Global longitudinal strain by feature tracking cardiovascular MRI predicts mortality in patients with end stage kidney disease

Alastair J. Rankin¹
Luke Zhu¹
Kenneth Mangion¹
Elaine Rutherford¹
Keith A. Gillis²
Jennifer S. Lees¹
Rosie Woodward³
Rajan K. Patel¹,²
Colin Berry¹
Giles Roditi¹,⁴
Patrick B. Mark¹

1. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
2. Renal and Transplant Unit, NHS Greater Glasgow and Clyde, Glasgow UK
3. Clinical Research Imaging, NHS Greater Glasgow and Clyde, Glasgow, UK
4. Department of Radiology, NHS Greater Glasgow and Clyde, Glasgow, UK

Correspondence to: Patrick B. Mark; E-mail: patrick.mark@glasgow.ac.uk
ABSTRACT

Background. Patients with end-stage kidney disease (ESKD) are at increased risk premature death, with cardiovascular disease being the predominant mode of death. We hypothesized that left ventricular global longitudinal strain (LV-GLS) measured by feature tracking cardiovascular magnetic resonance imaging (CMR) would be associated with all-cause mortality in patients with ESKD.

Methods. A pooled analysis of CMR studies in patients with ESKD acquired within a single centre between 2002 and 2016 was carried out. CMR parameters including left ventricular ejection fraction (LVEF), LV mass index (LVMI), left atrial emptying fraction (LAEF) and LV-GLS were measured. We tested independent associations of CMR parameters with survival using a multivariable Cox model.

Results. Among 215 patients (mean age: 54 years, 62% male), mortality was 53% over 5.0 years median follow-up. The median LVEF was 64.7% (IQR 58.5, 70.0) and median LV-GLS was -15.3% (-17.24, -13.6). While 90% of patients had preserved LVEF (>50%), 58% of this group had abnormal LVGLS (>−16%). On multivariable Cox regression, age (HR: 1.04, 95%CI: 1.02-1.05), future-renal transplant (HR 0.29 95%CI: 0.17-0.47), LAEF (HR: 0.98, 95%CI: 0.96-1.00) and LV-GLS (HR: 1.08, 95%CI: 1.01-1.16) were independently associated with mortality.

Conclusions. In this cohort of patients with ESKD, LV-GLS on feature tracking CMR and LAEF were associated with all-cause mortality, independent of baseline clinical variables and future renal transplantation. This effect was present even when >90% of the cohort had normal left ventricular ejection fraction (LVEF). Using LV-GLS, instead of LVEF, to diagnose cardiac dysfunction in patients with ESKD could result in a major advance in our understanding of cardiovascular disease in ESKD.

Keywords: cardiovascular, chronic renal failure, ESKD, left ventricular hypertrophy, magnetic resonance imaging, survival analysis
KEY LEARNING POINTS

What is already known about this subject?

- Left ventricular global longitudinal strain (LV-GLS) measures percentage muscle deformation during the cardiac cycle as a sensitive marker of myocardial function.
- LV-GLS measured on echocardiography is known to associate with mortality in patients with end-stage kidney disease (ESKD). The association of LV-GLS on cardiovascular MRI and survival has not been studied in patients with ESKD.

What this study adds?

- LV-GLS on cardiovascular MRI was associated with all-cause mortality, independent of baseline clinical variables and future renal transplantation.
- This effect was present even when >90% of the cohort had normal left ventricular ejection fraction (LVEF).
- The survival benefit of renal transplantation was evident even in the quartile of participants with the most severely impaired LV-GLS.

What impact this may have on practice or policy?

- Using LV-GLS, instead of LVEF, to diagnose cardiac dysfunction in patients with ESKD could result in a major advance in our understanding of cardiovascular disease and prognosis in ESKD
- LV-GLS in isolation is unlikely to be helpful when assessing an individual’s suitability for renal transplantation.
- Further studies exploring cardiovascular therapeutics in patients with ESKD who have impaired LV-GLS are warranted.
INTRODUCTION

Patients with chronic kidney disease (CKD) are at increased risk of death from all-causes compared to the general population (1). The majority of this increased risk is due to cardiovascular disease (2). While ischaemic heart disease is the most common form of cardiovascular disease in the general population, patients with CKD have relatively fewer atherosclerotic events but a disproportionate increase in the risk of sudden cardiac death and death from arrhythmogenic causes (3). This risk increases with severity of CKD (2), such that patients with CKD stage 5 are 3-4 times more likely to experience a cardiovascular event than age-standardized patients without CKD (4). This excess cardiovascular risk is intrinsically linked to cardiac structural and functional abnormalities, which start to develop early in CKD (5). These include left ventricular hypertrophy (LVH), cardiac dysfunction and myocardial fibrosis, which together are sometimes referred to as a ‘uraemic cardiomyopathy’ (6–8). The utility of cardiac magnetic resonance (CMR) imaging to detect these abnormalities has been an area of growing interest and CMR may prove to be a useful tool in the development of non-invasive novel biomarkers for future risk-stratification (9,10).

