAGS 2011



The internet is so fascinating!

That's the microwave!

Slap

Frailty: General Surgery

- 594 adults ≥ 65 yo undergoing general surgery
- Frailty Prevalence:
 - 10.4% frail
 - 31.3% intermediately frail
 - 58.3% nonfrail

Makary, Segev, JACS, 2010

Frailty: General Surgery

- 594 adults ≥ 65 yo undergoing general surgery
 - Frailty Prevalence:
 - 10.4% frail
 - 31.3% intermediately frail
 - 58.3% nonfrail
 - Adjusted Rate (full model):
 - Intermediately Frail
 - Frail
- | | Complications: | |
|------------------------------|----------------|-------|
| – 10.4% frail | 11.4% | 43.5% |
| – 31.3% intermediately frail | 7.3% | 33.7% |
| – 58.3% nonfrail | 3.9% | 19.5% |
- | | |
|------------------------|------------------|
| – Intermediately Frail | 2.06 (1.18-3.60) |
| – Frail | 2.54 (1.12-5.77) |

Makary, Segev, JACS, 2010

Frailty: General Surgery

- 594 adults ≥ 65 yo undergoing general surgery
- Frailty Prevalence:

	Length of Stay:	
– 10.4% frail	1.5d	7.7d
– 31.3% intermediately frail	1.2d	6.2d
– 58.3% nonfrail	0.7d	4.2d
- Adjusted Rate (full model):

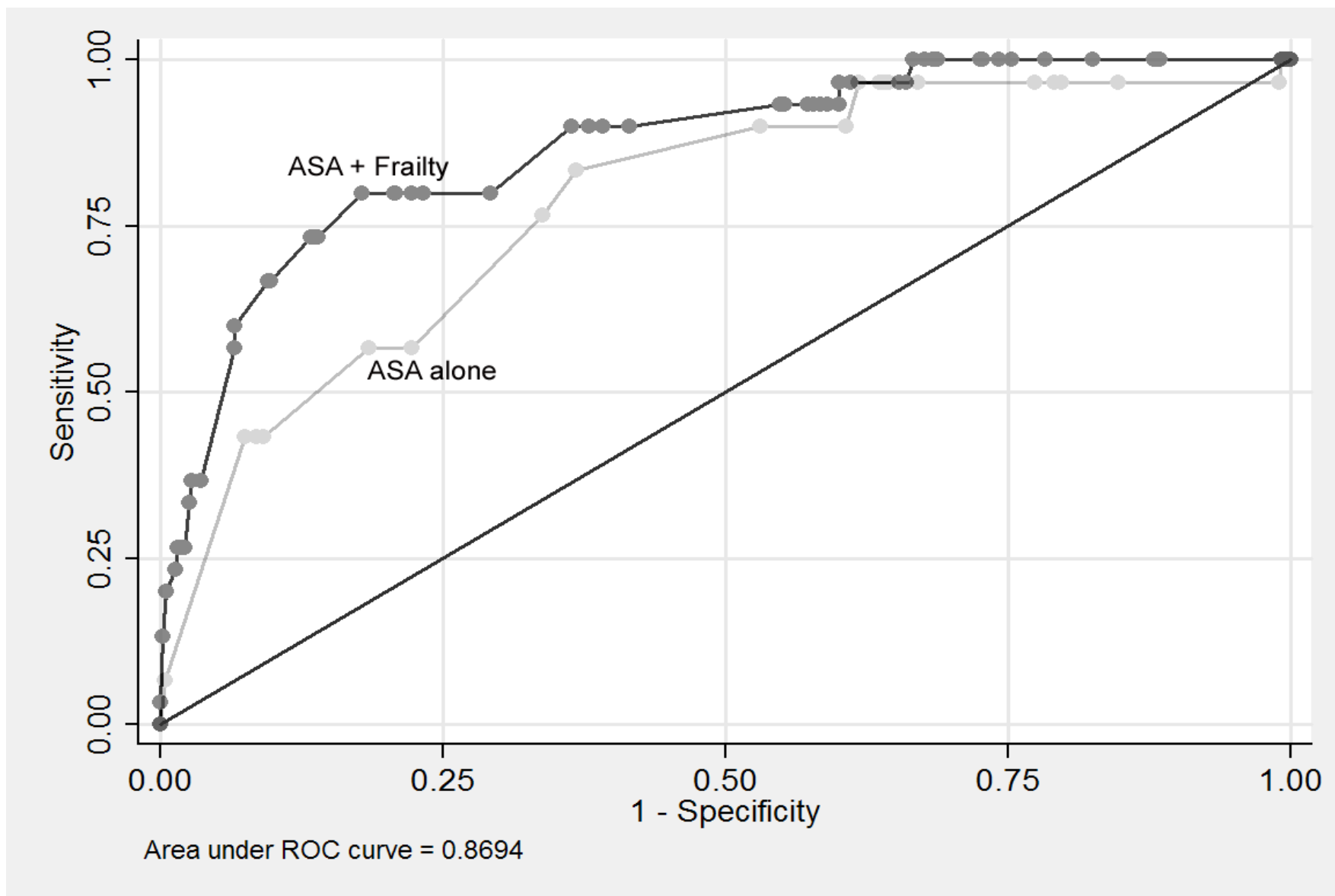
– Intermediately Frail	1.49 (1.24-1.80)
– Frail	1.69 (1.28-2.23)

