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Original Article

ORIGINAL ARTICLE

A registry-based retrospective study comparing pre-dialysis care and early outcomes in native vs transplant kidney failure

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ABSTRACT

Background. Starting dialysis is associated with morbidity and mortality. Outcomes for people with failed transplants can be poorer than for people with native kidney failure. We aimed to determine whether dialysis modality, place of initiation and mortality outcomes differed in the first 90 days between people starting dialysis for transplant and native kidney failure.

Methods. Retrospective cohort using linked UK Renal Registry data and Hospital Episode Statistics. Modality, place of initiation and outcomes compared with Day 90 for 16 417 adults starting dialysis in England between January 2018 and December 2019.

Results. Relative to those with native kidney failure (90.6%), those with transplant failure (9.4%) were younger (median 55.2 vs 66.3 years) and commenced more in-centre haemodialysis [86.8% vs 82.2%, adjusted odds ratio (OR) 1.72, 95% confidence interval (CI) 1.47–2.01; $P < .0001$]. Compared with individuals reported to have native chronic kidney disease, and accounting for age, sex, diabetes and ethnicity, those with transplant failure had increased odds of starting dialysis in hospital (adjusted OR 2.26, 95% CI 1.84–2.76; $P < .0001$), at higher estimated glomerular filtration rates (eGFRs) (8.9 vs 7.9 mL/min/1.73 m^2; $P = .0001$), and death [adjusted OR 1.95, 95% CI 1.31–2.90; $P = .001$).

Discussion. UK patients starting dialysis for transplant failure do so at higher eGFRs than those receiving specialist chronic kidney disease care. Those with transplant failure appear disproportionately likely to start as inpatients, receive haemodialysis or die within 90 days. These findings are likely to reflect differences between both patient groups and care pathways. Deeper understanding may inform improvements in care.

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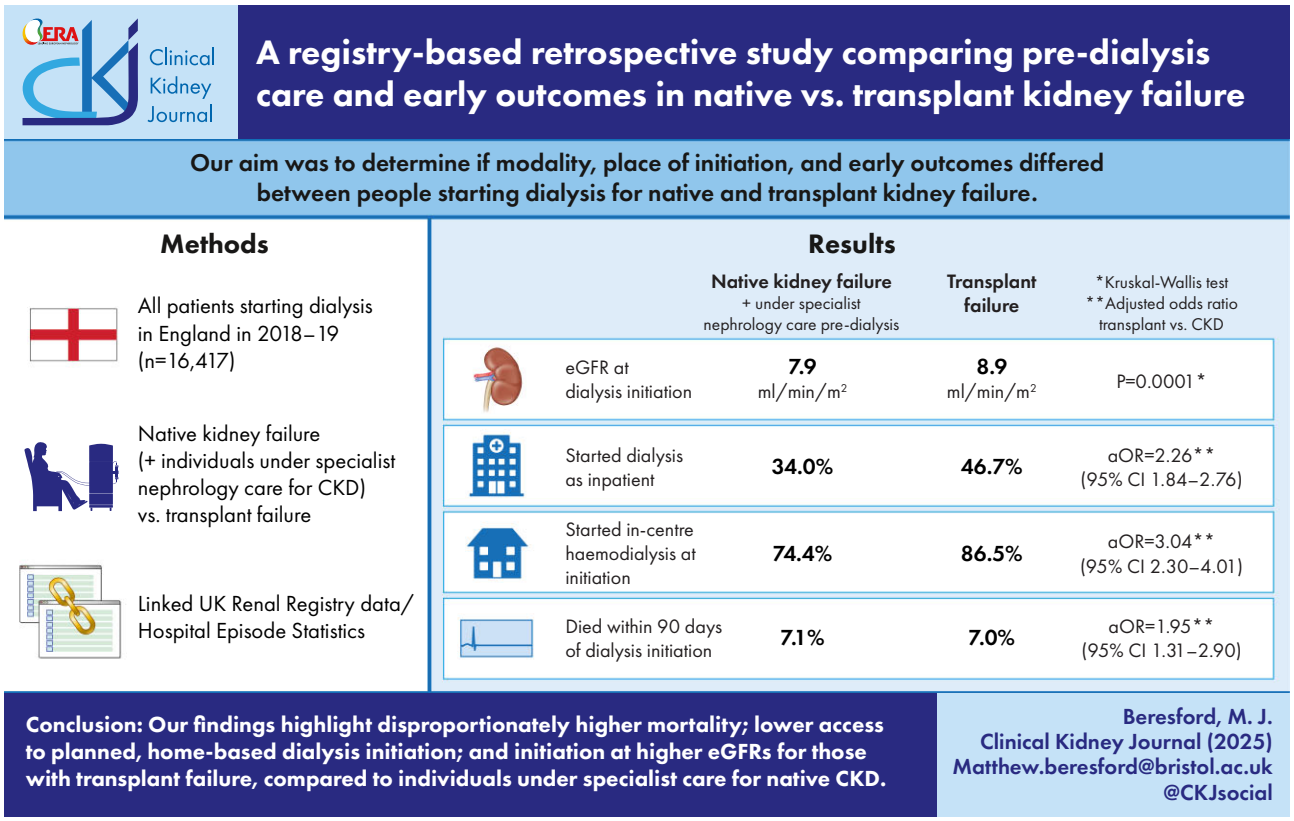
GRAPHICAL ABSTRACT



Keywords: dialysis, chronic renal failure, kidney transplantation, haemodialysis, AKI

KEY LEARNING POINTS

What was known:

- Initiation of dialysis for native or transplant kidney failure is associated with high early mortality and morbidity. Early mortality may reflect inadequate pre-dialysis nephrology care.
- Observational studies have shown individuals with transplant failure may initiate dialysis less optimally, with lower estimated glomerular filtration rates (eGFRs), and possibly experience higher mortality than individuals with native kidney failure.

