ORIGINAL ARTICLE

The impact of severe acute kidney injury requiring renal replacement therapy on survival and renal function of heart transplant recipients – a UK cohort study

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ABSTRACT

Severe acute kidney injury (AKI), defined as requiring renal replacement therapy (RRT), is associated with higher mortality postheart transplantation, but its long-term renal consequences are not known. Anonymized data of 3365 patients, who underwent heart transplantation between 1995 and 2017, were retrieved from the UK Transplant Registry. Multivariable binary logistic regression was performed to identify risk factors for severe AKI requiring RRT, Kaplan–Meier analysis to compare survival and renal function deterioration of the RRT and non-RRT groups, and multivariable Cox regression model to identify predicting factors of mortality and end-stage renal disease (ESRD). 26.0% of heart recipients received RRT post-transplant. The RRT group has lower survival rates at all time points, especially in the immediate post-transplant period. However, conditional on 3 months survival, older age, diabetes and coronary heart disease, but not post-transplant RRT, were the risk factors for long-term survival. The predicting factors for ESRD were insulin-dependent diabetes, renal function at transplantation, eGFR decline in the first 3 months post-transplant, post-transplant severe AKI and transplantation era. Severe AKI requiring RRT post-transplant is associated with worse short-term survival, but has no impact on long-term mortality. It also accelerates recipients' renal function deterioration in the long term.

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Key words
chronic kidney disease, end-stage renal disease, heart transplant, renal function, renal replacement therapy, survival

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Introduction

Heart transplantation is the gold standard treatment for selected patients with end-stage heart failure. Survival of heart transplant recipients worldwide has increased significantly in the past few decades [1], but long-term complications remain a concern.

Chronic kidney disease (CKD) is one of the common noncardiac complications experienced by heart transplant recipients. The incidence of CKD reported previously varies widely because of the usage of different definitions, study types and follow-up periods [2–5]. All of the studies agreed that CKD has an adverse impact on recipients' survival and quality of life [2–5]. Hence,

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it is crucial for clinicians to recognize, quantify, prevent and manage the risk factors contributing to CKD.

Prior to heart transplantation, the majority of patients on the waiting list have a degree of renal impairment [6], caused by a combination of reduced renal perfusion, fluid restriction, use of diuretics and renin–angiotensin–aldosterone system inhibitors, and comorbidities, such as diabetes mellitus and hypertension. Post-transplant, nephrotoxic calcineurin inhibitors are thought to be the main cause of renal function decline [2,4,7]. However, little is known about the impact of the events occurring at the peri-operative stage on the long-term renal function of heart transplant recipients.

In general population [8] and nontransplant postcardiac surgery patients [9,10], an episode of acute kidney injury (AKI) leads to an increased risk of mortality and developing CKD in the future. Only a few studies have looked at this problem in heart transplant recipients and identified severe AKI as a contributing factor to poorer outcomes [2,11,12]. To better understand the role of severe AKI, defined as the Kidney Disease: Improving Global Outcomes (KDIGO) classification stage 3 AKI requiring renal replacement therapy (RRT) within 30 days post-transplant, we used the UK Transplant Registry data to (i) identify the predictors of stage 3 AKI requiring RRT; (ii) study its impact on recipients' survival; and (iii) investigate its influence on recipient's long-term renal function.

Methods

Study design

This is a national multi-centre retrospective cohort study. All patients aged 16 years and older, undergoing heart transplantation between April 1995 and March 2017 in the UK, were included. Multi-organ transplants were excluded. Recipient and donor characteristics, operation details and post-transplant outcomes were collected from the UK Transplant Registry, which is maintained by the National Health Service Blood and Transplant (NHSBT). It captures all of the transplant activities across the UK, as data submission is mandatory. All the data in the registry have been validated. As this project did not involve patient identifiable information, a separate research ethics committee approval was not required [13].

Recipients' data included age, sex, ethnicity, pretransplant diabetes status, hypertension, cardiac pathology, urgency status for transplantation, pretransplant haemodynamic support, namely ventricular assist device (VAD), inotrope, intra-aortic balloon pump (IABP), and extra-corporeal membrane oxygenation (ECMO) prior to transplantation, and peri-transplant renal function. The peri-transplant renal function was measured as serum creatinine (SCr) immediately before the transplant operation, 3 and 12 months post-transplant, and annually afterwards. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease 4-variable equation [14]. Based on the eGFR, recipients' renal function was assigned to one of the National Kidney Foundation (NKF) chronic kidney disease (CKD) stages [15]. ΔeGFR was the difference in the eGFRs at transplantation and 3 months post-transplant. End-stage renal disease (ESRD) was defined as NKF CKD stage 5 (eGFR < 15 ml/min/1.37 m^2), or being listed for or received renal transplantation. Donors' data consisted of donor age and sex. The operation details were transplantation date, centre and allograft total ischaemic time. Transplants were categorized into four eras, namely era 1995–2000, era 2001–2005, era 2006–2010 and era 2011–2017, to study the changes in transplantation practice over time. The post-transplant outcomes were RRT within 30 days post-transplant, re-exploration, infection, and requirement of IABP and other mechanical assistance, recipients' survival status and length, and development of ESRD. In the registry data collection, the term RRT refers to both haemofiltration and haemodialysis.

Statistical analysis

The recipient cohort was divided into two groups, based on whether they developed severe AKI requiring RRT within 30-day post-transplant. To compare the means of continuous variables, Mann–Whitney *U*-test and two-sample *t*-test were used when appropriate. Chi-squared test was applied to compare frequencies of subgroups and test associations of categorical variables.

To identify the factors associated with RRT usage, univariable binary logistic regression was performed for the donor- and recipient-related variables, operative details, and development of post-transplant severe primary graft dysfunction (PGD). All factors with $P < 0.1$ were entered into the multivariable binary logistic regression.

Kaplan–Meier (KM) analysis was performed to compare the survival and freedom from ESRD post-transplant of the RRT and non-RRT groups. Multivariable Cox regression models for time to death and time to develop ESRD, in recipients who survived for at least 3 months post-transplant, were used to identify the respective predicting factors. 477 patients who did not

Table 1. Recipient and donor characteristics and operation details of the 3365 heart transplantations.

