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Impact of changing renal function, while waiting for a heart transplant, on post-transplant mortality and development of end stage kidney disease

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SUMMARY

Heart transplantation is a viable option for end stage heart disease but long-term complications such as chronic kidney disease are being increasingly recognized. We sought to investigate the effect of change in estimated glomerular filtration rate (eGFR) during the heart transplant waitlist period on post-transplant mortality and end stage kidney disease (ESKD). We analysed the United Network of Organ Sharing heart transplant database from 2000 to 2017. Multivariable Cox regression with restricted cubic splines and cumulative incidence competing risk (CICR) methods were used to compare the effects of change in eGFR on mortality and ESKD, respectively. A total of 19 412 patients met our inclusion criteria. Mortality increased with increasing loss of eGFR (adjusted hazard ratio increased from 1.02 [confidence interval (CI) 1.01–1.04, $P = 0.008$] for 10% loss to 1.15 (CI 1.06–1.26, $P = 0.001$) for 50% loss of eGFR. Similarly, risk of ESKD also increased monotonically with increasing loss of renal function [subdistribution hazard ratio increased from 1.12 (CI 1.09–1.14, $P < 0.001$) to 2.0 (CI 1.74–2.3, $P < 0.001$)] as loss of eGFR increased from 10% to 50%. Overall, we found that loss of >10% of eGFR resulted in higher risk of mortality and higher risk of ESKD.

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Key words
change in renal function, chronic kidney disease, complications, estimated glomerular filtration rate, heart clinical, outcome, waitlist

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Introduction

Orthotopic heart transplantation (OHT) has become a viable option for advanced heart failure and survival has steadily improved, with patients surviving decades after heart transplantation. Long-term complications such as declining renal function and end stage kidney disease (ESKD) are being increasingly recognized adding to the complexity of care and to morbidity [1,2]. Few retrospective studies have shown improved survival after simultaneous heart kidney transplantation (SHK) compared to isolated heart transplantation among patients with reduced kidney function [3–5], likely resulting in an increase of SHK being performed. In the past decade, there has been a nearly fivefold increase in SHK performed.

The ability to predict recovery of kidney function after an isolated heart transplant is difficult as kidney dysfunction in the waitlisted population is often multifactorial. However, this is an important area of study

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that could lead to fewer unnecessary kidney transplants at the time of heart transplant. Prior studies in adults have shown that renal function at the time of listing and at the time of heart transplantation predicts post-OHT ESKD as well as patient survival [6,7]. In the paediatric population, there is increasing recognition that worsening renal function during the waiting period is a significant risk factor for post-OHT ESKD and patient survival [8]. We undertook this study to determine the effect of changing eGFR in adults while on the waiting list for OHT on patient survival post-OHT and the risk of developing ESKD (defined as need for dialysis or receipt of a subsequent renal transplant).

Methods

De-identified heart transplant data from the United Network for Organ Sharing (UNOS) database (2000–2017) were included in the study. We excluded patients who were less than 18 years of age, were on the waitlist for less than 30 days (except as below), received multi-organ transplants, had a history of any prior solid organ transplant, or were on maintenance dialysis. Serum creatinine at the time of listing and at time of transplant were obtained from this data set and the Modification of Diet in Renal Disease (MDRD) equation was used to calculate estimated glomerular function rate (eGFR) at these two time points [9]. We excluded eGFR >200 ml/min/1.73 m^2 as erroneous data [10]. We looked at the effect of change in eGFR (measured continuously) during the waitlist period on mortality and risk of development of ESKD. We did a subgroup analysis of the effect of change in eGFR separately in patients with a listing eGFR of <30 ml/min/1.73 m^2, 30–59 ml/min/1.73 m^2 and ≥60 ml/min/1.73 m^2. We also looked at the effect of change in eGFR by amount of time spent on the waitlist (<30, 30–90 and >90 days; for this subgroup analysis alone we included patients who were on the waitlist for <30 days). Using clinical knowledge we identified potential confounders of the relationship between change in eGFR and mortality and ESKD for inclusion in the multivariable model. The relevant recipient factors (age, gender, race, ethnicity, body mass index (BMI), diabetes), donor characteristics (donor age, cold ischaemia time, donor diabetes, donor hypertension), waitlist and peri-transplant related variables (ventricular assist device (VAD), use of extra corporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), Inotropes, days on waitlist), and post-transplant characteristics (graft ejection fraction (EF), new onset diabetes, calcineurin inhibitor (CNI) use) were evaluated.

