

Myocardial Characterization in Pre-Dialysis Chronic Kidney Disease: A Study of Prevalence, Patterns and Outcomes

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Abstract

Background

Late gadolinium enhancement (LGE) using cardiac magnetic resonance (CMR) characterizes myocardial disease and predicts an adverse cardiovascular (CV) prognosis. Myocardial abnormalities, are present in early chronic kidney disease (CKD). To date there are no data defining prevalence, pattern and clinical implications of LGE-CMR in CKD.

Methods

Patients with pre-dialysis CKD (stage 2-5) attending specialist renal clinics at University Hospital Birmingham (UK) who underwent gadolinium enhanced CMR (1.5T) between 2005 and 2017 were included. The patterns and presence (LGEpos) / absence (LGENeg) of LGE were assessed by two blinded observers. Association between LGE and CV outcomes were assessed.

Results

In total, 159 patients received gadolinium (male 61%, mean age 55 years, mean left ventricular ejection fraction 69%, left ventricular hypertrophy 5%) with a median follow up period of 3.8 years [1.04-11.59]. LGEpos was present in 55 (34%) subjects; the patterns were: right ventricular insertion point n=28 (51%), mid wall n=18 (33%), sub-endocardial n=5 (9%) and sub-epicardial n=4 (7%). There were no differences in left ventricular structural or functional parameters with LGEpos. There were 12 adverse CV outcomes over follow up; 7 of 55 with LGEpos and 5 of 104 LGEneg. LGEpos was not predicted by age, gender, glomerular filtration rate or electrocardiographic abnormalities.

Conclusions

In a selected cohort of subjects with moderate CKD but low CV risk, LGE was present in approximately a third of patients. LGE was not associated with adverse CV outcomes. Further studies in high risk CKD cohorts are required to assess the role of LGE with multiplicative risk factors.

Background

Patterns of late gadolinium enhancement (LGE) identified by cardiac magnetic resonance (CMR) imaging are integral to characterizing myocardial disease and are predictive of adverse cardiovascular (CV) outcome in both ischaemic and non-ischaemic disease [1, 2] LGE correlates with expansion of the extracellular matrix of the myocardium through perivascular and replacement fibrosis and predicts increased mortality and CV hospitalisation independently of other routinely assessed CMR parameters including left ventricular ejection fraction (LVEF).[1–3] Furthermore, the absence of mid-wall fibrosis in non-ischaemic cardiomyopathy has been associated with improved reverse LV (left ventricular) remodelling following cardiac resynchronisation therapy and better long-term survival with both severe and mild-moderate degrees of systolic impairment.[1, 2, 4] Left ventricular hypertrophy (LVH), dilatation and systolic impairment constitute “uremic cardiomyopathy” and are thought to explain the disproportionate rates of heart failure and sudden death which constitute almost 50% of deaths in end-stage kidney disease (ESKD) compared to only 6.7% from myocardial infarction / ischaemia. [5, 6] Myocardial interstitial fibrosis is present on endomyocardial biopsy in ESKD and on CMR late gadolinium enhancement imaging (LGE-CMR) with sub-endocardial (14%) and mid-wall patterns (14%) in patients without diagnosed CV disease. [7, 8] Subsequent

observational CMR studies have confirmed that myocardial abnormalities of systolic deformation and interstitial fibrosis are detectable from the earliest stages of CKD, before development of LVH, or a reduction in LVEF, emphasising the potential importance of myocardial disease in driving adverse outcomes in this cohort.[9] The significance of LGE in CKD remains unknown.

Methods

Study design and population

A retrospective study of patients with pre-dialysis CKD (stages 2–5; estimated glomerular filtration rate (eGFR) 90 to <15ml/min/1.73m²) undergoing CMR as part of clinical research studies between 2005- 2017, see *Table S1* for details.[9, 10] Patients provided consent to take part and allow retrospective follow up. Detailed inclusion / exclusion study criteria and patient clinical characteristics are outlined in supplementary data *Table S1*. Patients were recruited from studies investigating the changes in non-ischaemic myocardial structure and function, including fibrosis, in early CKD. All patients were recruited from specialist renal clinics at a tertiary unit in Birmingham, UK and were followed up regularly. Trial exclusion criteria included; diagnosed coronary/ peripheral artery disease, LVEF <50%, and diabetes, with the aim of reducing possible confounding effects of atheromatous disease.

Data collection

Patient demographics, haematological and biochemical data were obtained from electronic patient records system (Clinical Portal©). Renal aetiology was confirmed on imaging or biopsy studies and eGFR calculated by the creatinine based Modification of diet in renal disease (MDRD) equation at baseline.[11]

Cardiac Magnetic Resonance Protocol

CMR (1.5T, MAGNETOM Symphony and Avanto: Siemens, Erlangen, Germany) was performed to assess LV and right ventricular (RV) volumes, function, and LV mass using standard breath-hold steady state free precession sequences. Gadolinium contrast (Magnevist®, Gadovist®) at a dose 0.15–0.2mmol/Kg was administered to subjects with eGFR >15ml/min/1.73m² between 2005–2012 and >30ml/min/1.73m² between 2012–2017 following a change in Medicines and Healthcare Products Regulatory Agency guidelines. Standard T1-weighted gradient echo inversion recovery images were performed at 7–10 minutes after contrast in standard long axis and short axis stack imaging.