	N = 3365
Donor sex	
Female	1136 (33.8)
Male	2228 (66.2)
Donor age (year)	36.3 ± 12.4
Recipient sex	
Female	763 (22.7)
Male	2601 (77.3)
Recipient age (year)	46.7 ± 12.8
Gender mismatch	
No	2457 (73.0)
Male donor to female recipient	268 (8.0)
Female donor to male recipient	639 (19.0)
Recipient ethnicity	
Asian	192 (5.8)
Black	56 (1.7)
White	3034 (91.6)
Others	30 (0.9)
Recipient diabetes status at registration	
No	2920 (91.0)
Yes, insulin dependent	124 (3.9)
Yes, noninsulin dependent	164 (5.1)
Recipient hypertension at registration	
No	2597 (81.3)
Yes	597 (18.7)
Recipient preop cardiac pathology	
Congenital heart disease	175 (5.2)
Coronary artery disease	948 (28.4)
Dilated cardiomyopathy	1674 (50.1)
Others	545 (16.3)
Recipient renal function at transplantation	
eGFR ≥ 60 ml/min/1.73 m^2	1682 (54.9)
CKD Stage 3	1278 (41.7)
CKD Stage 4	95 (3.1)
CKD Stage 5	11 (0.3)
Urgent status recipient at transplantation	1009 (30.0)
Recipient with VAD prior to transplantation	
None	1878 (85.5)
Left VAD	160 (7.3)
Right VAD	27 (1.2)
Bilateral VAD	132 (6.0)
Recipient on inotrope prior to transplantation	895 (41.5)
Recipient on IABP prior to transplantation	230 (10.5)
Recipient on ECMO prior to transplantation	28 (1.3)
Allograft total ischaemic time (h)	3.3 ± 1.1
Transplantation era	
Era 1995–2000	1330 (39.5)
Era 2001–2005	650 (19.3)
Era 2006–2010	501 (14.9)
Era 2011–2017	884 (26.3)
Transplantation centre	
Centre 1	520 (15.6)
Centre 2	107 (3.2)
Centre 3	808 (24.2)
Centre 4	613 (18.3)
Centre 5	131 (3.9)
Centre 6	438 (13.1)
Centre 7	427 (12.8)
Centre 8	300 (8.9)

Data are given as number (percentage) or mean ± SD, as appropriate.

survive beyond 3-month post-transplant and 56 patients with missing survival information were excluded from the analysis. The time point of 3 months was chosen because the survival behaviour of both RRT and non-RRT groups was very different before and after this time point. Also, 3 months is when the UK Transplant Registry records the first follow-up renal function. In addition, RRT and its interaction with transplantation era were included in the Cox model. The hazard ratios (HR) of the RRT group of era 2001–2005, era 2006–2010 and era 2011–2017 were calculated by the HR of era 1995–2000, 1.34, multiplied by the HRs of the non-RRT group and the interaction between era and RRT in the corresponding era, respectively. A step-down method guided by Akaike information criteria was used for model selection. Missing data were replaced by multiple imputation.

A subgroup analysis of the 361 recipients, who developed severe PGD, including severe PGD-left ventricle (LV) and PGD-right ventricle (RV), defined by the International Society for Heart and Lung Association Classification for PGD [16], was performed. A multivariable binary logistic regression was used to identify the predictors of death within 90 days post-transplant.

All statistical analyses were undertaken using the R programming language version 3.2.5 and IBM SPSS Statistics version 24 64-bit edition.

Results

Baseline characteristics

A total of 3365 patients aged 16 years and older underwent heart transplantation in eight centres during this 22-year period. The cohort was 77.3% male, with a mean age of 46.7 ± 12.8 years. 26.0% (876/3365) recipients required RRT within 30 days post-transplant. Table 1 summarizes the recipient characteristics and operation details of the cohort.

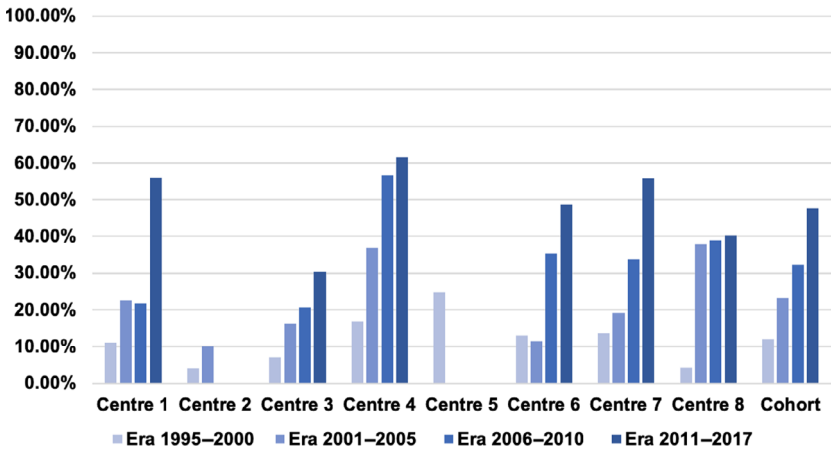


Figure 1 The percentage of recipients who developed stage 3 AKI requiring RRT post-transplant in the individual centres across the eras.

Table 2. Changes of donor and recipient characteristics across transplantation eras.

	Era 1995–2000 *N* = 1330	Era 2001–2005 *N* = 650	Era 2006–2010 *N* = 501	Era 2011–2017 *N* = 884
Donor age (year), mean ± SD	34.2 ± 12.2	36.3 ± 12.3	37.1 ± 12.0	39.1 ± 12.4
Recipient age (year), mean ± SD	48.6 ± 10.9	45.5 ± 13.5	45.1 ± 13.6	45.6 ± 13.9
Urgent status recipient at transplantation	22/1330 (1.7)	136/650 (20.9)	196/501 (39.1)	655/884 (74.1)
Recipient with VAD prior to transplantation				
None	658/676 (97.3)	363/415 (87.5)	289/352 (82.1)	568/754 (75.3)
Left VAD	11/676 (1.6)	28/415 (6.7)	25/352 (7.1)	96/754 (12.7)
Right VAD	1/676 (0.1)	3/415 (0.7)	7/352 (2.0)	16/754 (2.1)
Bilateral VAD	6/676 (0.9)	21/415 (5.1)	31/352 (8.8)	74/754 (9.8)
Recipient on inotrope prior to transplantation	161 /671 (24.0)	165/403 (40.9)	138/350 (39.4)	431/735 (58.6)
Recipient on IABP prior to transplantation	52/678 (7.7)	56/411 (13.6)	55/353 (15.6)	67/741 (9.0)
Recipient on ECMO prior to transplantation	0/677 (0)	5/411 (1.2)	5/352 (1.4)	18/740 (2.4)
Allograft total ischaemic time (h), mean ± SD	3.0 ± 1.0	3.6 ± 0.9	3.5 ± 0.9	3.3 ± 1.4

Data are given as number (percentage) or mean ± SD, as appropriate.

Renal replacement therapy usage had steadily increased from 12.0% (158/1312) in the era 1995–2000 to 47.7% (410/859) in the era 2011–2017. This temporal trend was observed across all centres (Fig. 1). The increase of RRT usage over time was accompanied by the rise in donor age, and recipients of urgent status and being supported by VAD, inotrope, IABP and ECMO prior to transplantation (Table 2). Moreover, RRT usage varied across centres, ranging from 4.7% (5/107) to 35.4% (217/613; Table 3).