Left ventricular global longitudinal strain (LV-GLS) measures percentage muscle deformation during the cardiac cycle as a sensitive marker of myocardial function [(11). Feature tracking CMR is a non-contrast post-processing technique that derives LV-GLS by tracking endo- and epicardial borders through successive images from routinely acquired cine CMR sequences (11). Normal values for LV-GLS measured by feature tracking CMR are approximately -20 +/- 4% (12–14). LV-GLS has been shown to be a strong correlate of mortality and clinical outcomes in patients with myocardial infarction (15), and improvements in LV-GLS have been reported following renal transplantation (16). In patients with CKD, utilizing echocardiography, GLS has been reported to predict clinical outcomes (17). However, CMR is considered the gold standard imaging modality in end-stage kidney disease (ESKD), as fluctuations in volume status with renal replacement therapy may have an undue influence on images obtained in a two-dimensional plane (18).
We hypothesised that LV-GLS on feature tracking CMR has incremental prognostic utility over clinical and conventional imaging parameters for predicting all-cause mortality in patients with ESKD.

MATERIALS AND METHODS

Participants

CMRs from research studies carried out in participants with ESKD within a regional renal and transplant centre between 2002 and 2016 were pooled. Patients for whom CMR images were available and who had consented for long term data follow-up were eligible for inclusion. All participants had CKD stage 5 (eGFR <15 ml/min/1.73m²) and were receiving, or estimated to be within 6 months of requiring, renal replacement therapy. Further details of the cohorts are described elsewhere (ClinicalTrials.gov ID NCT01951404) (19–21). Participants provided written informed consent and regional ethics committee approval was granted; the study was conducted in agreement with the Declaration of Helsinki.

Clinical data were manually collected via the West of Scotland Electronic Renal Patient Record database (Vitalpulse, Chelmsford, UK) by members of the team blinded to other aspects of the study. Baseline clinical variables included demographic characteristics and medical history. The primary outcome was all-cause mortality. The secondary outcome was cardiovascular mortality defined as death due to myocardial infarction, heart failure, sudden cardiac death, stroke and peripheral vascular disease (22).

CMR Image Acquisition

CMR acquisition was performed using 1.5 Tesla (T) (Sonata, Siemens Erlangen, Germany) and 3T MRI scanners (Magnetom Verio and Prisma, Siemens Erlangen, Germany). For
patients on haemodialysis, the scans were performed 24 hours following the end of their dialysis session. Imaging protocols were similar in all studies and were as described previously (19–21). In short, electrocardiograph-gating was used and the images were acquired in end-expiration. Following the acquisition of localiser images, balanced steady state free precession sequences were used to acquire left ventricular cines in three long axis planes, followed by a short axis stack from the apex to the atrio-ventricular ring. Additional details are available in supplementary materials S1.

CMR Image Analysis

All data analysis was carried out in a core lab, utilizing dedicated CMR software (cvi42 software (version 5.10, Circle Cardiovascular, Canada)). Routinely analysed CMR measures of left ventricular (LV) and right ventricular (RV) function were carried out according to current guidelines (23), with parameters of myocardial mass and ventricular volumes derived from the short-axis views and indexed to body surface area. Ventricular endocardial and epicardial contours were manually drawn at end-diastole. Left ventricular endocardial contours were drawn at end-systole, which was deemed to be the phase with the smallest blood pool cavity. Papillary muscles were excluded from myocardial mass and included in volumes. For the purposes of strain measurements, the manually drawn ventricular contours were propagated throughout the cardiac cycle using the software’s machine-learning algorithms. Automated contours were individually checked and corrected, where necessary. Global left ventricular strain (circumferential, longitudinal, and radial) and global right ventricular strain (longitudinal and radial) were derived using the tissue tracking module to derive values of peak strain and strain graphs following the manufacturer’s advised standard protocols (Figure 1). Atrial volumes were indexed to body surface area and derived from automated contours, with manual correction as needed. Left atrial emptying fraction (LAEF) was calculated as the percentage difference between maximal and minimal left atrial volume divided by maximal atrial volume. The primary observer (LYZ) performed all CMR analyses in a random order. A
second independent observer (AJR) analysed a random sample of >10% of the cohort to assess inter-observer variability. Both observers were blinded to clinical outcomes.

