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Original Article

ORIGINAL ARTICLE

Global longitudinal strain by feature-tracking cardiovascular magnetic resonance imaging predicts mortality in patients with end-stage kidney disease

Alastair J. Rankin [1], Luke Zhu[1], Kenneth Mangion [1], Elaine Rutherford [1], Keith A. Gillis[2], Jennifer S. Lees [1], Rosie Woodward[3], Rajan K. Patel[1,2], Colin Berry [1], Giles Roditi [1,4] and Patrick B. Mark [1]

[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 and [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 of premature death, with cardiovascular disease being the predominant cause of death. We hypothesized that left ventricular global longitudinal strain (LV-GLS) measured by feature-tracking cardiovascular magnetic resonance imaging (CMRI) would be associated with all-cause mortality in patients with ESKD.

Methods. A pooled analysis of CMRI studies in patients with ESKD acquired within a single centre between 2002 and 2016 was carried out. CMR parameters including LV ejection fraction (LVEF), LV mass index, 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 a median follow-up of 5 years. The median LVEF was 64.7% [interquartile range (IQR) 58.5–70.0] and the median LV-GLS was −15.3% (IQR −17.24 to −13.6). While 90% of patients had preserved LVEF (>50%), 58% of this group had abnormal LV-GLS (>−16%). On multivariable Cox regression, age {hazard ratio [HR] 1.04 [95% confidence interval (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 CMRI and LAEF 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 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

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INTRODUCTION

Patients with chronic kidney disease (CKD) are at increased risk of death from all causes compared with 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 the severity of CKD [2], such that patients with CKD Stage 5 are three to four 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 (LV) hypertrophy, cardiac dysfunction and myocardial fibrosis, which together are sometimes referred to as a 'uraemic cardiomyopathy' [6–8]. The utility of cardiovascular magnetic resonance imaging (CMRI) to detect these abnormalities has been an area of growing interest and CMRI may prove to be a useful tool in the development of non-invasive novel biomarkers for future risk stratification [9, 10].

LV global longitudinal strain (LV-GLS) measures the percentage of muscle deformation during the cardiac cycle as a sensitive marker of myocardial function [11]. Feature-tracking CMRI is a non-contrast post-processing technique that derives LV-GLS by tracking endocardial and epicardial borders through successive images from routinely acquired CMRI sequences [11]. Normal values for LV-GLS measured by feature-tracking CMRI are approximately $-20 \pm 4\%$ [12–14]. LV-GLS has been shown to be a strong correlate of mortality and clinical outcomes in patients with myocardial infarction (MI) [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, CMRI is considered the gold standard imaging modality in end-stage kidney disease (ESKD), as fluctuations in volume status with renal replacement therapy (RRT) may have an undue influence on images obtained in a two-dimensional plane [18].

We hypothesized that LV-GLS on feature-tracking CMRI has incremental prognostic utility over clinical and conventional imaging for predicting all-cause mortality in patients with ESKD.

MATERIALS AND METHODS

Participants

CMRIs 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 CMRIs were available and who had consented to long-term data follow-up were eligible for inclusion. All participants had CKD Stage 5 [estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2] and were receiving or were estimated to be within 6 months of requiring RRT. Further details of the cohorts are described elsewhere (ClinicalTrials.gov 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 MI, heart failure, sudden cardiac death, stroke or peripheral vascular disease [22].

CMRI acquisition

CMRI acquisition was performed using 1.5 T (Sonata, Siemens, Erlangen, Germany) and 3 T MRI scanners (Magnetom Verio and Prisma, Siemens Erlangen, Germany). For patients on haemodialysis, the scans were performed 24 h 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 localizer images, balanced steady-state free precession (SSFP) sequences were used to acquire LV images in three long-axis planes, followed by a short-axis stack from the apex to the atrioventricular ring. Additional details are available in the Supplementary data, Table S1.