Risk factors of severe AKI requiring RRT post-transplant

The results of the binary logistic regression, which aimed to identify variables predicting post-transplant RRT, were displayed in Table 4. With other factors controlled, male recipients [odds ratio (OR) 1.80, 95% confidence interval (CI): 1.33–2.43] were more likely to require RRT. The other recipient-related risk factors for RRT were requiring left VAD (OR 1.94, 95% CI: 1.22–3.08) and inotrope (OR 1.42, 95% CI: 1.05–1.92) prior to transplantation, renal function at the time of transplantation and development of severe PGD (OR 7.17, 95% CI: 4.99–10.30) post-transplant. Moreover, grafts from older donors increased the risk of RRT (OR 1.02, 95% CI: 1.01–1.03). Furthermore, RRT usage steadily increased with time, with the ORs for the latter three eras being 2.68 (95% CI: 1.69–4.26), 4.76 (95% CI: 2.94–7.70) and 7.66 (95% CI: 4.71–12.44), respectively. Moreover, recipients treated in centres 4 (OR 2.10, 95% CI: 1.38–3.19) were significantly more likely to receive

Table 3. Differences in donor and recipient characteristics and usage of RRT across centres.

	Centre 1 $N = 520$	Centre 2 $N = 107$	Centre 3 $N = 808$	Centre 4 $N = 613$	Centre 5 $N = 131$	Centre 6 $N = 438$	Centre 7 $N = 427$	Centre 8 $N = 309$
Percentage of RRT	27.0	4.7	18.0	35.4	24.8	28.8	33.6	22.2
Donor age (year), mean ± SD	36.9 ± 12.5	33.5 ± 11.9	37.3 ± 12.7	35.5 ± 12.4	32.5 ± 11.1	36.9 ± 12.1	36.0 ± 12.2	36.9 ± 12.3
Recipient age (year), mean ± SD	44.6 ± 14.2	52.2 ± 9.4	48.1 ± 12.4	46.1 ± 12.4	46.8 ± 11.5	45.5 ± 12.8	47.6 ± 12.2	48.3 ± 11.0
Urgent status recipient at transplantation	168 (32.3)	2 (1.9)	232 (28.7)	172 (28.1)	0(0)	178 (40.6)	171 (40.0)	82 (27.3)
Recipient with VAD prior to transplantation								
None	324 (86.6)	60 (56.1)	306 (78.7)	314 (74.1)	83 (100.0)	377 (92.6)	200 (85.8)	202 (94.4)
Left VAD	37 (9.9)	0 (0)	19 (4.9)	74 (17.5)	0 (0)	12 (2.9)	11 (4.7)	7 (3.3)
Right VAD	1 (0.3)	0 (0)	18 (4.6)	2 (0.5)	0 (0)	5 (1.2)	0 (0)	0 (0)
Bilateral VAD	12 (3.2)	0 (0)	46 (11.8)	34 (8.0)	0 (0)	13 (3.2)	22 (9.4)	5 (2.3)
Recipient on inotrope prior to transplantation	149 (40.8)	4 (7.0)	169 (45.2)	182 (43.8)	1 (1.2)	191 (46.9)	127 (54.5)	69 (32.7)
Recipient on IABP prior to transplantation	18 (4.9)	0 (0)	41 (10.6)	45 (10.7)	0 (0)	39 (9.6)	36 (15.5)	51 (23.8)
Recipient on ECMO prior to transplantation	2 (0.5)	0 (0)	7 (1.8)	2 (0.5)	0 (0)	12 (2.9)	1 (0.4)	2 (0.9)
Allograft total ischaemic time (h), mean ± SD	3.3 ± 0.8	2.8 ± 1.0	3.3 ± 1.0	3.4 ± 1.5	2.8 ± 0.9	3.1 ± 1.0	3.4 ± 0.8	3.3 ± 1.0

RRT, while recipients in centre 3 (OR 0.64, 95% CI: 0.42–0.98) were less likely.

Association between post-transplant complications and severe AKI requiring RRT

All of the recorded post-transplant complications, including re-exploration (OR 6.65, 95% CI: 5.55–7.96), infection (OR 3.07, 95% CI: 2.56–3.70), and requirement of IABP (OR 5.65, 95% CI: 4.71–6.79) and other mechanical support (OR 11.66, 95% CI: 9.02–15.06) were significantly associated with severe AKI requiring RRT (Table 5).

Survival analysis

Figure 2 shows the KM survival curves of the RRT and non-RRT groups. At all time points post-transplant, the survival rates of the RRT group were lower than that of the non-RRT group. The most-striking difference occurred in the immediate post-transplant period. The 30-day survival was 94.7% (95% CI: 93.8–95.6%) for the non-RRT group, but only 71.6% (95% CI: 68.7–74.7%) for the RRT group. The majority of the early deaths occurred within the first 3 months.

A multivariable Cox regression model of time to death was then used to identify factors associated with median-term and long-term survival, conditional on 3 months post-transplant survival (Table 6). Older recipient age (HR 1.01, 95% CI: 1.00–1.02), and both insulin-dependent (HR 1.54, 95% CI: 1.17–2.00) and non-insulin-dependent diabetes (HR 1.34, 95% CI: 1.03–1.75) were statistically significant predictors of survival post-transplant. Compared to those with congenital heart disease, recipients with coronary artery disease had increased risk of mortality (HR 1.62, 95% CI: 1.07–2.50). Survival rate differences across centres were generally not significant. Postoperative RRT, renal functional at transplantation and ΔeGFR did not have an adverse impact on long-term survival for patients who survived for at least 3 months post-transplant. There was a general trend of improvement in overall survival over time. For example, compared to the recipients of the non-RRT group in era 1995–2000, those recipients of the non-RRT group (HR 0.71, 95% CI: 0.54–0.92) and RRT group (HR 0.72) in era 2006–2010 had significantly better survival. A similar HR was observed in the non-RRT group in era 2011–2017 (HR 0.74, 95% CI: 0.52–1.04), though not at a statistically significant level, which was probably because of a shorter follow-up duration and smaller number of events in this group.

Table 4. Binary logistic regression for risk factors associated with post-transplant RRT.