This study adds:

- Patients in England starting dialysis after transplant failure had higher eGFRs and lower access to planned, home-based dialysis initiation compared with individuals with native chronic kidney disease under specialist nephrology care.
- After considering age, sex, ethnicity and diagnosed diabetes, early mortality after dialysis initiation was higher for individuals with transplant failure.

Potential impact:

- Our findings cannot fully account for baseline differences between populations but highlight a need for further research if we are to optimize systems treating those who experience transplant failure.
- Given the uncertainty around optimal management, future work should explore targeted interventions and changes to health service structures to improve outcomes.

INTRODUCTION

Dialysis initiation is associated with high early mortality and morbidity amongst individuals with native or transplant kidney failure [1, 2]. Early mortality may reflect inadequate pre-dialysis nephrology care.

Starting dialysis with planned access is associated with lower mortality [3, 4]. Some studies have suggested higher mortality and poorer anaemia management in individuals with transplant failure, compared with native kidney failure [5, 6], although there is limited evidence to support differences in robustly matched populations [7]. Several studies have shown individuals with transplant failure tend to start dialysis at similar or lower estimated glomerular filtration rates (eGFRs) [8–10].

People with native and transplant kidney failure are likely to differ in numerous ways. Factors such as age, primary kidney disease, duration of kidney failure, immunosuppression and residual allograft function may modify associations between dialysis initiation and outcomes [11]. Care pathways and health behaviours may also have impact [8]. UK practice patterns relating to the care of individuals with failing transplants are highly variable, reflecting a lack of high-quality evidence to guide clinicians [12]. In some centres, specialist clinics have emerged to prepare individuals with failing transplants for their next treatment. The impact of specialist transplant failure clinics on clinical outcomes has yet to be evaluated and questions remain regarding how to optimally manage patients [13–15].

Our aim was to determine whether modality, place of initiation and early outcomes differed between people starting dialysis for native and transplant kidney failure. We undertook a retrospective observational study using linked UK Renal Registry (UKRR) and Hospital Episode Statistics (HES) data, examining individuals with native and transplant kidney failure who started dialysis over a 2-year period. We focussed on individuals with transplant failure and individuals reported by nephrology centres to have native chronic kidney disease (CKD), given that both groups were receiving specialist kidney care before starting dialysis. Improved understanding of the circumstances of, and outcomes after, dialysis initiation may inform future research and service redesign.

MATERIALS AND METHODS

Study population

We included patients aged ≥18 years who were reported to the UKRR as having initiated haemodialysis, haemodiafiltration, haemofiltration or peritoneal dialysis (hereafter, referred to as 'dialysis') in any of the 51 English kidney centres between 1 January 2018 and 31 December 2019. Reflecting our intention to capture the full picture of dialysis initiation during this time, no exclusions were made based on outcomes following initiation, including dialysis discontinuation, recovery of native or transplant kidney function, death, or (re)transplantation. Individuals were included whether or not kidney replacement therapy was deemed permanent by their treating unit [16]. Individuals starting dialysis within 30 days of transplantation, likely comprising those with delayed graft function or primary non-function, were excluded.

We classified individuals as having:

(i) Native kidney failure if they commenced dialysis with no prior record of a kidney transplant. This included those initiating dialysis for the first time, and those restarting dialysis after one or more spells of dialysis of any type/duration.

(ii) Transplant failure if they started dialysis with timeline code indicating a kidney transplant. This group included individuals with early and late graft failure (although individuals starting dialysis within 30 days of transplantation were excluded, see above).

We used the UKRR CKD dataset to identify those with native CKD who were 'known to nephrology services' before dialysis initiation. Fourteen centres had been reliably submitting data on patients with CKD to the UKRR since July 2017, 6 months before the start of our inclusion period. A restricted cohort was formed of all patients starting dialysis in these 14 centres. Within this restricted cohort, those who started dialysis with native kidney failure were categorized as being 'known' or 'unknown to nephrology services before dialysis initiation'. Transplant centres were over-represented in the restricted cohort (n = 8/14) compared with the overall cohort (n = 19/51).

Outcomes of interest

We extracted data on eGFR at dialysis initiation; initial dialysis modality; presence of surgical access; place of dialysis initiation; and outcome 90 days after dialysis initiation. Outcomes at 90 days are widely reported in registry studies, reflecting international definitions of the transition between acute and chronic kidney disease.