CMR Analysis

Offline analysis was performed by experienced operators (NE, AP) using cvi42® software (version 5.3.4 cvi42, Circle Vascular Imaging, Canada). Analysis of LV function, volume and LV mass was performed with delineation of papillary muscles and trabeculations using thresholding.[12] LV hypertrophy was defined based on age and gender.[13] The presence and pattern of LGE was assessed qualitatively and quantitatively by both observers and defined as LGEpos if present on two or more contiguous short axis slices or on corresponding long axis images with appropriate phase swapping. Patterns were defined as; sub-endocardial, diffuse / mid wall, sub-epicardial and focal

right ventricular insertion point (RVIP) according to previous published descriptions.[14]. Quantification of LGE was determined using Full width half max methodology and expressed as the total percentage of the LV mass, see *Figure 1*. [15]

Follow up

Follow-up was defined from the date of CMR to the date of either the last outpatient clinic episode or the last known inpatient admission. Right censoring was used for survival analysis. Adverse events were recorded from electronic patient records systems. Major adverse CV clinical outcomes were defined as death from CV disease, myocardial infarction, stroke, peripheral vascular disease, or hospital admission with heart failure. Cause of death was classified according to 1a and 1b on the death certificate. Total admissions, renal admissions (defined as routine management of CKD such as intravenous iron infusions, access surgery or admissions related to transplantation) and non-renal admissions were recorded.

Statistical analysis

Statistical analysis was performed using IBM SPSS© version 23 Armonk, New York. Significance was classified as a p value < 0.05. Continuous parametric variables were analysed using unpaired t tests (Age, eGFR, blood pressure, body mass index, ventricular volumes and mass), non-parametric data such as N-terminal pro b-type natriuretic peptide (NTproBNP) was analysed after the data was logged. A one-way analysis of variance was used for continuous parametric variables with more than two groups. Binary variables such as immunosuppressive therapy, anti-hypertensive therapy, sex, presence of left ventricular hypertrophy and statin use were analysed using Fisher's exact tests. Chi square tests were used if there were several categories such as aetiology of renal disease. Kaplan Meier survival curves with Breslow and Log rank analysis were used to compare survival between those with and without LGE. Binary logistic regression was used to determine the influence of each variable on the presence of LGE. The results of the univariate analysis were displayed graphically as a forest plot. Forward regression was subsequently used for multivariate analysis. Absolute mean bias and interclass correlation coefficients were used to determine intra and inter observer variability.

Results

In total 159 patients underwent LGE-CMR with LGEpos present in 55 /159 subjects (34%). None of the 43 healthy controls had evidence of LGE.[9] Patient characteristics are presented in *Table 1*. There were no differences in demographics or blood pressure. Median follow up was 3.8 years [1.04–11.59].

CMR Data

Data are presented in *Table 2*. There were no differences in RV or LV volumes, function or mass between LGEpos and LGEneg subjects.

Patterns and quantification of LGE

Patterns of LGE were RVIP n = 28/55 (50.9%), mid wall n = 18/55 (32.7%), sub-endocardial n = 5/55 (9.1%) and sub-epicardial n = 4 (7.3%). Examples of these patterns are presented in *Figure 1*. There were no differences in demographic data, eGFR, blood pressure, ventricular function or mass between LGEpos and LGEneg subjects (*Table 1 and 2*) or between the different patterns of LGE in positive patients (see *Table S2* in supplemental materials). Sub-group analysis of LGEpos with exclusion of RVIP patterns (n = 27), demonstrated higher LV mass 69g/m² vs 63g/m² p = 0.029 and lower LVEF compared with LGEneg (69% vs. 66% p = 0.05). No specific pattern of LGE was associated with a defined aetiology. On multivariate modelling including demographics, CMR parameters and electrocardiogram (ECG) changes as variables, it was not possible to identify independent predictors of LGE (see *Figure 2*).

The diffuse and RVIP patterns of LGE limited quantification (38/55 patients) but accounted for a very small percentage of overall mass, 1.25 [0.67–2.02] %. Intra-observer variability (of 10 patients) gave an absolute mean bias of 0.46% ± 0.43%, interclass correlation coefficient 0.98 (95% confidence interval 0.91–0.99). Inter-observer variability (of 10 patients) gave an absolute mean bias of 0.46 ± 0.80%, interclass correlation coefficient 0.97 (95% confidence interval 0.90–0.99).

Eight subjects with LGEpos had abnormal ECGs (in the absence of known CVD) with varied renal aetiology. Three patients had pathological Q waves; two had RVIP LGE with inferior Q-waves and one subject had sub-endocardial LGE pattern corresponding to anterior Q-waves. Five patients had T wave inversion; three had RVIP LGE, one had mid wall and one had a sub-endocardial pattern.