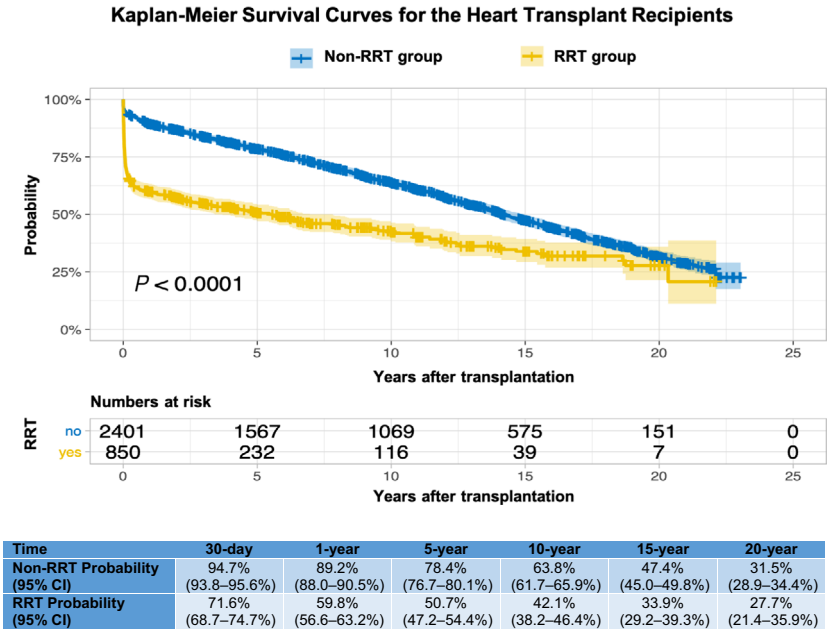
	Univariate analysis			Multivariate analysis		
	N	Odds Ratio	*P*-value	Odds Ratio	95% CI	*P*-value
Donor sex						
Female	1136	1.00	–			
Male	2228	0.99	0.9			
Donor age	3365	1.02	<0.001	1.02	1.01–1.03	0.001
Recipient sex						
Female	763	1.00	–	1.00	–	–
Male	2601	1.10	<0.001	1.80	1.33–2.43	<0.001
Recipient age	3365	1.00	0.9			
Gender mismatch						
No	2457					
Male donor to female recipient	268	1.05	0.7			
Female donor to male recipient	639	1.09	0.4			
Recipient ethnicity						
Asian	192	1.00	–			
Black	56	1.03	0.7			
White	3034	0.98	0.5			
Others	30	0.97	0.7			
Recipient diabetes status at registration						
No	2920	1.00	–			
Yes, insulin dependent	124	1.01	0.8			
Yes, noninsulin dependent	164	0.99	0.7			
Recipient hypertension at registration						
No	2597	1.00	–			
Yes	597	1.01	0.5			
Recipient preop cardiac pathology						
Congenital heart disease	175	1.00	–	1.00	–	–
Coronary artery disease	948	0.93	0.08	0.68	0.37–1.23	0.2
Dilated cardiomyopathy	1674	0.93	0.09	0.66	0.38–1.15	0.1
Others	545	0.96	0.4	1.08	0.59–1.97	0.8
Recipient renal function at transplantation						
eGFR $\geq$ 60 ml/min/1.73 m^2	1680	1.00	–	1.00	–	–
CKD Stage 3	1278	1.13	<0.001	2.21	1.71–2.86	<0.001
CKD Stage 4	95	1.27	<0.001	3.28	1.66–6.51	0.001
CKD Stage 5	11	1.41	0.07	7.13	1.17–43.64	0.03
Urgent status recipient at transplantation	1009	2.84	<0.001	0.84	0.59–1.20	0.3
Recipient with VAD prior to transplantation						
None	1878	1.00	–	1.00	–	–
Left VAD	160	3.94	<0.001	1.94	1.22–3.08	<0.001
Right VAD	27	2.56	0.02	1.52	0.55–4.25	0.3
Bilateral VAD	132	2.09	<0.001	1.25	0.76–2.05	0.4
Recipient on inotrope prior to transplantation	895	1.53	<0.001	1.42	1.05–1.92	0.02
Recipient on IABP prior to transplantation	230	0.97	0.9			
Recipient on ECMO prior to transplantation	28	5.70	<0.001	1.83	0.66–5.06	0.2
Allograft total ischaemic time	3231	1.02	0.006	1.11	0.99–1.24	0.07
Post-transplant severe PGD	3303	11.66	<0.001	7.17	4.99–10.30	<0.001
Transplantation era						
Era 1995–2000	1330	1.00	–	1.00	–	–
Era 2001–2005	650	1.11	<0.001	2.68	1.69–4.26	<0.001
Era 2006–2010	501	1.22	<0.001	4.76	2.94–7.70	<0.001
Era 2011–2017	884	1.46	<0.001	7.66	4.71–12.44	<0.001
Transplantation centre						
Centre 1	520	1.00	–	1.00	–	–
Centre 2	107	0.99	0.8	0.25	0.03–1.95	0.2

Table 4. Continued.

	Univariate analysis			Multivariate analysis		
	N	Odds Ratio	*P*-value	Odds Ratio	95% CI	*P*-value
Centre 3	808	0.94	0.02	0.64	0.42–0.98	0.04
Centre 4	613	1.13	<0.001	2.10	1.38–3.19	<0.001
Centre 5	131	1.14	0.01	2.05	0.76–5.56	0.2
Centre 6	438	1.03	0.2	1.00	0.67–1.50	0.9
Centre 7	427	1.07	0.01	1.52	0.98–2.38	0.06
Centre 8	300	0.98	0.6	0.89	0.53–1.48	0.6

Table 5. Association between post-transplant complications and severe AKI requiring RRT.

Complications	RRT group *n* (%) *N* = 876	Non-RRT group *n* (%) *N* = 2429	OR	95% CI	*P*-value
Return to theatre	415 (47.4)	290 (12.0)	6.65	5.55–7.96	<0.001
Infection	289 (34.7)	330 (14.7)	3.07	2.56–3.70	<0.001
Requirement of haemodynamic support					
IABP	369 (42.5)	280 (11.5)	5.65	4.71–6.79	<0.001
Other mechanical support	268 (30.8)	89 (3.7)	11.66	9.02–15.06	<0.001



Time	30-day	1-year	5-year	10-year	15-year	20-year
Non-RRT Probability (95% CI)	94.7% (93.8–95.6%)	89.2% (88.0–90.5%)	78.4% (76.7–80.1%)	63.8% (61.7–65.9%)	47.4% (45.0–49.8%)	31.5% (28.9–34.4%)
RRT Probability (95% CI)	71.6% (68.7–74.7%)	59.8% (56.6–63.2%)	50.7% (47.2–54.4%)	42.1% (38.2–46.4%)	33.9% (29.2–39.3%)	27.7% (21.4–35.9%)

Figure 2 Kaplan–Meier survival curves and survival rates for the heart transplant recipients in the non-RRT and RRT groups.

The characteristics of these 3-month survivors in the RRT and non-RRT groups were summarized in Table 7. The mean donor age of the RRT group was 2.8 years older, while the recipient age was comparable. The RRT group had more male patients (81.3% vs. 77.0%) and fewer patients with ischaemic cardiomyopathy (20.0% vs. 29.9%). The RRT group had worse renal function at transplantation, but similar percentages of other comorbidities, as the non-RRT group.

Among the whole cohort, 361 (10.9%) recipients developed severe PGD post-transplant. The percentages of the documented severe PGD increased with time, being 3.6% (47/1312), 10.8% (70/647), 13.7% (67/488) and 20.7% (177/856) in the four eras, respectively.

Table 6. Multivariate Cox regression model for time to death in patients who survived at least 3 months post-transplant.