Chronic Kidney Disease Epidemiology Collaboration eGFR was calculated for individuals using the most recent serum creatinine before dialysis initiation. We only present eGFR data where the latest available measurement was within 30 days of the dialysis start date. In the main analyses, we removed eGFR data points >20 mL/min/1.73 m^2 to mitigate against the risk of including falsely elevated eGFR recordings. Such readings potentially reflect blood samples that postdated dialysis initiation. A sensitivity analysis (Supplementary data, Fig. S1) is provided that includes eGFR values >20 mL/min/1.73 m^2. For reference, of those with creatinine data in the overall cohort, 82 (6.2%) with native kidney failure and 54 (10.3%) with transplant failure had an eGFR >20 mL/min/1.73 m^2 on the last measurement before the reported date of dialysis initiation.

Access type in individuals that started ICHD was derived from sessional haemodialysis data and enriched with data from the annual dialysis access survey performed by the UKRR for people starting dialysis after native kidney failure. Access was classified as surgical (arteriovenous fistula or arteriovenous graft) or non-surgical (tunnelled or non-tunnelled central venous catheter).

Outcomes 90 days after initiation included dialysis modality, death, loss to follow-up and 'alive, not on dialysis'. This last category included all individuals who had discontinued dialysis before Day 90 and were alive and not receiving dialysis on Day 90 [17]. UKRR data did not allow us to differentiate individuals who had withdrawn from dialysis without recovery and were alive from those who had recovered native or transplant kidney function, in the first 90 days after dialysis initiation. Dialysis modality at initiation was categorized as [home therapy—including peritoneal dialysis and home haemodialysis or in-centre haemodialysis (ICHD)]. The odds of ICHD vs home therapy were compared between groups as a marker of planned dialysis initiation because the proportion receiving home treatments is audited as part of care quality assurance [18].

HES data were used to identify the place of dialysis initiation. An inpatient initiation was defined as one in which the patient spent three or more nights in hospital, including the date of

Table 1: Clinicodemographic characteristics of overall and restricted cohorts, grouped into native kidney failure and transplant failure.

	Main cohort				Restricted cohort		
	Total cohort	Native kidney failure	Transplant failure	*P*-value	Total cohort	Native kidney failure	Transplant failure
N	16 417	14 880	1537		5359	4841	518
Age [median (IQR)]	65.2 (52.6–74.8)	66.3 (53.9–75.6)	55.2 (43.2–65.3)	<.0001	65.3 (53.1–74.9)	66.4 (54.2–75.6)	55.6 (43.9–65.8)
Sex (% male)	63.9	64.4	58.8	<.0001	64.1	64.5	60.2
Ethnicity[a] (%)				<.0001			
Asian	13.3	13.2	14.5		12.3	12.1	13.5
Black	7.7	7.3	10.9		6.1	5.8	8.7
Other	3.5	3.5	3.1		3.3	3.3	3.1
White	75.5	75.9	71.6		78.4	78.8	74.7
Missing	0.6	0.6	0.0		0.5	0.6	0.0
Primary kidney disease[a] (%)				<.0001			
Diabetes	29.3	31.4	13.9		27.9	30.2	13.0
Glomerulonephritis	13.6	12.0	25.2		14.2	12.4	25.2
Hypertension	7.3	7.4	6.7		5.9	5.9	5.7
Other	18.3	18.2	18.6		18.4	17.9	22.1
Polycystic kidney disease	5.8	5.5	8.4		6.4	6.2	7.9
Pyelonephritis	5.7	4.8	11.6		5.7	5.0	10.4
Renovascular disease	4.9	5.4	1.3		6.2	6.9	1.8
Uncertain	15.2	15.3	14.3		15.3	15.5	14.0
Missing	23.7	26.1	1.1		30.1	33.1	1.9
Diabetic (%)[b]	46.8	47.6	39.0	<.0001	46.3	47.3	37.1

Percentages represent column percentages. *P*-values based on Kruskal–Wallis (continuous variables) and Chi-squared (categorical variables) tests.
[a]Percentages exclude missing patients.
[b]as recorded in HES data at any time prior to dialysis initiation.

initiation; or if the admission was coded as 'admitted patient care' and the patient died in hospital within 2 days from admission. Individuals were classified as having started dialysis on critical care if their HES record indicated initiation during, or within 3 days of discharge from a critical care unit stay.

HES data were used to identify the date that an individual first presented to nephrology services. Treatment specialty codes (treatspef or mainspef) were used to discern inpatient or outpatient encounters under a consultant nephrologist (code 361). Individuals with kidney transplants were assumed to be under regular nephrology follow-up.

We used the Master Patient Index (MPI) dataset [19] to identify patients with a rising serum creatinine who triggered a stage 1–3 acute kidney injury (AKI) alert as per the National Health Service (NHS)-approved algorithm [19] used by all English laboratories. We stratified individuals in the restricted cohort according to whether they had an AKI-alert in the year before dialysis initiation, as the presence of AKI may reduce an individual's opportunity to transition to dialysis in a planned manner. For those with transplant failure, only AKI alerts occurring after the date of the most recent transplant were counted.

Statistical analysis

Percentages were calculated for categorical variables, medians and interquartile ranges (IQRs) for continuous variables. Non-normally distributed continuous variables were compared using Kruskal–Wallis tests, and categorical variables using Chi-squared tests. To calculate odds ratios for outcomes of interest, we undertook multivariable logistic regression adjusted for age (as a continuous variable), sex, ethnicity and presence/absence of diabetes (as coded in HES). Ethnicity was classified as White, Black, Asian, Mixed/Other or Missing, as per the UK Office of National Statistics [20]. HES diagnosis codes were used to identify individuals with diabetes.

