The value of cardiopulmonary exercise testing and stress echocardiography in the prediction of all-cause mortality in adults with end stage renal disease

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Abstract

We aimed to assess the prognostic utility of different parameters routinely assessed from cardiopulmonary exercise testing (CPET) and exercise echocardiography in adults with end-stage renal disease (ESRD). Forty-two ESRD (37 male) individuals (age: 58±13 years, height: 169.30±8.30 cm, weight: 81±15 kg, body surface area: 1.92±0.20m^2) underwent a maximal/symptom limited CPET, with a full cross-sectional echocardiogram performed at baseline and peak exercise. All participants were prospectively followed over a 10-year period, with all-cause mortality as the primary endpoint. After the follow-up period, a total of 19 participants (45%) died. Left atrial size (4.70±0.70 vs. 3.65±0.50 cm, P<0.001) and anteroseptal wall thickness (1.28±0.40 vs. 1.06±0.02 cm, P=0.002) were significantly greater in those that died, while peak heart rate was significantly lower (108±12 vs. 128±14 bpm, P<0.001). The prevalence of myocardial ischaemia (13 vs. 8 participants, P=0.03) was significantly greater, while peak VO_2 (9.80±2.10 vs. 15.90±4.30 $ml \cdot kg^{-1} \cdot min^{-1}$, P<0.001) was significantly lower in those that died. Following multivariate cox regression, myocardial ischaemia (Hazard Ratio 3.08; 95% Confidence Interval 1.09 – 8.70; P=0.03) and peak VO_2 (HR 0.73; 95% CI 0.64 – 0.84; P<0.001) were significant independent predictors of 10-year all-cause mortality. This is the first study to establish peak VO_2 as powerful marker of all-cause mortality when assessed with clinical, resting and stress echocardiography parameters in people with ESRD over a 10-year follow up period. This observation indicates that, in clinical practice, CPET and exercise echocardiography may serve as valuable tools for the risk stratification of individuals with ESRD.

Key words: end-stage renal disease, chronic kidney disease, stress echocardiography, cardiopulmonary exercise testing, mortality.

Highlights

- We aimed to assess the prognostic utility of cardiopulmonary exercise testing (CPET) and exercise echocardiography in end-stage renal disease (ESRD) with 10-year mortality.
- Peak aerobic capacity and the presence of ischaemic heart disease were independently associated with all-cause mortality.
- This observation indicates that, in clinical practice, CPET and exercise echocardiography may serve as valuable tools for the risk stratification of individuals with end-stage renal disease.

Introduction

Chronic kidney disease (CKD) results from structural renal damage and progressively diminished renal function characterized by a reduction in glomerular filtration rate (GFR) [1]. CKD may eventually lead to end stage renal disease (ESRD) requiring renal replacement therapy such as dialysis or transplantation [1,2]. The prevalence of CKD is estimated to be between 11 to 13%, and while ESRD is only estimated to represent 0.1% of these cases, these patients are the most prognostically vulnerable [3]. In the ESRD population, 77% of patients are treated with haemodialysis or peritoneal dialysis, while the remaining will have a kidney transplant [4]. Individuals with ESRD demonstrate a pronounced risk for cardiovascular disease (CVD), with CV mortality accounting for approximately 40-50% of all deaths in ESRD [2,5], including young adult patients [6]. The association between ESRD and CVD is multifaceted and highly complex with the varying pathophysiological effects of traditional risk factors, renal hormone, enzyme and cytokine excretion, haemodynamic changes and inflammation [1,2]. These complex mechanisms often lead to vascular calcification and disease [2], as well as direct myocardial effects such as left ventricular hypertrophy (LVH) [7], systolic and diastolic dysfunction, dilated cardiomyopathy, and myocardial ischaemia [8,9].

Exercise intolerance is a hallmark of ESRD, even at low intensities such as those encountered during daily actives [10]. Studies have consistently evidenced that reductions in exercise capacity augment CVD risk and serves as a significant predictor of mortality in ESRD [11–14]. Cardiopulmonary exercise testing (CPET) is the gold standard for assessing functional capacity and unmasking physiological mechanisms of exercise intolerance [15]. While the role of cardiovascular assessment in asymptomatic patients that are awaiting transplantation remains controversial, given the prevalence of CVD and myocardial alterations in ESRD, the use of simultaneous echocardiography may provide useful insight into the detection of early signs of otherwise silent CVD with subsequent implications for long-term outcome risk. Previous work has evidenced the prognostic value of CPET derived measures of cardiorespiratory fitness and standard resting echocardiographic parameters in ESRD [16]; however, no research to date has investigated the predictive utility of combined exercise echocardiography and CPET variables in this population. This is especially important given the validity of stress echocardiography in the detection and diagnosis of ischaemic heart disease [17] which remains a leading cause of mortality in adults with ESRD [18,19].