CMRI analysis

All data analysis was carried out in a core lab utilizing dedicated CMR software (cvi42, version 5.10; Circle Cardiovascular Imaging, Calgary, AB, Canada). Routinely analysed CMRI measures of LV and right ventricular (RV) function were carried out according to current guidelines [23], with parameters of myocardial mass and ventricular volume derived from the short-axis views and indexed to body surface area. Ventricular endocardial and epicardial contours were manually drawn at end diastole. LV 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 volume. 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 LV strain (circumferential, longitudinal and radial) and global RV strain (longitudinal and radial) were derived using the tissue tracking module to determine 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 (LA) emptying fraction (LAEF) was calculated as the percentage difference between maximal and minimal LA volume divided by maximal atrial volume. The primary observer (L.Y.Z.) performed all CMRI analyses in a random order. A second independent observer (A.J.R.) analysed a random sample of $>10\%$ of the cohort to assess interobserver variability. Both observers were blinded to clinical outcomes.

Statistical analysis

Continuous data with a normal distribution are presented as mean ± standard deviation and median and interquartile range

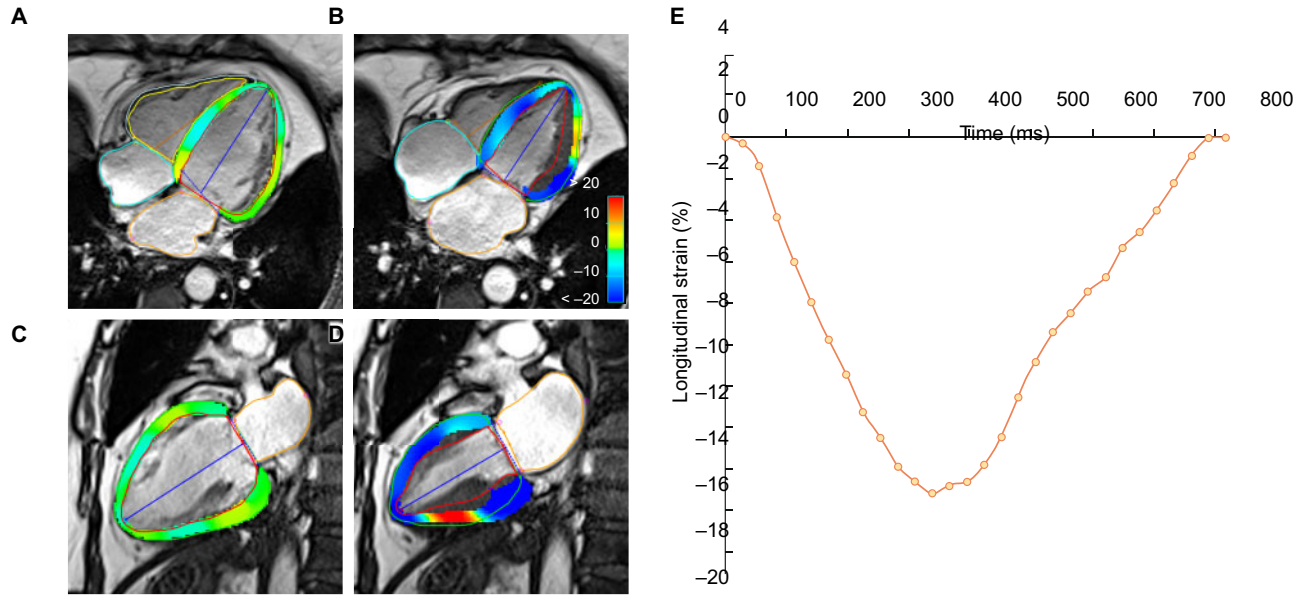

FIGURE 1: Representative images showing two-dimensional GLS derivation using cvi42 software version 5.10 (Circle Cardiovascular Imaging). Panels show horizontal long-axis view at (A) diastoleand (B) systoleand vertical long-axis views at (C) diastoleand (D) systoleand (E) the resultant curve displaying peak GLS (%) by time (ms).

(IQR) for skewed data, with normality defined according to the 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. The Kruskal–Wallis test was used to compare LV-GLS by the year of scan. Univariable Cox proportional hazards analysis was performed to identify CMRI 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 MI. Future renal transplantation was added to the model as a time-dependent 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 backward 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. CMRI 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 subgroup analyses based on future renal transplantation. Intra- and interobserver variability was assessed by the intraclass correlation (ICC) coefficient (two-way mixed effect, average measures). Receiver operating characteristics (ROC) curve analysis was used to identify an optimal prognostic threshold for LV-GLS. Statistical analysis was performed using SPSS version 26 (IBM, Armonk, NY, USA).