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) within the UKRR. Approval to conduct this work using the UKRR's audit and research permissions was granted by the UKRR's Research Methods Study Group. The UKRR has Human Research Authority (HRA) Confidentiality Advisory Group section 251 approvals to perform both audit and research analyses, as well as HRA Research Ethics Committee approval of its research database and the use of linked HES data. Data were analysed and reported in line with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidance and a checklist is provided as Supplementary data, File S1.

RESULTS

Clinicodemographic characteristics

After excluding 133 individuals who commenced dialysis within 30 days of transplantation, a total of 16 417 adults started dialysis in England between 1 January 2018 and 31 December 2019, comprising 14 880 (90.6%) individuals with native kidney failure and 1537 (9.4%) with transplant failure (Table 1). A total of 5359 individuals (32.6% of the total cohort) initiated dialysis in the 14-centre 'restricted cohort'. Clinicodemographic characteristics were similar in the overall and restricted cohorts (Table 1). Those with native kidney failure were older (median age 66.3 years vs 55.2 years, $P < .0001$), and more likely to be male (64.4% vs 58.8%, $P < .0001$), diabetic (47.6% vs 39.0% $P < .0001$) and of White

Table 2: Dialysis initiation and Day 90 outcomes for individuals with native kidney failure and transplant failure.

	Total	Native kidney failure	Transplant failure	P-value[a]	Adjusted OR (95% CI) transplant/native[a]
N	16 417	14 880	1537		
Dialysis at Day 0					
ICHD at initiation (%)	82.6	82.2	86.8	<.0001	1.72 (1.47–2.01)
KRT At Day 90					
ICHD (%)	58.6	57.2	72.2	<.0001	2.26 (1.98–2.58)
Home therapy (%)	17.1	17.4	14.1		
Transplanted (%)	1.1	1.1	1.2		
Alive, not on dialysis (%)	14.3	15.2	5.7		
Died (%)	9.0	9.2	6.8	.16	1.17 (0.94–1.45)
Place of KRT initiation					
Inpatient (%)	50.0	50.6	44.3	.007	0.86 (0.77–0.96)
Of which, critical care (%)	19.5	20.1	13.7	<.0001	0.55 (0.44–0.69)

Percentages represent column percentages.
[a]ORs and *P*-values derived from logistic regression model adjusted for age, sex, diabetes and ethnicity.

ethnicity (75.9% vs 71.6%, $P < .0001$) compared with those with transplant failure. The distribution of primary kidney disease differed between native kidney and transplant failure ($P < .0001$). Diabetes mellitus was the most common diagnosis in native kidney failure (31.4%) and glomerulonephritis in transplant failure (25.2%).

Comparing dialysis initiation in native and transplant kidney failure in the main cohort

A total of 8203 individuals (50.0% of overall cohort) started dialysis during an inpatient stay, and 19.5% of these ($n = 1601$) started dialysis in critical care (Table 2). Inpatient initiation was more common in native than transplant kidney failure [50.6 vs 44.3%; adjusted odds ratio (OR) 0.86, 95% confidence interval (CI) 0.77–0.96; $P = .007$], as was initiation in critical care (20.1% vs 13.7%; adjusted OR 0.55, 95% CI 0.44–0.69; $P < .0001$).

At initiation, 2857 individuals (17.4% of overall cohort) received home dialysis, the remainder receiving ICHD. In the transplant failure group, the adjusted odds of receiving ICHD at initiation were nearly double those in the native kidney failure group (OR 1.72, 95% CI 1.47–2.01; $P < .0001$) (Table 2).

On Day 90, 2801 individuals (17.1%) were receiving a home therapy, 1470 (9.0%) had died, 2344 (14.3%) were alive but no longer receiving dialysis and 176 (1.1%) had been (re)transplanted (Table 2). Again, in the transplant failure group, the adjusted odds of ICHD at Day 90 were twice those in the native kidney failure group (OR 2.26, 95% CI 1.98–2.58, $P < .0001$). The proportion of individuals dying before Day 90 was lower in transplant than native kidney failure (6.8 vs 9.2%), but there was no evidence to support a mortality difference after adjusting for age, sex, ethnicity and diabetic status (adjusted OR 1.17, 95% CI 0.94–1.45; $P = .16$). Data for eGFR at dialysis initiation were only available for 10.3% so are not provided for the main cohort.

Comparing subgroups of the restricted cohort

The restricted cohort of 5359 individuals included 2999 (56.0%) known to nephrology services with native CKD before initiation, 1283 (23.9%) who started dialysis after an AKI alert but without known native CKD, 518 (9.7%) who started dialysis after transplant failure and 559 (10.4%) individuals who started dialysis without being reported to the UKRR before initiation (Fig. 1). eGFR data were available for 37.9% of individuals in the restricted cohort. The median eGFR at dialysis initiation for the restricted cohort was 8.1 mL/min/1.73 m2 (IQR 6.4–10.5).