Therefore, this novel study aims to determine whether routinely assessed parameters from CPET and exercise echocardiography can provide prognostic information on the risk of mortality in ESRD with 10-year follow-up.

Methods

Study population and inclusion criteria

The study population consisted of 42 ESRD (37 male) participants (age 58±13.90 years, height 169.30±8.30 cm, weight 81±15 kg and body surface area of 1.92+0.20m^2) who were recruited from Ealing Hospital, North West London University Healthcare NHS Trust, which is a district general hospital. The inclusion criteria for the study were male and female adults >18 years of age with ESRD that were able to exercise on an upright cycle ergometer. ESRD was characterised as an eGFR <15 $mL \cdot min^{-1} \cdot 1.73m^2$. Participants were excluded if they were unable to consent, had known coronary artery disease (CAD) (≥70% stenosis), had unstable angina, were not in sinus rhythm, or had moderate to severe valvular heart disease (regurgitation and/or stenosis across any valve, using qualitative, semi-quantitative and/or quantitative echocardiographic assessment).

Participants enrolled in the study underwent medical examination to identify any comorbidities or physical conditions that would contraindicate or exclude them from participation. Their family histories were questioned, and a list of their current cardiac medications were recorded. Blood samples were taken and tested for total cholesterol ($mg \cdot dL^{-1}$) and triglycerides ($mg \cdot dL^{-1}$). The eGFR was calculated from collections of serum creatine and applying the Modification of Diet in Renal Disease equation [20]. This investigation conformed to the Declaration of Helsinki principles. All participants provided written informed consent before testing and the local research ethics committee approved the study (09/HO710/22).

Experimental protocol

All participants underwent a maximal/symptom limited CPET, with a full cross-sectional echocardiogram performed at baseline and peak exercise. 12-lead electrocardiography and blood pressure (BP) were recorded during testing. Participants were seated at rest for 5 minutes prior to any exertion and performed 2 minutes of unloaded cycling before resistance was added. Studies were performed 24 hours after dialysis, when participants were closest to their euvolemic state. At yearly intervals, (±2-week period of the month recruited) the

participants were clinically assessed for changes related to medication, admissions to hospital and mortality.

Baseline and stress echocardiography

Two-dimensional transthoracic echocardiography was used to obtain conventional views and measurements [21] using a portable ultrasound Philips iE33 system (Philips Medical, Best, Netherlands) with a 1.5-3.6MHz phased array transducer. Images were acquired at rest and immediately following the exercise test whilst the participant was still on the cycle ergometer. Stress (exercise) was conducted on an upright cycle ergometer (Lode Corival; Lode, Groningen, Netherlands), using a standard 15W ramp protocol while maintaining a cadence of ~60rpm until volitional fatigue was evident, despite being encouraged by investigators. Stress echocardiography was performed in accordance with British Society of Echocardiography stress protocol [22]. Standard parasternal long axis, parasternal short axis, apical four, two, and three chamber views were acquired at rest and peak work rate. The left ventricle (LV) was divided using a 17-segment model for qualitative analysis and wall motion was scored using a 4-point wall motion scale (1, normal wall motion; 2, hypokinesis; 3, akinetic; and 4, dyskinetic) as is standard. An abnormal response was described as the exercise-induced akinesia or dyskinesia in one or more segments, and/or a worsening of wall motion in one or more resting hypokinetic segments. The peak wall motion score index was calculated for each participant. Using this, participants were categorised as ischaemic or non-ischaemic. Pulsed wave doppler recordings were used to assess transmitral Doppler, and tissue Doppler imaging [23], as well as M-mode echocardiography for tricuspid annular plane systolic excursion. LV and left atrial (LA) volume and ejection fraction (LVEF) were calculated using the Simpsons biplane method of discs [24].

Cardiopulmonary Exercise Testing

A metabolic cart (Ultima CPX, MedGraphics Corporation, St. Paul, MN) was used to perform breath by breath gas exchange analysis. From this, measures of peak oxygen consumption (peak VO_2) ($ml \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$), gas exchange threshold ($ml \cdot kg \cdot^{-1} min^{-1}$), peak O_2 pulse ($ml \cdot beat^{-1}$), and minute ventilation ($ml \cdot min^{-1}$) were acquired. Peak VO_2 was defined as the average oxygen consumption recorded during the final 10-seconds of the test.