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 NCT01951404)]. There was no difference in survival or LV-GLS by the 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 the 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 RRT, of whom 8 (4%) had a functioning renal transplant [median eGFR 10.5 (IQR 9.1–13.3) mL/min/1.73 m^2]. The remaining 34 (16%) patients had CKD Stage 5 with a median eGFR of 10.4 (IQR 8.6–12.8) mL/min/1.73 m^2. During a median follow-up of 5.0 years (range 1 day–16.9 years), there were 115 deaths (53%). A 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 and 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 a similar sex distribution and body mass index (Table 1). Deceased patients were significantly more likely to have diabetes at baseline (37% versus 22%; $P = 0.014$); however, the history of cardiac disease including MI and heart failure were similar (Table 1).

Table 2 summarizes the CMRI results for the cohort. Seven patients had a reduced LV ejection fraction (LVEF) <40%, while a further 14 patients had a mid-range ejection fraction between 40% and 49%, as defined by the 2016 European Society of Cardiology guidelines [24, 25]. A total of 112 patients with preserved LVEF >50% had abnormal LV-GLS when defined as >−16.0% [12]. Intra- and interobserver reproducibility were excellent for LA, right atrial (RA) and LV parameters (ICC >0.92) and moderate for RV parameters (ICC 0.57–0.74) (Supplementary data, Table S2) [26].

CMRI parameters and all-cause mortality

On univariable analysis with each variable entered separately, LV-GLS, LV global radial strain (LV-GRS), RV global longitudinal strain (RV-GLS), RV global radial strain (RV-GRS), minimum LA

Table 1. Baseline demographics

Characteristics	All (N = 215)	Alive (n = 100)	Dead (n = 115)	P-value
Age (years), mean (SD)	54 (12)	51.2 (11.7)	56.2 (12.2)	0.005
Gender (male), n (%)	133 (62)	62 (62)	71 (62)	0.97
Body mass index (kg/m2), median (IQR)	25.6 (22.4–30.1)	25.0 (22.2–29.2)	26.6 (22.4–31.6)	0.06
Diabetes mellitus, n (%)	65 (30)	22 (22)	43 (37)	0.01
Previous MI, n (%)	32 (15)	14 (14)	18 (16)	0.73
Heart failure, n (%)	2 (1)	1 (1)	1 (1)	0.92
Primary renal diagnosis, n (%)				
Diabetes mellitus	48 (22)	15 (15)	33 (27)	–
Glomerulonephritis	44 (20)	25 (25)	19 (17)	–
Hypertension/renal vascular disease	18 (8)	8 (8)	10 (9)	–
Polycystic kidney disease	23 (11)	13 (13)	10 (9)	–
Pyelonephritis	19 (9)	9 (9)	10 (9)	–
Unknown	32 (15)	18 (18)	14 (12)	–
Other (defined)	31 (14)	12 (12)	19 (17)	0.01
CKD status at time of CMRI, n (%)				
Haemodialysis	136 (63)	72 (72)	64 (56)	–
Peritoneal dialysis	37 (17)	8 (8)	29 (25)	–
Functioning transplant	8 (4)	5 (5)	3 (3)	–
CKD Stage 5 (pre-dialysis)	34 (16)	15 (15)	19 (17)	–
Previous renal transplant (non-functioning)	26 (12)	15 (15)	11 (10)	0.04
RRT vintage at time of CMRI (years), median (IQR)	1.7 (0.6–4.6)	2.1 (0.6–5.3)	1.3 (0.6–4.3)	0.37

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 backward stepwise elimination, LV-GLS and LAEF were the only CMRI 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% and 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). When compared with 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 with participants in the third and fourth quartiles of LAEF (Figure 2; P = 0.003 and 0.03, respectively).

On 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 an LV-GLS cut-off of −14.1% would yield 77% sensitivity and 67% specificity. However, when 2-year mortality was examined the AUC decreased to 0.52.