Outcome measures

There were 15/159 patient deaths over follow up (9%); n = 6 (10.9%) in LGEpos patients and n = 9 (8.5%) in LGEneg. The cause of death was ascertained in 10 patients; 6 deaths were due to advanced carcinoma, one patient died of pneumonia, one patient died of acute cardiac failure secondary to ischaemic and hypertensive cardiac disease, one patient died of myocardial infarction and one patient died of a brain stem haemorrhage secondary to hypertension. A Kaplan Meier curve for all-cause mortality did not demonstrate a significant difference in mortality between the two groups (see *Figure 3*). Cardiovascular morbidity was also low in this cohort (7%) with no difference between LGEpos and LGEneg; cardiac events (including heart failure) n = 5 vs. n = 2, stroke n = 1 vs. n = 2 and peripheral vascular disease n = 1 vs. n = 1. Hospital admissions occurred in 51 subjects (32%) although 26 of these were renal related admissions and only 4 subjects were admitted with cardiac causes (all those with chest pain were admitted for investigations and subsequent angiograms). The remaining admissions were non-cardiac and included admissions for a range of medical and surgical complaints including seizures, urinary tract infections, hernias and fractures.

Subgroup analysis

Further analysis was conducted to compare subgroups of LGE in an attempt to determine whether those with RVIP patterns had a different risk profile in CKD to other patterns of LGE. When comparing the patients with LGEneg or RVIP LGE (n = 132) to all other remaining patterns of LGE (n = 27) there was no significant difference in survival (Log rank p = 0.316, Breslow p = 0.397). There was also no difference in cardiac events, heart failure, stroke or peripheral vascular disease. Similarly when those with RVIP (n = 28) were compared to all other types of LGE (n =

27) there was no difference in survival (Log rank $p = 0.404$ Breslow $p = 0.299$) cardiac events, heart failure, stroke or peripheral vascular disease.

Discussion

This large retrospective CMR study has examined the prevalence, patterns and clinical significance of LGE in patients with pre-dialysis CKD. Over a third of subjects had evidence of LGE with normal LVEF and low rates of LVH. However, LGE, did not predict adverse cardiac events and did not offer incremental risk stratification in this population. This finding may reflect that over half of the LGE was focal at the right ventricular insertion points, a pattern shown to be associated with a better prognosis and correlated on histology with myocardial disarray, increased collagen and fat between fibre bundles but not replacement fibrosis.[16] Only 18/159 (11%) patients had a mid-wall / diffuse pattern in keeping with myocardial interstitial fibrosis from a non-coronary aetiology which is far lower than the reported ~30% seen in non-ischaemic dilated cardiomyopathy (NI-DCM) where LGE has prognostic stratification. [17] CMR plays an increasingly important role in characterizing heart disease in CKD and an appreciation of the myocardial changes frequently present are important for clinicians. The observed low cardiac event rate over intermediate follow up might also offer a degree of reassurance to clinicians when assessing CKD patients without high risk CV markers such as diabetes or proteinuria.

RVIP-LGE has been reported not only in NI-DCM, pulmonary hypertension and hypertrophic cardiomyopathy but also in athletes [18–20]. It is thought to represent plexiform fibrosis related to interdigitation of RV and LV fibers as these form the septum rather than myocardial fibrosis and represents only 1–3% of overall LV mass [21]. The natural history of RVIP-LGE in CKD remains unknown. Our finding of isolated RVIP-LGE and a more benign phenotype is supported in a recent prospective observational study examining patterns of LGE in NI-DCM with severe LV impairment and a mean LVEF of 25% over 46 months follow up. RVIP-LGE was present in 14% of the cohort and was associated with higher systolic and diastolic blood pressure but did not increase the risk of adverse cardiac event or arrhythmic events compared to patients with no LGE. Furthermore, there was a lower incidence of heart failure than observed with myocardial LGE [16]. In pulmonary hypertension, observational studies have also shown that RVIP-LGE does not predict mortality in contrast to more extensive LGE extending into the interventricular septum [20].

In contrast, there are extensive data to support the role of myocardial LGE as a marker of risk in ischaemic and non-ischaemic cardiomyopathies even when the LVEF is normal.[1, 17]. Myocardial LGE correlates on histology with expansion of the extracellular space, increased collagen deposition and ultimately irreversible fibrosis.[22] The latter serves as a substrate for ventricular arrhythmias and promotes adverse ventricular remodelling.[22] In CKD, histological data showing myocardial interstitial fibrosis and disarray on endomyocardial biopsy was first reported in the 1990s and the subsequent use of LGE-CMR demonstrated 14% of patients with ESKD had evidence of mid-wall reparative fibrosis [7, 8]. Unlike other disease cohorts, large outcome studies demonstrating the prognostic role of LGE in CKD have not followed and further gadolinium LGE-CMR studies have been restricted since 2006 with regulatory changes to reflect the reported association between gadolinium-based contrast agents used for magnetic resonance imaging (MRI) procedures and nephrogenic systemic fibrosis (NSF).

