

Survival after graft failure

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Overview

- Background
- Survival after transplant failure (UK)
- Defining a proxy group
- European analyses
- Future work

Background

- In 2009:
 - 23,284 prevalent renal transplant patients
 - 2.9% experienced graft failure (excluding death as cause of graft loss)
 - Evidence (mostly North American) that kidney transplant loss associated with significant mortality and morbidity
- Why is this important?
 - Growing transplant population
 - Young patients
 - Limited guidelines/ evidence for best practice
 - Some deaths may be preventable
 - Quality of life
 - Financial implications

Survival analyses

- UKRR and NHSBT data
- **Cases** = Patients starting dialysis after 1st transplant failure (>90 days function) 01/01/2000 - 31/12/2008
- **Controls** = Patients starting RRT on dialysis 01/01/2000 - 31/12/2008, and wait-listed for transplantation within 2 years
- Followed to death, or loss to follow up, or 31/12/2010
- Censored if transplanted
- Exclusions: <18 yrs, missing primary renal diagnosis
- Hazard ratios (case/control) for specific time periods calculated. Adjusted for age, gender, DM, ethnicity and modality

Final cohort

Controls

UK incident adult RRT patients (1st Jan 2000 - 31st Dec 2008) in UK (n= 46,793)

Pre-emptive
transplants (n=1,645)

Not listed (n=31,863)

Listed >2 years from
RRT start (n=1,543)

**Controls included in
analysis (n= 11,742)**

Cases

UK adult patients with failure of 1st transplant (1st Jan 2000 – 31st Dec 2008) (n=3,568)

Pre-emptive re-
transplants (n=93)

1st transplant
<90days duration
(n=416)

**Cases included in
analysis (n=3,059)**

Demographics

	Cases	Controls	P value
Number of subjects	3,059	11,742	
Age mean (SD)	48.2 (15.0)	47.4 (13.5)	0.003
Sex (% male)	60.9	61.4	n.s.
Ethnicity – White (%)	86.3	81.4	<0.0001
Ethnicity – Asian (%)	7.1	10.2	
Ethnicity – Black (%)	4.5	5.7	
Ethnicity – Other (%)	2.1	2.7	
Ethnicity – Missing N (%)	63 (2.1)	77 (0.7)	
Diabetes as PRD (%)	9.6	15.6	<0.0001
Missing PRD N (%)	34 (1.1)	160 (1.4)	
Dialysis modality (% HD)	77	58	<0.0001
Mean duration 1st transplant (yrs) (SD)	9.4 (6.5)	N/A	
Mean duration dialysis pre-transplant (yrs)(SD)	1.7 (2.1)	N/A	
Mean duration on dialysis (yrs) (SD)	2.3 (1.9)	2.2 (1.6)	n.s.

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Survival: UK

Hazard ratio (case/control)	Un-adjusted	+age	+gender	+DM and DM*age	+ ethnicity	+modality
0-90 days	25.0 (11.1-56.3)	23.9 (10.6-53.8)	23.9 (10.6-53.8)	23.1 (10.2-52.1)	23.4 (10.3-52.8)	17.0 (7.5-38.5)
90-365 days	6.5 (4.7-9.2)	6.3 (4.5-8.9)	6.3 (4.5-8.9)	6.5 (4.6-9.1)	6.3 (4.4-8.8)	5.9 (4.1-8.4)
1-2 years	4.0 (3.2-5.1)	4.1 (3.2-5.1)	4.1 (3.2-5.2)	4.3 (3.4-5.5)	4.2 (3.3-5.3)	3.9 (3.0-4.9)
2-3 years	2.5 (2.0-3.1)	2.8 (2.2-3.4)	2.8 (2.2-3.5)	3.2 (2.5-4.0)	3.0 (2.4-3.8)	3.1 (2.4-3.9)
3-5 years	1.4 (1.1-1.7)	1.7 (1.3-2.0)	1.7 (1.3-2.0)	1.8 (1.5-2.3)	1.8 (1.5-2.2)	1.8 (1.4-2.2)
>5 years	0.8 (0.6-1.2)	1 (0.7-1.5)	1 (0.7-1.5)	1.2 (0.8-1.7)	1.3 (0.8-1.7)	1.2 (0.9-1.8)