		Multivariate analysis		Final model		
	N	Hazard Ratio	*P*-value	Hazard Ratio	95% CI	*P*-value
Recipient sex						
Female	627	1.00	–			
Male	2204	1.03	0.7			
Recipient age	2832	1.01	0.02	1.01	1.00–1.02	0.005
Recipient ethnicity						
Asian	159	1.00	–			
Black	50	2.10	0.01			
White	2549	1.47	0.03			
Others	27	1.55	0.3			
Recipient diabetes status at registration						
No	2487	1.00	–	1.0	–	–
Yes, insulin dependent	100	1.56	0.004	1.54	1.17–2.00	0.002
Yes, noninsulin dependent	131	1.30	0.08	1.34	1.03–1.75	0.03
Recipient hypertension at registration						
No	2215	1.00	–			
Yes	490	0.99	0.9			
Recipient preop cardiac pathology						
Congenital heart disease	134	1.00	–			
Coronary artery disease	786	1.93	0.01	1.62	1.07–2.50	0.02
Dilated cardiomyopathy	1462	1.40	0.2	1.18	0.78–1.77	0.4
Others	435	1.75	0.03	1.44	0.94–2.20	0.09
Recipient renal function at transplantation						
eGFR $\geq$ 60 ml/min/1.73 m^2	1465	1.00	–			
CKD Stage 3	1062	0.91	0.2			
CKD Stage 4	67	1.01	1			
CKD Stage 5	3	2.80	0.3			
Allograft total ischaemic time	2724	0.97	0.4			
Recipient ΔeGFR	2576	1.00	0.4			
RRT	552					
Era 1995–2000						
Non-RRT	1030	1.00	–	1.00	–	–
RRT	66	1.22	0.3	1.34	0.95–1.87	0.09
Era 2001–2005						
Non-RRT	464	1.06	0.5	0.99	0.84–1.17	0.9
RRT	83	–	–	0.92	–	–
Era 2006–2010						
Non-RRT	309	0.75	0.04	0.71	0.54–0.92	0.009
RRT	99	–	–	0.72	–	–
Era 2011–2017						
Non-RRT	436	0.75	0.1	0.74	0.52–1.04	0.08
RRT	304	–	–	1.51	–	–
Interaction between transplantation era and RRT						
Era 1995–2000 and RRT		1.00	–	1.00	–	–
Era 2001–2005 and RRT		0.71	0.2	0.69	0.41–1.14	0.1
Era 2006–2010 and RRT		0.83	0.6	0.76	0.42–1.37	0.4
Era 2011–2017 and RRT		1.65	0.1	1.52	0.89–2.60	0.1
Transplantation centre						
Centre 1	416	1.00	–	1.00	–	–
Centre 2	98	1.02	0.9	0.90	0.65–1.24	0.5
Centre 3	713	0.92	0.4	0.88	0.72–1.09	0.2
Centre 4	489	0.82	0.1	0.81	0.64–1.01	0.06
Centre 5	101	0.94	0.7	0.94	0.69–1.28	0.7

Table 6. Continued.

		Multivariate analysis		Final model		
	N	Hazard Ratio	*P*-value	Hazard Ratio	95% CI	*P*-value
Centre 6	374	1.37	0.02	1.29	1.02–1.63	0.03
Centre 7	381	1.37	0.01	1.33	1.07–1.67	0.01
Centre 8	243	1.03	0.9	0.99	0.76–1.28	0.9

ΔeGFR, recipient eGFR at transplantation – recipient eGFR at 3-month post-transplant.

54.8% (198/361) of these patients died within 90 days post-transplant. Severe AKI requiring RRT (OR 8.08, 95% CI: 2.58–25.20) was a significant risk factor of early death in this subgroup (Table 8). Other risk factors include older recipient age (OR 1.07, 95% CI: 1.03–1.11), preop bilateral VAD (OR 4.91, 95% CI: 1.21–19.97) and IABP (OR 6.30, 95% CI: 1.27–31.31), and longer ischaemic time (OR 1.58, 95% CI: 1.12–2.22).

Renal function analysis

The recipients were also followed up in terms of their renal function. 86.2% (2901/3365) of the patients had at least 1 postoperative SCr documented. The median follow-up time was 6 years [interquatile range (IQR): 1.6–13.0 years].

Immediately prior to transplantation, the means of eGFR of the RRT and non-RRT groups were comparable, 67.1 ± 32.3 and 67.9 ± 27.3 ml/min/1.73 m^2, respectively ($P = 0.5$). At 3 months post-transplant, a slightly bigger drop in eGFR was observed in the RRT group compared to the non-RRT group (the mean ΔeGFR was 13.0 ± 37.5 and 9.3 ± 24.3 ml/min/1.73 m^2, respectively, $P = 0.026$). After the initial 3 months, recipients' renal function gradually deteriorated with time, as evident by the Kaplan–Meier analysis of the freedom from development of ESRD (Fig. 3). The time to development of ESRD was significantly shorter for the recipients who required post-transplant RRT. Among the patients who developed ESRD, a total of 79 patients were registered for renal transplantation. The median duration from the heart transplantation to being registered for renal transplantation was 8.3 years (IQR: 4.3–11.1 years). 60.8% (48/79) of them received renal transplantation. The median duration from the heart transplantation to the renal transplantation was 8.8 years (IQR: 4.4–13.2 years).

Table 9 showed the results of the multivariable Cox regression model for time to develop ESRD in patients who survived at least 3 months post-transplant. Recipients with insulin-dependent diabetes at registration (HR 2.61, 95% CI: 1.44–4.81) had increased risk of ESRD. Recipients' renal function at transplantation was also an independent predictor of ESRD [HR 2.12 (95% CI: 1.45–2.90) for recipients with CKD stage 3, 4.81 (95% CI: 2.31–9.92) for CKD stage 4 and 58.03 (95% CI: 6.32–541.01) for CKD stage 5]. A drop in the renal function at 3 months post-transplant was associated with a long-term deterioration in renal function, though the effect was small (HR 1.01, 95% CI: 1.01–1.02). RRT, recent transplantation era and the interaction between them were significantly associated with increased probability of ESRD. Compared to the non-RRT group in the era 1995–2000, all the non-RRT groups in the more recent eras had much reduced risks of developing ESRD (HR 0.44, 95% CI: 0.27–0.71 for the non-RRT group in the era 2001–2005, HR 0.42, 95% CI: 0.19–0.92 for those the in era 2006–2010 and HR 0.23, 95% CI: 0.05–0.99 for those in the era 2011–2017). For the RRT groups, the HR of developing ESRD gradually increased with time (HR 1.16, 1.66 and 1.68 for the RRT groups in the era 2001–2005, era 2006–2010 and era 2011–2017, respectively). As a result, the difference between HR of the non-RRT and RRT groups within the same era widened with time.

There were also significant differences in the risks of ESRD across centres. Recipients treated in centres 2, 4, 5 and 6 were at greater risk of post-transplant ESRD. Last, interestingly, the total ischaemic time statistically had a protective effect on the development of ESRD (HR 0.85, 95% CI: 0.72–0.99). Other recipient-related factors such as sex, age, ethnicity, hypertension and preoperative cardiac pathology did not have an effect on renal function post-transplant.

Discussion

This study reviewed a 22-year experience of heart transplantation in the UK and demonstrated that the stage 3 AKI requiring RRT within 30 days post-transplant is

Table 7. Comparison of the characteristics of the patients who survived at least 3 months post-transplant in the RRT and non-RRT groups.