The gas exchange threshold was estimated by applying the V-slope method and ventilatory equivalents [25]. Both Peak VO_2 and gas exchange threshold were indexed to participants body mass. Peak respiratory exchange ratio was calculated as VO_2/VCO_2. Exercise time (mins) and peak work rate (watts) were recorded at the end of the study. During the CPET, oxygen saturations were monitored continuously using a pulse oximetry probe, which was positioned on the index finger. Throughout baseline, exercise and recovery a 12-lead ECG was recorded using GE Marquette Hellige (Milwaukee, Wisconson, USA). Standard setup was applied with a paper speed of 25mm·s^{-1} [26]. Heart rate was measured continuously using the ECG, which was used to ascertain baseline heart rate and peak heart rate (b·min^{-1}). At baseline and at 3-minute intervals thereafter, BP was recorded using a stethoscope and pressure gauge (Belmalia Aneroid, Berlin). Measures of baseline and peak systolic and diastolic BP were recorded. Prior to each test, the equipment was calibrated using a 3-litre syringe and standard reference gases. The American Thoracic Society recommendations for exercise test termination were followed [27].

Follow up

After the testing session, participants were followed up via contact with the transplant unit and review of inpatient and outpatient medical records. Data was collated by contacting participants, family, general practitioners and reviewing hospital records to inquire about hospital admissions, cardiovascular events, or deaths. The study was observational; therefore, changes in treatment policy were not contemplated. The primary end point was all-cause mortality with a follow-up period of 10-years.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation and categorical variables as n (%). Group comparisons were based on 2-sample *t* test for continuous variables and χ^2 test was used for categorical variables. The optimal cut-off value for peak VO_2 was determined from receiver operator characteristic curve analysis. Kaplan-Meier survival curves were constructed and compared using the log-rank test and a P-value of <0.05 was used to report statistical significance. The survival curves were stratified according to a peak VO_2 of ≥ 10.1 ml·kg^{-1}·min^{-1} and <10.1 ml·kg^{-1}·min^{-1} (sensitivity of 0.84 and specificity of 0.91) and the

presence or absence of myocardial ischaemia. Previous research performed in clinically vulnerable populations has also used this peak VO_2 threshold cut off [28,29].

Multivariable adjusted cox proportional hazard models were constructed to ascertain predictors of all-cause mortality. For model building, significant univariate parameters were evaluated for their association with all-cause mortality. Age and cardiovascular disease (CVD) risk factors were included in all models. Forward stepwise selection procedures were used to compare models for goodness-of-fit and a P-value of <0.01 was used for retention in the final model. The final multivariate model consisted of 2 variables (peak VO_2 and myocardial ischaemia). Hazard ratios (HR) and corresponding 95% confidence intervals (CI) are reported. All analyses were conducted using the statistical package for social sciences (SPSS 26 release version of SPSS for Windows; SPSS Inc., Chicago IL, USA).

Results

All 42 ESRD participants completed the exercise stress test with no reports of any side effects or ill health. The characteristics of all participants stratified into event-free and all-cause mortality groups are described in Table 1.

Medical therapy was broadly similar across both groups, although significantly more all-cause mortality participants were taking beta blockers (P=0.002). Most participants were engaged with lipid lowering and anti-hypertensive medical therapy, with 75% on lipid-lowering agents, 35% taking ACE inhibitors and 48% on beta-blockers. There were no significant differences in the prevalence of CVD risk factors or prior coronary revascularisation between the groups. The overall prevalence of hypertension, diabetes and hypercholesterolaemia were 45%, 55%, and 62% respectively. Fourteen percent of the recruited participants had a previous MI, PCI, and/or CABG.

Survival

Survival status was determined at the end of the mean 10-year follow-up period. The study end point of death occurred in a total of 19 (45%) participants. The clinical parameters and respective statistical significance of each are detailed in Table 1. While there was no gender difference, unsurprisingly, those who were older were significantly more likely to die than those of a younger age (65±14 vs. 53±11 years, P<0.001). Of interest, the study end points of all-cause mortality at 1 and 5-years of follow-up time occurred in a total of 4 (10%) and 12 (29%) participants, respectively.

Echocardiographic Parameters

The all-cause mortality group had a significantly greater LA size (P<0.001) and significantly greater anteroseptal wall thickness (P=0.002), than participants who were alive. In regard to stress echocardiography parameters, twenty-one participants had ischaemia (50%), and the presence of ischemia was significantly greater in those who died (P=0.03). However, in both resting and stress echocardiography, there was no significant difference between groups for LVEF, systolic and diastolic diameters, diastolic parameters (Mitral E, Mitral E/A, Mitral E deceleration time) or peak/resting wall motion score index (WMSI).

CPET Parameters

Several CPET parameters were significantly different between all-cause mortality and those who were alive. These included a lower peak heart rate, shorter exercise time, lower peak VO_2, lower peak O_2 pulse, lower minute ventilation, lower VO_2/work rate slope, and lower peak work rate (all $P<0.05$). However, baseline heart rate, nor baseline and peak systolic and diastolic BP were significantly different between the two groups. All tests were terminated due to physical exhaustion.