**Statistical Analysis**

Continuous data with a normal distribution are presented as mean ± standard deviation (SD), and median and interquartile range (IQR) for skewed data, with normality defined according to Shapiro-Wilk test. Exploratory analyses using independent Student’s t-tests, Mann Whitney U test, and Pearson’s Chi-squared test, as appropriate, were performed on baseline variables of clinical significance. Kruskal-Wallis test was used to compare LV-GLS by year of scan. Univariable Cox proportional hazards analysis was performed to identify CMR variables associated with outcome. Parameters that were significantly associated with outcome were then entered into a model including pre-specified baseline clinical variables of age, sex, diabetes, heart failure, and previous myocardial infarction. Future renal transplantation was added to the model as a time-dependant covariate. The proportional hazards assumption was tested for continuous variables using Schoenfeld’s residuals and deemed satisfied when the p value was >0.05. A backwards stepwise regression model using Wald’s statistic was performed with an exclusion threshold of p > 0.1. An assessment of model fit was not performed due to the necessary inclusion of future renal transplantation as a time-dependent covariate. CMR variables of independent significance in the multivariable model were divided into quartiles and compared using Kaplan-Meier survival analysis and the log-rank test, including sub-group analyses based on future renal transplantation. Intra- and interobserver variability was assessed by the intra-class correlation (ICC) coefficient (two-way mixed effect, average measures). Receiver-operator curve analysis was used to identify an optimal prognostic threshold for LV-GLS. Statistical analysis was performed using SPSS (version 26, IBM Corp, New York).
RESULTS

Participant characteristics

A total of 215 patients were included (144 of whom were being considered for renal transplant(19,21), and 71 incident dialysis patients without overt heart failure (33 from Rutherford et al (20) and 38 locally acquired baseline scans from a recent trial of allopurinol therapy in dialysis patients (ClinicalTrials.gov ID NCT01951404)). There was no difference in survival or LV-GLS by year of scan (log rank test p=0.99, and Kruskal Wallis test H=2.77, p=0.60, respectively).

In total, 133 (62%) were male and mean age was 54.0 ± 12.1 years (Table 1). The majority of participants were white (200; 93%), with 11 Asian, 3 black and 1 other. At the time of scanning, 181 (84%) patients were receiving renal replacement therapy, of whom 8 (4%) had a functioning renal transplant (median eGFR 10.5 (IQR 9.1 - 13.3) ml/min/1.73m²). The remaining 34 (16%) patients had CKD stage 5 with median eGFR 10.4 (IQR 8.6 - 12.8) ml/min/1.73m². During a median follow-up of 5.0 years (range 1 day – 16.9 years), there were 115 deaths (53%). Specific cause of death was available for 96 (83%) patients and included 34 (35%) due to infection, 33 (34%) cardiovascular (22 cardiac, 9 peripheral vascular disease, 4 stroke), 13 (14%) cancer, 7 (7%) withdrawal of dialysis, and 9 (9%) other causes. Participants who survived were younger (51.6 +/- 11.7 versus 56.2 +/-12.2 years, p = 0.005), with similar sex distribution and body mass index (Table 1). Deceased patients were significantly more likely to have diabetes at baseline (37% vs 22%, p = 0.014), however history of cardiac disease including myocardial infarction and heart failure were similar (table 1).

Table 2 summarises the CMR results for the cohort. Seven patients had reduced left ventricular ejection fraction (LVEF) <40%, while a further 14 patients had mid-range ejection fraction between 40-49%, as defined by the 2016 European Society of Cardiology guidelines.
One hundred twelve patients with preserved LVEF >50% had abnormal LV-GLS when defined as >-16.0% (12). Intra-and inter observer reproducibility were excellent for left atrial (LA), right atrial (RA) and LV parameters (ICC >0.92) and moderate for RV parameters (ICC 0.57-0.74) (Supplementary material table S2) (26).

CMR parameters and All-cause Mortality

On univariable analysis with each variable entered separately, LV-GLS, LV-GRS, RV-GLS, RV-GRS, minimum left atrial volume and LAEF were significantly associated with all-cause mortality (Table 3). A multivariable model was created of these variables combined with the pre-specified clinical variables of gender, age, diabetes, heart failure, previous MI and future renal transplant. Following backwards stepwise elimination, LV-GLS and LAEF were the only CMR parameters that remained independently associated with mortality, in combination with gender, age, and future renal transplantation (Table 3). All other variables were excluded.

Patients were divided into quartiles according to LV-GLS and LAEF. The quartiles for LV-GLS are as follows: first quartile < -17.24% (best), second quartile -17.25% to -15.28%, third quartile -15.29 to -13.62%, fourth quartile > -13.61% (worst). The quartiles for LAEF were: first quartile <50.12 % (worst), second quartile 50.13-57.30%, third quartile 57.31-64.94%, and fourth quartile >64.94% (best). Compared to the best quartile of LV-GLS, participants in the worst quartile had significantly poorer outcomes (p=0.03, Figure 2), with no difference between the other quartiles. Similarly, the first quartile of LAEF had significantly worse survival compared to participants in the 3rd and 4th quartiles of LAEF (Figure 2, p= 0.003 and 0.03).