	RRT group (N = 552), n (%)	Non-RRT group (N = 2239), n (%)	P-value
Donor sex			
Female	178 (32.3)	737 (32.9)	0.8*
Male	373 (67.7)	1502 (67.1)	
Donor age (year), mean ± SD	38.0 ± 12.3	35.2 ± 12.4	<0.001†
Recipient sex			
Female	103 (18.7)	516 (23.0)	0.03*
Male	448 (81.3)	1723 (77.0)	
Recipient age (year), mean ± SD	46.5 ± 13.0	46.6 ± 12.7	0.9†
Gender mismatch			
No	404 (73.3)	1650 (73.7)	0.1*
Male donor to female recipient	37 (6.7)	184 (8.2)	
Female donor to male recipient	110 (20.0)	405 (18.1)	
Recipient ethnicity			
Asian	40 (7.3)	113 (5.1)	0.02*
Black	16 (2.9)	34 (1.5)	
White	483 (88.5)	2031 (92.4)	
Others	7 (1.3)	20 (0.9)	
Recipient diabetes status at registration			
No	490 (91.1)	1960 (91.5)	0.7*
Yes, insulin dependent	23 (4.3)	77 (3.6)	
Yes, noninsulin dependent	25 (4.6)	105 (4.9)	
Recipient hypertension at registration			
No	434 (81.3)	1743 (81.8)	0.8*
Yes	100 (18.7)	387 (18.2)	
Recipient preop cardiac pathology			
Congenital heart disease	44 (8.0)	89 (4.0)	<0.001*
Coronary artery disease	110 (20.0)	665 (29.9)	
Dilated cardiomyopathy	302 (54.8)	1140 (51.2)	
Others	95 (17.2)	331 (14.9)	
Recipient renal function at transplantation			
eGFR ≥ 60 ml/min/1.73 m^2	278 (52.3)	1166 (57.4)	0.01*
CKD Stage 3	230 (43.3)	820 (40.3)	
CKD Stage 4	21 (4.0)	46 (2.3)	
CKD Stage 5	2 (0.4)	1 (0.0)	
Urgent status recipient at transplantation	303 (54.9)	547 (24.4)	<0.001*
Recipient with VAD prior to transplantation			
None	328 (76.1)	1248 (90.2)	<0.001*
Left VAD	61 (14.2)	59 (4.3)	
Right VAD	9 (2.1)	14 (1.0)	
Bilateral VAD	33 (7.6)	62 (4.5)	
Recipient on inotrope prior to transplantation	216 (51.2)	532 (39.1)	<0.001*
Recipient on IABP prior to transplantation	38 (8.9)	145 (10.5)	0.3*
Recipient on ECMO prior to transplantation	10 (2.4)	6 (0.4)	<0.001*
Allograft total ischaemic time (h), mean ± SD	3.4 ± 1.2	3.2 ± 1.0	0.001‡
Post-transplant severe PGD	101 (18.3)	53 (2.4)	<0.001*
Transplantation era			
Era 1995–2000	66 (12.0)	1030 (46.0)	<0.001*
Era 2001–2005	83 (15.0)	464 (20.7)	
Era 2006–2010	99 (17.9)	309 (13.8)	
Era 2011–2017	304 (55.1)	436 (19.5)	

Table 7. Continued.

	RRT group (N = 552), n (%)	Non-RRT group (N = 2239), n (%)	P-value
Transplantation centre			
Centre 1	81 (14.8)	334 (15.0)	<0.001*
Centre 2	1 (0.2)	97 (4.4)	
Centre 3	91(16.7)	589 (26.4)	
Centre 4	129 (23.6)	357 (16.0)	
Centre 5	13 (2.4)	87 (3.9)	
Centre 6	87 (15.9)	287 (12.9)	
Centre 7	111 (20.3)	270 (12.1)	
Centre 8	33 (6.0)	207 (9.3)	

SD, standard deviation.

*Analysed by chi-squared test.

†Analysed by Mann–Whitney U-test.

‡Analysed by independent-samples t-test.

associated with higher short-term mortality rate and predicts increased risk of developing ESRD in future, but does not influence long-term survival.

The baseline characteristics of our cohort are comparable to that of other large-scale registry data [2,5,16]. The reported rate of stage 3 AKI requiring RRT in the postoperative period varies considerably from 3.0% to 34.2% [2,11,17–22]. In addition to variable practice and criteria for post-transplant RRT utilization adopted by different centres, this rate appears to have a temporal trend. For example, the lowest published incidence of postoperative RRT, 3.0%, came from a cohort operated between 1990 and 2000 [2], while the highest incidence, 34.2%, was from a cohort operated between 2009 and 2014 [22]. This temporal trend was also observed in our cohort. Those receiving RRT increased from 12.0% in the era 1995–2000 to 47.7% in the era 2011–2017. There are several possible explanations for this. An urgent list for heart transplantation, aiming to prioritize the haemodynamically unstable and unwell patients, who require inotropic and mechanical support, although introduced in 1999, was only formally implemented with defined clinical criteria in the UK in 2008. The percentage of recipients who were of urgent status at transplantation increased dramatically from 1.7% in the era 1995–2000 to 74.1% in the era 2011–2017. Similarly, the percentage of recipients supported by VADs, inotropes, IABP and ECMO increased. With more recipients of higher risk undergoing heart transplantation, especially those with left and bilateral VADs and on ECMO, the incidence of postoperative stage 3 AKI requiring RRT increased [12]. In addition, the donor criteria had been extended in recent years [23], as evident in our cohort with the mean donor age rising continuously over time. Changes in donor and recipient characteristics are likely to result in a higher risk of post-transplant haemodynamic instability and complications including stage 3 AKI requiring RRT. The increased availability of and easier access to RRT in the more recent eras may have also contributed to the more frequent use of RRT in heart recipients.

Apart from transplantation centre and era, donor age, recipient sex, renal function at transplantation, and support from left and bilateral VAD and ECMO were found to be the predictors of stage 3 AKI requiring RRT. Impaired preoperative renal function had been recognized as a risk factor for severe AKI post-transplant in several previous studies [19,21,24,25], suggesting that steps to preserve recipients' renal function could potentially reduce the risk of stage 3 AKI requiring RRT post-transplant. Heart transplant for recipients with VAD or on ECMO is of higher risk, leading to increased likelihood of post-transplant complications, which are closely associated the requirement of RRT.