Statistical analysis

Baseline characteristics between the groups were compared using chi-squared tests for categorical variables and analysis of variance (ANOVA) for continuous variables. Multivariable Cox regression with restricted cubic splines was used to assess the effect of change in eGFR on mortality [11,12]. The cumulative incidence competing risk (CICR) method was used to compare the effect of change in eGFR on the development of ESKD (with death as a competing risk) and subdistribution hazards approach was used to adjust for independent variables associated with ESKD [13]. Potential confounder variables were included in the multivariable analysis if they were associated ($P < 0.20$) in simple Cox regression for continuous variables and the Logrank test for categorical variables. We adjusted for patient's age, gender, race, BMI, diabetes, VAD use, ECMO, IABP, inotropes use, eGFR at listing, listing status, days on waitlist, donor hypertension, donor diabetes, CNI use, graft EF and new onset diabetes. Statistical analysis was performed using STATA 16.1 (StataCorp LP, College Station, TX, USA). Statistical significance was set at $P < 0.05$.

Results

During the study period, we had 19412 patients who met the inclusion criteria. 3551 (18.29%) had no change in their eGFR; 4932 (25.4%), 2803 (14.4%) and 637 (3.3%) had loss of up to 25%, 26–50% and >50% of eGFR, respectively, during the waiting period. 3502 (18.0%), 2082 (10.7%), 1905 (9.8%) patients had up to 25%, 26–50% and >50% improvement in their eGFR, respectively, while waiting for a heart transplant. Baseline characteristics of these seven groups are shown in Table 1.

Loss of renal function during the waiting period was associated with higher mortality. The adjusted hazard ratio (HR) was 1.02 [confidence interval (CI) 1.01–1.04, $P = 0.008$] for patients who lost just 10% of their listing eGFR. The adjusted hazard ratio increased to 1.15 (CI 1.06–1.26, $P = 0.001$) and 1.31 (CI 1.11–1.55, $P < 0.001$) for patients who lost 50 % and 90% of their listing eGFR, respectively, (Fig. 1). In subgroup analysis, based on listing eGFR, mortality was higher in patients who lost more than 10% of their listing eGFR when the starting eGFR was ≥60 ml/min/1.73 m^2 or between 59 ml/min/1.73 m^2 and 30 ml/min/1.73 m^2 (Table 2).

Table 1. Baseline characteristics based on percentage change in listing eGFR.

