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# Pre-orthotopic heart transplant estimated glomerular filtration rate predicts post-transplant mortality and renal outcomes: An analysis of the UNOS database

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**KEYWORDS:**
estimated glomerular filtration rate;
heart transplant outcome;
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**BACKGROUND:** Pre-orthotopic heart (OHT) serum creatinine correlates with post-OHT outcomes, but there is limited information on the relationship between pre-OHT estimated glomerular filtration rate (eGFR) and adjusted short- and long-term survival and renal outcomes post-OHT.

**METHODS:** Using the United Network of Organ Sharing (UNOS) database we estimated pre-OHT eGFR using the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in patients aged ≥18 years who underwent OHT between 1988 and 2013. Patients were stratified into 5 eGFR categories (≥90, 60 to 89, 45 to 59, 30 to 44 and <30 ml/min/1.73 $m^2$) using each equation. The primary outcome was to determine whether pre-OHT eGFR independently predicted post-OHT mortality.

**RESULTS:** A total of 30,090 patients were included in the study; of these, 46.1% and 39.9% had an eGFR <60 ml/min/1.73 $m^2$ by MDRD and CKD-EPI, respectively. Compared with eGFR ≥90 ml/min/1.73 $m^2$, the adjusted hazard ratio of mortality was 1.09 (95% confidence interval [CI] 1.02 to 1.26) for eGFR 45 to 59 ml/min/1.73 $m^2$, 1.22 (95% CI –1.23 to 1.31) for eGFR 30 to 44 ml/min/1.73 $m^2$ and 1.55 (95% CI 1.41 to 1.70) for eGFR <30 ml/min/1.73 $m^2$ by MDRD. There was no advantage for CKD-EPI over MDRD in determining post-OHT mortality. Pre-OHT eGFR by either equation was predictive of post-OHT end-stage renal disease (ESRD) and the need for kidney transplantation, with the highest risk in those with pre-OHT eGFR <30 ml/min/1.73 $m^2$ by either equation.

**CONCLUSIONS:** Pre-OHT eGFR was independently associated with mortality, ESRD and kidney transplantation after OHT. There was no advantage of CKD-EPI over MDRD in determining post-OHT mortality or renal outcomes.

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Pre-orthotopic heart transplant (OHT) kidney function has a strong impact on waitlist mortality and post-OHT patient and graft survival rates, even in recipients of combined heart and kidney transplantation.[1–5] Kilic and

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colleagues demonstrated that each 1-mg/dl increase in pre-OHT serum creatinine is associated with a 58% increase in the adjusted odds of graft failure 1 year after OHT in 671 patients who underwent heart re-transplantation.[2] Data from the International Society for Heart and Lung Transplantation (ISHLT) 2015 annual report show a direct correlation between pre-OHT serum creatinine and 1-year post-OHT mortality, with a pre-OHT serum creatinine of $\geq 2.5$ mg/dl being associated with almost double the mortality risk 1 year after OHT.[6] These reports, however, were limited to 1-year post-OHT outcomes and either used serum creatinine to assess kidney function or did not adjust for other important factors that affect post-OHT survival. Therefore, the independent effect of pre-OHT kidney function based on estimates of glomerular filtration rate on long-term post-OHT survival remains unclear.

Serum creatinine is a dynamic variable and is affected by various factors, including hydration status and diuretic use as well as patients' muscle mass, gender and ethnicity. In patients with heart failure with reduced ejection fraction, there is often difficulty distinguishing between renal and pre-renal causes of serum creatinine elevation. Serum creatinine is therefore an inaccurate tool for assessing pre-OHT kidney function, especially in heart failure patients with cachexia and muscle wasting, which alter creatinine generation. Obtaining estimated glomerular filtration rate (eGFR) using readily available equations that employ surrogate markers, such as serum creatinine or cystatin C, is the most commonly used method for assessing GFR in the general population, but the utility of eGFR in OHT candidates has not been well studied. Moreover, it is unclear which GFR equation will better predict post-OHT outcomes. The current ISHLT guidelines recommend assessing pre-OHT renal function using eGFR, but they do not specify a particular eGFR equation.[7] These ISHLT recommendations were designated Level C evidence indicating only expert opinion, due to the lack of studies linking pre-OHT eGFR with post-OHT outcomes. Using the United Network for Organ Sharing (UNOS) database, we sought to examine and compare the independent effects of pre-OHT kidney function, as assessed by both the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, on post-OHT patient mortality and renal outcomes, including end-stage renal disease (ESRD) and need for kidney transplantation.

