Trends in Pancreas After Kidney (PAK) Transplant: Understanding Graft Loss

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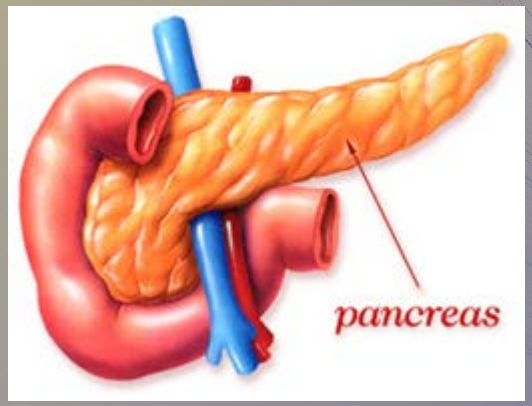

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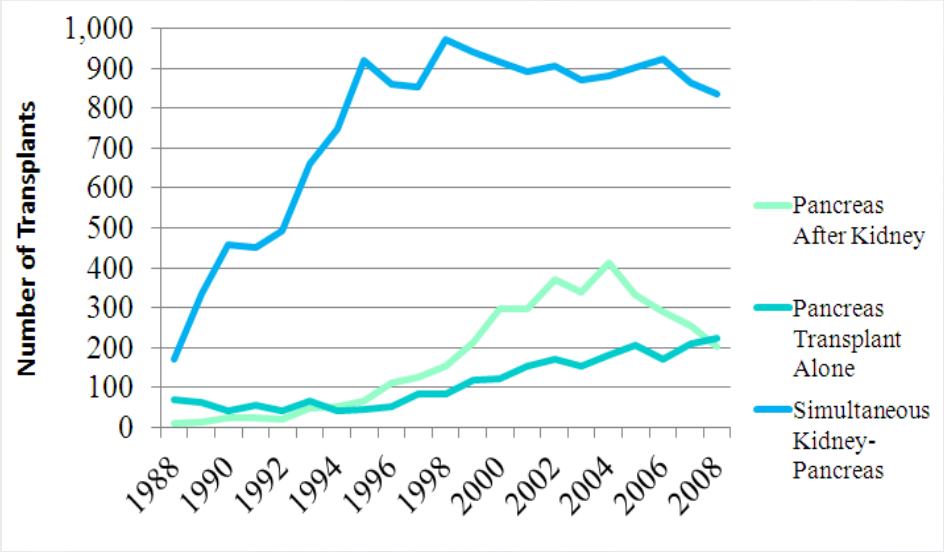
Background

- Patients with type I DM and renal failure have 4 options
  - Simultaneous Kidney-Pancreas Transplant (SPK)
  - Pancreas after kidney transplant (PAK)
  - Islet after kidney transplant
  - Kidney transplant alone
- SPK has dominated PAK as a result of historically better outcomes



Background

- Differential in PAK vs. SPK outcomes
  - Donor quality
  - Immunologic monitoring using serum creatinine
- Causes of graft loss
  - Early thrombosis
  - Infection
  - Acute rejection
  - Chronic rejection
  - Death

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Background: Pancreas Donor Risk Index

Donor Characteristics	Reference Donor (DRI = 1.00)	Change Donor Characteristic to:	DRI
Gender	Male	Female	0.87
Age	28	45	1.56
Black Race	No	Yes	1.27
Asian Race	No	Yes	1.17
BMI	24	30	1.17
Height (cm)	170	190	0.90
COD: CVA/Stroke	No	Yes	1.23
COD: CVA/Stroke (PAK)	No	Yes	0.93
Preservation Time (hrs)	12	20	1.13
DCD	No	Yes	1.39
SCr >2.5	No	Yes	1.22

