

Clinical Outcomes of People With Fabry Disease – ANZDATA Registry Study



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Fabry disease (FD) is an X-linked lysosomal storage disease caused by a deficiency in the enzyme, α -galactosidase A. FD has neurologic, cardiovascular, and kidney manifestations. Kidney dysfunction contributes significantly to mortality in people with FD. Analysis of the Fabry Registry showed that 57% of people with FD who died from cardiovascular causes had previously received kidney replacement therapy (KRT).¹ Recombinant α -galactosidase A can be used to replace endogenous α -galactosidase A and has been available since 2001.² To date, there has been limited information about the prognostic predictors and outcomes of people with FD on KRT, or about the effect of enzyme replacement therapy (ERT) in KRT populations. Furthermore, the absence of a control group (nontreated people with FD or transplant recipients without FD) makes the effect of ERT on posttransplantation clinical outcomes difficult to assess.^{3,4}

The Australian and New Zealand Dialysis and Transplant (ANZDATA) registry captures clinical outcomes information for people receiving KRT in Australia and New Zealand. The primary aim was to compare the characteristics and outcomes of those with FD on KRT compared to those without FD. Secondary analyses aimed to determine if people commencing KRT after the introduction of ERT (2001) had altered mortality risk.

RESULTS

Dialysis Population

Thirty-five people with FD and 79,400 people without FD were included in the dialysis cohort (Table S1,

Figure S1). In people with FD, 1-year, 3-year, and 5-year mortality rates were 9%, 26%, and 43%, respectively, whereas in people without FD, they were 11%, 28%, and 40%, respectively. The main cause of death for people with and without FD was cardiovascular disease. People with FD on dialysis had increased mortality risk compared to people without FD on dialysis in univariable (hazard ratio [HR], 1.78; 95% confidence interval [CI], 1.11–2.86) and multivariable analysis (adjusted HR, 2.22; 95% CI, 1.38–3.57) (Table 1). Any cigarette smoking, body mass index (BMI) < 18.5 kg/m², diabetes, KRT initiation before ERT availability, and later dialysis commencement date were associated with increased mortality risk. BMI > 25 kg/m² and non-white ethnicity were associated with reduced mortality risk. Time-stratified analyses confirmed these findings even after accounting for missing values (Table S2).

Transplant Population

Twenty people with FD and 26,511 people without FD were included in the transplant cohort (Table S3, Figure S1). Nineteen people with FD received both dialysis and kidney transplant. All of these people received dialysis before kidney transplantation. In people with FD, 1-year, 3-year, and 5-year mortality rates were 10%, 15% and 20%, respectively, whereas for people without FD, they were 6%, 10%, and 14%, respectively. Respective 1-year, 3-year, and 5-year graft failure rates were 10%, 10%, and 10% in people

Table 1. Unadjusted and adjusted hazard ratios and 95% confidence intervals for the association between Fabry disease and mortality for the dialysis cohort

Effect	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Disease status	$\chi^2_{(LRT)} = 0.24, df = 1, P = 0.62$		$\chi^2_{(LRT)} = 0.22, df = 1, P = 0.64$	
Fabry	1.78*	1.11-2.86	2.22 [†]	1.38-3.57
Non-Fabry	Reference	—	Reference	—
Sex	$\chi^2_{(LRT)} = 0.47, df = 1, P = 0.5$		NA	
Male	Reference	—	NA	NA
Female	1.00	0.98-1.02	NA	NA
Ethnicity	$\chi^2_{(LRT)} = 204, df = 1, P < 0.001$		NA	
White	Reference	—	NA	NA
Non-white	0.88 [‡]	0.87-0.90	NA	NA
Smoking status	$\chi^2_{(LRT)} = 989.01, df = 2, P < 0.001$		$\chi^2_{(LRT)} = 964.79, df = 2, P < 0.001$	
Never	Reference	—	Reference	—
Former	1.41 [‡]	1.38-1.44	1.37 [‡]	1.34-1.40
Current	1.27 [‡]	1.24-1.31	1.23 [‡]	1.19-1.26
BMI, kg/m ²	$\chi^2_{(LRT)} = 83.05, df = 3, P < 0.001$		$\chi^2_{(LRT)} = 32.78, df = 3, P < 0.001$	
<18.5	0.86 [‡]	0.81-0.90	1.09 [†]	1.03-1.15
18.5-24.9	Reference	—	Reference	—
25-29.9	1.05 [‡]	1.03-1.08	0.94 [‡]	0.92-0.96
>30	1.06 [‡]	1.04-1.09	0.83 [‡]	0.80-0.85
Diabetes	$\chi^2_{(LRT)} = 487, df = 1, P < 0.001$		$\chi^2_{(LRT)} = 3015.95, df = 1, P < 0.001$	
Absent	Reference	—	Reference	—
Present	1.82 [‡]	1.79-1.86	1.60 [‡]	1.57-1.64
Dialysis modality	$\chi^2_{(LRT)} = 61.1, df = 1, P < 0.001$		$\chi^2_{(LRT)} = 1.16, df = 1, P = 0.28$	
Hemodialysis	Reference	—	Reference	—
Peritoneal dialysis	0.97 [†]	0.95-0.99	0.98 [†]	0.95-1.00
Dialysis commencement date relative to ERT availability (2001)	$\chi^2_{(LRT)} = 109, df = 1, P < 0.001$		$\chi^2_{(LRT)} = 0.44, df = 1, P = 0.51$	
Pre-ERT	1.01	0.99-1.03	1.42 [‡]	1.38-3.57
Post-ERT	Reference	—	Reference	—
Dialysis vintage	$\chi^2_{(LRT)} = 29.64, df = 4, P < 0.001$		$\chi^2_{(LRT)} = 294.50, df = 3, P < 0.001$	
1991–1995	Reference	—	Reference	—
1996–2000	1.06 [†]	1.02-1.09	1.22 [‡]	1.17-1.26
2001–2005	1.11 [‡]	1.07-1.15	1.31 [‡]	1.27-1.36
2006–2010	1.03	1.00-1.07	1.20 [‡]	1.16-1.24
2011–2017	0.89 [‡]	0.86-0.92	NA	NA