Makary, Segev, JACS, 2010

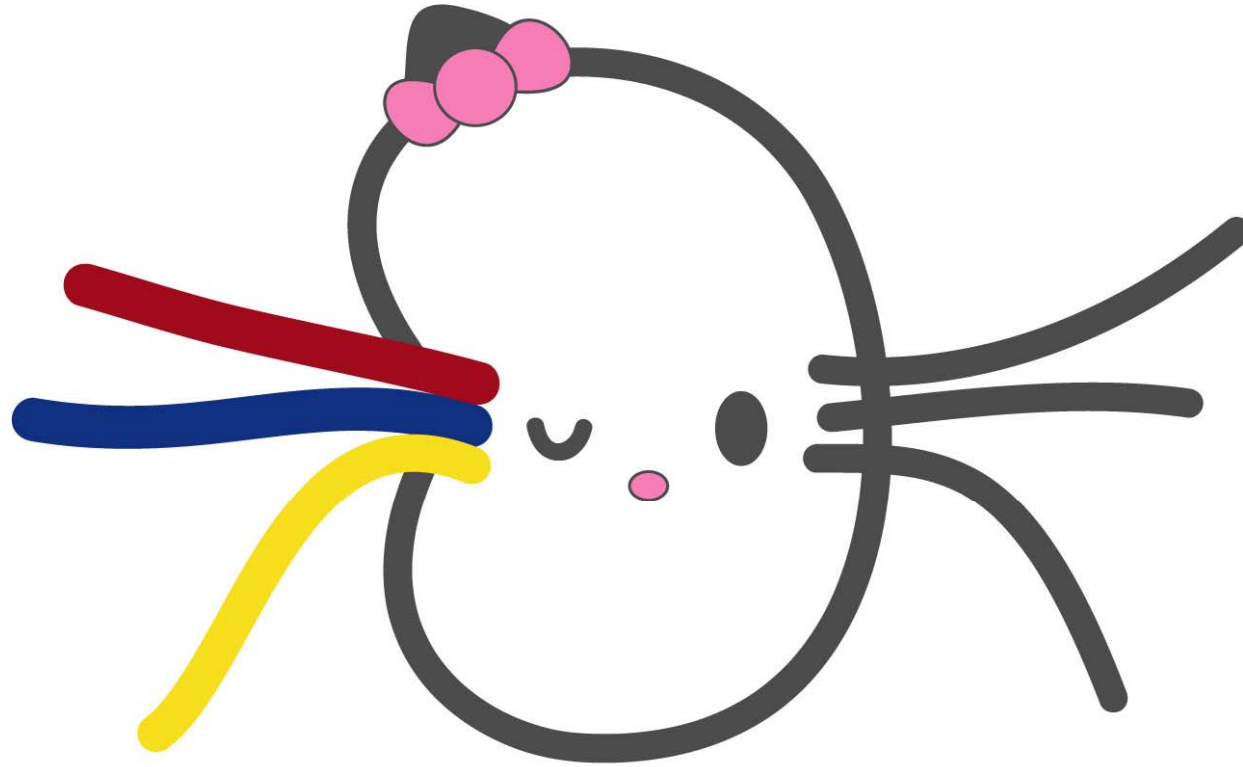
Frailty: General Surgery

- 594 adults ≥ 65 yo undergoing general surgery
- Frailty Prevalence: Discharge to Non-Home:
 - 10.4% frail 17.4% 42.1%
 - 31.3% intermediately frail 0.0% 12.2%
 - 58.3% nonfrail 0.8% 2.9%
- Adjusted Rate (full model):
 - Intermediately Frail 3.16 (1.00-9.99)
 - Frail 20.48 (5.54-75.68)