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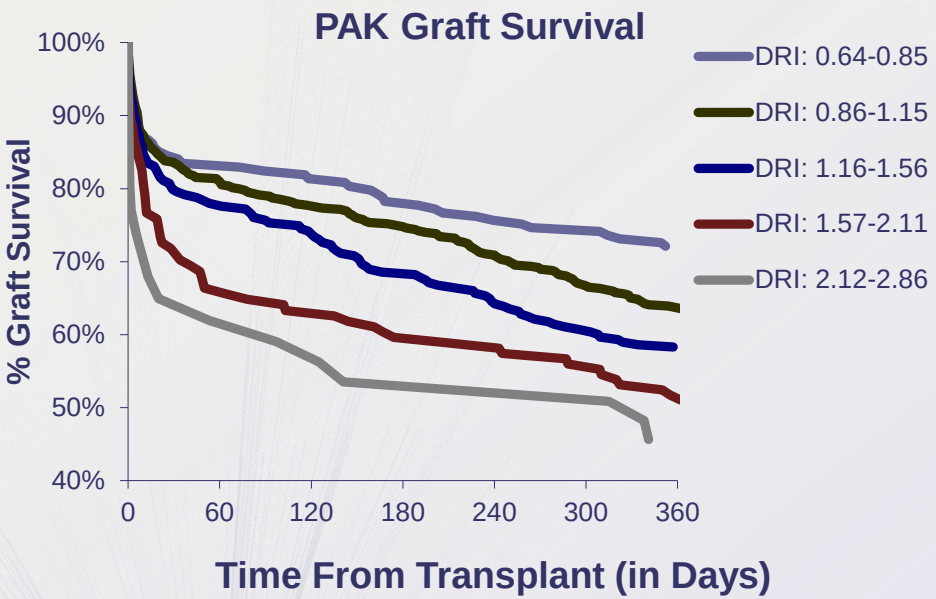
Pancreas Allograft Outcomes

	1 Year Graft Survival		
pDRI	SPK	PAK	PTA
0.64-0.85	88%	84%	84%
0.86-1.15	87%	77%	82%
1.16-1.56	82%	75%	70%
1.57-2.11	78%	69%	68%
2.12-2.86	77%	67%	80%



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Research Aims

- Describe the outcomes of PAK over time:
  - *Are Pancreas after Kidney transplant outcomes improving?*
- Assess the factors associated with PAK graft loss:
  - *Are high risk factors modifiable through intervention or policy?*
- Determine the relationship between kidney allograft characteristics, PAK outcome, and patient death:
  - *Is it really all about the kidney?*

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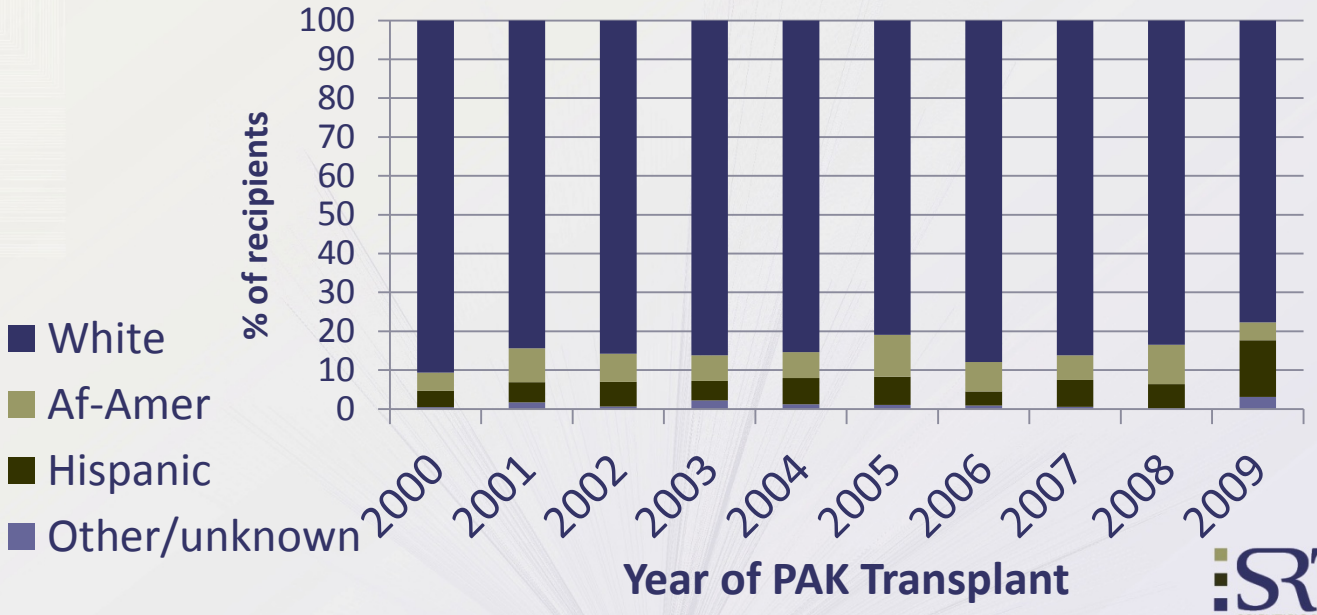
Methods