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0-90 days	25 .0 (11.1-56.3)	23.9 (10.6-53.8)	23.9 (10.6-53.8)	23.1 (10.2-52.1)	23.4 (10.3-52.8)	17.0 (7.5-38.5)
90-365 days	6.5 (4.7-9.2)	6.3 (4.5-8.9)	6.3 (4.5-8.9)	6.5 (4.6-9.1)	6.3 (4.4-8.8)	5.9 (4.1-8.4)
1-2 years	4.0 (3.2-5.1)	4.1 (3.2-5.1)	4.1 (3.2-5.2)	4.3 (3.4-5.5)	4.2 (3.3-5.3)	3.9 (3.0-4.9)
2-3 years	2.5 (2.0-3.1)	2.8 (2.2-3.4)	2.8 (2.2-3.5)	3.2 (2.5-4.0)	3.0 (2.4-3.8)	3.1 (2.4-3.9)
3-5 years	1.4 (1.1-1.7)	1.7 (1.3-2.0)	1.7 (1.3-2.0)	1.8 (1.5-2.3)	1.8 (1.5-2.2)	1.8 (1.4-2.2)
>5 years	0.8 (0.6-1.2)	1 (0.7-1.5)	1 (0.7-1.5)	1.2 (0.8-1.7)	1.3 (0.8-1.7)	1.2 (0.9-1.8)

Re wait-listing analysis

Of the 3,059 cases, 1,610 were listed for repeat transplantation within 2 yrs

Hazard ratio (re wait-listed cases/control)	Adjusted	P value
0-365 days	3.1 (1.3-7.3)	0.009
1-2 years	1.6 (1.0-2.6)	0.04
2-3 years	2.3 (1.6-3.2)	<0.0001
3-5 years	1.5 (1.1-2.1)	0.007
>5 years	0.72 (0.4-1.3)	0.3

Discussion

- As would be predicted the greatest risk of death is in the first few weeks following transplant failure but persists until at least 5 years post transplant failure
- Even if only patients listed for further transplantation (i.e. fitter cases) are considered, an excess mortality risk is seen
- Limitations: choice of control group, lack of comorbidity data, data capture issues

Proxy group Analyses

Background

- Evolved from plans to undertake a European study
- ERA-EDTA registry doesn't normally collect wait-listing data
- Is it possible (from the data available) to design a “proxy” cohort of patients fit for transplantation?
- Preliminary analyses using UK data
- Who would be likely to be fit for transplantation?
 - <50 years old
 - Non-diabetics

Cases vs. proxy controls (1)

- 01/01/2000-31/12/2008
- Cases = as before, limiting to patients <50 years, non-diabetic
- Controls = incident dialysis patients <50 years, non-diabetic
- HR (Case/control) calculated
- Adjusted for age, gender, ethnicity and modality at start

Cases vs. proxy controls (2)

Hazard ratio (case/ control)	Adjusted HR	P value
0-90 days	1.7 (1.3-2.3)	0.0002
90-365 days	1.5 (1.2-1.9)	<0.0001
2-5 years	1.0 (0.8-1.3)	0.9

**Why are the results
so different?**

Cases vs. proxy controls (3)

	Cases	Proxy controls	P value
Number of subjects	1474	8057	
Age at dialysis start mean	37.0	37.7	n.s
Sex (% male)	907 (61.5)	4,832 (60)	n.s
GN as PRD (%)	399 (27.1)	1689 (21.0)	<0.0001
Missing as PRD (%)	12 (0.8)	427 (5.3)	
Uncertain as PRD (%)	301(20.5)	1924 (23.9)	
Dialysis modality (% HD)	72.9	67.0	<0.0001

- UK wait-listing data used to split proxy group into true and proxy controls

Cases vs. proxy controls (4)

	Cases	True controls	Proxy controls	P values
Number of subjects	1474	5407	2681	
Age at dialysis start mean (SD)	37 (8.7)	37 (8.7)	39.2 (8.3)	
Sex (% male)	61.5	60.8	57.9	0.02
Ethnicity – White (%)	86.3	78.3	73.7	<0.0001
Ethnicity – Missing N (%)	8 (0.5)	47 (0.9)	374 (14.0)	
GN as PRD (%)	27.1	25.3	15.1	<0.0001
HTN as PRD (%)	3.9	6.8	7.1	
Pyelonephritis as PRD (%)	22.9	13.2	12.8	
Uncertain as PRD (%)	20.5	23.5	28.8	
Missing PRD N (%)	12 (0.8)	73 (1.4)	201 (7.5)	
Dialysis modality (% HD)	72.9	59.2	83.1	
% who died (censoring at transplant)	12.1	2.4	27.5	<0.0001
% who died (not censored)	13.2	4.0	27.8	<0.0001