On receiver-operator curve (ROC) analysis, there was no single threshold of LV-GLS with meaningful prognostic value for all-cause mortality. When 1-year mortality was examined, the area under the curve (AUC) for LV-GLS was 0.71 from which a LV-GLS cut-off of -14.1% would yield 77% sensitivity and 67% specificity. However, when 2-year mortality was examined the AUC fell to 0.52.
LV-GLS differed by sex within the cohort, with females having greater contractility than males (median GLS -16.17% (females) vs -14.52% (males); Mann-Whitney U test p<0.001). There was no difference in mortality by sex (log rank p=0.48). When only female patients were studied, LV-GLS was significantly associated with all-cause mortality (HR 1.21 (1.08-1.35, p=0.001) but the association was not detected when only male patients were studied (HR 1.08 (-.99-1.18, p=0.09)). There was no difference in LAEF by sex (Mann Whitney U test p=0.15).

CMR parameters and Cardiovascular mortality
With regards the secondary outcome of cardiovascular mortality, LV-GLS (HR 1.17 (95% CI: 1.00-1.25)) and LAEF (HR 0.949 (95% CI: 0.92-0.98)) were the only CMR parameters that significantly associated with outcome on univariable analysis. Following backwards elimination, LAEF was the only CMR parameter that remained significantly associated with cardiovascular mortality in the multivariable model containing age: HR 1.08 (95% CI: 1.04-1.12); diabetes: HR 2.30 (95% CI: 1.12-4.71); future renal transplant: HR 0.35 (95% CI: 0.13-0.95); LAEF: HR 0.96 (95% CI: 0.93-0.99).

CMR parameters and future Renal Transplantation
A total of 106 (49%) of patients received a renal transplant during the follow-up. Of these, 33 patients died. Patients who received a transplant had lower median LV-GLS than those who did not (-15.63% (-17.32 - -14.18) compared to -14.88% (-16.82- -13.08) p=0.04). There was no difference in LAEF between those who did and did not receive a future renal transplant (p=0.10). The survival benefit of renal transplantation was evident on Kaplan-Meier survival analysis across all quartiles of LV-GLS and LAEF (Figure 3 and Supplementary Material Figure S3).
DISCUSSION

This large, retrospective study of CMR in patients with ESKD found that LV-GLS by feature tracking CMR and LAEF have significant association with all-cause mortality, independent of baseline clinical variables and future renal transplantation. Importantly, these associations were present even when the majority of the cohort had normal cardiac function as defined by traditional parameters (i.e. LVEF).

Benefits of Using Feature Tracking CMR for Strain Analysis

CMR is the gold standard for the assessment of cardiac volumes and mass in patients with renal failure (10,18). Although strain imaging by echocardiography is likely to be more accessible, it can be limited by poor availability of acoustic windows, image quality, expertise required and inter-operator variability. Fluid shifts associated with dialysis may further impair the accuracy and reliability of this measure. The ability to quantify LV-GLS accurately and quickly using CMR supports the superiority of CMR over echocardiography. Feature tracking is a technique that measures strain using routinely acquired steady state free procession (SSFP) sequences and obviates the need for acquisition of bespoke CMR strain sequences such as myocardial tagging. Feature tracking strain has been validated against myocardial tagging (27,28) with the additional advantage that it is able to generate this data in less than a quarter of the time needed by tagging. We believe feature tracking CMR is at the intersection of accuracy and ease of acquisition and have demonstrated its utility in this cohort.