- SRTR registry data for PAK recipients of deceased donor transplants
- PAK recipients transplanted 1/1/00-12/31/09
  - Excluded previous SPK recipients who received a PAK (N=490)
  - Recipients who did not have records with UNOS for their previous kidney transplant were excluded (N=32).
- The final cohort (N=2349), followed until 9/30/10.

Recipient Demographic Characteristics

Characteristic	Average / Percent
Age	42.0 yrs
Male	58.4%
Type I DM	93 %
Living donor kidney	70.4%



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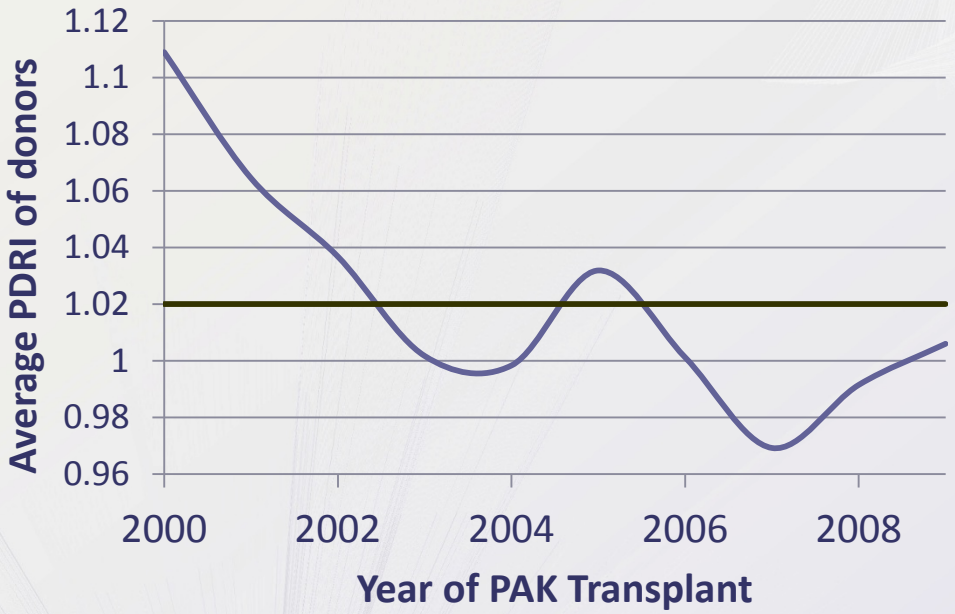
Donor Demographic Characteristics

- Ave. donor age: 25.4
- Ave. donor BMI: 24.1
- Race/Ethnicity:
  - 72.5% white
  - 12.0% AA
  - 13.4% Hispanic/Latino
  - 2.1% other/unknown



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Analytical Approach

- Cox Proportional Hazards Models were used to model outcomes:
  - All-cause and death censored pancreas graft failure
  - All-cause and death censored kidney graft failure
  - Patient survival.
- Start of observation time: pancreas transplant
- Use time-dependent covariates of pancreas failure during follow-up for kidney; kidney failure during follow-up for pancreas; and both during follow-up for patient survival.