The largest study to date in CKD was a retrospective analysis of 966 “all comers” undergoing LGE-CMR between 2006–2008 with a serum creatinine measured within 30 days of CMR. Patients were stratified according to eGFR greater or less than 70ml/min/1.73m². [23] The authors demonstrated lower eGFR to be associated with more LGE even after adjustment for demographics, coronary disease and diabetes. Stratification of survival based on eGFR

demonstrated higher mortality with LGEpos and $eGFR < 70 \text{ ml/min/1.73m}^2$ with a hazard ratio of 1.8 (1.07–3.04, $p = 0.03$) compared to LGEneg subjects. [23] This cohort was a very different population to our study. Firstly, subjects were ‘all comers’ who had all undergone CMR for clinical reasons and most subjects had coronary artery disease (54%) or diabetes (16%). [23] This contrasts with those recruited to our study, the majority of whom were identified a priori based on the presence of renal disease confirmed on biopsy/imaging and without cardiovascular disease. Secondly, the predominant pattern of LGE found in 88% was sub-endocardial ‘coronary’ infarct, suggesting that the study by Dandamudi et al was of a cohort of clinical patients with ischaemic heart disease and mild secondary renal impairment (mean $eGFR 73 \text{ ml/min/1.73m}^2$). [23] The ratio of sub-endocardial LGE in their study is disproportionate not only to the amount of a non-coronary pattern seen in our study but also that in the landmark study by Mark et al. [7]

There are several potential reasons why LGE did not predict adverse outcomes in our study of CKD contrary to the near universal finding in non-ischaemic cardiomyopathies where “LGE is bad”. Firstly, our cohort was selected as part of research trials to investigate the impact of CKD on changes in myocardial structure and function, and hence specifically excluded subjects with diagnosed cardiovascular disease and diabetes. Secondly, although the majority of our cohort were male, hypertensive and many were prescribed lipid lowering therapy, most also had only early stage CKD and the overall CV adverse event rate was low. It is possible that the follow-up period was too short to identify adverse outcomes related to myocardial LGE but it may also be that the impact of myocardial fibrosis in CKD may be most adverse in those with an incremental number of risks, perhaps including sub-clinical ischaemia. The latter hypothesis is consistent with the recent scientific statement from the American Heart Association, concluding that multiple mechanisms contribute to the progression of uremic cardiomyopathy rather than this being driven solely by a decline in $eGFR$ [24]. The impact of multiplicative CV risk factors including hypertension, calcium-phosphate metabolism and diabetes on LGE prevalence remains to be established in higher risk CKD cohorts.

Limitations and clinical implications

There are several limitations of our study; the data were retrospectively acquired and are observational from pre-defined and selected research cohorts. The small sample size, long follow up and small number of events makes this study vulnerable to type two statistical error. The low number of adverse clinical outcomes is partly due to a highly selected patient group and single centre data which might have precluded identification of an independent association of adverse events with LGE. It is also possible that clinical events have been missed in patients presenting to other hospitals. We acknowledge a selection bias in our cohort. Patients recruited into our studies are a highly selected group with controlled blood pressure and without diabetes and many comorbidities. The aetiology is also most commonly primary glomerulonephritis or adult polycystic kidney disease. We also acknowledge that the duration of CKD would be expected to affect the prevalence of myocardial disease. However, it was not possible to reliably establish this vintage in pre-dialysis patients many of whom were only referred from primary care at a stage of more rapid decline or falling below $eGFR$ referral cut offs. Further studies will require the enrolment of unselected subjects with CKD and longer follow up times to assess the prognostic implications of LGE in CKD. It is noteworthy that we have no reported cases of NSF in over 10 years of CKD based research. However, precautions are taken to minimise dose (0.15–0.2mmol/kg), newer low risk gadolinium agents are used (Gadovist®) and contrast is avoided in patients with acute kidney injury and when $eGFR < 30 \text{ ml/min/1.73m}^2$. The absence of any cases of NSF is reassuring but, our sample size is too small and NSF is too rare to draw conclusions.

Recruitment and data collection commenced before widespread availability of newer non-contrast T1 mapping CMR sequences. These sequences have undoubtedly allowed better detection of diffuse fibrosis which can be “missed” with LGE inversion recovery sequences due to limited spatial resolution.[25] Observational data in CKD cohorts have been consistent in demonstrating elevated native T1 times in early stage CKD and ESKD on dialysis [9, 26, 27]. However, to date there is not histological correlation with T1 in CKD. Indeed a recent proof of concept study correlating the extent of myocardial fibrosis on LGE with absolute native T1 signal failed to identify “cut off” thresholds in a validation model [28]. To date, the most comprehensive assessment of myocardial fibrosis and its clinical impact appears to be through combining multi-parametric CMR biomarkers of LGE, T1 and ECV. This approach was recently used in a cohort with aortic stenosis and successfully identified patients with worse LV remodelling, adverse blood biomarkers such as NT pro-BNP and worse functional capacity. [29] Continued restrictions on use of gadolinium in CKD means T1 mapping endpoints will potentially have increasing importance for longitudinal follow up and outcome prediction.