Amongst those known to nephrology services with native CKD before starting dialysis, 1728 (57.6%) also had an AKI alert in the year before dialysis initiation. For those with transplant failure, the comparable figure was 325 (62.7%). Some 1842 individuals starting dialysis for native kidney failure were not reported as being under nephrology care for native CKD prior to initiation. Of these, 1586 (86.1%) had an inpatient or outpatient nephrology encounter at some point prior to dialysis, with 28.5% having their first encounter more than one year before dialysis initiation (Fig. 2).

Comparing individuals reported by nephrology services as having native CKD before dialysis to those with transplant failure

In the restricted cohort, 98.2% ($n = 2945$) of individuals with native CKD had been seen in renal outpatients before dialysis initiation. Most individuals (87.4%) with native CKD had their first inpatient or outpatient encounter more than 1 year before dialysis, with only 3% being seen for the first time in the 3 months prior to initiation.

The median eGFR at initiation was higher, with a broader distribution, in transplant failure compared with native CKD: median 8.9 mL/min/1.73 m^2 (IQR 7.0–11.9) vs 7.9 mL/min/1.73 m^2 (IQR 6.4–10.1), $P < .0001$ (Table 3, Fig. 3).

A quarter (25.6%) of individuals with native CKD started dialysis on a home therapy, compared with 13.5% of those with transplant failure. The odds for receiving ICHD (vs a home therapy) at dialysis initiation were higher in transplant failure (OR 3.04, 95% CI 2.30–4.01; $P < .0001$). In the absence of AKI alerts, individuals with transplant failure had nearly four times the odds of initiating dialysis as an inpatient (OR 4.08, 95% CI 2.88–5.77; $P < .0001$): the difference remained, but was attenuated, in individuals with AKI alerts (OR 1.59, 95% CI 1.23–2.05; $P = .0004$). For ICHD starters with data for initial dialysis access, surgical access was recorded in 47.8% of those with native CKD and 49.5% of those with transplant failure. However, many individuals were missing data for initial dialysis access, especially in the cohort with transplant failure (7.3% missing for native CKD, 38.5% for transplant failure) who were not covered by the dialysis access survey.

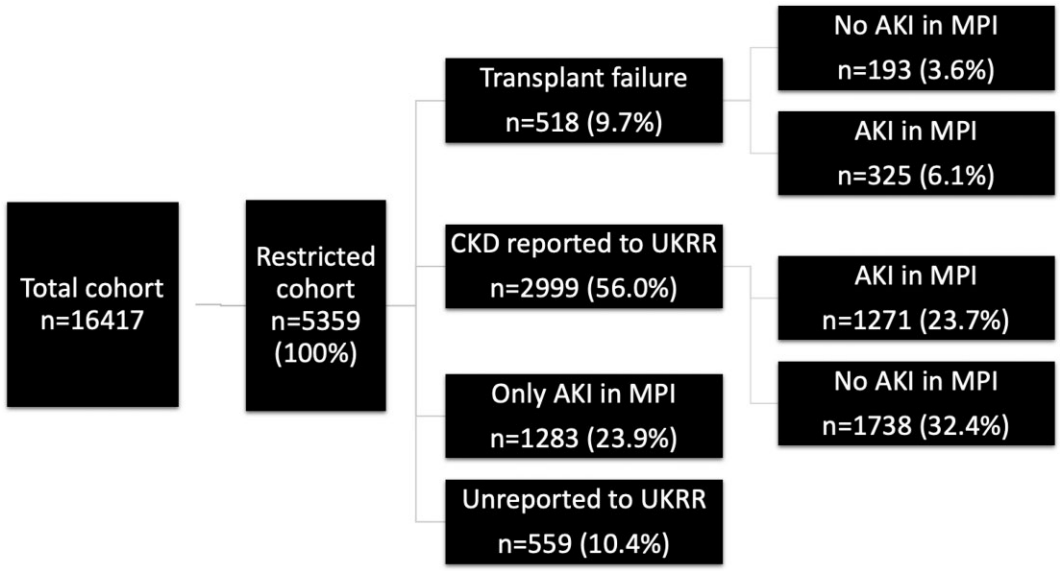


Figure 1: Flowchart depicting the composition of the 'restricted' cohort of individuals initiating dialysis who belonged to renal centres ($n = 16$) submitting historical CKD data to the UKRR.

