


## 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.

*Transplant International* 2020; 33: 1650–1666

## Key words

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

Received: 7 January 2020; Revision requested: 30 January 2020; Accepted: 9 June 2020; Published online: 3 July 2020

## 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,

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].  $\Delta$ eGFR 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/1.73 m<sup>2</sup>), 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    |             |

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 multi-variable 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

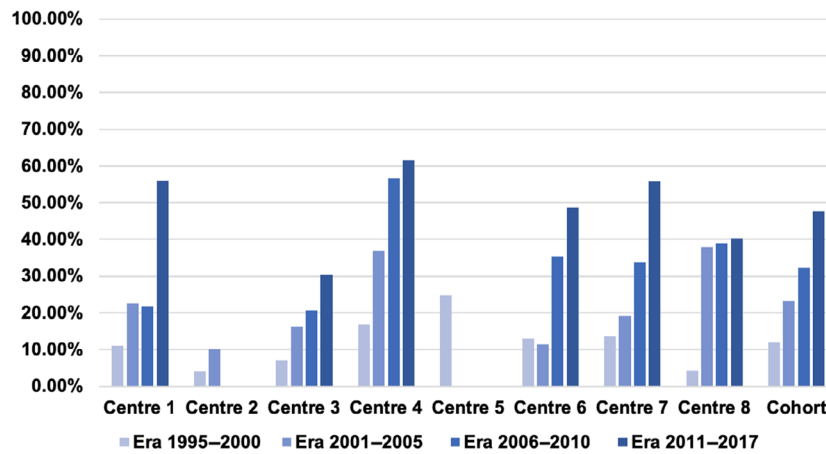
### Baseline characteristics

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.

**Table 1. Continued.**

|  | N = 3365    |
|--|-------------|
| 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 <sup>2</sup>           | 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.



**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<br>N = 1330 | Era 2001–2005<br>N = 650 | Era 2006–2010<br>N = 501 | Era 2011–2017<br>N = 884 |
|---|---------------------------|--------------------------|--------------------------|--------------------------|
| Donor age (year), mean $\pm$ SD                   | 34.2 $\pm$ 12.2           | 36.3 $\pm$ 12.3          | 37.1 $\pm$ 12.0          | 39.1 $\pm$ 12.4          |
| Recipient age (year), mean $\pm$ SD               | 48.6 $\pm$ 10.9           | 45.5 $\pm$ 13.5          | 45.1 $\pm$ 13.6          | 45.6 $\pm$ 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 $\pm$ SD | 3.0 $\pm$ 1.0             | 3.6 $\pm$ 0.9            | 3.5 $\pm$ 0.9            | 3.3 $\pm$ 1.4            |

Data are given as number (percentage) or mean  $\pm$  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<br>N = 520 | Centre 2<br>N = 107 | Centre 3<br>N = 808 | Centre 4<br>N = 613 | Centre 5<br>N = 131 | Centre 6<br>N = 438 | Centre 7<br>N = 427 | Centre 8<br>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 $\pm$ SD                   | 36.9 $\pm$ 12.5     | 33.5 $\pm$ 11.9     | 37.3 $\pm$ 12.7     | 35.5 $\pm$ 12.4     | 32.5 $\pm$ 11.1     | 36.9 $\pm$ 12.1     | 36.0 $\pm$ 12.2     | 36.9 $\pm$ 12.3     |
| Recipient age (year), mean $\pm$ SD               | 44.6 $\pm$ 14.2     | 52.2 $\pm$ 9.4      | 48.1 $\pm$ 12.4     | 46.1 $\pm$ 12.4     | 46.8 $\pm$ 11.5     | 45.5 $\pm$ 12.8     | 47.6 $\pm$ 12.2     | 48.3 $\pm$ 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 $\pm$ SD | 3.3 $\pm$ 0.8       | 2.8 $\pm$ 1.0       | 3.3 $\pm$ 1.0       | 3.4 $\pm$ 1.5       | 2.8 $\pm$ 0.9       | 3.1 $\pm$ 1.0       | 3.4 $\pm$ 0.8       | 3.3 $\pm$ 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  $\Delta$ eGFR 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.

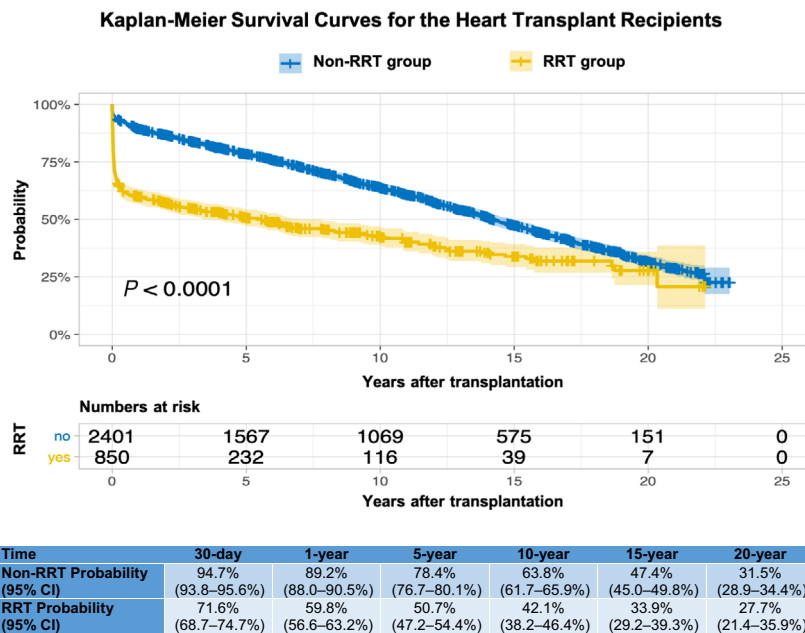
|  | Univariate analysis |            |         | Multivariate analysis |            |         |
|--|---------------------|------------|---------|-----------------------|------------|---------|
|  | N                   | Odds Ratio | P-value | Odds Ratio            | 95% CI     | P-value |
| Donor sex                                      |                     |            |         |                       |            |         |
| 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 ≥ 60 ml/min/1.73 m <sup>2</sup>           | 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 (%)<br>N = 876 | Non-RRT group n (%)<br>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  |