Conclusions

LGE is common in patients with pre-dialysis CKD who do not have clinical ischaemic heart disease. The predominant pattern was in the RVIP distribution with lower rates of mid-wall fibrosis than is reported in non-ischaemic cardiomyopathy. In this low risk, stable cohort, rates of CV events were low and LGE did not predict an adverse prognosis. This study does not exclude an association between mid-wall/myocardial LGE and adverse prognosis in those with advanced CKD and multiple risk factors.

Abbreviations

BMI: Body mass index.

CMR: Cardiovascular magnetic resonance.

CV: Cardiovascular.

CKD: Chronic kidney disease.

NI-DCM: Non ischaemic dilated cardiomyopathy.

eGFR: Estimated glomerular filtration rate.

ECG: Electrocardiogram.

ESKD: end stage kidney disease.

KDIGO: Kidney Disease Improving Global Outcomes.

LGEpos: Patients with late gadolinium enhancement.

LGENeg: Patients without late gadolinium enhancement.

LV: Left ventricular.

LVEDVI: Left ventricular end diastolic ventricular volume index.

LVESVI: Left ventricular end systolic ventricular volume index.

LVSV: Left ventricular stroke volume.

LVEF: Left ventricular ejection fraction.

LVMI: Left ventricular mass index.

LGE: Late gadolinium enhancement.

LGE-CMR: Late gadolinium cardiovascular magnetic resonance.

LVH: Left ventricular hypertrophy.

MRI: Magnetic resonance imaging.

MDRD: Modification of diet in renal disease.

NSF: Nephrogenic systemic fibrosis.

NTproBNP: N-terminal pro b-type natriuretic peptide.

RV: Right ventricular.

RVIP: Right ventricular insertion point.

RVEDVI: Right ventricular end diastolic volume index.

RVESVI: Right ventricular end systolic volume index.

RVSV: Right ventricular systolic volume.

RVEF: Right ventricular ejection fraction.

Declarations

Ethics approval and consent to participate

Data was collated and accessed for this retrospective analysis in accordance with the previous studies ethical approvals, see *Table S1*. Further informed consent was not required as data reviewed was collected as part of clinical care. This is in agreement with the United Kingdom National Research Ethics Service guidance.

Consent for publication

Not applicable.

Availability of data and materials

The data set used during this study are available from the corresponding author on reasonable request.

Competing interests

None

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Author's contributions

AMP made contributions to acquisition, analysis and interpretation of the data and drafting the manuscript. MKH, RV and SAF made contributions to the acquisition of data. WEM, MKH, RV, SAF, CJF, JNT and RPS revised the manuscript critically for important intellectual content. NCE made contributions to the conception and design, interpretation of data, drafting the manuscript and revising it critically. All authors have read and approved the final manuscript.

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References

- 1.Halliday B, Gulati A, Ali A, Guha K, Newsome SJ, Arzanauskaite M, Vassiliou VS, Lota AS, Izgi C, Tayal U *et al*: *Association Between Mid-Wall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients with Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction. Circulation* 2017, *135*(22):2106–2115.
- 2.Leyva F, Taylor RJ, Foley PWX, Umar F, Mulligan LJ, Patel K, Stegemann B, Haddad T, Smith REA, Prasad SK: *Left Ventricular Midwall Fibrosis as a Predictor of Mortality and Morbidity After Cardiac Resynchronization Therapy in Patients With Nonischemic Cardiomyopathy. Journal of the American College of Cardiology* 2012, *60*(17):1659–1667.
- 3.Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA, Pennell DJ: *Cardiovascular Magnetic Resonance, Fibrosis, and Prognosis in Dilated Cardiomyopathy. Journal of the American College of Cardiology* 2006, *48*(10):1977–1985.
- 4.Masci PG, Doulaptsis C, Bertella E, Del Torto A, Symons R, Pontone G, Barison A, Droogné W, Andreini D, Lorenzoni V *et al*: *Incremental Prognostic Value of Myocardial Fibrosis in Patients With Non–Ischemic Cardiomyopathy Without Congestive Heart Failure. Circulation: Heart Failure* 2014, *7*(3):448–456.