Global Longitudinal Strain as a Predictor of Mortality and Cardiac Dysfunction

In patients with CKD, LV-GLS measured by echocardiography has consistently been shown to be an independent predictor of mortality. Associations have been demonstrated in patients with CKD stage 3B-5D (17), CKD stage 4-5D (29), and patients on dialysis (30). LV-GLS has theoretical advantages over LVEF for the assessment of cardiac function in patients with CKD: reduced LVEF has been shown to occur late in the development of the uraemic cardiomyopathy (31), a finding that is supported by the high prevalence of heart failure with
preserved ejection fraction in ESKD populations (32). This is likely explained by the differential aspects of myocardial function that the 2 techniques measure. While LVEF simply assesses the difference in volume at end diastole and systole, LV-GLS assesses the function of subendocardial fibres, which more directly correlates to the extent of interstitial myocardial fibrosis (30). In our study, 112 (58%) of 194 patients with preserved LVEF (>50%) had abnormal LV-GLS when defined as >-16% (a threshold chosen based on the normal LV-GLS in healthy subjects being -20% +/-4% (12–14)). This may partly explain the extreme cardiovascular risk seen in ESKD populations, despite relatively low prevalence of heart failure. Accordingly, there would be an argument to investigate cardiovascular therapeutics, especially those with anti-fibrotic properties (such as mineralocorticoid receptor antagonists) in patients with ESKD who have impaired LV-GLS. Mineralocorticoid receptor antagonists have previously been studied in ESKD populations with no effect on LVMI but LV-GLS was not assessed (33,34). Given the high prevalence of impaired LV-GLS in ESKD populations, and the expected high frequency of events, we believe these trials would be of significant interest. The difference in LV-GLS between men and women is well recognised (14). Sex was accounted for in the multivariable model which found LV-GLS to independently associated with mortality, nevertheless our subgroup analysis suggests a greater prognostic ability of LV-GLS in women, compared to men, and this requires further study. The lack of association between LVEF and mortality in this cohort is likely explained by the low prevalence of reduced LVEF resulting in reduced statistical power. This is partly due to the entry criteria of the pooled studies which excluded patients with known severe left ventricular systolic dysfunction. On the contrary, the fact that LV-GLS associated with mortality, even when the vast majority of patients did not have heart failure, is striking. The lack of clear threshold of LV-GLS in predicting mortality on the ROC analysis suggests that LV-GLS alone is unlikely to be a useful prognostic tool, albeit there are numerous explanations for the lack of association including the observed influence of renal transplantation on survival and the long follow-up with high overall mortality.
Left Atrial Emptying Fraction as a Predictor of Mortality

LAEF was strongly correlated with mortality in our study on univariable and multivariable analyses. This was an unexpected finding and LAEF has not been extensively studied within this population. LAEF has been shown to associate with adverse cardiovascular events in the general population (35), elderly (36) and in patients with heart failure (37,38). Furthermore, there is extensive evidence correlating left atrial volumes with mortality, including in patients on haemodialysis (21,39). It is not clear if left atrial impairment is directly involved in the pathophysiology of the excess mortality, or if it is a surrogate marker, perhaps for volume overload or left ventricular diastolic dysfunction (40,41).

CMR in the assessment of suitability for transplant

Renal transplantation, where appropriate, is the optimal treatment for patients with ESKD. However, transplants are a limited resource and have potential to cause some patients net harm due to the risks of surgery and long-term immunosuppression. Cardiovascular assessment (albeit to varying degrees) is standard practice in pre-transplant assessment and is recommended by international guidelines (42). However, the evidence supporting this practice is scant and so it is becoming increasingly controversial (43). We hypothesised that LV-GLS on CMR may be helpful for cardiovascular risk assessment when considering renal transplant suitability. LV-GLS significantly associated with mortality in the multivariable model, even when future renal transplantation was accounted for. However, the overwhelming survival benefit of renal transplantation was evident across all quartiles of LV-GLS (Figure 3), suggesting that there is no LV-GLS too poor (or too good) for a patient to reap survival benefit from a transplant, if not otherwise contraindicated. Regression of myocardial fibrosis following kidney transplant may account for part of this improved survival (7,44). This retrospective observation will be heavily biased due to selection bias and immortal time bias, but as randomised controlled trials assessing this will never be ethically feasible, we feel the present data are sufficient to say that LV-GLS is unlikely to be helpful when assessing the majority of patients for transplant suitability. The utility of stress CMR protocol using GLS at peak stress
has not been investigated and advances in free breathing cine acquisitions might make this feasible.

**Limitations**

This is a retrospective analysis of pooled studies, albeit at a single centre using consistent imaging protocols. The cohort combines patients scanned at both 1.5T and 3T. While the influence from field strength on LV-GLS is likely to be negligible (12), we accept there may be a small, unquantified difference in cine parameters between the acquisitions from different scanners. Inclusion from source studies was incomplete and unquantified for the studies published in 2006 (19) and 2010 (21) due to a combination of overlap in participants between the 2 studies and inability to retrieve some CMRs from archiving. The nature of the source studies has resulted in a younger than expected mean age (54 +/- 12 years) within this cohort and an under-representation of older, prevalent dialysis patients. Further studies to confirm our findings in different populations of patients with ESKD are required. It was not possible to examine non-fatal cardiovascular outcomes as data from historic patients were insufficient to allow reliable examination of cardiovascular events. The source data for our primary outcome of all-cause mortality are robust, but the data on cause of death were incomplete resulting in reduced power to examine of our secondary outcome of cardiovascular mortality. Nevertheless, the weaker association between LV-GLS and cardiovascular mortality, as opposed to all-cause mortality, is surprising given the cardio-centric nature of LV-GLS and warrants further study. It is plausible that reduced functional myocardial reserve in ESKD would impair the ability to recover from other critical illness, such as severe infection, but we accept that any future interventional trials targeting LV-GLS as a surrogate marker would be expected to address cardiovascular mortality and events. Previous studies examining LV-GLS by echocardiography have found associations with all-cause mortality(17,29) and cardiovascular mortality (29,30).
CONCLUSION