LV-GLS differed by sex within the cohort, with females having greater contractility than males [median GLS −16.17% (females) versus −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 (95% CI 1.08–1.35); P = 0.001], but the association was not detected when only male patients were studied [HR 1.08 (95% CI −0.99–1.18); P = 0.09]. There was no difference in LAEF by sex (Mann–Whitney U test P = 0.15).

CMRI parameters and cardiovascular mortality

With regards to 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 CMRI parameters that were significantly associated with outcome on univariable analysis. Following backwards elimination, LAEF was the only CMRI parameter that remained significantly associated with cardiovascular mortality in the multivariable model containing age [HR 1.08 (95% CI 1.0–1.12)], diabetes [HR 2.30 (95% CI 1.12–4.71)], future renal transplant [HR 0.35 (95% CI 0.13–0.95)] and LAEF [HR 0.96 (95% CI 0.93–0.99)].

CMRI parameters and future renal transplantation

A total of 106 (49%) 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% (IQR −17.32 to −14.18) compared with −14.88% (IQR −16.82 to −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; Supplementary data, Figure S3).

DISCUSSION

This large, retrospective study of CMRI in patients with ESKD found that LV-GLS by feature-tracking CMRI and LAEF have a 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).

Table 2. CMRI characteristics

Characteristics	All ($N = 215$)	Alive ($n = 100$)	Dead ($n = 115$)	P-value
LVMI (g/m^2)	70.2 (56.4–84.8)	–	–	–
LV-EDVI (mL/m^2)	82.7 (67.3–101.2)	–	–	–
LV-ESVI (mL/m^2)	28.8 (21.0–39.3)	–	–	–
LVM/LV-EDV (g/mL)	0.83 (0.71–0.95)	–	–	–
LVEF (%)	64.7 (58.5–70.0)	–	–	–
LV-GLS (%)	−15.3 (−17.24 to −13.6)	–	–	–
LV-GRS (%)	24.9 (21.1–29.6)	–	–	–
LV-GCS (%)	−16.0 (−17.8 to −13.8)	–	–	–
RV-GLS (%)	−21.1 (−21.1 to −17.7)	−22.1 (−18.39 to −20.7)	−20.7 (−23.3 to −16.5)	0.008
RV-GRS (%)	44.2 (34.4–56.0)	48.7 (36.0–60.8)	42.8 (33.1–53.7)	0.05
$LAVI_{min}$ (mL/m^2)	14.0 (9.9–20.6)	13.1 (8.8–18.4)	15.0 (11.2–23.1)	0.002
$LAVI_{max}$ (mL/m^2)	33.6 (26.1–45.9)			
LAEF (%)	57.5 (50.1–65.1)	62.6 (55.8–67.6)	54.3 (47.1–60.7)	0.001
$RAVI_{min}$ (mL/m^2)	16.7 (11.9–22.8)	–	–	–
$RAVI_{max}$ (mL/m^2)	33.5 (26.7–43.0)	–	–	–
RAEF (%)	48.3 (41.3–58.3)	–	–	–

Values presented as median (IQR). P-value refers to Mann–Whitney U test comparing baseline CMRI parameters for alive versus dead. For simplicity, only those variables for which a statistically significant difference with a P-value <0.05 are presented.
LV-EDVI, LV end-diastolic volume index; LV-ESVI, LV end-systolic volume index; LVM/LVEDV, ratio of LV mass to LV end-diastolic volume; LV-GCS, LV global circumferential strain; $LAVI_{min}$, minimum LA volume index; $LAVI_{max}$, maximum LA volume index; $RAVI_{min}$, minimum RA volume index; $RAVI_{max}$, maximum RA volume index; RAEF, RA ejection fraction.