BMI, body mass index; CI, confidence interval; ERT, enzyme replacement therapy; HR, hazard ratio; LRT, likelihood ratio test; NA, not applicable.

* <0.05 .

[†] <0.01 .

[‡] <0.001 .

with FD; and 11%, 14% and 17% in people without FD. The main cause of death for people with and without FD was cardiovascular disease (25% and 12%, respectively) (Table S3). The main cause of graft failure for people with and without FD was chronic allograft nephropathy (10% and 16%, respectively).

Kidney transplant recipients with FD had an increased risk of mortality compared to transplant recipients without FD in both unadjusted (HR, 2.32; 95% CI, 1.04-5.17) and adjusted analyses (adjusted HR, 2.59; 95% CI, 1.16-5.79) (Table 2). Any cigarette smoking, BMI > 25 kg/m², KRT initiation before ERT availability, and diabetes were associated with higher mortality. Female gender, BMI < 18.5 kg/m², pre-emptive transplantation, and living-donor kidney transplantation were associated with reduced mortality. Time-stratified

sensitivity analyses completed with available variables confirmed these findings even after accounting for missing values (Table S4). Competing risk analyses showed similar death-censored graft failure and increased graft failure-censored mortality risks in recipients with FD (Table S5).

DISCUSSION

This study is the first in-depth analysis of the characteristics and clinical outcomes of adults with FD receiving KRT in Australia and New Zealand. The mortality rates reported in this study are similar to previously reported values from the United States Renal Data System⁵ and lower than that reported by the

Table 2. Unadjusted and adjusted hazard ratios and 95% confidence intervals for the association between Fabry disease and mortality in the transplant cohort

Effect	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Disease status	$\chi^2_{(LRT)} = 0.30$, df = 1, $P = 0.58$		$\chi^2_{(LRT)} = 2.31$, df = 1, $P = 0.13$	
Fabry	2.32*	1.04-5.17	2.59*	1.16-5.79
Non-Fabry	Reference	—	Reference	—
Sex	$\chi^2_{(LRT)} = 0.03$, df = 1, $P = 0.86$		NA	
Male	Reference	—	NA	NA
Female	0.86†	0.80-0.92	NA	NA
Ethnicity	$\chi^2_{(LRT)} = 11.10$, df = 1, $P < 0.001$		NA	
White	Reference	—	NA	NA
Non-white	0.92	0.84-1.00	NA	NA
Smoking status	$\chi^2_{(LRT)} = 287.67$, df = 2, $P < 0.001$		$\chi^2_{(LRT)} = 276.51$, df = 2, $P < 0.001$	
Never	Reference	—	Reference	—
Former	1.67†	1.56-1.79	1.47†	1.37-1.58
Current	1.87†	1.70-2.05	1.62†	1.47-1.78
BMI, kg/m ²	$\chi^2_{(LRT)} = 190.66$, df = 3, $P < 0.001$		$\chi^2_{(LRT)} = 155.90$, df = 3, $P < 0.001$	
<18.5	0.58†	0.50-0.68	0.75†	0.65-0.88
18.5-24.9	Reference	—	Reference	—
25-29.9	1.27†	1.18-1.36	1.25†	1.16-1.35
>30	1.51†	1.38-1.65	1.40†	1.28-1.53
Diabetes	$\chi^2_{(LRT)} = 3.15$, df = 1, $P = 0.08$		$\chi^2_{(LRT)} = 356.77$, df = 1, $P < 0.001$	
Absent	Reference	—	Reference	—
Present	2.30†	2.14-2.48	2.04†	1.89-2.20
Dialysis modality	$\chi^2_{(LRT)} = 208.72$, df = 2, $P < 0.001$		$\chi^2_{(LRT)} = 58.58$, df = 2, $P < 0.001$	
Hemodialysis	Reference	—	Reference	—
Peritoneal dialysis	0.96	0.90-1.03	1.00	0.93-1.08
Pre-emptive transplantation	0.41†	0.36-0.47	0.59†	0.51-0.68
Dialysis commencement date relative to ERT availability (2001)	$\chi^2_{(LRT)} = 5.99$, df = 1, $P = 0.01$		$\chi^2_{(LRT)} = 76.36$, df = 1, $P < 0.001$	
Pre-ERT	1.44†	1.34-1.54	1.39†	1.23-1.56
Post-ERT	Reference	—	Reference	—
Donor source	$\chi^2_{(LRT)} = 1.37$, df = 1, $P = 0.24$		$\chi^2_{(LRT)} = 169.66$, df = 1, $P < 0.001$	
Deceased	Reference	—	Reference	—
Live donor	0.49†	0.45-0.52	0.67†	0.61-0.72
Transplant era	$\chi^2_{(LRT)} = 29.64$, df = 4, $P < 0.001$		$\chi^2_{(LRT)} = 12.95$, df = 4, $P = 0.01$	
1991–1995	Reference	—	Reference	—
1996–2000	0.94	0.86-1.03	1.07	0.97-1.19
2001–2005	0.82†	0.75-0.91	1.15*	1.02-1.30
2006–2010	0.79†	0.71-0.89	1.10	0.94-1.29
2011–2017	0.74†	0.65-0.85	0.96	0.80-1.16