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Results: Pancreas Graft Failure

- Graft Failure: 42.4% (n=997)
  - Average length of follow-up: 688 days (22.6 months)
  - 7.9% (n=229) died prior to graft failure
  - 32.7% (n=768) experienced graft failure prior to death
- Lost-to-Follow-up: 0.6% (n=15)
- Survived with function : 56.9% (n=1337)
  - Average length of follow-up: 1706 days (56 months)
- **Risk adjusted hazard ratio for graft loss has decreased over time (HR 0.96 P=.007) per year**

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Pancreas Graft Failure Model

Risk factor	Impact on risk
Kidney failure	↑
PDRI	↑ as PDRI ↑
Age < 30	↑ with age
Use of CNI and mTOR	↓ vs. neither
Years between KTx and PTx	↓
Recipient GFR > 65	↓ vs. GFR < 65
PVOD	↑
Type I vs. Type II	↓
Karnofsky Score	↑ if total assist
Local donor	↓
Donor eGRF	↓ as eGFR ↑
Transplant year	↓ as year ↑
Recipient BMI > 31	↑ vs. 20-31
DGF of KTx	↑

Index of Concordance (95% CI: 61.3% (59.4, 63.1)

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Predicted Outcomes

Covariate	Person 1, low risk	Person 2, medium-risk	Person 3, high risk
PDRI, linear	0.80	1.0	1.5
Age	>30	>30	<30
Local pancreas	Yes	No	No
Years between kidney and pancreas transplants	1 year	2 years	3 years
CNI and mTOR	Both	CNI only	mTOR only
eGFR at pancreas transplant	65.1-76.8	55.1-65	45.1-55
History of PVD	No	No	No
Delayed Graft Function of Kidney	No	No	Yes
Year of pancreas transplant	2006	2006	2006
Pancreas donor eGFR	110	110	90
Karnofsky functional status	No limitations	No limitations	Some limitations
Diabetes type	Type 1	Type 1	Type 1
Estimated 5-yr PTx graft survival	68.6 (60.7, 77.5)	55.0 (49.9, 60.8)	29.3 (14.8, 58.0)

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Kidney Graft Failure Model

Risk factor	Impact on risk
Pancreas failure	↑
BMI	↑ <25 or > 30
Age	↑ with age
Kidney donor age	↑ with age
Use of CNI	↓ vs. CNI & mTOR
Recipient eGFR > 65	↓ vs. GFR < 65
Donor eGFR <75 or >115	↑ vs. 75-115
Recipient race	↑ if AA, ↓ if Hispanic
Kidney donor type	↓ if live donor
Total HLA mismatch	↑ if > 1
Local donor	↓
eGFR post kidney txp	↓ if > 40
Prememptive kidney txp	↓

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Kidney Graft Failure: Cause

Cause of Kidney Graft Failure	Living Kidney Donor Recipients	Deceased Kidney Donor Recipients
Acute Rejection	2.4%	4.2%
Graft Thrombosis	1.3%	0.5%
Infection	2.1%	1.4%
Recurrent Disease	1.6%	0.5%
Chronic Rejection	22.5%	24.0%
BK Virus	3.0%	1.4%
Other cause	9.4%	9.7%
Death, no other cause given	47.2%	46.5%
Cause missing, graft failure preceding death	10.5%	12.0%
Total	22.6%	31.2%

Index of Concordance (95% CI: 65% (62.6-67.1)