Makary, Segev, JACS, 2010



Makary, Segev, JACS, 2010



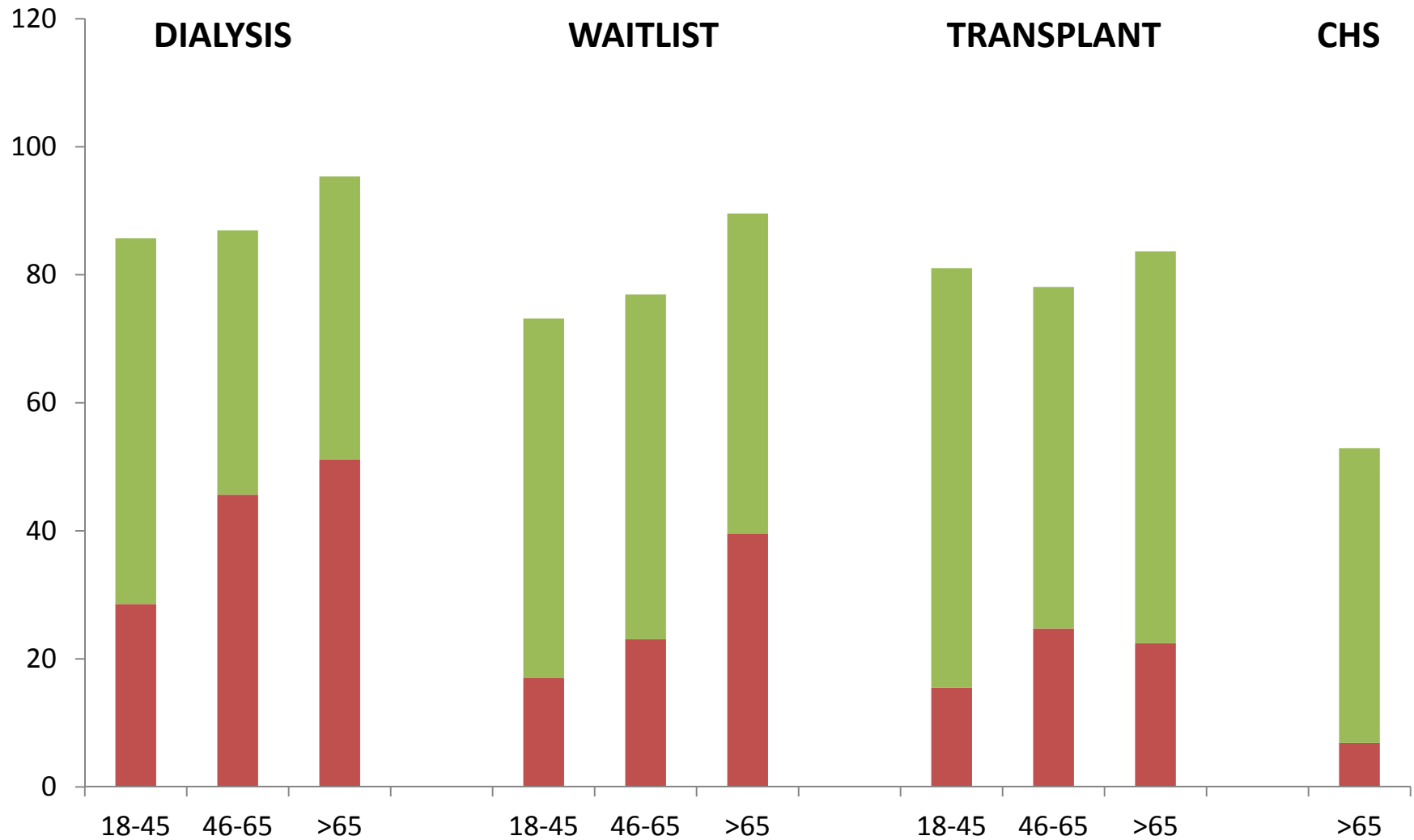
HELLO KIDNEY

Segev, 2006: "Surviving MAFAT by doodling"