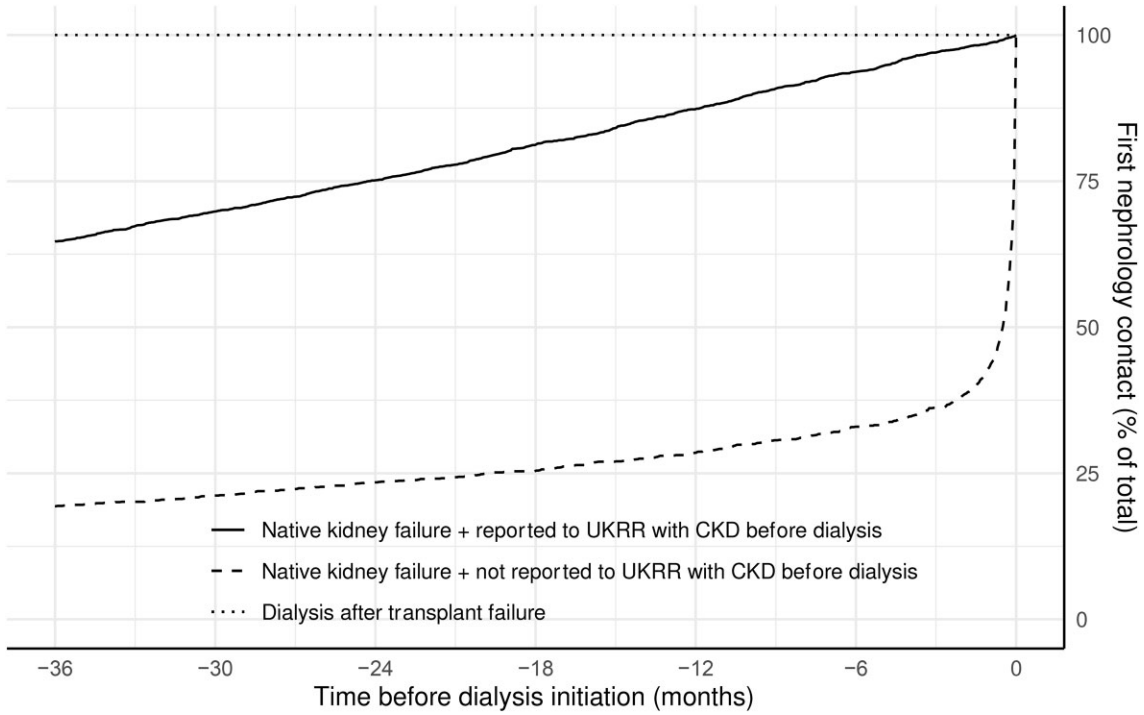


Figure 2: Cumulative frequency plot showing the timing of the first nephrology encounter (inpatient or outpatient) relative to dialysis initiation. Individuals shown belong to restricted cohort and are grouped into those with a prior transplant, those with native kidney failure reported to the UKRR with CKD prior to dialysis initiation and all others. Dotted line for the transplant cohort is indicative (as transplant recipients were known to nephrology prior to transplantation by definition). Grey shaded box represents 3 months prior to initiation, which is defined by the UKRR as late presentation.

Ninety days after dialysis initiation, 36 individuals (7.0%) in the transplant failure cohort ($n = 518$) and 214 individuals (7.1%) with native CKD ($n = 2999$) had died. In the adjusted analysis, the odds of death were higher in transplant failure (OR 1.95, 95% CI 1.31–2.90; $P = .0009$). This increased risk continued to reach conventional thresholds for statistical significance amongst those with AKI alerts (OR 1.84, 95% CI 1.17–2.88; $P = .008$), but not for those without AKI alerts (OR 1.84, 95% CI 0.78–4.35; $P = .16$). Most (92.4%) individuals who survived 90 days remained on dialysis. At Day 90, rates of dialysis discontinuation were 6.8% amongst those with transplant failure and 5.0% in native CKD. Rates of transplantation were 0.8% and 2.0%, respectively. In transplant

Table 3: Dialysis initiation and Day 90 outcomes for in the restricted cohort, comparing individuals reported to have CKD prior to dialysis initiation and individuals with transplant failure.

	Overall				No AKI alerts (in the year before dialysis start)				≥1 AKI alerts (in the year before dialysis start)			
	Native CKD	Transplant failure	Adjusted OR (95% CI), transplant vs CKD	*P*-value	Native CKD	Transplant failure	Adjusted OR (95% CI), transplant vs CKD	*P*-value	Native CKD	Transplant failure	Adjusted OR (95% CI), transplant vs CKD	*P*-value
N	2999	518			1271	193			1728	325		
eGFR pre-start[a]												
Median (mL/min/1.73 m^2)	7.9	8.9		<.0001[a]	7.9	9.5		.0006[a]	8.0	8.7		.012[a]
(IQR)	(6.4–10.1)	(7.0–11.9)			(6.4–9.6)	(7.1–12.2)			(6.4–10.6)	(6.9–11.8)		
Missing (%)	64.3	49.6			63.7	53.9			64.7	47.1		
Dialysis at Day 0												
ICHD at initiation (%)	74.4	86.5	3.04 (2.30–4.01)	<.0001[b]	68.5	82.9	2.99 (1.97–4.53)	<.0001[b]	78.8	88.6	3.00 (2.05–4.38)	<.0001[b]
ICHD starters using surgical access at Day 0 (%)	47.8	49.5			64.5	55.4			36.7	46.1		
ICHD starters missing access data (%)	7.3	38.5			5.4	37.7			8.5	39.0		
KRT At Day 90												
ICHD (%)	61.3	71.4	2.09 (1.65–2.65)	<.0001[b]	60.0	72.0	2.21 (1.53–3.20)	<.0001[b]	62.3	71.1	1.99 (1.46–2.71)	<.0001[b]
Home therapy (%)	24.5	14.1			30.5	18.1			20.2	11.7		
Transplanted (%)	2.0	0.8			2.0	0.5			2.0	0.9		
Alive, not on dialysis (%)	5.0	6.8			3.4	5.7			6.2	7.4		
Died (%)	7.1	7.0	1.95 (1.31–2.90)	.0009[b]	4.2	3.6	1.84 (0.78–4.35)	.16[b]	9.3	8.9	1.84 (1.17–2.88)	.008[b]
Place of KRT initiation												
Inpatient (%)	34.0	46.7	2.26 (1.84–2.76)	<.0001[b]	19.6	44.6	4.08 (2.88–5.77)	<.0001[b]	44.7	48.0	1.59 (1.23–2.05)	.0004[b]
Of which, critical care (%)	16.2	13.6	0.88 (0.58–1.34)	.54[b]	12.9	14.0	1.10 (0.51–2.37)	.82[b]	17.2	13.5	0.83 (0.50–1.38)	.47[b]

Individuals with and without AKI alerts in the year preceding dialysis initiation are shown separately.