Survival Analysis

The Kaplan-Meier curves for the cumulative survival are presented in Figure 1 and Figure 2. ESRD participants with a peak VO_2 $\geq$10.1 ml·min·$^{-1}$kg^{-1} had a significantly greater survival rate compared to those with a peak VO_2 <10.1 ml·min·$^{-1}$kg^{-1} ($P<0.001$, Figure 1). Similarly, participants without myocardial ischaemia had a significantly greater survival rate than those with myocardial ischaemia ($P=0.03$, Figure 2). The Cox regression proportional hazard model analysis demonstrated that myocardial ischaemia (HR: 3.08; 95% CI 1.09-8.7; $P=0.03$) and peak aerobic capacity (HR: 0.73; 95% CI 0.64-0.84; $P=0.001$) are independent predictors of all-cause mortality at the 10-year follow up time. At 1 and 5-years of follow-up, the Cox regression proportional hazard model analysis demonstrated that peak aerobic capacity (HR: 0.98; 95% CI 0.98-0.99; $P=0.013$ and HR: 0.94; 95% CI 0.93-0.96; $P=0.006$, respectively) was the only independent predictor of all-cause mortality.

Discussion

This study is the first to investigate the predictive utility of routinely assessed CPET with exercise stress echocardiography on 10-year all-cause mortality in adults with ESRD. Both peak VO_2 and myocardial ischaemia are independently associated with an increased risk of all-cause long-term mortality in ESRD. These findings were observed independent of age, CVD risk factors and prior coronary revascularisation. Previous studies using CPET in ESRD did not also use stress echocardiography, which has multiple parameters that predict outcome [8,17]. These novel results demonstrate the clinical utility of CPET combined with stress echocardiography for the prediction of mortality risk in adults with ESRD.

Cardiorespiratory fitness remains a leading prognostic marker in the heterogeneous general population [30] as well as various clinical sub-populations [31,32]. Indeed, the present analysis demonstrated a 27% increased risk of all-cause mortality in those ESRD adults with a peak VO_2 <10.1 $ml \cdot kg^{-1} \cdot min^{-1}$. These findings support that of previous work from Sietsema et al. [31] who found significantly lower survival rates in ESRD with a reduced peak VO_2, even with a higher threshold of 17.5 $ml \cdot kg^{-1} \cdot min^{-1}$. Ting et al. [16] also performed comparable work in participants waitlisted for kidney transplantation, evidencing significant differences in peak VO_2 between survivors and non-survivors, with the gas exchange threshold at percentage predicted peak VO_2 demonstrating the greatest predictive ability as a measure of cardiorespiratory fitness [16]. Similarly, we also found a significantly lower gas exchange threshold in those who died. While a degree of exercise limitation is highly prevalent and generally expected in renal populations [33], the pathophysiological mechanisms driving significant exercise intolerance in ESRD are not entirely understood. Inter-participant variations in peak VO_2 are generally the result of complex changes in cardiovascular function, metabolism, anaemia, pulmonary health and neurocirculatory control, which are all influenced by comorbidities, general disease state and age; although it should be noted that the predictive capacity of peak VO_2 in the present study was independent of age [33–35]. Many individuals with ESRD are also vulnerable to generalized skeletal muscle dysfunction/sarcopenia and cachexia, which carry implications for oxygen extraction via mitochondrial dysfunction and other skeletal muscle related metabolic processes [35,36]. Ultimately, such systemic physiological decline inhibits oxygen transportation and/or utilization, subsequently presenting as an impaired functional capacity [34]. Importantly, peak O_2 pulse and heart rate, which both centrally contribute to oxygen delivery and thus peak VO_2, were also significantly lower in the all-cause mortality group. These heart rate findings

are indicative of a blunted chronotropic response as is common in more advanced disease states and is understood as a primary contributor to exercise intolerance in ESRD [37], especially considering the prevalence of beta-blockade in this population. Future work should consider the addition of other non-invasive physiological methods, such as impedance cardiography, which may provide advanced mechanistic insight into the exercise intolerance in these individuals.

LA size was also significantly smaller in survivors. Previous studies both in the general population [38,39] and in ESRD participants [40,41] have shown LA size to be a significant predictor of adverse outcomes. As an easily, reliably, and reproducibly acquired measure using standard 2-D echocardiography, routinely acquired LA size may provide further prognostic information in ESRD participants. Separately, this study demonstrated significantly greater anteroseptal wall thickness and borderline-significant inferolateral wall thickness in those who died. The increase in LV wall thickness seen in ESRD is thought to not only parallel the high prevalence of hypertension, but also act as a compensatory adaptation to chronic pressure and volume overload [16,35], potentially via CKD-specific risk factors that remain poorly categorized [42]. Given that hypertension was not significantly different between groups in this cohort, this may have reduced the prevalence and thus the statistical power of inferolateral LV wall thickness as a marker of mortality. Such LV geometric changes are well-established as highly prevalent in ESRD with independent associations to adverse long-term outcomes [43,44]. Specifically, Suh et al. [44] reported stringent linear correlations between relative wall thickness and all-cause mortality, which was significant independent of the presence or absence of overall LVH.