- 5.Saran R, Li Y, Robinson B, Abbott KC, Agodoa LYC, Ayanian J, Bragg-Gresham J, Balkrishnan R, Chen JLT, Cope E *et al: US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. American Journal of Kidney Diseases* 2016, 67(3, Supplement 1):A7-A8.
- 6.Edwards NC, Moody WE, Chue CD, Ferro CJ, Townend JN, Steeds RP: *Defining the Natural History of Uremic Cardiomyopathy in Chronic Kidney Disease: The Role of Cardiovascular Magnetic Resonance. JACC: Cardiovascular Imaging* 2014, 7(7):703–714.
- 7.Mark PB, Johnston N, Groenning BA, Foster JE, Blyth KG, Martin TN, Steedman T, Dargie HJ, Jardine AG: *Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. Kidney Int* 2006, 69(10):1839–1845.
- 8.Mall G, Huther W, Schneider J, Lundin P, Ritz E: *Diffuse Intermyocardiocytic Fibrosis in Uraemic Patients. Nephrology Dialysis Transplantation* 1990, 5(1):39–44.
- 9.Edwards NC, Moody WE, Yuan M, Hayer MK, Ferro CJ, Townend JN, Steeds RP: *Diffuse Interstitial Fibrosis and Myocardial Dysfunction in Early Chronic Kidney Disease. American Journal of Cardiology* 2015, 115(9):1311–1317.
- 10.Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townend JN: *Effect of Spironolactone on Left Ventricular Mass and Aortic Stiffness in Early-Stage Chronic Kidney Disease: A Randomized Controlled Trial. Journal of the American College of Cardiology* 2009, 54(6):505–512.
- 11.Levey AS, Coresh J, Greene T, *et al.:* *Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals of Internal Medicine* 2006, 145(4):247–254.
- 12.Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R, Plein S, Tee M, Eng J, Bluemke DA: *Normal values for cardiovascular magnetic resonance in adults and children. J Cardiovasc Magn Reson* 2015, 17(29).
- 13.Maceira AM, Prasad SK, Khan M, Pennell DJ: *Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson* 2006, 8:17–26
- 14.Schietinger BJ, Brammer GM, Wang H, Christopher JM, Kwon KW, Mangrum AJ, Mangrum JM, Kramer CM: *Patterns of Late Gadolinium Enhancement in Chronic Hemodialysis Patients. JACC: Cardiovascular Imaging* 2008, 1(4):450–456.
- 15.Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, Muthurangu V, Moon JC: *Evaluation of Techniques for the Quantification of Myocardial Scar of Differing Etiology Using Cardiac Magnetic Resonance. JACC: Cardiovascular Imaging* 2011, 4(2):150–156.
- 16.Yi J-E, Park J, Lee H-J, Shin DG, Kim Y, Kim M, Kwon K, Pyun WB, Kim YJ, Joung B: *Prognostic implications of late gadolinium enhancement at the right ventricular insertion point in patients with non-ischemic dilated cardiomyopathy: A multicenter retrospective cohort study. PLOS ONE* 2018, 13(11):e0208100.
- 17.Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M: *Late Gadolinium Enhancement on CMR Predicts Adverse Cardiovascular Outcomes in Non-ischemic Cardiomyopathy: A Systematic Review and Meta-analysis. Circulation: Cardiovascular Imaging* 2013, 7(2): 250–258.

- 18.van de Schoor FR, Aengevaeren VL, Hopman MTE, Oxborough DL, George KP, Thompson PD, Eijsvogels TMH: *Myocardial Fibrosis in Athletes. Mayo Clinic Proceedings* 2016, 91(11):1617–1631.
- 19.Zhu Y, Park E-A, Lee W, Kim H-K, Chu A, Chung JW, Park JH: *Extent of late gadolinium enhancement at right ventricular insertion points in patients with hypertrophic cardiomyopathy: relation with diastolic dysfunction. European Radiology* 2015, 25(4):1190–1200.
- 20.Swift AJ, Rajaram S, Capener D, Elliot C, Condliffe R, Wild JM, Kiely DG: *LGE Patterns in Pulmonary Hypertension Do Not Impact Overall Mortality. JACC: Cardiovascular Imaging* 2014, 7(12):1209–1217.
- 21.Moon JCC, Reed E, Sheppard MN, Elkington AG, Ho S, Burke M, Petrou M, Pennell DJ: *The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Journal of the American College of Cardiology* 2004, 43(12):2260–2264.
- 22.Bogun F, Desjardins B, Good E, Gupta S, Crawford T, Oral H, Ebinger M, Pelosi F, Chugh A, Jongnarangsin K *et al*: *Delayed-Enhanced Magnetic Resonance Imaging in Non-Ischemic Cardiomyopathy: Utility For Identifying the Ventricular Arrhythmia Substrate. Journal of the American College of Cardiology* 2009, 53(13):1138–1145.
- 23.Dandamudi S SJ, Hodge DO, Glockner JF and Chen HH: *The Prognostic Significance of Late-Gadolinium Enhancement Identified by Cardiac MRI in Association with Renal Function. Journal of Molecular Biology and Molecular Imaging* 2015, 2(2):1021.
- 24.Rangaswami J, Bhalla V, Blair John EA, Chang Tara I, Costa S, Lentine Krista L, Lerma Edgar V, Mezue K, Molitch M, Mullens W *et al*: *Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Circulation* 2019, 139:e840-e878.
- 25.aus dem Siepen F, Baumgärtner C, Müller-Hennessen M, André F, Messroghli D, Ochs M, Riffel J, Giannitsis E, Katus HA, Friedrich MG *et al*: *Variability of cardiovascular magnetic resonance (CMR) T1 mapping parameters in healthy volunteers during long-term follow-up. Open Heart* 2018, 5(1):e000717.
- 26.Rutherford E, Talle MA, Mangion K, Bell E, Rauhalammi SM, Roditi G, McComb C, Radjenovic A, Welsh P, Woodward R *et al*: *Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping. Kidney International* 2016, 90(4):845–852.
- 27.Graham-Brown MPM, March DS, Churchward DR, Stensel DJ, Singh A, Arnold R, Burton JO, McCann GP: *Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. Kidney International* 2016, 90(4):835–844.
- 28.Graham-Brown M, S. Singh A, S. Gulsin G, Levelt E, A. Arnold J, J. Stensel D, Burton J, P. McCann G: *Defining myocardial fibrosis in haemodialysis patients with non-contrast cardiac magnetic resonance. BMC Cardiovascular disorders* 2018, 18 (1): 145
- 29.Treibel TA, López B, González A, Menacho K, Schofield RS, Ravassa S, Fontana M, White SK, DiSalvo C, Roberts N *et al*: *Reappraising myocardial fibrosis in severe aortic stenosis: an invasive and non-invasive study in 133 patients. European Heart Journal* 2017, 39(8):699–709.
- 30.Price A, Ferro CJ, Hayer MK, Steeds RP, Edwards NC, Townend JN: *Premature Coronary Artery Disease and Early Stage Chronic Kidney Disease. QJM: An International Journal of Medicine* 2017, 111(10):683–686.