Table 3. Association between clinical and CMRI parameters and all-cause mortality (Cox proportional hazards model)

	Univariable		Multivariable	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (female)	1.14 (0.79–1.67)	0.48	1.43 (0.95–2.17)	0.09
Age	1.04 (1.02–1.06)	<0.001	1.04 (1.02–1.05)	<0.001
Diabetes	1.43 (0.98–2.08)	0.07	–	–
Heart failure	0.83 (0.11–5.78)	0.83	–	–
Previous myocardial infarction	1.23 (0.75–2.04)	0.41	–	–
Future renal transplant[a]	0.23 (0.14–0.38)	<0.001	0.29 (0.17–0.47)	<0.001
LVMI (g/m^2)	1.00 (0.99–1.01)	0.30	–	–
LVEDVI (mL/m^2)	1.00 (1.00–1.001)	0.47	–	–
LVESVI (mL/m^2)	1.01 (1.00–1.02)	0.11	–	–
LVM/LVEDV (g/mL)	1.25 (0.49–3.21)	0.65	–	–
LVEF (%)	0.99 (0.97–1.01)	0.18	–	–
LVGLS (%)	1.10 (1.03–1.16)	0.003	1.08 (1.01–1.16)	0.03
LVGRS (%)	0.97 (0.94–0.99)	0.03	–	–
LVGCS (%)	1.02 (0.96–1.08)	0.49	–	–
RVGLS (%)	1.05 (1.01–1.08)	0.007	–	–
RVGRS (%)	0.99 (0.98–1.00)	0.02	–	–
$LAVI_{min}$ (mL)	1.03 (1.01–1.04)	0.002	–	–
$LAVI_{max}$ (mL)	1.01 (1.00–1.02)	0.15	–	–
LAEF (%)	0.97 (0.95–0.99)	0.001	0.98 (0.96–1.00)	0.03
$RAVI_{min}$ (mL)	1.01 (1.00–1.03)	0.13	–	–
$RAVI_{max}$ (mL)	1.01 (1.00–1.02)	0.16	–	–
RAEF (%)	1.00 (0.99–1.02)	0.75	–	–

[a]Time-dependent covariate.
The multivariable model was created using pre-specified clinical variables including sex, age, diabetes mellitus, previous MI, heart failure and future renal transplantation, combined with CMRI parameters that significantly associated with mortality on univariable analysis. Backward stepwise elimination (Wald's) was used to select the optimal variables in the final model displayed here.

Benefits of using feature-tracking CMRI for strain analysis

CMRI is the gold standard for the assessment of cardiac volume 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 interoperator 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 CMRI supports the superiority of CMRI over echocardiography. Feature tracking is a technique that measures strain using routinely acquired SSFP sequences and obviates the need for acquisition of bespoke CMRI strain