Of interest, we also found myocardial ischaemia to be a significant predictor of all-cause mortality. The importance of this finding lies within its predictive capacity independent of the long-established prognostic value of peak VO_2. As such, the finding of a more than 3-fold increased risk in those with myocardial ischaemia, is clinically important. However, this finding should be interpreted in the context of a wide confidence interval and thus more data of a larger scale is warranted. ESRD is well-recognized as a major risk factor for ischaemic heart disease, with such patients largely exposed to nontraditional uremia-related CAD risk factors such as oxidative stress and calcium-phosphorus metabolism in addition to traditional risk factors [19]. While the findings of this work highlight the importance of CAD management in adults with ESRD, the recent landmark ISCHEMIA-CKD trial reported no significant mortality, nonfatal MI or angina-related health status differences in 777 patients randomized

to invasive or conservative treatment of CAD in advanced CKD [18]. Thus, while the findings of the present study highlight the strong prognostic value of myocardial ischaemia in ESRD, the evidence that a more aggressive treatment approach towards CAD will offset such mortality risk in this population remains unfounded. Indeed, outcome data at 1 and 5 years did not demonstrate a significant prognostic role of myocardial ischaemia, indicating that the mean follow-up period of 2.2 years in the ISCHEMIA-CKD trial may not have been sufficient to translate into changes in clinical outcomes [18]. However, peak aerobic capacity remained a statistically significant predictor of all-cause mortality at 1 and 5 years, suggesting its superior prognostic value for earlier outcomes.

Limitations

This work is limited by a small sample size, which has implications for multivariate analysis. As such, some degree of caution in the interpretation of these results is advised. Furthermore, participants were recruited from a single centre Dialysis Unit and therefore this work may suffer from selection/inclusion bias. As such, future work should aim for multi-centre designs performed in larger-scale study populations to confirm our findings. This study also provides no information on participant transplant status and thus we are unable to provide data on any parameters reflecting this. All participants performed a standardised protocol of 15W increments with no familiarisation testing. Thus, this work may have benefited from individualized work rates and a familiarisation CPET. Nonetheless, this study demonstrated that a single CPET, which is routine practice, is of clinical importance. In addition, this work may have benefited from the application of more novel predictive measures such as myocardial strain and work. Finally, this work involved a male dominant sample, which is not reflective of the ESRD prevalence across the sexes [45] and thus future female-focused research is needed.

Conclusion

This study demonstrates that obtainable and routinely assessed CPET and stress echocardiographic information, particularly peak VO_2 and myocardial ischaemia, can be utilized for the prediction of mortality risk in adults with ESRD. Such findings may have clinical implications in the utilization of early clinical decision making and high-risk patient management.

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Competing Interests

The authors report there are no competing interests to declare.

References

1. Webster AC, Nagler E v., Morton RL, Masson P. Chronic Kidney Disease. *Lancet*. 2017;389(10075):1238-1252. doi:10.1016/S0140-6736(16)32064-5

2. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease. *Circulation*. 2021;143(11):1157-1172. doi:10.1161/CIRCULATIONAHA.120.050686

3. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. *PLoS One*. 2016;11(7). doi:10.1371/JOURNAL.PONE.0158765

4. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. *American Journal of Kidney Diseases*. 2017;69(3):A7-A8. doi:10.1053/j.ajkd.2016.12.004

5. Thompson S, James M, Wiebe N, et al. Cause of Death in Patients with Reduced Kidney Function. *J Am Soc Nephrol*. 2015;26(10):2504-2511. doi:10.1681/ASN.2014070714

6. Modi ZJ, Lu Y, Ji N, et al. Risk of Cardiovascular Disease and Mortality in Young Adults With End-stage Renal Disease: An Analysis of the US Renal Data System. *JAMA Cardiol*. 2019;4(4):353-362. doi:10.1001/JAMACARDIO.2019.0375

7. Sharma R, Gaze DC, Pellerin D, et al. Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T. *Heart*. 2006;92(6):804-809. doi:10.1136/HRT.2005.069666

8. Sharma R, Gaze DC, Pellerin D, et al. Evaluation of ischaemia-modified albumin as a marker of myocardial ischaemia in end-stage renal disease. *Clin Sci (Lond)*. 2007;113(1):25-32. doi:10.1042/CS20070015