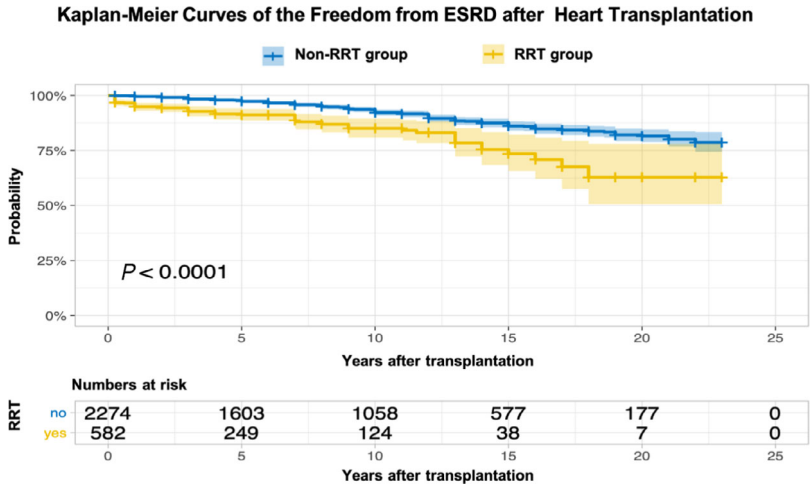
The Kaplan–Meier survival curves showed a striking difference in survival rates over time of the two groups. The major separation of the two survival curves occurred in the immediate post-transplant period. Evidence from previous studies showed that severe AKI was closely associated with other significant complications, such as tamponade, acute right ventricular failure and major bleeding, in the immediate postoperative period [12,22]. Therefore, stage 3 AKI requiring RRT is often a part of multi-organ failure, which is associated with very poor short-term prognosis [12,18,19]. Our data supported this finding, as stage 3 AKI requiring

Table 8. Binary logistic regression for risk factors of early death in recipients with severe PGD.

		Multivariate Analysis		
	N	Odds Ratio	95% CI	*P*-value
Donor sex				
Female	146	1.00	–	–
Male	214	0.49	0.15–1.65	0.5
Donor age	361	1.03	0.99–1.06	0.1
Recipient sex				
Female	94	1.00	–	–
Male	267	2.31	0.60–8.91	0.2
Recipient age	361	1.07	1.03–1.11	<0.001
Gender mismatch				
No	252	1.00	–	–
Male donor to female recipient	29	0.75	0.10–5.83	0.8
Female donor to male recipient	80	0.72	0.08–4.58	0.7
Recipient ethnicity				
Asian	28	1.00	–	–
Black	9	0.05	0.00–0.72	0.03
White	321	0.61	0.15–2.54	0.5
Others	2	–	–	–
Recipient diabetes status at registration				
No	315	1.00	–	–
Yes, insulin dependent	22	1.13	0.21–6.01	0.9
Yes, noninsulin dependent	14	3.74	0.48–29.02	0.2
Recipient hypertension at registration				
No	277	1.00	–	–
Yes	69	0.40	0.14–1.16	0.09
Recipient preop cardiac pathology				
Congenital heart disease	25	1.00	–	–
Coronary artery disease	80	0.13	0.01–1.38	0.09
Dilated cardiomyopathy	183	0.12	0.01–1.09	0.06
Others	67	0.13	0.01–1.35	0.09
Recipient renal function at transplantation				
eGFR $\geq$ 60 ml/min/1.73 m^2	197	1.00	–	–
CKD Stage 3	138	1.16	0.47–2.83	0.8
CKD Stage 4	9	0.95	0.04–22.84	0.9
CKD Stage 5	2	–	–	–
Urgent status recipient at transplantation	160	0.21	0.06–0.76	0.02
Recipient with VAD prior to transplantation				
None	170	1.00	–	–
Left VAD	48	0.72	0.23–2.32	0.6
Right VAD	6	0.11	0.01–8.36	0.3
Bilateral VAD	41	4.91	1.21–19.97	0.03
Recipient on inotrope prior to transplantation	101	1.58	0.58–4.31	0.4
Recipient on IABP prior to transplantation	22	6.30	1.27–31.31	0.03
Recipient on ECMO prior to transplantation	13	0.39	0.05–3.28	0.4
Allograft total ischaemic time	341	1.58	1.12–2.22	0.009
Transplantation era				
Era 1995–2000	47	1.00	–	–
Era 2001–2005	70	0.79	0.08–7.48	0.8
Era 2006–2010	67	1.49	0.15–15.17	0.7
Era 2011–2017	177	0.31	0.03–3.30	0.3
Transplantation centre				
Centre 1	61	1.00	–	–
Centre 2	2	–	–	–
Centre 3	45	0.02	0.02–0.66	0.02

Table 8. Continued.

		Multivariate Analysis		
	N	Odds Ratio	95% CI	*P*-value
Centre 4	97	0.19	0.08–1.63	0.2
Centre 5	1	0.18	0.07–1.64	0.2
Centre 6	49	0.01	0.02–0.50	0.005
Centre 7	62	0.08	0.04–1.21	0.08
Centre 8	37	–	–	–
Postop severe AKI requiring RRT				
No	89	1.00	–	–
Yes	268	8.07	2.58–25.20	<0.001



Time	3-month	1-year	5-year	10-year	15-year	20-year
Non-RRT Probability (95% CI)	99.9% (99.7–100%)	99.5% (99.2–99.8%)	97.4% (96.7–98.1%)	92.2% (90.8–93.6%)	86.1% (84.0–88.2%)	81.6% (78.7–84.6%)
RRT Probability (95% CI)	96.7% (95.3–98.2%)	94.8% (93.0–96.7%)	91.2% (88.6–93.9%)	85.1% (80.9–89.5%)	73.5% (65.8–82.1%)	62.8% (50.6–78.0%)

Figure 3 Kaplan–Meier curves of the freedom from ESRD for the heart transplant recipients in the non-RRT and RRT groups.

RRT was significantly associated with all of the documented complications in the immediate post-transplant periods. In addition, among the recipients who developed severe PGD post-transplant, those required RRT was of an increased risk of 90-day mortality. This finding was consistent with that reported by Sabatino *et al.* [26]. While severe PGD leads to post-transplant haemodynamic instability and thus higher risk of developing severe AKI, the requirement of RRT indicates worse systemic morbidity and predicts mortality in the recipients with severe PGD.

Interestingly, the gap between the two survival curves gradually reduced over time, indicating that the subgroup of recipients in the RRT group, who had survived through the initial post-transplant period, had a lower subsequent attrition rate. The differences in the characteristics of the 3-month survivors in the RRT and non-RRT groups could not explain this phenomenon, which had never been discussed in the literature either. Other factors that were not considered in this study, such as frailty [27,28], might shed light on the difference in the long-term attrition rate between the two groups. We hypothesized that these recipients in the RRT group, who survived through the haemodynamic instability and other major complications in the initial post-transplant period, were perhaps a group of self-selected patients with better physiological 'reserve'.

In contrast to most of the studies about peri-operative renal function and survival [21,29], we found that none of the renal function-related factors peri-transplant had a statistical effect on long-term survival. The adverse impact of stage 3 AKI requiring RRT was purely on the short-term survival, as shown by the finding of the Kaplan–Meier survival analysis. This observation reflects

Table 9. Multivariate Cox regression model for time to develop ESRD in patients who survived at least 3 months post-transplant.