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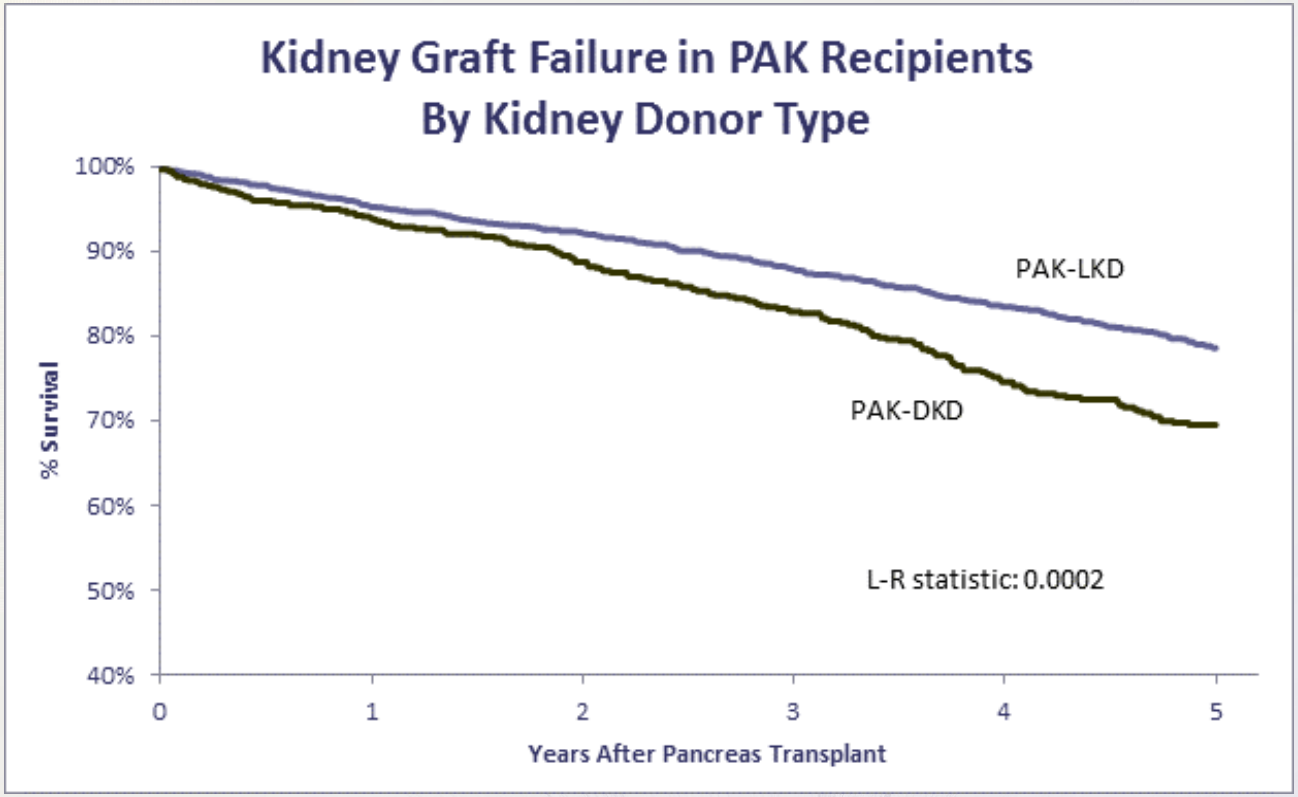
Kidney Graft Survival: by Kidney Donor Type



The log-rank statistic indicates a significant difference in the observed survival curves over time.

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Patient Survival Model

Risk factor	Impact on risk
Kidney or Pancreas failure	↑↑
BMI	↑ <20
Age	↑ with age
Private Insurance	↓
Recipient eGFR > 65	↓ vs. GFR < 65
Kidney donor age	↑
eGFR post kidney txp	↓ if > 30 or <90
Karnofsky Score at KTx	↑ if total assist
Pancreas donor BMI	↓ if BMI 25-27
Pancreas donor eGFR	↓ as eGFR ↑

Index of Concordance and 95% confidence interval: 73.2% (70.6, 75.8)