BMI, body mass index; CI, confidence interval; ERT, enzyme replacement therapy; HR, hazard ratio; LRT, likelihood ratio test; NA, not applicable.

* <0.05 .

† <0.001 .

European Renal Association–European Dialysis and Transplant Association (Table S6).⁶

KRT commencement in the post-ERT era was associated with reduced mortality in people with FD on dialysis. This could be attributed to reduced progression of extrarenal disease. In an open-label, nonrandomized study of nine people on dialysis, ERT was associated with reduced gastrointestinal pain and slope of left ventricular mass increase.⁷ This result may have been confounded by dialysis vintage. However, in this study, dialysis initiation date was not associated with incremental improvements in mortality risk.

In transplant recipients, FD was associated with increased mortality HR in multivariable and competing

risk analyses. This aligns with analysis of kidney-only transplant recipients from the Organ Procurement Transplant Network (USA) (Table S6).⁸ Similar to those on dialysis without FD, the major cause of death among people with FD on dialysis was cardiovascular disease, suggesting that the excess mortality risk was likely secondary to FD disease progression in non-kidney tissues.⁹

In multivariable analysis, KRT commencement post-ERT era was associated with superior posttransplantation mortality rates, suggesting a beneficial effect of ERT therapy. This aligns with the findings from observational studies of transplant recipients, with FD demonstrating similar mortality rates compared to non-FD

transplant recipients^{S1} and improved cardiac indices compared to untreated people after ERT.^{4,S2} It is possible that the observed mortality benefit of commencing KRT in the post-ERT era may have been confounded by transplantation era. However, each transplantation era after 2001 was not associated with improved mortality rates.

The shortcomings of this study involved the use of observational data, small FD sample due to disease rarity, and time-dependent classification of ERT exposure. The use of retrospective observational data exposed this study to confounding by unmeasured factors and measurement bias. This is particularly applicable to disease classifications as primary kidney disease classifications in ANZDATA are based on clinician classification and are not always biopsy or genetically proven. Furthermore, FD is also underdiagnosed in KRT populations with targeted screening programs usually finding new and confirmed FD in up to 1:100 people with kidney failure.^{S3-4}

The use of KRT commencement relative to ERT availability as a surrogate indicator of ERT exposure was also a flaw of this analysis. People who commenced KRT pre-ERT later gained access to ERT and vice versa. For example, Lidove *et al.*² found that only 50% of people with FD enrolled in international registries received ERT as of 2006.^{S5} In the Fabry Outcomes Survey, only 66% of kidney transplant recipients received ERT.⁴ Further studies investigating people with FD on KRT with documented ERT exposure status are required to determine the efficacy of ERT in this subpopulation.

Australian and New Zealand people with FD receiving dialysis had increased mortality compared to those without FD. Although post-transplantation mortality in those with FD was higher compared to those without FD, people with FD should still be considered for kidney transplantation as their mortality rate posttransplantation was superior to those on dialysis, and FD was not observed to recur in kidney grafts. KRT commencement post ERT availability was associated with superior mortality rate in people on KRT; however, this result may have been confounded by KRT initiation era and small sample size.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Supplementary Methods

Figure S1. Flow chart demonstrating stratification of patient cohorts.

Table S1. Socio-demographic characteristics and medical conditions of the dialysis cohort.

Table S2. Time stratified analyses for hazard ratios and 95% confidence intervals for the association between Fabry disease and mortality for the dialysis cohort.

Table S3. Socio-demographic characteristics and medical conditions of the transplant cohort.

Table S4. Time stratified analyses for hazard ratios and 95% confidence intervals for the association between Fabry disease and mortality for the transplant cohort.

Table S5. Competing risk analysis — adjusted subdistribution hazard ratios and 95% confidence intervals for death-censored graft failure and graft failure-censored mortality.

Table S6. Comparison to published clinical outcomes in other registry-based FD populations.

Table S7. Modified STROBE statement.

Supplementary References

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