9. Stewart GA, Mark PB, Johnston N, et al. Determinants of hypertension and left ventricular function in end stage renal failure: a pilot study using cardiovascular magnetic resonance imaging. *Clin Physiol Funct Imaging*. 2004;24(6):387-393. doi:10.1111/J.1475-097X.2004.00583.X

10. MacDonald JH, Fearn L, Jibani M, Marcora SM. Exertional fatigue in patients with CKD. *Am J Kidney Dis*. 2012;60(6):930-939. doi:10.1053/J.AJKD.2012.06.021

11. Kirkman DL, Muth BJ, Stock JM, Townsend RR, Edwards DG. Cardiopulmonary exercise testing reveals subclinical abnormalities in chronic kidney disease. *Eur J Prev Cardiol*. 2018;25(16):1717-1724. doi:10.1177/2047487318777777

12. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int*. 2004;65(2):719-724. doi:10.1111/J.1523-1755.2004.00411.X

13. Martins P, Marques EA, Leal D v., Ferreira A, Wilund KR, Viana JL. Association between physical activity and mortality in end-stage kidney disease: a systematic review of

observational studies. *BMC Nephrol*. 2021;22(1):1-11. doi:10.1186/S12882-021-02407-W/FIGURES/2

14. Johansen KL. Exercise in the End-Stage Renal Disease Population. *Journal of the American Society of Nephrology*. 2007;18(6):1845-1854. doi:10.1681/ASN.2007010009

15. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults. *Circulation*. 2010;122(2):191-225. doi:10.1161/CIR.0B013E3181E52E69

16. Ting SMS, Iqbal H, Kanji H, et al. Functional cardiovascular reserve predicts survival pre-kidney and post-kidney transplantation. *Journal of the American Society of Nephrology*. 2014;25(1):187-195. doi:10.1681/ASN.2013040348/-/DCSUPPLEMENTAL

17. Sharma R, Pellerin D, Gaze DC, et al. Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates. *Nephrology Dialysis Transplantation*. 2005;20(10):2207-2214. doi:10.1093/NDT/GFI005

18. Bangalore S, Maron DJ, O'Brien SM, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. *New England Journal of Medicine*. 2020;382(17):1608-1618. doi:10.1056/NEJMOA1915925/SUPPL_FILE/NEJMOA1915925_DATA-SHARING.PDF

19. Sarnak MJ, Amann K, Bangalore S, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;74(14):1823-1838. doi:10.1016/J.JACC.2019.08.1017

20. Levey AS, Coresh J, Bolton K, et al. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. G. Balint, Antala B, Carty C, Mabieme JMA, Amar IB, Kaplanova A, eds. *American Journal of Kidney Diseases*. 2002;39(2 SUPPL. 1):i-ii+S1-S266. doi:10.2/JQUERY.MIN.JS

21. Harkness A, Ring L, Augustine DX, Oxborough D, Robinson S, Sharma V. Normal reference intervals for cardiac dimensions and function for use in echocardiographic practice: a guideline from the British Society of Echocardiography. *Echo Res Pract*. 2020;7(1):X1. doi:10.1530/ERP-19-0050

22. Becher H, Chambers J, Fox K, et al. BSE procedure guidelines for the clinical application of stress echocardiography, recommendations for performance and interpretation of stress echocardiography. *Heart*. 2004;90(suppl 6):vi23-vi30. doi:10.1136/HRT.2004.047985

23. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17(12):1321-1360. doi:10.1093/EHJCI/JEW082

24. Lang RM, Badano LP, Victor MA, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14. doi:10.1016/J.ECHO.2014.10.003

25. Reinhard U, Mueller PH, Schmuelling RM. Determination of anaerobic threshold by the ventilation equivalent in normal individuals. *Respiration*. 1979;38(1):36-42. doi:10.1159/000194056

26. Spodick DH. Diagnostic Electrocardiography and Vectorcardiography. *JAMA*. 1971;216(12):2019-2019. doi:10.1001/JAMA.1971.03180380073031

27. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211-277. doi:10.1164/RCCM.167.2.211

28. Oliveira RB, Myers J, Araújo CGS, et al. Does Peak Oxygen Pulse Complement Peak Oxygen Uptake in Risk Stratifying Patients with Heart Failure? *Am J Cardiol*. 2009;104(4):554. doi:10.1016/J.AMJCARD.2009.04.022

29. Goda A, Lund LH, Mancini D. The Heart Failure Survival Score outperforms the peak oxygen consumption for heart transplantation selection in the era of device therapy. *The Journal of Heart and Lung Transplantation*. 2011;30(3):315-325. doi:10.1016/J.HEALUN.2010.09.007

30. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing. *JAMA Netw Open*. 2018;1(6):e183605-e183605. doi:10.1001/JAMANETWORKOPEN.2018.3605

31. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int*. 2004;65(2):719-724. doi:10.1111/J.1523-1755.2004.00411.X

32. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *Am Heart J*. 2004;147(2):354-360. doi:10.1016/J.AHJ.2003.07.014

33. Pella E, Theodorakopoulou MP, Boutou AK, et al. Cardiopulmonary reserve examined with cardiopulmonary exercise testing in individuals with chronic kidney disease: A systematic review and meta-analysis. *Ann Phys Rehabil Med*. 2022;65(5). doi:10.1016/J.REHAB.2021.101588

34. Lim K, McGregor G, Coggan AR, Lewis GD, Moe SM. Cardiovascular Functional Changes in Chronic Kidney Disease: Integrative Physiology, Pathophysiology and Applications of Cardiopulmonary Exercise Testing. *Front Physiol*. 2020;11. doi:10.3389/FPHYS.2020.572355

35. Pella E, Boutou A, Boulmpou A, Papadopoulos CE, Papagianni A, Sarafidis P. Cardiopulmonary exercise testing (CPET) in patients with end-stage kidney disease (ESKD): principles, methodology and clinical applications of the optimal tool for exercise tolerance evaluation. *Nephrol Dial Transplant*. Published online April 6, 2021. doi:10.1093/NDT/GFAB150

36. O'Driscoll JM, Slee AD, Sharma R. Body mass index mortality paradox in chronic kidney disease patients with suspected cardiac chest pain. *JCSM Clin Rep*. 2017;2(1):1-8. doi:10.17987/JCSM-CR.V2I1.10

37. McGuire S, Horton EJ, Renshaw D, Chan K, Krishnan N, McGregor G. Ventilatory and chronotropic incompetence during incremental and constant load exercise in end-stage renal disease: a comparative physiology study. *Am J Physiol Renal Physiol*. 2020;319(3):F515-F522. doi:10.1152/AJPRENAL.00258.2020

38. Patel DA, Lavie CJ, Gilliland YE, Shah SB, Dinshaw HK, Milani R v. Prediction of all-cause mortality by the left atrial volume index in patients with normal left ventricular filling pressure and preserved ejection fraction. *Mayo Clin Proc*. 2015;90(11):1499-1505. doi:10.1016/j.mayocp.2015.07.021

39. Li T, Li G, Guo X, Li Z, Yang J, Sun Y. Predictive value of echocardiographic left atrial size for incident stoke and stroke cause mortality: a population-based study. *BMJ Open*. 2021;11(3):e043595. doi:10.1136/BMJOPEN-2020-043595

40. Tripepi G, Benedetto FA, Mallamaci F, Tripepi R, Malatino L, Zoccali C. Left Atrial Volume Monitoring and Cardiovascular Risk in Patients with End-Stage Renal Disease: A Prospective Cohort Study. *Journal of the American Society of Nephrology*. 2007;18(4):1316-1322. doi:10.1681/ASN.2006080881

41. Patel RK, Jardine AGM, Mark PB, et al. Association of left atrial volume with mortality among ESRD patients with left ventricular hypertrophy referred for kidney transplantation. *Am J Kidney Dis*. 2010;55(6):1088-1096. doi:10.1053/J.AJKD.2009.12.033

42. Sárközy M, Gáspár R, Zvara Á, et al. Chronic kidney disease induces left ventricular overexpression of the pro-hypertrophic microRNA-212. *Scientific Reports 2019 9:1*. 2019;9(1):1-16. doi:10.1038/s41598-018-37690-5

43. Silberberg JS, Barre PE, Prichard SS, Sniderman SD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int*. 1989;36(2):286-290. doi:10.1038/KI.1989.192

44. Suh SH, Oh TR, Choi HS, et al. Association Between Left Ventricular Geometry and Renal Outcomes in Patients With Chronic Kidney Disease: Findings From Korean Cohort Study for Outcomes in Patients With Chronic Kidney Disease Study. *Front Cardiovasc Med*. 2022;0:996. doi:10.3389/FCVM.2022.848692

45. Tomlinson LA, Clase CM. Sex and the Incidence and Prevalence of Kidney Disease. *Clinical Journal of the American Society of Nephrology*. 2019;14(11):1557-1559. doi:10.2215/CJN.11030919

Figure legends

Figure 1: Kaplan-Meier curve for the cumulative survival according to aerobic capacity.

Figure 2: Kaplan-Meier curve for the cumulative survival according to the presence and absence of myocardial ischaemia.

Table 1. Characteristics of Patients According to Alive vs. All-Cause Mortality.