[a]*P*-values based on Kruskal–Wallis test and [b]regression model adjusted for age, sex, diabetes, ethnicity. ORs not calculated for presence of surgical access at ICHD initiation due to high proportion of missing data.

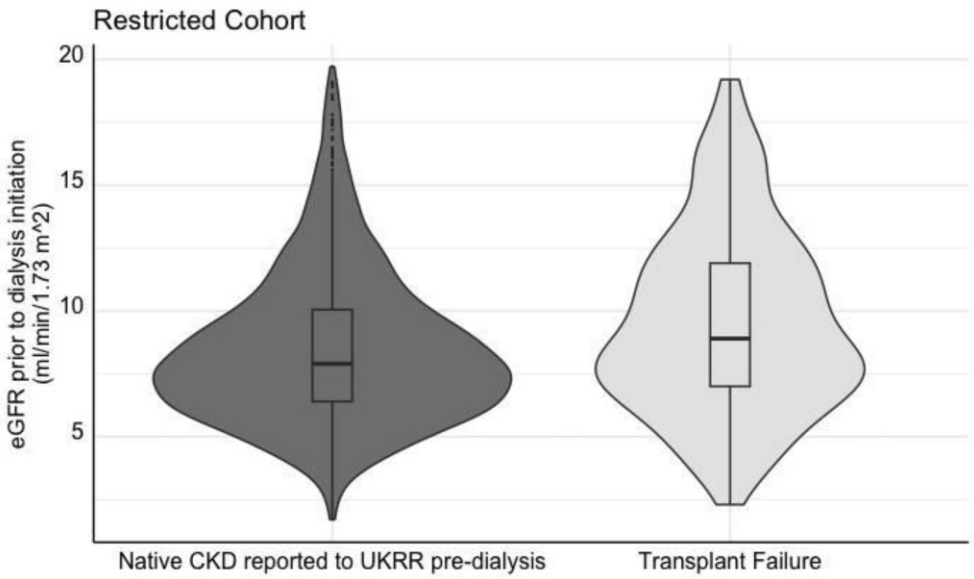


Figure 3: Violin plot with nested box-and-whiskers plot showing eGFR (mL/min/1.73 m^2) at dialysis initiation for individuals reported to UKRR with native CKD and transplant failure in the restricted cohort. Only includes values where eGFR measurement was within 30 days of dialysis start and <20 mL/min/1.73 m^2.

failure, the odds of being on ICHD at 90 days were approximately twice that of native CKD (OR 2.09, 95% CI 1.65–2.65; $P = .0001$).

DISCUSSION

In this analysis of UK adults, of every 10 individuals starting dialysis, 1 started because of transplant failure and 9 with native kidney disease. Of the nine with native kidney failure, six were reported to be known to nephrology services with CKD before dialysis initiation. Compared with those reported to have native CKD, individuals with transplant failure started dialysis with higher eGFRs, had higher rates of ICHD use and were more likely to start as inpatients. While the proportion of individuals surviving to 90 days was similar in each subgroup, the risk of death was disproportionately high amongst those with transplant failure after adjusting for the differences in age, sex, ethnicity and diabetic status.

The reasons for the observed differences can only be speculated in this retrospective registry study. Whilst comparisons were adjusted for age, sex, ethnicity and diabetic status, those with transplant and native kidney failure represent different populations, and differences likely reflect the influence of multiple factors. These include variations in patient characteristics, causes of kidney failure, patient preferences, clinician behaviours, immunosuppression and health system factors.

The proportion of individuals who died within 90 days of dialysis initiation was similar in transplant failure and amongst individuals known to nephrology services with native CKD, but adjusted mortality was higher in transplant failure. The inability to adjust for important confounders, including prior periods of dialysis and prior immunosuppression, may contribute at least partly to the observed differences [21]. Other observational work suggests that mortality is highest amongst individuals with native kidney failure where transplantation is contraindicated, intermediate in those with transplant failure, and lowest in those who are transplant-naïve and waitlisted [5, 22]. Individuals with transplant failure are at greater risk of infection around the time of dialysis initiation, and this may provide another explanation for the observed mortality differences.

Our finding that individuals with transplant failure start dialysis at higher eGFRs than individuals known to nephrology services with native CKD contrasts with results from three small (<150 participants), non-UK observational studies. These showed comparable [9, 10] or lower [8] eGFRs at dialysis initiation amongst individuals with transplant failure. Possible explanations for our findings include variations in practice patterns, earlier emergence of symptoms in transplant failure and/or overestimation of transplant GFR when using eGFR formulae validated in native kidney disease [23]. Unpicking these associations is important to improve care for individuals transitioning between treatments. Higher eGFRs at dialysis initiation have been associated with increased mortality in transplant failure [2] and while observational studies are subject to confounding by indication, similar patterns were seen in propensity-matched studies in the healthiest subgroups [24].