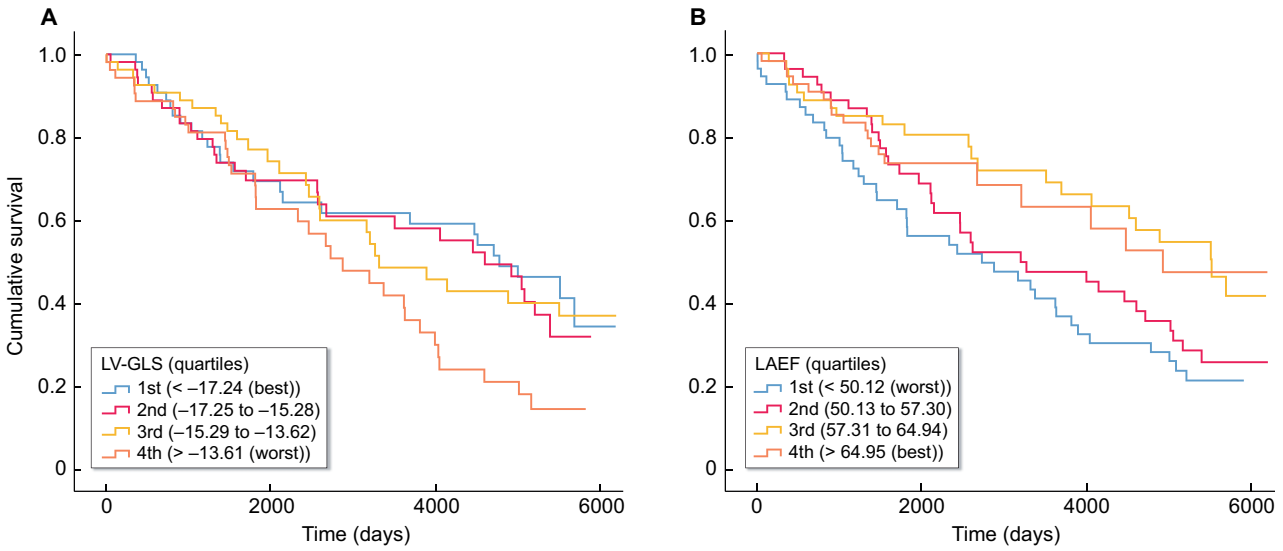

FIGURE 2: Kaplan–Meier curves of all-cause mortality by quartiles of (**A**) peak LV-GLS (%) and (**B**) LAEF (%). Compared with the best quartile of LV-GLS, participants in the worst quartile had significantly poorer outcomes (log-rank test P = 0.03) with no difference between the other quartiles. For LAEF, the first quartile had significantly worse survival compared with the third and fourth quartiles (log-rank test P = 0.003 and 0.03, respectively).

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 these data in less than a quarter of the time needed for tagging. We believe feature-tracking CMRI is at the intersection of accuracy and ease of acquisition and have demonstrated its utility in this cohort.

GLS 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 Stages 3B–5D [17], CKD Stages 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 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 two 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 the relatively low prevalence of heart failure. Accordingly, there would be an argument to investigate cardiovascular therapeutics, especially those with antifibrotic 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 LV mass index (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 recognized [14]. Sex was accounted for in the multivariable model, which found LV-GLS to be independently associated with mortality. Nevertheless, our subgroup analysis suggests a greater prognostic ability of LV-GLS in women compared with 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 LV systolic dysfunction. In contrast, 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 a 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, although 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.

LA emptying fraction as a predictor of mortality

LAEF was strongly correlated with mortality in our study in both 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], the elderly [36] and in patients with heart failure [37, 38]. Furthermore, there is extensive evidence correlating LA volumes with mortality, including in patients on haemodialysis [21, 39]. It is unclear if LA impairment is directly involved in the pathophysiology of the excess mortality or if it is a surrogate marker, perhaps for volume overload or LV diastolic dysfunction [40, 41].

CMRI 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 the potential to cause some patients net harm due to the risks of surgery and long-term