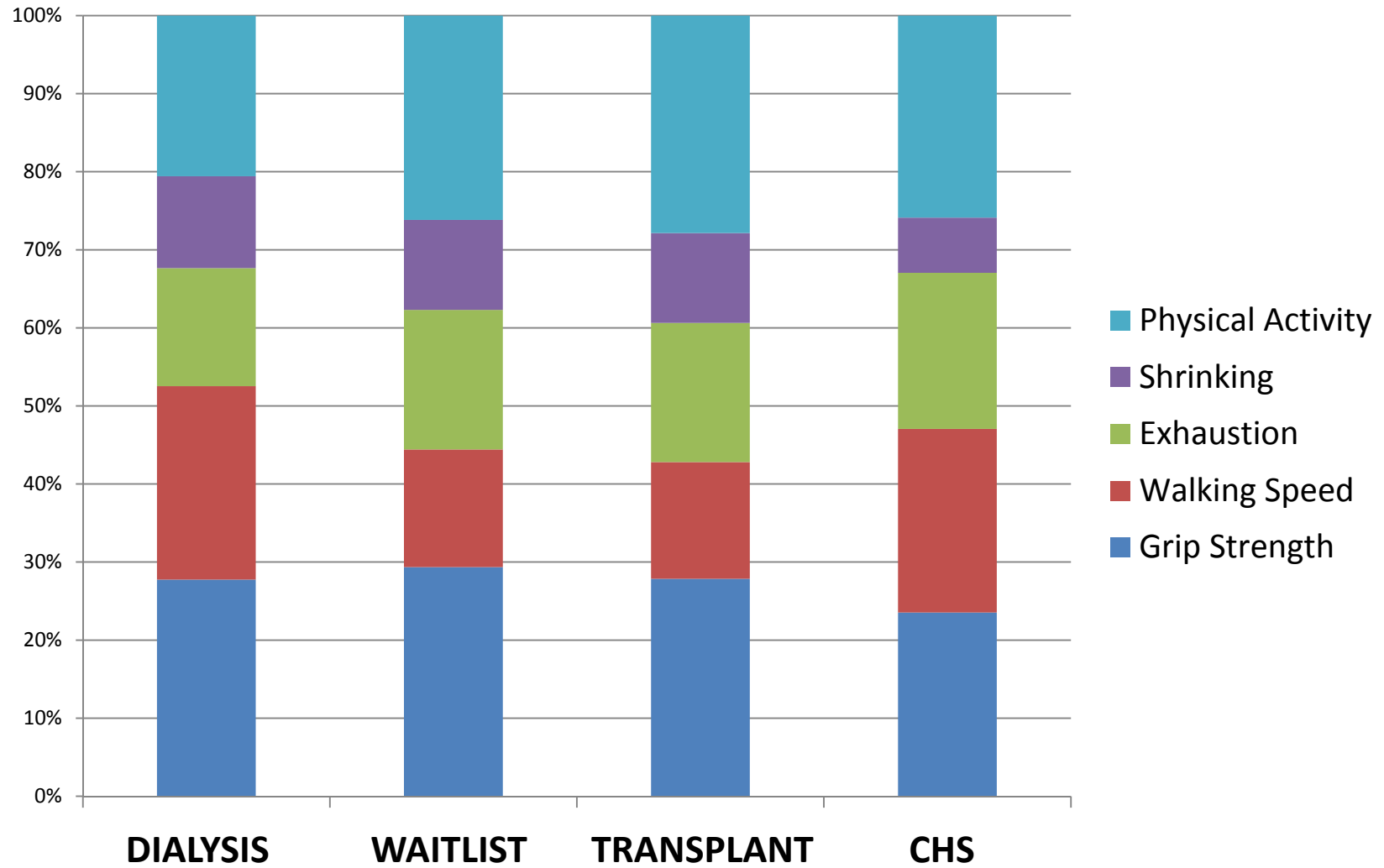
Frailty Prevalence: By Cohort, All Ages

	DIALYSIS	WAITLIST	TRANSPLANT	CHS
Non-Frail	9.6%	19.7%	20.1%	46.0%
Intermediately Frail	44.2%	53.5%	58.4%	46.0%
Frail	46.2%	26.8%	21.5%	6.9%

Frailty Prevalence: By Cohort, By Age



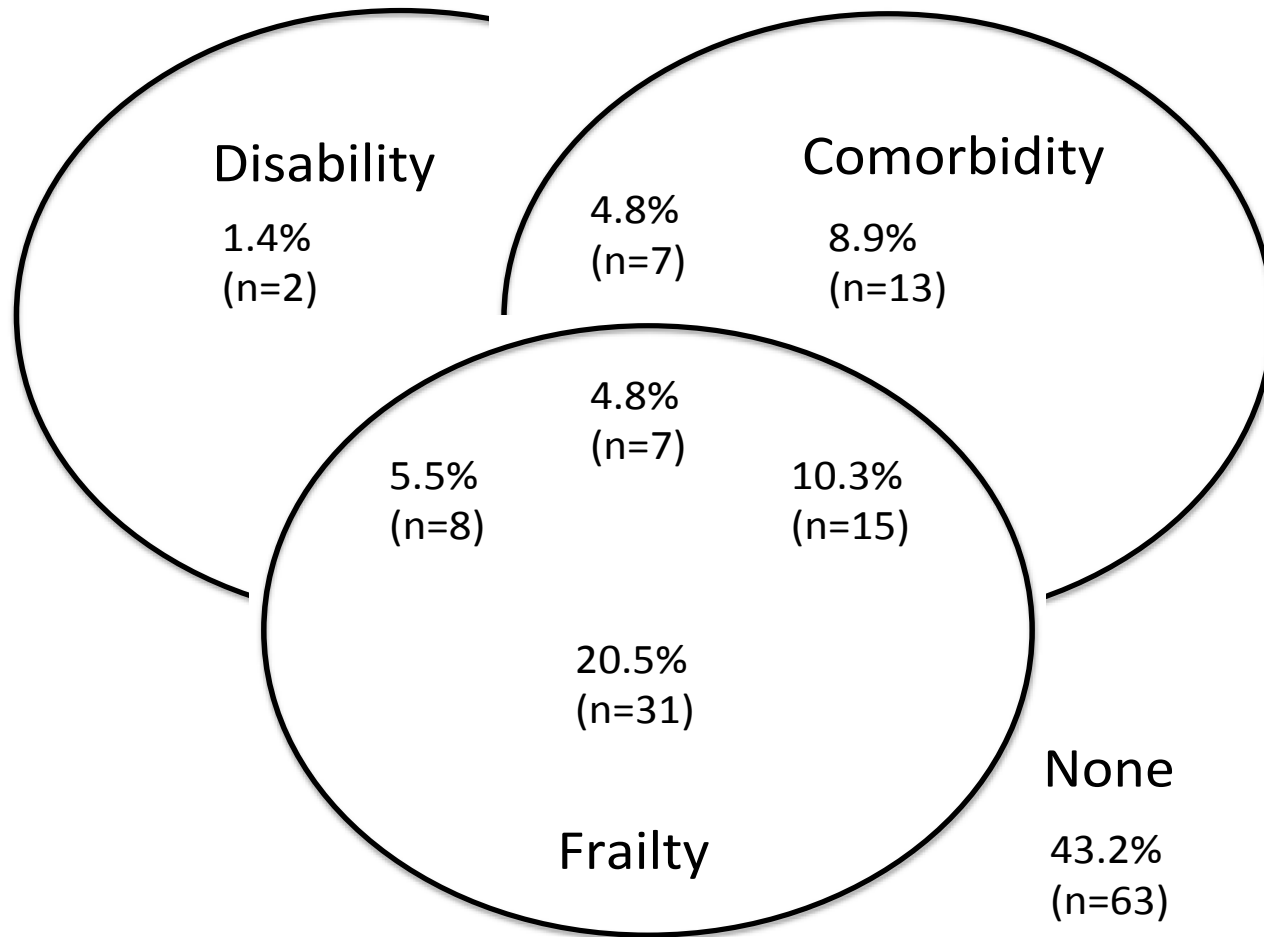
Frailty Components, Normalized



Frailty: Prevalent ESRD Patients

- 146 prevalent dialysis patients; 43.8% age \geq 65
- Frailty Prevalence:
 - 41.8% frail
 - 32.2% intermediately frail
 - 26.0% nonfrail (expanded definition)

Frailty: Prevalent ESRD Patients



McAdams-DeMarco/Segev, JAGS, In Press

Frailty: Prevalent ESRD Patients

- 146 prevalent dialysis patients; 43.8% age \geq 65
- Frailty Prevalence:

	3-Year Mortality:
– 41.8% frail	40.2%
– 32.2% intermediately frail	34.4%
– 26.0% nonfrail	16.2%

McAdams-DeMarco/Segev, JAGS, 2013

Frailty: Prevalent ESRD Patients

- 146 prevalent dialysis patients; 43.8% age \geq 65
- Frailty Prevalence: 3-Year Mortality:
 - 41.8% frail 40.2%
 - 32.2% intermediately frail 34.4%
 - 26.0% nonfrail 16.2%
- Adjusted Rate (full model):
 - Intermediately Frail 2.68 (1.02-7.07)
 - Frail 2.60 (1.04-6.49)

McAdams-DeMarco/Segev, JAGS, 2013

Frailty: Prevalent ESRD Patients

- 146 prevalent dialysis patients; 43.8% age \geq 65
- Frailty Prevalence: Hospitalization:
 - 41.8% frail 60.7%
 - 32.2% intermediately frail 44.7%
 - 26.0% nonfrail 46.2%
- Adjusted Rate (full model):
 - Intermediately Frail 0.76 (0.49-1.16)
 - Frail 1.43 (1.01-2.03)

McAdams-DeMarco/Segev, JAGS, 2013

Frailty: Prevalent ESRD Patients

- 146 prevalent dialysis patients; 43.8% age \geq 65
- Frailty Prevalence: # Falls in 6 months:
 - 41.8% frail
 - 32.2% intermediately frail
 - 26.0% nonfrail
- Adjusted Rate (full model):
 - Intermediately Frail 1.19 (0.44-3.24)
 - Frail 3.09 (1.38-6.90)

McAdams-DeMarco/Segev, BMC Nephrology, 2013



Frailty: KT Recipients

- 183 KT recipients; 22.1% age \geq 65
- Frailty Prevalence:
 - 25.1% frail
 - 74.9% not frail

Frailty: KT Recipients

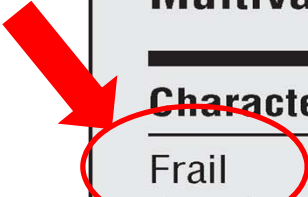
- 183 KT recipients; 22.1% age \geq 65
 - Frailty Prevalence:
 - 25.1% frail
 - 74.9% not frail
- DGF:
30%
15%

Frailty: KT Recipients

- 183 KT recipients; 22.1% age \geq 65
 - Frailty Prevalence:
 - 25.1% frail
 - 74.9% not frail
 - Adjusted Rate (full model):
 - Frail
- DGF:
30%
15%
- 1.94 (1.13-3.36)

Frailty: KT Recipients

Table 4. Relative Risk of Delayed Graft Function, Multivariate Model



Characteristic	RR (95% CI)	P Value
Frail	1.94 (1.13-3.36)	.02
Age, in decades	0.94 (0.74-1.20)	.62
Donor creatinine level ^a	1.26 (1.10-1.44)	.001
Cold ischemia time		
Live donor	1 [Reference]	
Deceased donor <12 h	4.46 (0.82-23.93)	.08
Deceased donor 12-24 h	6.92 (1.45-33.2)	.02
Deceased donor >24 h	8.47 (1.75-41.12)	.008
Extended criteria donor ^b	1.44 (0.74-2.80)	.28
Donor after cardiac death ^b	2.24 (0.88-5.74)	.09
BMI > 30	1.42 (0.79-2.60)	.24
African American	1.26 (0.64-2.48)	.50
Diabetes	1.04 (0.60-1.80)	.88
Preemptive transplant	0.25 (0.04-1.80)	.17