Our data showed that individuals with transplant failure and native CKD known to nephrology services were under regular outpatient follow-up. Approximately the same proportion of individuals with native CKD and transplant failure triggered AKI alerts before starting dialysis. This suggests opportunities to prepare for the possibility of dialysis initiation were similar. While dialysis initiation in unplanned settings may reflect acute illness, this is true for both groups. The lower rates of home therapy and outpatient initiation may indicate missed opportunities to support individuals with transplant failure to start dialysis in a way that suits them best and may impact clinical outcomes [2].

For individuals starting ICHD, presence of surgical dialysis access can be marker of preparedness. While we extracted data on access at dialysis initiation, missingness was too high to draw confident conclusions about whether rates of surgical access differed meaningfully between groups.

While not the primary focus, our analysis identified an important subgroup of dialysis starters who were not reported by nephrology centres as having CKD, but who had been seen by a nephrologist more than 1 year before dialysis initiation. These

individuals may have been discharged following nephrology input. Given prior nephrology contact, and evidence of AKI, these individuals should not be misclassified as having undiagnosed kidney disease. Further examination of the clinical and health service phenotypes within this group may indicate a population with unmet specialist care needs.

Our study has several strengths. To our knowledge, it is the first to use multiple, linked, routinely collected data sources to examine a UK cohort of dialysis starters, and the first publication to arise from the UKRR CKD dataset. Analyses were based on a large, contemporary cohort of UK dialysis starters, with adjustment for important confounders.

We are aware of several limitations. As we included only those who started dialysis, others who underwent pre-emptive transplantation/re-transplantation, or who opted for conservative management were not included. Individuals with native CKD and transplant failure may have differential access to pre-emptive treatments and this could bias the comparisons of the remaining patients who transitioned to dialysis. A decision to include all individuals who received dialysis, with the exception of individuals starting dialysis within 30 days of transplantation, means our cohort included individuals with potentially recoverable kidney disease, which is not the typical approach for registry analyses [17, 18]. This reflected our intention to gain a full picture of dialysis initiation, rather than make exclusions based on events, such as 'chronicity', which cannot always be foreseen at the time of initiation. Our approach was consistent across groups. The group of individuals 'alive, not on dialysis' at 90 days included a heterogenous mix of those withdrawing from dialysis without recovery of native or transplant kidney function but remaining alive, and those with recovery of native and transplant kidney function. Unfortunately, UKRR data do not allow these groups to be readily distinguished at 90 days after dialysis initiation. The restricted cohort was formed from a convenience sample of centres, which may have differed systemically from the whole cohort of UK centres, limiting the generalizability of our findings. The demographics of the patients included in the restricted cohort were comparable to the national case mix, but we cannot account for differences in unmeasured factors such as practice patterns. Whilst we used all available sources to enhance data completeness, no attempt was made to interpolate missing data. Furthermore, categorization of individuals in UKRR data meant we were unable to distinguish individuals who withdrew from dialysis following recovery of native kidney function from those whose death went on to come earlier than it would have, had their dialysis been continued. Since the UKRR did not receive data from all UK biochemical laboratories at the time of study, some individuals with AKI will have been misattributed to the subgroup without AKI. We adjusted for important confounders available in UKRR data but could not account for unmeasured differences between subgroups. The UKRR collects other data that may be relevant to dialysis initiation, including residual urine volume and immunosuppressive drug levels, but high levels of missingness precluded their use.

Our findings highlight disproportionately higher mortality; lower access to planned, home-based dialysis initiation; and initiation at higher eGFRs for those under specialist care with transplant failure, compared with individuals with native CKD. Our analysis cannot fully account for baseline differences between individuals with native and transplant kidney failure. Instead, our findings should be seen as indicative of the need for explanation, if we are to optimize systems treating those who experience transplant failure. Our group is conducting mixed-methods research to explore this further, including DEFINE, a national prospective cohort study examining the indications for dialysis initiation after transplant failure, and INvestigating the experiences and management of individuals with FAiling Kidney Transplants, a qualitative evaluation of the experience and management of transplant failure from the perspective of patients, their families and clinicians [25].

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

B.H., M.B., A.C. and D.N. contributed to conceptualization, methodology, analysis and manuscript preparation. All other authors were involved with data analysis and interpretation, and manuscript review. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data for this study is held by the UK Renal Registry. Sharing of individual participant data is not possible due to the national ethical permissions governing the operation of the UK Renal Registry (section 251, NHS Act 2006). Aggregate data is available on request from the study team.

CONFLICT OF INTEREST STATEMENT

G.G. has received speaker fees from SwissTransplant. R.H. has received speaker honoraria from Sandoz and serves on an advisory board for Takeda. S.G. has received personal remuneration for lectures from CSL Vifor, support to attend meetings from Alexion, and participates in advisory boards for Elodon Pharmaceuticals, CSL Vifor, Chiesi, and Alexion. All other authors have no conflicts of interest to declare.

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