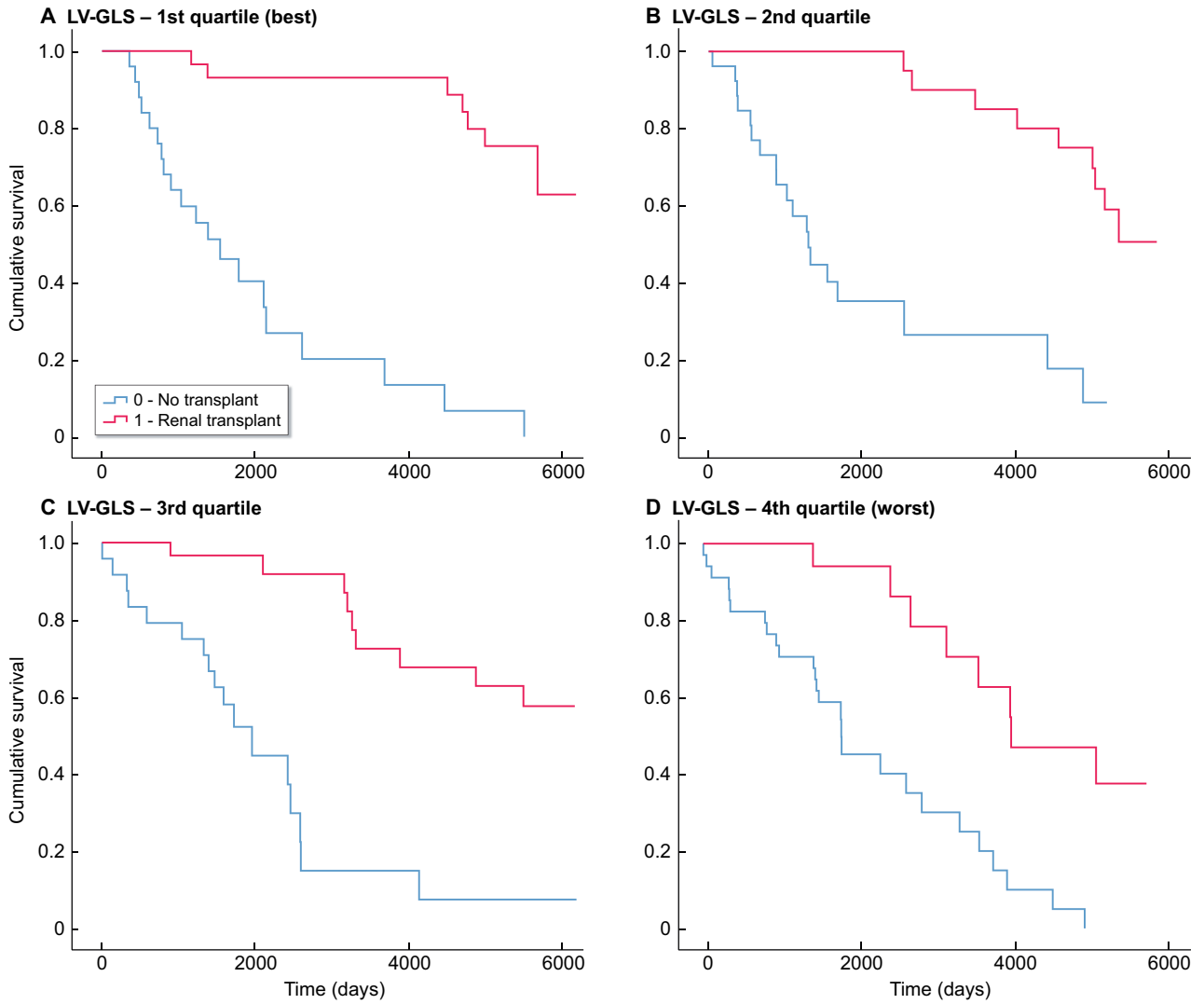

FIGURE 3: Kaplan–Meier curves of all-cause mortality comparing participants who did and did not receive a renal transplant during follow-up for each quartile of LV-GLS. The survival benefit of renal transplantation was most marked in those in the best quartile of LV-GLS but was still significant in participants within the worst quartile of LV-GLS (log-rank test $P < 0.001$ for all groups).

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 hypothesized that LV-GLS on CMRI 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 randomized 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 the stress CMRI protocol using GLS at peak stress has not been investigated and advances in free-breathing image acquisitions might make this feasible.

Limitations

This is a retrospective analysis of pooled studies at a single centre using consistent imaging protocols. The cohort combines patients scanned at both 1.5 T and 3 T. 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 image parameters between 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 two studies and inability to retrieve some CMRIs 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 underrepresentation 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 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 cardiocentric nature of LV-GLS and warrants further study. It is plausible that reduced functional myocardial reserve in ESKD impairs the ability to recover from other critical illnesses, 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.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

All authors reviewed and contributed to this manuscript. P.B.M., A.J.R., E.R. and K.M. conceived the idea for this study and designed the analysis plan. P.B.M., R.P. and E.R. recruited participants to the contributing studies. L.Y.Z. analysed the CMRIs. A.J.R. performed the data analysis and analysed a sample of the CMRIs. A.J.R. and L.Y.Z. wrote the manuscript. K.M., G.R. and C.B. advised on CMRI analysis and critically reviewed the manuscript. R.W. led image acquisition. K.G. and J.L. assisted with data collection and analysis and critically reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests relevant to this study. K.G. reports speaker honoraria from Napp and consultancy fees from Vifor, outside the present work. J.L. reports speaker honoraria from Vifor-Fresenius, AstraZeneca, Bristol Myers Squibb and Pfizer, outside the present work. P.M. reports speaker honoraria from Vifor-Fresenius, AstraZeneca, Janssen, Napp, Novartis and Bristol Myers Squibb; research grants from Boehringer Ingelheim and non-financial support from Pharmacosmos, outside the present work. The University of Glasgow holds research and consultancy agreements for work done by C.B. 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.

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