Garonzik-Wang/Segev, Archives Surgery, 2012

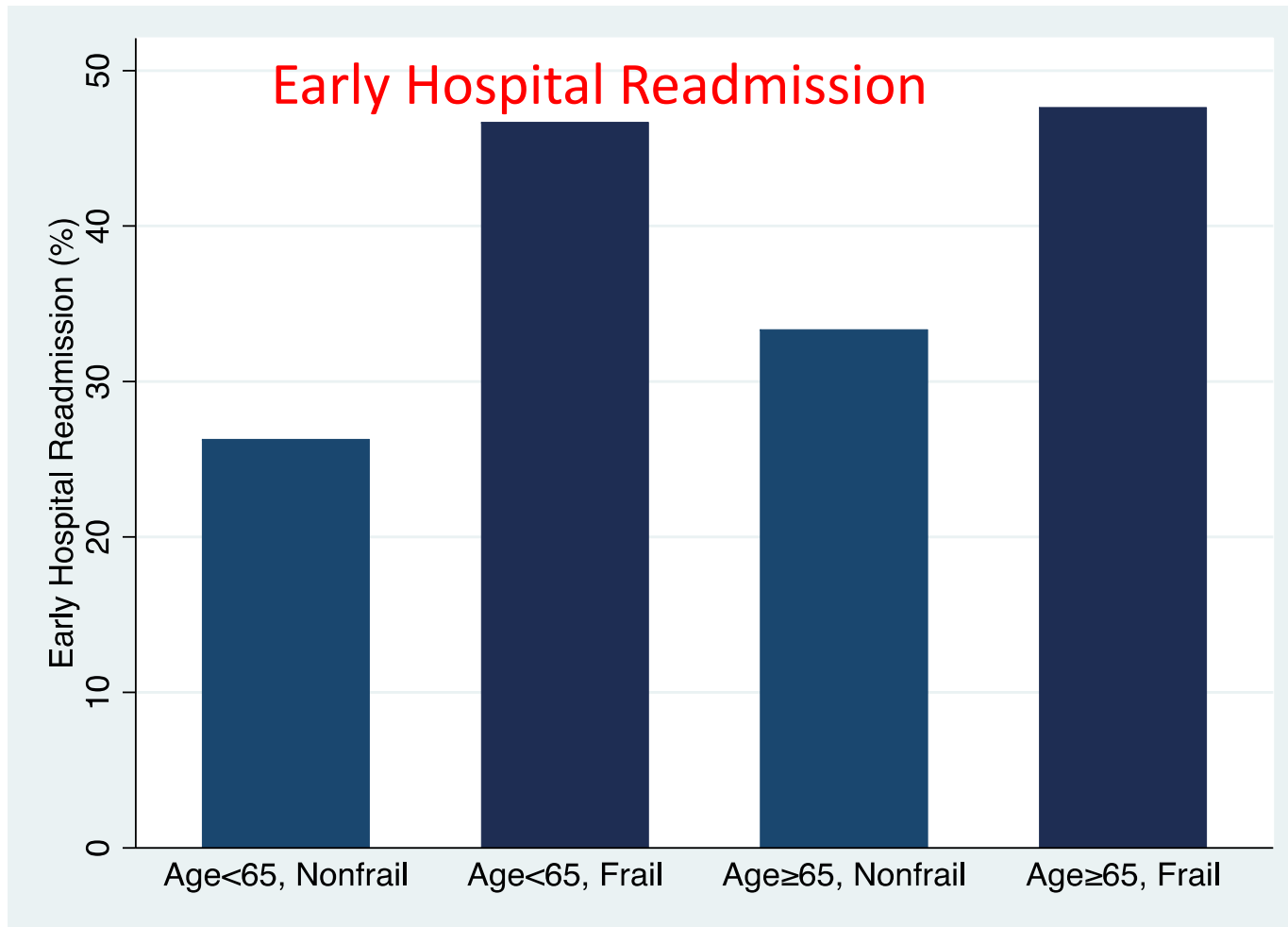
Frailty: KT Recipients

- 383 KT recipients
- Frailty Prevalence:
 - 18.8% frail
 - 81.2% not frail
- Early Readmission:
 - 45.8%
 - 28.0%

Frailty: KT Recipients

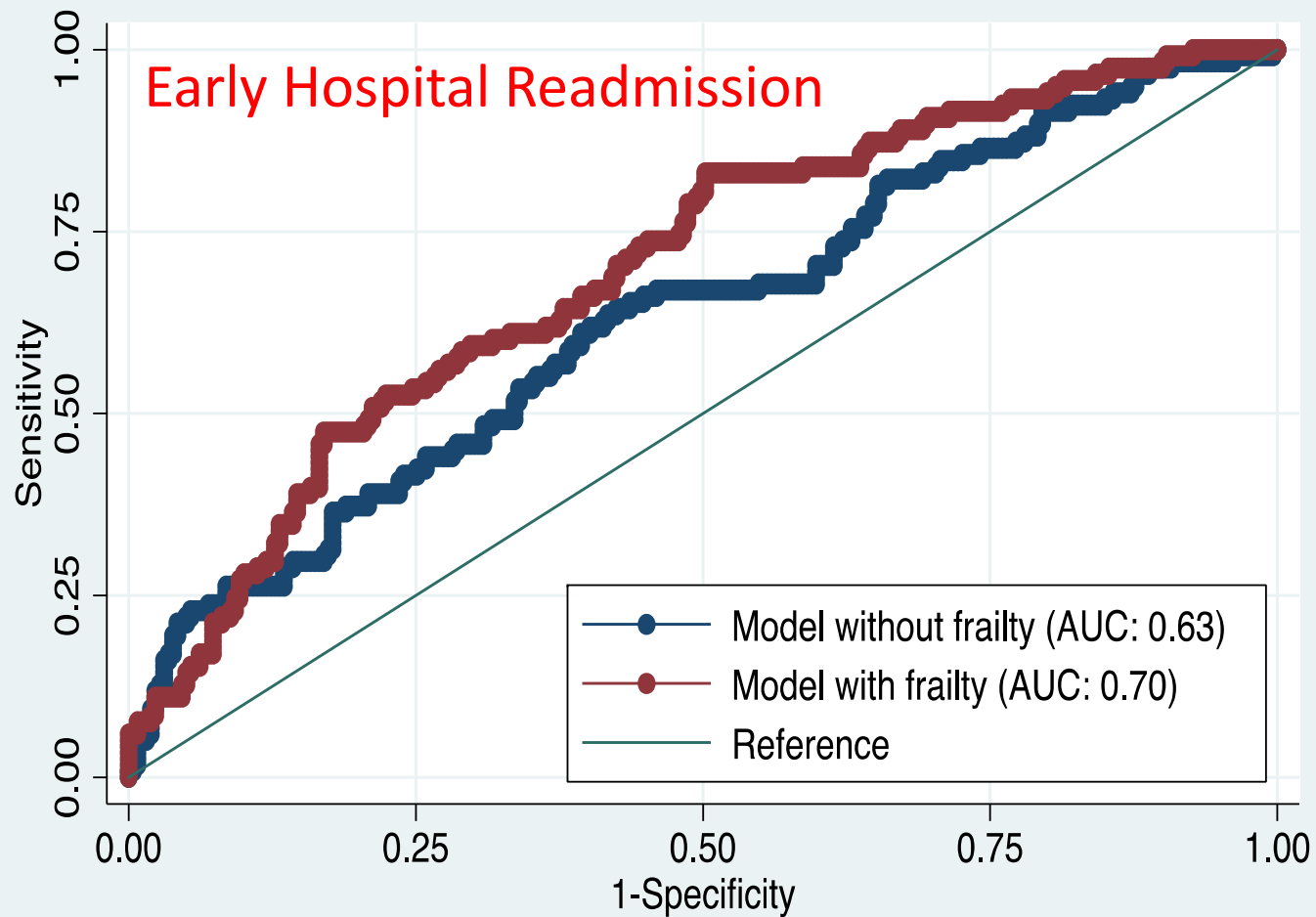
- 383 KT recipients
 - Frailty Prevalence:
 - 18.8% frail
 - 81.2% not frail
 - Adjusted Rate (full model):
 - Frail
- Early Readmission:
45.8%
28.0%
- 1.61 (1.18-2.19)