Characteristics		Alive (n=23)	All-Cause Mortality (n=19)	P Value
Demographics				
	Age, years	53±11	65±14	**0.004***
	Men	22 (95.7)	15 (78.9)	1
History				
	Hypertension	10 (43.5)	9 (47.4)	0.80
	Diabetes mellitus	11 (47.8)	12 (63.2)	0.32
	Hypercholesterolaemia	13 (56.5)	13 (68.4)	0.43
	Family history of CVD	0 (0)	1 (5.3)	0.27
	Prior myocardial infarction	2 (8.7)	4 (21)	0.26
	PCI	2 (8.7)	4 (21)	0.26
	CABG	3 (13)	3 (15.8)	0.80
Long term cardiac medication				
	ACEI	8 (34.8)	7 (36.8)	0.89
	Angiotensin II receptor antagonist	11 (47.8)	10 (52.6)	0.76
	Aspirin	16 (69.6)	9 (47.4)	0.15
	Beta Blockers	6 (26)	14 (73.7)	**0.002***
	Calcium antagonists	6 (26)	7 (36.8)	0.45
	Diuretic	7 (30.4)	3 (15.8)	0.27
	Lipid-lowering agents	17 (73.9)	15 (78.9)	0.70
	Warfarin	1 (4.3)	0 (0)	0.36
Baseline Echocardiography Data				
	LA Size (cm)	3.65±0.5	4.17±0.7	**0.011***
	LVESD (cm)	3.21±1	3.04±1	0.59
	LVEDD (cm)	5.11±0.9	4.86±0.9	0.35
	LVEF (%)	53.7±15	52.8±12	0.84
	Anteroseptal Wall Thickness (cm)	1.06±0.2	1.28±0.4	**0.024***
	Inferolateral Wall Thickness (cm)	1.01±0.2	1.17±0.3	0.05
	Mitral E	0.8±0.29	0.85±0.37	0.59
	Mitral A	0.78±0.32	0.78±0.34	0.98
	Mitral E/A	1.31±1.25	1.44±1.13	0.74
	Mitral E Deceleration (ms)	213.8±59	222.3±67	0.67
	Mitral E/Ea	4.78±2.1	5.32±1.5	0.36
	Resting wall motion score index	1.17±0.26	1.01±0.16	0.20
Exercise Echocardiography Data				
	LVEF (%)	62.4±19	59.1±15.9	0.55
	Mitral E	0.98±0.26	0.97±0.39	0.95
	Mitral A	0.8±0.29	0.85±0.34	0.61
	Mitral E/A	1.47±0.93	1.34±0.77	0.65
	Mitral E Deceleration (ms)	200.1±57.9	192.1±60.4	0.66
	Mitral E/Ea	5.57±2.5	5.58±1.7	0.98
	Peak wall motion score index	1.22±0.3	1.26±0.23	0.63
	Myocardial Ischaemia	8 (34.8)	13 (68.4)	**0.03***
Cardiopulmonary Exercise Test Data				
	Baseline heart rate ($b \cdot min^{-1}$)	87±16.8	78.6±14.5	0.09
	Peak heart rate ($b \cdot min^{-1}$)	128.2±14.4	108.9±12.5	**<0.001***
	Baseline sBP (mmHg)	131.2±26.2	134±37.6	0.78
	Peak sBP (mmHg)	157.6±34.3	150.1±26.5	0.44

Baseline dBP (mmHg)	82.9±14.5	77.5±22	0.59
Peak dBP (mmHg)	81.7±14.5	74.6±14.1	0.12
Exercise Time (min)	9.96±2.8	5.78±1.7	**<0.001***
Peak VO_2 ($ml \cdot min^{-1}$)	1251.1±377	791.1±119	**<0.001***
Peak VO_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)	15.9±4.3	9.8±2.1	**<0.001***
Peak VO_2 (% of predicted)	53.8±12.6	42.7±18.7	**0.03***
Gas Exchange Threshold ($ml \cdot min^{-1}$)	810.3±293	574±155.6	**0.003***
Gas Exchange Threshold ($ml \cdot min^{-1} \cdot kg^{-1}$)	10.1±2.6	7.1±2.3	**<0.001***
Peak O_2 Pulse ($ml \cdot beat^{-1}$)	10.5±2.9	8.1±2.1	**0.003***
Minute Ventilation ($L \cdot min^{-1}$)	44±11.9	26.2±6.6	**<0.001***
V_E/VCO_2 Slope	32.3±5.1	37±5.8	0.69
VO_2/Work Rate Slope	9±0.6	7.4±1	**<0.001***
Peak Respiratory Exchange Ratio	1.22±0.1	1.15±0.1	0.070
Peak Work Rate (Watts)	100.4±39.8	65.9±27.3	**0.003**

CVD, cardiovascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEI, angiotensin converting enzyme inhibitor; LA, left atrium; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; sBP, systolic blood pressure.