In this cohort of patients with ESKD, LV-GLS and LAEF were associated with all-cause mortality, independent of baseline clinical variables and future renal transplantation. Conversely, conventional imaging biomarkers, such as LVMI and LVEF, did not associate with mortality. Using LV-GLS, instead of LVEF, to diagnose cardiac dysfunction in patients with ESKD could result in a major advance in our understanding of cardiovascular disease in ESKD and may be a more relevant measure in this population. Despite this, the survival benefit of renal transplantation was evident across all quartiles of LV-GLS, suggesting that in the absence of other contraindications to renal transplant, LV-GLS is unlikely to be helpful when assessing patients’ suitability for renal transplantation. Further studies are warranted to explore the potential role of LV-GLS as a sample enrichment tool and surrogate outcome measure in future clinical trials examining therapeutics to improve survival in patients with ESKD.
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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests relevant to the present study. Outside the present work: Keith Gillis reports speaker honoraria from Napp and consultancy fees from Vifor. Jennifer Lees reports speaker honoraria from Vifor-Fresenius, Astra Zeneca, Bristol Myers-Squibb and Pfizer. Patrick Mark reports speaker honoraria from Vifor-Fresenius, Astra Zeneca, Janssen, Napp, Novartis and Bristol Myers-Squibb, research grants from Boehringer Ingelheim and non-financial support from Pharmacosmos. The University of Glasgow holds research and consultancy agreements for work done by Colin Berry in the course of his employment with companies that have interests in cardiovascular disease. They include AstraZeneca, Abbott Vascular, Boehringer Ingelheim, HeartFlow, Novartis, Menarini, and Siemens Healthcare.

AUTHORS’ CONTRIBUTIONS

All authors have reviewed and contributed to this manuscript. PBM, AJR, ER, and KM conceived the idea for this study and designed the analysis plan. PBM, RP and ER recruited participants to the contributing studies. LYZ analysed the CMRs. AJR performed the data analysis and analysed a sample of CMRs. AJR and LYZ wrote the manuscript. KM, GR and CB advised on CMR analysis and critically reviewed the manuscript. RW led image acquisition. KG and JL assisted with data collection, analysis and critically reviewed the manuscript.
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### Tables and Figures

#### Table 1. Baseline demographics

<table>
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<th>ALL (N= 215)</th>
<th>Alive (n = 100)</th>
<th>Dead (n = 115)</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Age, years (mean (SD))</strong></td>
<td>54 (+/- 12)</td>
<td>51.2 (+/- 11.7)</td>
<td>56.2 (+/- 12.2)</td>
<td>0.005</td>
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<tr>
<td><strong>Gender, male (n (%))</strong></td>
<td>133 (62%)</td>
<td>62 (62%)</td>
<td>71 (62%)</td>
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<td><strong>Body mass index (median, (IQR)), kg/m²</strong></td>
<td>25.6 (22.4-30.1)</td>
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<td>26.6 (22.4-31.6)</td>
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<td><strong>Diabetes Mellitus (n, (%))</strong></td>
<td>65 (30%)</td>
<td>22 (22%)</td>
<td>43 (37%)</td>
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<tr>
<td><strong>Previous myocardial infarction (n, (%))</strong></td>
<td>32 (15%)</td>
<td>14 (14%)</td>
<td>18 (16%)</td>
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<td><strong>Heart failure (n, (%))</strong></td>
<td>2 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
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**Primary Renal Diagnosis N, (%)**

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<th>Alive (15%)</th>
<th>Dead (27%)</th>
<th>P-value</th>
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<td>48 (22%)</td>
<td>15 (15%)</td>
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<tr>
<td>Glomerulonephritis</td>
<td>44 (20%)</td>
<td>25 (25%)</td>
<td>19 (17%)</td>
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<td>Hypertension / Renal vascular disease</td>
<td>18 (8%)</td>
<td>8 (8%)</td>
<td>10 (9%)</td>
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<tr>
<td>Polycystic kidney disease</td>
<td>23 (11%)</td>
<td>13 (13%)</td>
<td>10 (9%)</td>
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<tr>
<td>Pyelonephritis</td>
<td>19 (9%)</td>
<td>9 (9%)</td>
<td>10 (9%)</td>
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<td>Unknown</td>
<td>32 (15%)</td>
<td>18 (15%)</td>
<td>14 (12%)</td>
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<tr>
<td>Other (defined)</td>
<td>31 (14%)</td>
<td>12 (12%)</td>
<td>19 (17%)</td>
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**CKD status at time of CMR N, (%)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>ALL (63%)</th>
<th>Alive (72%)</th>
<th>Dead (56%)</th>
<th>P-value</th>
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<tr>
<td>Haemodialysis</td>
<td>37 (17%)</td>
<td>8 (8%)</td>
<td>29 (25%)</td>
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<tr>
<td>Peritoneal dialysis</td>
<td>8 (4%)</td>
<td>5 (5%)</td>
<td>3 (3%)</td>
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<td>Functioning transplant</td>
<td>34 (16%)</td>
<td>15 (15%)</td>
<td>19 (17%)</td>
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</tr>
<tr>
<td>CKD stage 5 (pre-dialysis)</td>
<td>26 (12%)</td>
<td>15 (15%)</td>
<td>11 (10%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous renal transplant (non-functioning)</td>
<td>1.7 (0.6-4.6)</td>
<td>2.1 (0.6-5.3)</td>
<td>1.3 (0.6-4.3)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Presented as: mean +/- standard deviation (SD), or median and interquartile range (IQR).