**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.

|   | N    | Multivariate analysis |         | Final model  |           |         |
|---|------|-----------------------|---------|--------------|-----------|---------|
|   |      | 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 <sup>2</sup>       | 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 $\Delta$ eGFR                         | 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.

|          | N   | Multivariate analysis |         | Final model  |           |         |
|----------|-----|-----------------------|---------|--------------|-----------|---------|
|          |     | 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     |

$\Delta$ eGFR, 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 [interquartile range (IQR): 1.6–13.0 years].

Immediately prior to transplantation, the means of eGFR of the RRT and non-RRT groups were comparable,  $67.1 \pm 32.3$  and  $67.9 \pm 27.3$  ml/min/1.73 m<sup>2</sup>, 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  $\Delta$ eGFR was  $13.0 \pm 37.5$  and  $9.3 \pm 24.3$  ml/min/1.73 m<sup>2</sup>, 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 in the 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 pre-operative 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<br>(N = 552), n (%) | Non-RRT group<br>(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 <sup>†</sup> |
| 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 <sup>†</sup>    |
| 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 <sup>2</sup>           | 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 <sup>‡</sup>  |
| 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<br>( <i>N</i> = 552), <i>n</i> (%) | Non-RRT group<br>( <i>N</i> = 2239), <i>n</i> (%) | <i>P</i> -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.

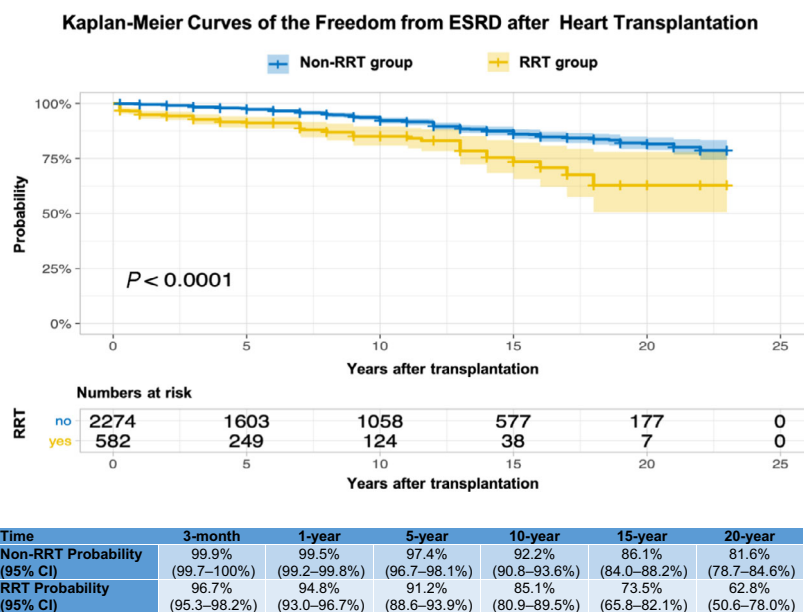
The Kaplan–Meier survival curves showed a striking difference in survival rates over time of the two groups. The major separation of the two survival curves occurred in the immediate post-transplant period. Evidence from previous studies showed that severe AKI was closely associated with other significant 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.

|  | N   | Multivariate Analysis |            |         |
|--|-----|-----------------------|------------|---------|
|  |     | 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 <sup>2</sup>      | 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.

|                                 | N   | Multivariate Analysis |            |         |
|---------------------------------|-----|-----------------------|------------|---------|
|                                 |     | 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  |

**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.

|   | N    | Multivariate analysis |         | Final model  |             |         |
|---|------|-----------------------|---------|--------------|-------------|---------|
|   |      | 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 <sup>2</sup>       | 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 $\Delta$ eGFR                         | 2576 | 1.01                  | <0.001  | 1.01         | 1.01–1.02   | <0.001  |
| RRT   |      |                       |         |              |             |         |
| 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.

|          | N   | Multivariate analysis |         | Final model  |           |         |
|----------|-----|-----------------------|---------|--------------|-----------|---------|
|          |     | 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     |

$\Delta$ eGFR, 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,  $\Delta$ eGFR 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.

## Fundings

The research was funded by the National Institute for Health Research (NIHR) Blood and Transplant Research Unit (BTRU) in Organ Donation and Transplantation at the University of Cambridge in collaboration with Newcastle University and in partnership with

NHSBT. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or NHSBT.

## Conflicts of interests

The authors declare no conflicts of interests.

## Acknowledgements

The authors are grateful to all the transplant centres in the UK, who contributed data on which this article is based. The authors thank the statisticians at the NHSBT for their contribution to data acquisition.

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