	Improvement in eGFR by >50% (1905)	Improvement in eGFR by 26–50%	Improvement in eGFR up to 25%	No change in eGFR	Loss of eGFR up to 25%	Loss of eGFR by 26–50%	Loss of eGFR by >50%	*P* value
N (19 412)	1905	2082	3502	3551	4932	2803	637	
Recipient characteristics								
Male gender* (%)	1453 (76.2)	1590 (76.3)	2737 (78.1)	2649 (74.6)	3813 (77.3)	2133 76.2)	474 (74.4)	0.014
Age (median with range)†	53 (18–78)	54 (18–73)	53 (18–77)	55 (18–78)	55 (18–77)	55 (18–76)	54 (18–72)	<0.001
White race* (%)	1307 (68.6)	1479 (71.0)	2511 (71.7)	2650 (74.6)	3464 (70.2)	1991 (71.0)	427 (67.0)	<0.001
Black race (%)	383 (20.1)	390 (18.7)	643 (18.3)	530 (14.9)	965 (19.5)	533 (19.0)	132 (20.7)	
Hispanic	149 (7.8)	147 (7.0)	219 (6.2)	250 (7.0)	325 (6.5)	193 (6.8)	54 (8.4)	
Days on Waitlist (median with range)†	135 (30–3467)	145 (30–4004)	155 (30–3833)	115 (30–3580)	160 (30–3989)	162 (30–4598)	184 (30–2739)	<0.001
Listing status 1A* (%)	431 (22.6)	317 (15.2)	457 (13.0)	473 (13.3)	688 (13.9)	418 (14.9)	114 (17.9)	<0.001
Ischaemic heart failure* (%)	758 (39.7)	836 (40.1)	1460 (41.6)	1569 (44.1)	2127 (43.1)	1190 (42.4)	266 (41.7)	0.014
BMI (median with range)†	26.5 (15–47)	27.1 (15–43)	27.1 (15–51)	26.6 (15–44)	27.4 (15–44)	27.1 (15–43)	27.6 (15–43)	<0.001
Cold ischaemic time (h) (median with range)†	3.21 (0.39–8.9)	3.19 (0.5–8.7)	3.16 (0.4–12)	3.1 (0.38–10.1)	3.14 (0.2–12)	3.14 (0.23–8.0)	3.13 (0.38–8.4)	0.008
Creatinine at the time of listing (median with range)†	1.6 (0.6–16)	1.33 (0.5–5.8)	1.25 (0.55–4.5)	1.1 (0.4–4.0)	1.1 (0.4–4.1)	1.0 (0.4–4.5)	1.0 (0.4–6.1)	<0.001
eGFR at time of listing (median with range)†	44.7 (3.12–122)	54.5 (12–147)	59.8 (14–159)	66.0 (15.4–186)	67.7 (15–192)	75.7 (13–198)	78 (11.9–191)	<0.001
eGFR at time of transplant (median with range)†	85.3 (22.7–196)	74.7 (16–186)	68.0 (16.4–196)	66.0 (15.4–186)	57.7 (13.7–173)	48.4 (7.7–141)	31.2 (2.2–89)	<0.001
Diabetes* (%)	491 (25.7)	537 (25.7)	923 (26.3)	852 (23.9)	1327 (26.9)	719 (25.6)	184 (28.8)	0.005
Donor age (median with range)†	29 (8–71)	30 (8–72)	30 (11–70)	29 (3–64)	30 (9–73)	29 (9–70)	29 (10–64)	0.07
Other variables at the time of transplant								
VAD use* (%)	1212 (63.6)	1071 (51.4)	1684 (48.0)	1636 (46.0)	2313 (46.9)	1416 (50.5)	374 (58.7)	<0.001
Inotropes* (%)	632 (33.1)	724 (34.7)	1256 (35.7)	1384 (38.9)	1793 (36.3)	1035 (36.9)	241 (37.8)	0.001
IABP* (%)	97 (5.0)	82 (3.9)	122 (3.4)	115 (3.2)	163 (3.3)	104 (3.7)	30 (3.7)	0.008
Post-transplant variables								
% Ejection fraction (median with ranges)†	60 (10–87)	60 (10–80)	60 (5–84)	60 (9–80)	60 (5–90)	60 (5–81)	60 (20–76)	0.11
CNI use* (%)	1713 (89.9)	1898 (91.1)	3201 (91.4)	3263 (91.8)	4506 (91.3)	2514 (89.6)	502 (78.8)	<0.001

Numbers missing: cold ischaemia time, 577; Diabetes, 44; Ejection fraction, 2019; ESKD, 1198.

*Categorical variables compared with chi-square.

†Continuous variables compared with ANOVA.

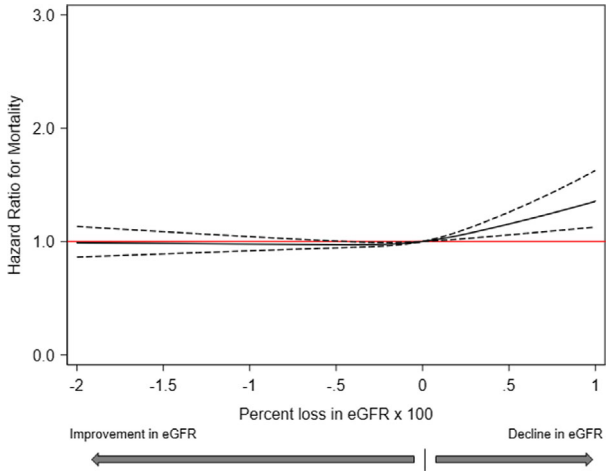

Figure 1 Overall adjusted hazard ratio for mortality. Multivariable cox regression with restricted cubic splines illustrating relationship between change in renal function during the waitlist period and post-transplant mortality.

For the same level of loss of eGFR, patients who had a lower starting eGFR had higher hazard ratio for mortality. There were very few patients with listing eGFR <30 ml/min/1.73 m^2 who had decline of their listing eGFR, therefore a valid conclusion could not be drawn in this group. When stratifying our data based on the amount of time spend on the waitlist, mortality was higher in patients who lost >10% of eGFR on the waitlist only if they were on the list for >90 days (Table 2). In the overall model for mortality, improvement in eGFR was not protective and they had similar mortality as compared to our reference group (no change in eGFR while on the waitlist).