KM survival

Survival function

True controls

Cases

Proxy controls

Days post dialysis start

Discussion

- Very hard to define a proxy group
- Higher proportion of missing data in non-listed proxy controls (previous UKRR work has shown missing data is associated with poorer outcomes)
- Accurate clinical reasoning – physicians do well at selecting patients suitable for transplants
- Local-level audit to generate some ideas

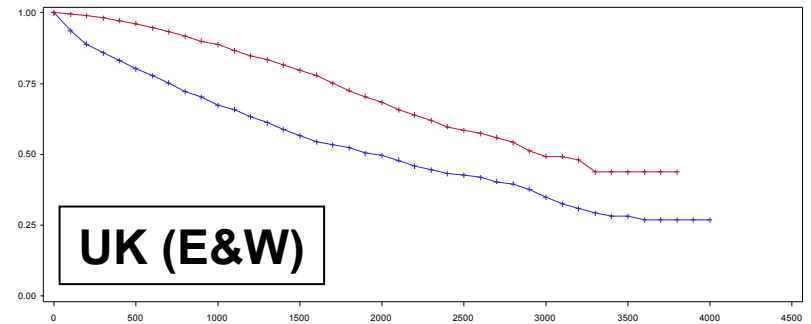
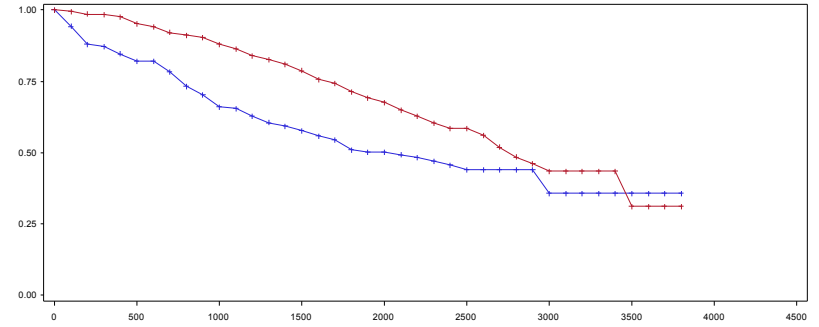
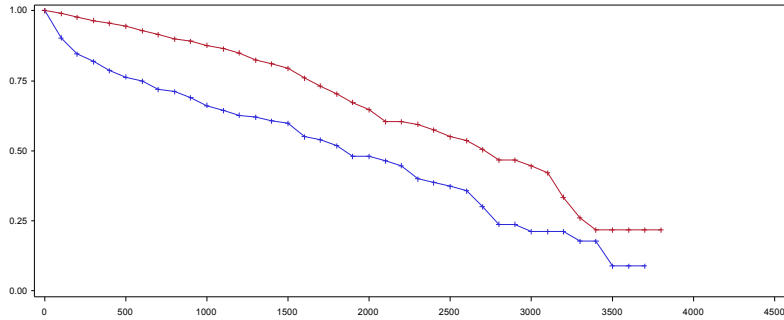
European Analyses

European analyses

- ERA-EDTA wait-listing data (1998-2005) for:
 - Norway
 - Netherlands
 - Austria
 - Scotland
- Group A
 - >18yrs old
 - Starting dialysis after failure of 1st transplant (>90days function)
 - 01/01/1998-31/12/2003
- Group B
 - Incident dialysis patients >18yrs commencing dialysis
 - Wait-listed pre or within 2 yrs of RRT start
- Censoring:
 - Transplantation/re-transplantation
 - Lost to follow-up
 - End of study 31/12/2008

KM survival (adjusted)

↑
Survival function



Cases (Group A)

Controls (Group B)

Days →

Discussion

- There appears to be significant variation in outcomes after graft failure between countries
 - Access to transplantation
 - Transplantation practices
 - Survival on dialysis
 - Prevalence of comorbidities (e.g. High DM rate in Austria)

Future work

Future work

- Questionnaire examining centre-level practices
 - Service provision and staffing
 - Service design
 - Research and audit
 - IT facilities
- Explore cause of death data and compare with MRIS death certificate information
- Funding for a case-control study

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