		Multivariate analysis		Final model		
	N	Hazard ratio	*P*-value	Hazard ratio	95% CI	*P*-value
Recipient sex						
Female	627	1.00	–			
Male	2204	1.20	0.4			
Recipient age	2832	0.99	0.9			
Recipient ethnicity						
Asian	159	1.00	–			
Black	50	3.05	0.06			
White	2549	1.12	0.8			
Others	27	0.00	1			
Recipient diabetes status at registration						
No	2487	1.00	–	1.00	–	–
Yes, insulin dependent	100	2.41	0.007	2.61	1.44–4.81	0.002
Yes, noninsulin dependent	131	1.24	0.6	1.26	0.61–2.64	0.5
Recipient hypertension at registration						
No	2215	1.00	–			
Yes	490	0.99	0.9			
Recipient preop cardiac pathology						
Congenital heart disease	134	1.00	–			
Coronary artery disease	786	1.52	0.5			
Dilated cardiomyopathy	1462	1.32	0.6			
Others	435	1.29	0.7			
Recipient renal function at transplantation						
eGFR $\geq$ 60 ml/min/1.73 m^2	1465	1.00	–	1.00	–	–
CKD Stage 3	1062	2.11	<0.001	2.12	1.45–2.90	<0.001
CKD Stage 4	67	5.02	<0.001	4.81	2.31–9.92	<0.001
CKD Stage 5	3	76.04	<0.001	58.03	6.32–541.01	<0.001
Allograft total ischaemic time	2724	0.85	0.04	0.85	0.72–0.99	0.04
Recipient ΔeGFR	2576	1.01	<0.001	1.01	1.01–1.02	<0.001
RRT	552					
Era 1995–2000						
Non-RRT	1030	1.00	–	1.00	–	–
RRT	66	1.20	0.6	1.21	0.58–2.51	0.6
Era 2001–2005						
Non-RRT	464	0.43	0.001	0.44	0.27–0.71	0.001
RRT	83	–	–	1.16	–	–
Era 2006–2010						
Non-RRT	309	0.42	0.04	0.42	0.19–0.92	0.03
RRT	99	–	–	1.66	–	–
Era 2011–2017						
Non-RRT	436	0.24	0.06	0.23	0.05–0.99	0.05
RRT	304	–	–	1.68	–	–
Interaction between transplantation era and RRT						
Era 1995–2000 and RRT		1.00	–	1.00	–	–
Era 2001–2005 and RRT		2.20	0.1	2.20	0.77–6.44	0.1
Era 2006–2010 and RRT		3.30	0.05	3.30	1.02–11.01	0.05
Era 2011–2017 and RRT		6.10	0.05	6.10	1.07–34.03	0.04
Transplantation centre						
Centre 1	416	1.00	–	1.00	–	–
Centre 2	98	2.91	0.002	3.12	1.58–6.01	0.001
Centre 3	713	0.51	0.05	0.56	0.29–1.08	0.08
Centre 4	489	1.77	0.05	1.77	1.02–3.11	0.04
Centre 5	101	2.20	0.03	2.31	1.12–4.82	0.02

Table 9. Continued.

		Multivariate analysis		Final model		
	N	Hazard ratio	*P*-value	Hazard ratio	95% CI	*P*-value
Centre 6	374	2.31	0.008	2.41	1.32–4.31	0.005
Centre 7	381	1.69	0.09	1.66	0.91–3.03	0.1
Centre 8	243	0.88	0.8	0.89	0.42–1.89	0.8

ΔeGFR, recipient eGFR at transplantation – recipient eGFR at 3-month post-transplant.

that in carefully selected heart transplant recipients, their pretransplant renal function is largely influenced by the prerenal factors, rather than intrinsic renal pathology.

Despite the lack of influence on long-term survival, all renal function-related factors, including renal function at transplantation, ΔeGFR and stage 3 AKI requiring RRT were significant predictors of ESRD. Moreover, there was a significant reduction in the risk of developing ESRD in the non-RRT groups over time. This could be potentially explained by that in the earlier eras, there was a proportion of recipients with severe post-transplant renal impairment who did not receive RRT because of lack of access. They had more rapid renal decline compared to their peers in the non-RRT groups who did not have an as significant renal insult in the immediate post-transplant period. With an increased availability of RRT in the later eras, most of the recipients, who would benefit from RRT for renal or other indications, would have received it and thus belong to the RRT groups. If this assumption is correct, compared to that of the era 1995–2000, the non-RRT group in the era 2011–2017 would include fewer recipients with significant post-transplant renal injury. Therefore, the risk of ESRD for the non-RRT groups decreased with time.

The discrepancy in the risks of developing ESRD across transplantation centres may be explained by the different practices, such as immunosuppression strategies and threshold of initiating post-transplant RRT, adopted by different centres. Unfortunately, with the limited data available from the registry, we could not explore this hypothesis further.

The counter-intuitive small protective effect of long total ischaemic time on renal function deterioration was first observed by Thomas *et al.* [3], who reported on the earlier half of our cohort. With an additional 10 years of data, this effect persists. It is independent of other variables, such as recipients' age and cardiac pathologies. We speculate that with an anticipated long ischaemic time, the selection of donor hearts would be more cautious. Therefore, proportionally, there would be few extended-criteria donor hearts with longer ischaemic time. Better donor heart quality reduced recipients' renal function deterioration in the long term.

Our study benefits from a large national cohort with long follow-up period and relatively comprehensive database. However, the analysis was limited by the number of variables collected by the UK Transplant Registry. Some relevant factors, such as pretransplant proteinuria and post-transplant immunosuppression therapies, were not available. As no SCr or eGFR in the immediate post-transplant period was recorded in the registry, the severity of post-transplant renal injury not requiring RRT could not be graded using either the KDIGO classification or the RIFLE criteria. The use of RRT indicates severe AKI, but is subject to variation in clinical practice. In addition, although most of the variables in the registry had less than 10% missing data, the data about haemodynamic support required prior to transplantation, including inotrope, VAD, IABP and ECMO, were missing in 35.8% (1205/3365) of recipients.

In conclusion, this study confirmed that stage 3 AKI requiring RRT post-transplant is a prevalent problem for heart transplant recipients. It is associated with significantly worse short-term survival, but has no impact on long-term mortality. However, it accelerates renal function deterioration in the long term. There are two potential therapeutic gains from this analysis. Optimizing recipients' preoperative renal function may help reduce the risk of severe AKI post-transplant, especially for male recipients with poor pretransplant renal function and supported by left VAD or ECMO. In addition, for recipients who required post-transplant RRT, their renal function needs to be closely monitored. They are more likely to benefit from renal-sparing immunosuppressive regimes, such as Everolimus instead of the nephrotoxic Calcineurin inhibitors [30,31].

Authorship

JHD, GP and NS: contributed to the conception and design of the study. SNR: made substantial contribution to data acquisition and interpretation. TW and LW:

performed the statistical analysis. LW: wrote the first draft of the manuscript. All authors agree to be accountable for all aspects of the work and resolve any questions related to the accuracy of the manuscript, revised the manuscript and approved the final version of the manuscript.

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Conflicts of interests

The authors declare no conflicts of interests.

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