Frailty: KT Recipients



McAdams-Demarco/Segev, AJT, 2013

Frailty: KT Recipients



McAdams-Demarco/Segev, AJT, 2013

KT Outcomes, by Frailty (N=537)

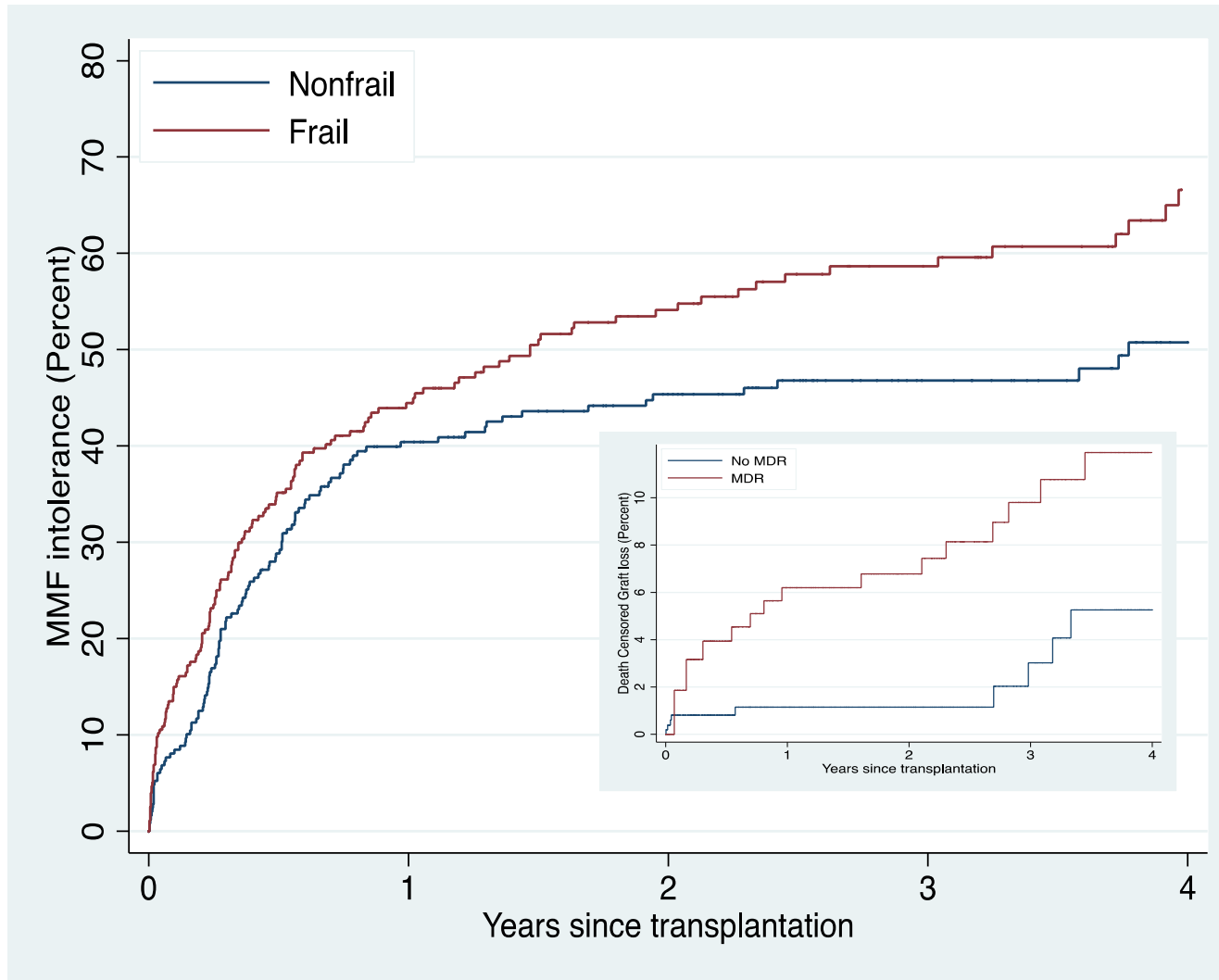
	Nonfrail	Intermediately Frail	Frail
Graft Loss	Ref	1.91 (0.75, 4.82)	2.50* (1.00, 6.23)
Mortality	Ref	1.59 (0.71, 3.57)	2.19* (1.00, 4.80)