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Predicted Patient Outcomes

Covariate	Person 1, low risk	Person 2, medium risk	Person 3, high risk
Age at PTx	30	45	55
Insurance	Private	Private	Public or other
Recipient eGFR	65.1- 76.8	55.1-65	≤45
Recipient BMI	20.1-31	>31	≤20
Karnofsky at KTx	No limitations	No limitations	No limitations
Kidney donor age	35	45	60
Pancreas donor BMI	27.1-30	20.1-25	≤20
Pancreas donor eGFR	110	100	100
Recipient eGFR at discharge, after KTx	60-90	30-60	0-30
Kidney or pancreas failure during follow-up	Neither	Neither	Neither
Estimated 5-year survival (95% CI)	97.6 (96.5, 98.7)	90.5 (86.6, 94.6)	60.8 (47.3, 78.1)

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Summary

- Graft failure
  - Graft failure rates have declined over time for PAK
  - Kidney graft failure predicts pancreas graft failure
  - Pancreas graft failure predicts kidney graft failure.
  - Both effects were much stronger when the outcome was all-cause graft failure versus death-censored graft survival
- Kidney and pancreas graft failure were definitive predictors of patient death.
  - Magnitude of kidney failure's was greater
  - Pancreas failure alone was a highly significant predictor of patient death ($P<0.0001$)

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Summary, cont.

- PDRI was highly predictive of pancreas outcomes but not kidney or patient survival
- Cold ischemic time:
  - Marginally reduced hazard for <6 hours
  - No differences among cold times between 6-30 hours
- Young patients were at **significantly higher risk** of death-censored pancreas graft failure than older patients.
  - The trend diminished for all-cause graft failure

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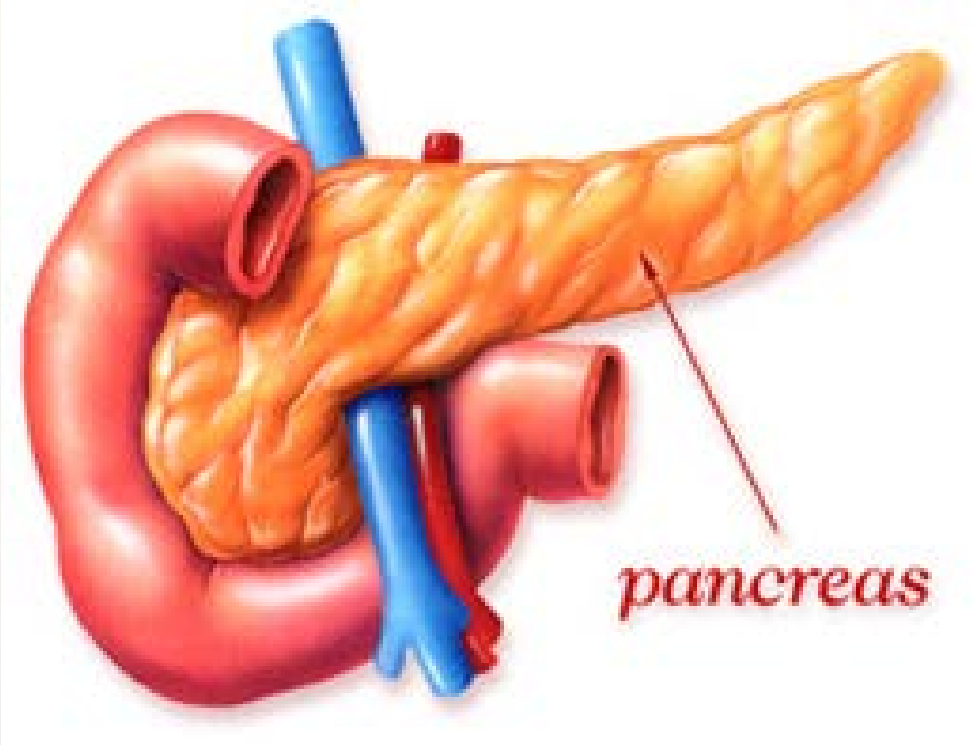
Questions?



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