A total of 1689 (8.7%) of the patients developed ESKD in the follow-up period. Table 3 lists the absolute number of ESKD events by percentage loss of eGFR during the waiting period. After adjusting for multiple confounders, we found that loss of eGFR by even 10% during the waiting period was associated with higher risk of ESKD (subdistribution hazard ratio (SHR) of 1.12 (CI 1.09–1.14, $P < 0.001$). The risk for ESKD continued to increase with increasing loss of eGFR and the SHR increased to 2.00 (CI 1.74–2.30, $P < 0.001$) and 3.68 (CI 2.84–4.79, $P < 0.001$) by the time there was a loss of 50% and 90% of listing eGFR, respectively (Fig. 2). Improvement in eGFR during the waiting period for heart transplant lowered the risk of ESKD. The confounders included in the model for development of ESKD was Black race or Hispanic ethnicity, recipient diabetes, donor age, CNI use, eGFR at listing, post-transplant diabetes and post-transplant EF.

Table 2. Adjusted hazard ratio with confidence interval and p value for mortality based on listing eGFR and time spent on the waitlist (Comparison group is patients with no change in eGFR).

Change in renal function	Listing eGFR ≥60 ml/min/m^2	Listing eGFR 59–30 ml/min/m^2	Time on waitlist >90 days	Time on waitlist 90–30 days	Time on waitlist <30 days
50% improvement	0.91 (0.82–1.02)	0.96 (0.91–1.02)	0.95 (0.91–0.99)	1.02 (0.97–1.07)	1.01 (0.97–1.05)
	0.09	0.16	0.51	0.43	0.63
20% improvement	0.96 (0.93–0.99)	0.97 (0.94–1.0)	0.97 (0.95–0.99)	0.99 (0.97–1.02)	1.01 (0.99–1.04)
	0.03	0.05	0.24	0.44	0.43
10% improvement	0.98 (0.96–1.0)	0.98 (0.96–1.0)	0.98 (0.97–0.99)	0.99 (0.98–1.01)	1.01 (0.99–1.03)
	0.05	0.05	0.03	0.19	0.32
10 % decline	1.02 (1.01–1.4)	1.03 (1.0–1.05)	1.03 (1.01–1.04)	1.01 (0.99–1.04)	0.99 (0.96–1.01)
	0.008	0.01	<0.001	0.43	0.44
20% decline	1.05 (1.01–1.08)	1.06 (1.01–1.11)	1.06 (1.02–1.1)	1.04 (0.98–1.09)	0.97 (0.93–1.02)
	0.004	0.02	0.002	0.14	0.24
50% decline	1.13 (1.01–1.25)	1.17 (1.01–1.34)	1.18 (1.06–1.31)	1.11 (0.95–1.30)	0.91 (0.78–1.06)
	0.04	0.03	0.002	0.19	0.23

Table 3. Absolute number of events (death and eskd (with percentages)).

Change in eGFR (total number)	Improvement in eGFR by >50% (1905)	Improvement in eGFR by 26–50% (2082)	Improvement in eGFR up to 25% (3502)	No change in eGFR (3551)	Loss of eGFR up to 25% (4932)	Loss of eGFR by 26-50% (2803)	Loss of eGFR by >50% (637)
Death (%)	667 (35.0)	717 (34.4)	1054 (30.0)	1368 (38.5)	1593 (32.4)	963 (34.3)	297 (46.6)
ESKD (%)	167 (8.7)	175 (8.4)	276 (7.8)	321 (9.0)	387 (7.8)	264 (9.4)	99 (15.5)

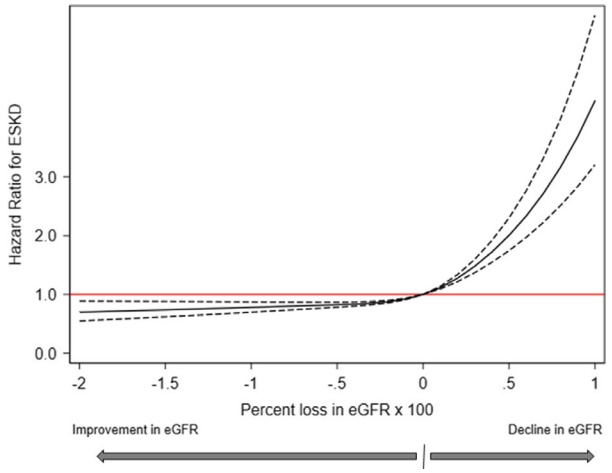

Figure 2 Subdistribution hazard ratio for end stage kidney disease (ESKD). Cumulative incidence competing risk (CICR) model illustrating the relationship between change in renal function during the waitlist period and post-transplant development of ESKD (with death as a competing event).