Abbreviations: CKD = chronic kidney disease; CMR = Cardiovascular magnetic resonance imaging; RRT = renal replacement therapy
Table 2. Cardiovascular MRI characteristics

<table>
<thead>
<tr>
<th></th>
<th>ALL n=215</th>
<th>Alive n=100</th>
<th>Dead n=115</th>
<th>p-value</th>
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<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
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<tr>
<td>LVMI (g/m²)</td>
<td>70.2</td>
<td>56.4, 84.8</td>
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<tr>
<td>LV-EDVI (ml/m²)</td>
<td>82.7</td>
<td>67.3, 101.2</td>
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<tr>
<td>LV-ESVI (ml/m²)</td>
<td>28.8</td>
<td>21.0, 39.3</td>
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<tr>
<td>LVM/LV-EDV (g/ml)</td>
<td>0.83</td>
<td>0.71, 0.95</td>
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<tr>
<td>LVEF (%)</td>
<td>64.7</td>
<td>58.5, 70.0</td>
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<tr>
<td>LV-GLS (%)</td>
<td>-15.3</td>
<td>-17.2, -13.6</td>
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<tr>
<td>LV-GRS (%)</td>
<td>24.9</td>
<td>21.1, 29.6</td>
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<tr>
<td>LV-GCS (%)</td>
<td>-16.0</td>
<td>-17.8, -13.8</td>
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<tr>
<td>RV-GLS (%)</td>
<td>-21.1</td>
<td>-21.1, -17.7</td>
<td>-22.1</td>
<td>-18.39, -20.7</td>
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<tr>
<td>RV-GRS (%)</td>
<td>44.2</td>
<td>34.4, 56.0</td>
<td>48.7</td>
<td>36.0, 60.8</td>
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<tr>
<td>LAVI min (ml/m²)</td>
<td>14.0</td>
<td>9.9, 20.6</td>
<td>13.1</td>
<td>8.8, 18.4</td>
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<tr>
<td>LAVI max (ml/m²)</td>
<td>33.6</td>
<td>26.1, 45.9</td>
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<tr>
<td>LAEF (%)</td>
<td>57.5</td>
<td>50.1, 65.1</td>
<td>62.6</td>
<td>55.8, 67.6</td>
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<tr>
<td>RAVI min (ml/m²)</td>
<td>16.7</td>
<td>11.9, 22.8</td>
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<tr>
<td>RAVI max (ml/m²)</td>
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<td>26.7, 43.0</td>
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<tr>
<td>RAEF (%)</td>
<td>48.3</td>
<td>41.3, 58.3</td>
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</table>

Presented as median and interquartile range (IQR). P-value refers to Mann-Whitney U test comparing baseline cardiovascular MRI parameters for alive versus dead. For simplicity, only those variables for which a statistically significant difference with a p value <0.05 are presented.

Abbreviations:
LVMI = left ventricular mass index
LV-EDVI = left ventricular end diastolic volume index
LV-ESVI = left ventricular end systolic volume index
LVM/LVEDV = ratio of left ventricular mass to left ventricular end diastolic volume
LVEF = left ventricular ejection fraction
LV-GLS = left ventricular global longitudinal strain
LV-GRS = left ventricular global radial strain
LV-GCS = left ventricular global circumferential strain
RV-GLS = right ventricular global longitudinal strain
RV-GRS = right ventricular global radial strain
LAVI min = minimum left atrial volume index
LAVI max = maximum left atrial volume index
LAEF = left atrial emptying fraction
RAVI min = minimum right atrial volume index
RAVI max = maximum right atrial volume index
RAEF = right atrial ejection fraction
Table 3. Association between clinical and CMR parameters and all-cause mortality (Cox Proportional Hazards Model)