Tables

Table 1: Baseline patient characteristics according to presence or absence of late gadolinium enhancement on cardiac MRI

	LGEpos	LGENeg	P value
	n=55	n=104	
Age (years)	57 ± 12	53 ± 13	0.069
Male sex <i>n</i> (%)	38 (69)	59 (57)	0.171
BMI	28 ± 4	27 ± 4	0.088
eGFR (ml/min/1.73m ²)	54 ± 15	52 ± 16	0.502
KDIGO stage <i>n</i> (%)			0.649
2 (eGFR 60-89 ml/min/1.73m ²)	22 (40)	32 (31)	
3a (eGFR 45-59 ml/min/1.73m ²)	17 (30)	35 (33)	
3b (eGFR 30-44 ml/min/1.73m ²)	14 (26)	29 (28)	
4 (eGFR 15-29 ml/min/1.73m ²)	2 (4)	8 (8)	
Aetiology <i>n</i> (%)			0.117
Vasculitis	7 (13)	9 (9)	
GN	15 (27)	49 (47)	
Hereditary	10 (18)	13 (12)	
Systemic	8 (14)	9 (8)	
Infective	2 (4)	4 (4)	
Obstruction	4 (7)	3 (3)	
Hypertensive	1 (2)	5 (5)	
Interstitial	0 (0)	6 (6)	
Vascular	1 (2)	1 (1)	
Unknown	7 (13)	5 (5)	
Systolic BP (mmHg)	128 ± 17	126 ± 14	0.431
Diastolic BP (mmHg)	78 ± 11	77 ± 10	0.710
Haemoglobin (g/L)	138 ± 14	132 ± 22	0.057

Total cholesterol (mg/dL)	90 ± 18	90 ± 18	0.575
NTproBNP (pg/mL)	55 [34-93]	59 [17- 161]	0.656
Immunosuppression usage <i>n</i> (%)	16 (29)	22 (21)	0.326
Anti-hypertensive usage <i>n</i> (%)	45 (82)	83 (80)	0.822
Statin usage <i>n</i> (%)	24 (46)	39 (37)	0.388
ECG <i>n</i> (%)			
Q waves	3 (5)	4 (4)	0.931
T inversion	5 (9)	12 (11)	0.789

Continuous variables are presented as mean ± SD if normally distributed or medians and [25th-75th percentile] for skewed variables. Categorical variables are presented as *n* (valid %). Significant p values are bold.

BMI: Body mass index, BP: blood pressure, eGFR: estimated glomerular filtration rate. GN: Glomerulonephritis. KDIGO: Kidney Disease Improving Global Outcomes. LGEpos: Patients with late gadolinium enhancement. LGENeg: Patients without late gadolinium enhancement.

Table 2: Cardiac MRI data according to presence or absence of late gadolinium enhancement.

	LGEpos	LGENeg	P value
	n=55	n=104	
LVEDVI (ml/m ²)	61 ± 12	59 ± 12	0.484
LVESVI (ml/m ²)	19 ± 8	18 ± 7	0.336
LVSV (ml)	82 ± 16	77 ± 17	0.095
LVEF (%)	68 ± 10	70 ± 8	0.382
LVMI (g/m ²)	66 ± 14	62 ± 14	0.193
RVEDVI (ml/m ²)	67 ± 14	68 ± 13	0.690
RVESVI (ml/m ²)	28 ± 11	31 ± 10	0.057
RVSV (ml)	78 ± 17	74 ± 16	0.219
RVEF (%)	62 ± 9	61 ± 7	0.405
LVH	4 (7.3)	4 (3.8)	0.449

Continuous variables are presented as mean ± SD if normally distributed or medians [25-75th percentile] for skewed variables. Categorical variables are presented as n (valid %). Significant p values are bold.