When investigating the effect of change in eGFR on ESKD risk based on the listing eGFR, we found that loss of 10% or more of starting eGFR lead to significant higher risk of ESKD if starting eGFR was ≥60 ml/min/1.73 m^2 or if starting eGFR was between 59 ml/min/1.73 m^2 and 30 ml/min/1.73 m^2 (Table 4). As with mortality, we also found that for similar loss of eGFR the hazard ratio for ESKD was higher if the starting eGFR was lower. The number of patients with loss of eGFR if the listing eGFR was <30 ml/min/1.73 m^2 was too few to come to any meaningful conclusion. In the subgroup analysis, looking at the effect of wait time and change in eGFR we found that loss of >10% or more of eGFR had a significant impact on the risk of ESKD in all the subgroups (time spend on the waitlist ≤30 days, 31–90 days or >90 days (Table 4).

Discussion

In this UNOS database analysis of nearly 20 000 OHT patients, we examined pre- and postheart transplant risk factors for mortality. We found that, while waiting for a heart transplant, a 10% decline in renal function was associated with an increased risk of both post-transplant mortality and ESKD. Further, these risks monotonically increased with increasing loss in renal function.

Overall, our adjusted models showed that decline in eGFR by 10% or more translated to higher risk of future ESKD. It is important to note that this was true even when patients were on the list for short period of time (<30 days). We looked at percentage changes in eGFR during the wait time, knowing that at lower eGFR small absolute changes will give rise to higher percentage changes, and our findings suggest that even smaller absolute changes in eGFR at lower starting eGFR are significant. Other studies have identified worse mortality in nontransplant adult patients with heart failure who have a decline in their renal function [14–16]. Acute kidney injury in the perioperative period, renal function at one year postheart transplant and development of ESKD post-transplant have each been shown to predict higher long-term patient mortality [17–21]. Our analysis shows that worsening renal function (>10%) while on the waitlist for heart transplant is associated with an increased risk of ESKD, even if patients are on the list for short periods of time (<30 days). These data suggest that a potentially reversible condition such as cardiorenal syndrome was playing a smaller role and that kidney function decline continues in this subgroup following OHT and leads to ESKD.

Several studies have now shown better outcomes with combined heart kidney transplantation as compared to heart transplantation alone in recipients with reduced eGFR [3–5,22]. These emerging data could be prompting an increase in the number of simultaneous heart kidney transplantation (nearly fivefold increase from 2004 to 2018) [23]. Moreover, because of the current allocation algorithm recipients undergoing simultaneous heart kidney transplant likely receive a higher quality deceased donor kidney compared to a subsequent isolated deceased donor kidney transplant [24]. This creates an imbalance between beneficence and utility and can place patients in need of a kidney transplant alone at a relative disadvantage [23]. Furthermore, some

Table 4. Subdistribution hazard ratio with confidence interval and p value for ESKD based on listing eGFR and time spent on the waitlist (comparison group is patients with no change in eGFR).

Change in renal function	Listing eGFR ≥60 ml/min/m^2	Listing eGFR 59–30 ml/min/m^2	Time on waitlist >90 days	Time on waitlist 90–30 days	Time on waitlist <30 days
50% improvement	0.82 (0.67–1.0)	0.72 (0.67–0.78)	0.83 (0.78–0.89)	0.81 (0.74–0.88)	0.83 (0.77–0.91)
	0.05	<0.001	<0.001	0.004	0.008
20% improvement	0.90 (0.84–0.96)	0.84 (0.81–0.87)	0.89 (0.86–0.91)	0.86 (0.83–0.90)	0.89 (0.86–0.93)
	0.002	<0.001	<0.001	<0.001	<0.001
10% improvement	0.94 (0.91–0.96)	0.91 (0.89–0.93)	0.93 (0.91–0.95)	0.92 (0.89–0.94)	0.94 (0.91–0.96)
	0.005	<0.001	<0.001	<0.001	<0.001
10 % decline	1.10 (1.07–1.13)	1.12 (1.09–1.15)	1.11 (1.08–1.14)	1.13 (1.09–1.17)	1.09 (1.05–1.13)
	<0.001	<0.001	<0.001	<0.001	<0.001
20% decline	1.24 (1.17–1.31)	1.27 (1.19–1.35)	1.26 (1.19–1.34)	1.31 (1.21–1.42)	1.22 (1.12–1.32)
	<0.001	<0.001	<0.001	<0.001	<0.001
50% decline	1.87 (1.56–2.24)	1.85 (1.55–2.22)	1.95 (1.64–2.31)	2.14 (1.69–2.70)	1.73 (1.37–2.19)
	<0.001	<0.001	<0.001	<0.001	<0.001