All models adjusted for recipient, transplant and donor risk factors using the hybrid registry-augmented regression

* P<0.05

McAdams-Demarco/Segev, AJT, 2015

MMF Dose Reduction

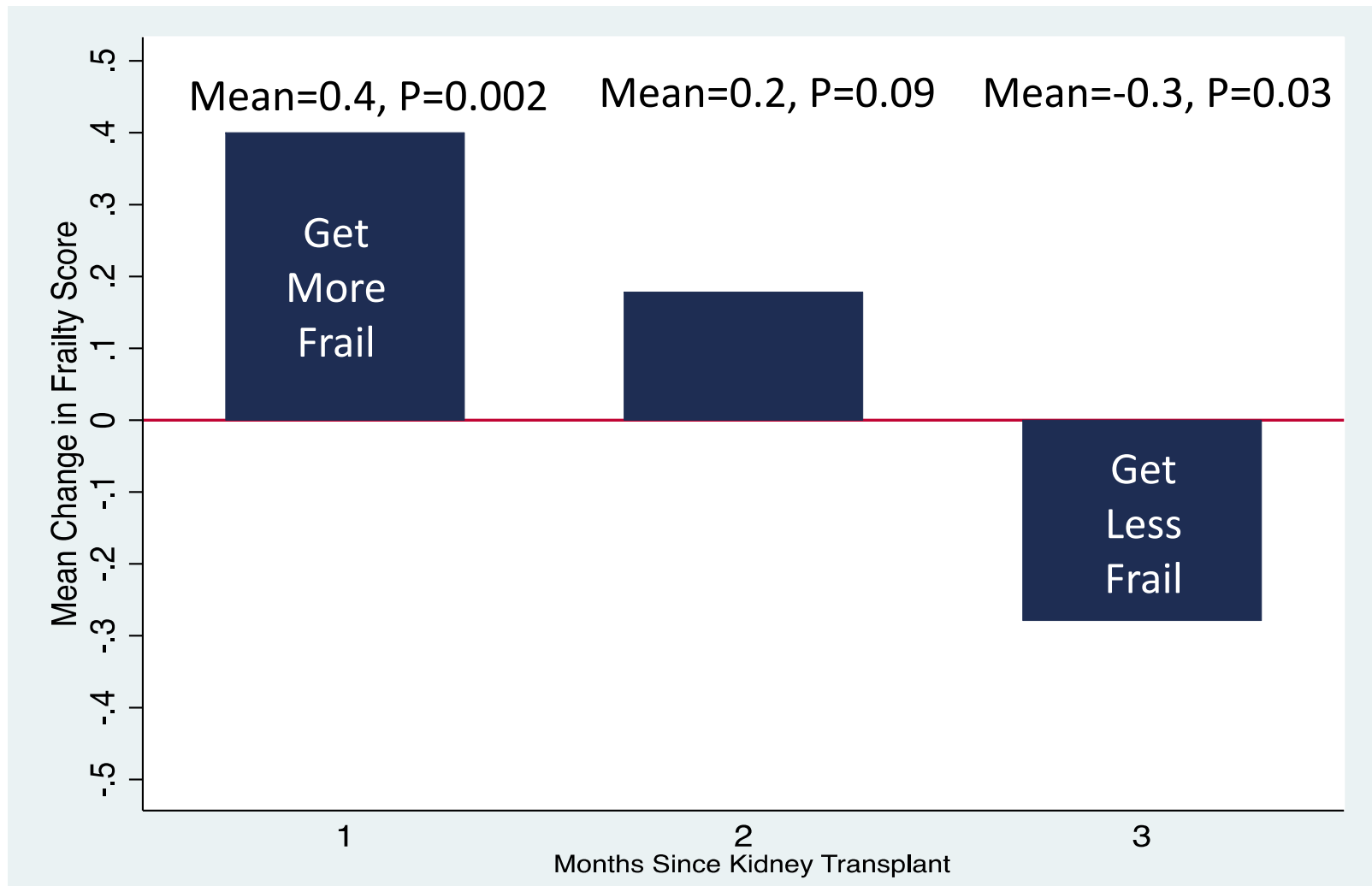


McAdams-Demarco/Segev, Transplantation, in press

Frailty and Length of Stay (N=589)

	Ratio (95% CI) of days hospitalized		OR (95% CI) of 2 week LOS	
	Without DGF	With DGF	Without DGF	With DGF
Frail vs. Nonfrail	1.15 (1.02-1.29)	1.15 (1.02-1.29)	1.67 (1.15-2.43)	1.60 (1.08-2.37)
P-value	0.02	0.02	0.007	0.02

Change in Frailty after KT



McAdams-Demarco/Segev, JAGS, in revision

Next Steps

- Better understand frailty and cognitive decline in this population
- Better understand frailty trajectories (on dialysis, with transplant)
- Integrate into clinical practice
- Develop a disease-specific frailty measure
- Prehabilitation

Funding

- American Geriatrics Society
- NKF of Maryland
- Doris Duke Charitable Foundation
- K23AG032885
- R21DK085409
- R01AG042504

Epidemiology Research Group in Organ Transplantation (D Segev, Director)

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ID Faculty; R01 Pending
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Surgery: Collaborator
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Elliott Haut, MD PhD
Surgery: Mentee (KL2; PCORI)
Kim Steele, MD PhD
Surgery: Mentee (K23)
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