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<th>Multivariable</th>
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<td>P-value</td>
<td>HR</td>
<td>CI</td>
<td>P-value</td>
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<td>0.79-1.67</td>
<td>0.48</td>
<td>1.43</td>
<td>0.95-2.17</td>
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<td>Age</td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>&lt;0.001</td>
<td>1.04</td>
<td>1.02-1.05</td>
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<tr>
<td>Diabetes</td>
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<td>0.98-2.08</td>
<td>0.07</td>
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<td>Heart failure</td>
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<td>0.11-5.78</td>
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<td>Previous</td>
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<td>0.75-2.04</td>
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<td>myocardial</td>
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<td>Future</td>
<td>0.23</td>
<td>0.14-0.38</td>
<td>&lt;0.001</td>
<td>0.29</td>
<td>0.17-0.47</td>
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<td>renal transplant*</td>
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<td>LVMI (g/m²)</td>
<td>1.00</td>
<td>0.99-1.01</td>
<td>0.30</td>
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<td>LVEDVI (ml/m²)</td>
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<td>LVESVI (ml/m²)</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.11</td>
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<tr>
<td>LVM/LVE DV (g/ml)</td>
<td>1.25</td>
<td>0.49-3.21</td>
<td>0.65</td>
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<tr>
<td>LVEF (%)</td>
<td>0.99</td>
<td>0.97-1.01</td>
<td>0.18</td>
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<tr>
<td>LVGLS (%)</td>
<td>1.10</td>
<td>1.03-1.16</td>
<td>0.003</td>
<td>1.08</td>
<td>1.01-1.16</td>
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<tr>
<td>LVGRS (%)</td>
<td>0.97</td>
<td>0.94-0.99</td>
<td>0.03</td>
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<tr>
<td>LVGCS (%)</td>
<td>1.02</td>
<td>0.96-1.08</td>
<td>0.49</td>
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<td>RVGLS (%)</td>
<td>1.05</td>
<td>1.01-1.08</td>
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<td>RVGRS (%)</td>
<td>0.99</td>
<td>0.98-1.00</td>
<td>0.02</td>
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<td>Description</td>
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<td>p-value</td>
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<tr>
<td>LAVI min (ml)</td>
<td>1.03</td>
<td>1.01-1.04</td>
<td>0.002</td>
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<tr>
<td>LAVI max (ml)</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.15</td>
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<tr>
<td>LAEF (%)</td>
<td>0.97</td>
<td>0.95-0.99</td>
<td>0.001</td>
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<tr>
<td>RAVI min (ml)</td>
<td>1.01</td>
<td>1.00-1.03</td>
<td>0.13</td>
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<tr>
<td>RAVI max (ml)</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.16</td>
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<tr>
<td>RAEF (%)</td>
<td>1.00</td>
<td>0.99-1.02</td>
<td>0.75</td>
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</tbody>
</table>

*time dependent covariate

The multivariable model was created using pre-specified clinical variables including sex, age, diabetes mellitus, previous myocardial infarction, heart failure and future renal transplantation, combined with CMR parameters that significantly associated with mortality on univariable analysis. Backwards stepwise elimination (Wald's) was used to select the optimal variables in the final model displayed here.

Abbreviations:

LVMI = left ventricular mass index
LV-EDVI = left ventricular end diastolic volume index
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FIGURE 1: Representative images showing 2D global longitudinal strain derivation using Cvi42 software (version 5.10, Circle Cardiovascular, Canada). Panels show horizontal long axis view at diastole (A) and systole (B) and vertical long axis views at diastole (C) and systole (D) and the resultant curve displaying peak global longitudinal strain (%) by time (milliseconds) (E).
FIGURE 2: Kaplan-Meier Curves of All-Cause Mortality by quartiles of: A) peak left ventricular global longitudinal strain (LV-GLS) (%), B) left atrial emptying fraction (LAEF) (%). Compared to the best quartile of LV-GLS, participants in the worst quartile had significantly poorer outcomes (log rank test p=0.03) with no difference between the other quartiles. For LAEF, the first quartile had significantly worse survival compared to participants in the 3rd and 4th quartiles (log rank test p = 0.003 and 0.03, respectively).
FIGURE 3: Kaplan-Meier curves of all-cause mortality comparing participants who did and did not receive a renal transplant during follow-up for each quartile of left ventricular global longitudinal strain (LV-GLS). Survival benefit of renal transplantation was most marked in those in the best quartile of LV-GLS but was still significant in participants within the worst quartile of LV-GLS (log rank test p<0.001 for all groups).
REFERENCES


20. Rutherford E, Talle MA, Mangion K et al. Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1


44. Conti MM, Fregonesi Barbosa M, Del Carmen A et al. Kidney transplantation is associated with reduced myocardial fibrosis. A cardiovascular magnetic resonance study with native T1 mapping. Available from: https://doi.org/10.1186/s12968-019-0531-x
173x254mm (300 x 300 DPI)
173x254mm (300 x 300 DPI)
Kaplan-Meier curves of all-cause mortality comparing participants who did and did not receive a renal transplant during follow-up for each quartile of left atrial emptying fraction (LAEF). Survival benefit of renal transplantation was present, and of similar magnitude, across all quartiles of LAEF (log rank test p<0.001).