## Methods

UNOS provided de-identified waiting list and transplant data on all heart transplant candidates registered on the United States waiting list via the UNOS Standard Transplant Analysis and Research (STAR) file. Patients $\geq 18$ years of age who were transplanted from 1988 to 2013 were included in the study. Those patients who received simultaneous heart–kidney transplant or pre-OHT kidney transplant and those on dialysis at the time of OHT were excluded from the study. Immediate pre-OHT serum creatinine was obtained from the UNOS heart transplant database and was utilized to calculate patients' pre-transplant GFR using the equations given for MDRD and CKD-EPI. Each equation utilizes the following 4 variables: gender; age; race; and serum creatinine. Patients missing any of these variables were excluded from the study.

The following equations were utilized:

$$For\ MDRD:\ eGFR = 175 \times standardized\ sCr^{-1.154} \times age^{-0.203} \times 1.212\ (if\ black) \times 0.742\ (if\ female).$$

$$For\ CKD\text{-}EPI:\ eGFR = 141 \times min(sCr/\kappa, 1)^{\alpha} \times max(sCr/\kappa, 1)^{n1.209} \times 0.993^{age} \times 1.018\ (if\ female) \times 1.159\ (if\ black).$$

where sCr is serum creatinine, $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is $-0.329$ for females and $-0.411$ for males, min indicates the minimum of sCr/$\kappa$ or 1 and max indicates the maximum of SCr/$\kappa$ or 1.[4]

The data were stratified by clinically relevant eGFR categories based on each respective equation as follows (M representing eGFR by MDRD and C representing eGFR by CKD-EPI): M1/C1 = eGFR $\geq 90$ ml/min/1.73 m$^2$; M2/C2 = eGFR 60 to 89 ml/min/1.73 m$^2$; M3/C3 = eGFR 45 to 59 ml/min/1.73 m$^2$; and M4/C4 = eGFR 30 to 44 ml/min/1.73 m$^2$; and M5/C5 = eGFR $<30$ ml/min/1.73 m$^2$. Given that the number of patients with GFR $<15$ ml/min/1.73 m$^2$ was small, these patients were combined with those in the M5/C5 group.

Our primary aim was to assess the effect of pre-OHT eGFR on long-term post-OHT survival. Our secondary aims were to: (1) determine whether GFR determination using the CKD-EPI equation will impact GFR category in OHT candidates; (2) determine whether GFR reclassification using CKD-EPI will alter post-OHT survival compared with MDRD; and (3) assess the effect of pre-OHT kidney function on post-OHT ESRD and the need for kidney transplantation.

## Statistical analysis

The baseline characteristics of the population were compared based on MDRD eGFR categories using the chi-square or Fisher's exact test for categorical variables and Student's *t*-test or Wilcoxon's rank sum test for continuous variables. We then reclassified the population based on CKD-EPI eGFR categories and compared the net reclassification difference between the 2 equations. A crude net reclassification index was constructed and evaluated for each of the end-points, as described elsewhere.[8]

We constructed Kaplan–Meier curves to compare the effect of the 5 different eGFR categories and 2 eGFR cut-offs ($<60$ ml/min/1.73 m$^2$ and $<45$ ml/min/1.73 m$^2$) using the MDRD and CKD-EPI equations on post-OHT survival. Cox proportional hazards models were used to investigate the relationship of these factors to the post-OHT end-point. In addition, the following recipient- and transplant-related variables were adjusted for in this analysis: age; gender; ethnicity; body mass index (BMI); cold ischemia time; diabetes; inotrope use; era of transplant (Era 0: OHT between 1988 and 1998; Era 1: OHT between 1999 and 2006; Era 2: OHT between 2007 and 2013); listing status; and ventricular assist device (VAD). Due to the large number of patients without information on hypertension, we did not include history of hypertension in this analysis. Given the high correlation between VAD, inotrope use and listing status, these models were run separately, and the results for both models were included. In a separate model, we assessed the effect of pre-OHT serum creatinine alone, without using eGFR, on post-OHT survival after adjusting for the aforementioned factors. Statistical analysis was performed using SAS (version 9.3). $p < 0.05$ was considered statistically significant.