patients who receive a simultaneous heart/kidney transplant may recover native kidney function making that kidney transplant unnecessary and consequential to those remaining on the kidney transplant waitlist. However, it is difficult to predict renal recovery after heart transplantation as reduced renal function in end stage heart failure is multifactorial and sometimes irreversible. Reduced kidney perfusion, increased venous pressures, enhanced proinflammatory signalling and stimulation of fibrosing pathways from an activated renin–angiotensin–aldosterone system are few of the many pathophysiological mechanisms [25,26]. In the heart failure population although studies have shown adverse outcome with worsening kidney function as noted above, there are other studies like the ESCAPE and EVEREST trials in which decongestion and hemoconcentration with treatment was associated with decline in renal function but improved survival, highlighting the complexity of the problem [27,28].

Mechanical circulatory support in the heart failure population has been shown to improve early renal function but the effect seemed to be largely transient [29]. It is also unknown if improvement in renal function with ventricular assist devices in end stage heart failure population translates into renal recovery postheart transplantation. Recent studies have, however, shown some benefit of using levosimendan to improve renal function in patients waiting for a heart transplant as well as in the early post-transplant period [30,31]. In prior studies, pretransplant renal function, Black race, diabetes, post-transplant heart function, post-transplant diabetes, CNI use were associated with high risk of development of ESKD. We now report that worsening renal function while waiting for heart transplant is also an important risk factor for ESKD. This finding has important implication for clinicians caring for patients waitlisted for heart transplant as avoiding progressive kidney injury and focusing on renoprotective therapies during this period may help prevent later ESKD. Those that show continued kidney function decline, while waiting, may need to be prioritized for a combined heart kidney transplant or placed in a safety net for a subsequent kidney transplant if ESKD develops a short time after OHT.

Several important limitations should be considered when interpreting the results of this database analysis. In all retrospective studies, there is a possibility of selection bias and the results could have been affected by missing data. In our study cohort, there is a possibility that patients with significant deterioration of kidney function may have gone on to receive a combined heart

kidney transplantation or may have been completely removed from the heart transplant list which can introduce selection bias. Aetiology of chronic kidney disease in heart failure and also post-OHT is multifactorial and registry analysis does not allow us to comment on the cause of ESKD in this population. Data regarding use of medication like diuretics and angiotensin-converting enzyme inhibitors which can affect kidney function were not available. Measured GFR is not the same as eGFR and there is variability in the measured and calculated GFR in patients waiting for heart transplant [9]. This could be secondary to loss of lean body mass, however, it is not practical to measure GFR in each patient. Registry data also suffers from missing data and errors in data entry. There were 1242 patients with missing eGFR at the time of listing and about 1576 who had eGFR greater than 200 which we excluded from the analysis. We also did not have data on proteinuria or urine chemistry, which provides valuable information on glomerular and tubular function and the potential for recovery of renal disease. cPRA and crossmatch data were also missing in majority of cases and its effect could not be analysed. Finally, retrospective analysis cannot prove causality and can only demonstrate associations.

In conclusion, even minor loss of eGFR (>10%) between listing and transplant in OHT was associated with an increased risk of post-OHT mortality. Worsening renal function (>10%) during the waiting time even for a short duration was associated with higher risk of post-OHT ESKD while improvement in renal function reduced the risk. A multidisciplinary approach may help preserve renal function while waiting and thus the development of ESKD post-OHT.

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Authorship

Every individual who is included as a co-author contributed to this manuscript. AK and CP conceived the study, AK and LB conducted the database analysis and statistical studies and AK, LB and CP interpreted the data analysis and wrote the manuscript.

Conflict of interest

The authors have declared no conflicts of interest.

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