LVEDVI: Left ventricular end-diastolic ventricular volume index. LVESVI: Left ventricular end systolic ventricular volume index. LVSV: Left ventricular stroke volume. LVEF: Left ventricular ejection fraction. LVMI: Left ventricular mass index. LVH: Left ventricular hypertrophy. RVEDVI: Right ventricular end diastolic volume index. RVESVI: Right ventricular end systolic volume index. RVSV: Right ventricular systolic volume. RVEF: Right ventricular ejection fraction.

Supplementary Tables

Table S1: A summary of details of each study included in this cohort.

Study name and ethical approval	Exclusion/Inclusion criteria	Methods of excluding ischaemic heart disease	Gadolinium dose, generic brand	Scan parameters	Patient demographics of those recruited
Chronic Renal Impairment in Birmingham II CRIB II [1] Approved by South Birmingham Local Research Ethics Committee	<p>Inclusion:</p> <ul style="list-style-type: none"> · CKD stage 2 (eGFR 60 to 89 ml/min/1.73 m² with other evidence of kidney disease. · Stage 3 (eGFR 30 to 59 ml/min/1.73 m²), and stage 4 (15 to 29 ml/min/1.73 m²) <p>Exclusion:</p> <ul style="list-style-type: none"> · Cardiovascular disease or symptoms · Valvular heart disease · AF · Diabetes 	Clinical history, ECG, Echocardiography	Magnevist® 0.2mmol/kg	1.5 Tesla LV function LV mass Aortic distensibility LGE	<p>Average age: 53yrs</p> <p>~60% male</p> <p>Average eGFR: 50ml/min/1.73m²</p> <p>Average office blood pressure: 130/77 mmHg</p> <p>Left ventricular hypertrophy 8%</p> <p>69% taking angiotensin converting enzyme inhibitors</p>
Diffuse fibrosis in CKD.[2] Approved by the National Research Ethics Service—South Birmingham (12/WM/0250)	<ul style="list-style-type: none"> · As in CRIB II <p>Healthy controls</p> <ul style="list-style-type: none"> · Normotensive or well controlled hypertension · No history of CVD · Renal function within expected range for age. 	Clinical history, ECG	Gadovist ® 0.15mmol/Kg	1.5 Tesla LV function LV mass T1 mapping LGE	<p>Average age: 57yrs</p> <p>~56% male</p> <p>Average eGFR: 50ml/min/1.73m² (CKD cohort)</p> <p>Average office blood pressure: 127/69 mmHg</p> <p>Left ventricular hypertrophy 5%</p> <p>>80% taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers</p> <p>37% Glomerular nephropathy. 21% Adult polycystic kidney disease.</p>
Left Ventricular Disease in Chronic Kidney Disease.	<p>Inclusion:</p> <ul style="list-style-type: none"> · >18 years of age. · CKD stage 2 to 5 plus other evidence of 	Stress Echo Cardiopulmonary exercise test.	Gadovist ® 0.15mmol/Kg	1.5 Tesla LV function LV mass T1 mapping	<p>Average age: 52 yrs</p> <p>~60% male</p>

CKD-Fibrosis NCT03176862	kidney disease i.e. proteinuria.	LGE if eGFR >30ml/min	Average office systolic blood pressure 134mmHg
Approved by the National Research Ethics Service – East Midlands (15/EM/0280)	Exclusion <ul style="list-style-type: none"> · Diabetes · Any previous cardiovascular disease · Cerebrovascular disease. · Peripheral vascular disease. · Pregnancy · Reno vascular disease. 		93% on anti- hypertensives
			Majority of patients had primary glomerulonephritis or adult polycystic kidney disease

AF; Atrial fibrillation. CKD; Chronic Kidney Disease. eGFR; estimated glomerular filtration rate.
ECG; Electrocardiogram

Table S2: Demographics and CMR data according to patterns of LGE.

	RVIP n=28	Mid- wall n=18	Subendocardial n=5	Subepicardial n=4
Age (years)	57 ± 13	57 ± 10	55 ± 14	59 ± 9
Male sex <i>n</i> (%)	21 (75)	11 (61)	4 (80)	2 (50)
BMI (kg/m ²)	28 ± 3	27 ± 3	30 ± 2	30 ± 7
eGFR (ml/min/1.73m ²)	55 ± 17	56 ± 13	41 ± 6	58 ± 9

				Total	LGEpos	LGENeg	P
				n=161	n=55	n=106	value
LVEDV				60 ± 13	61 ± 12	60 ± 14	0.78
(ml/m ²)							
LVESV				19 ± 9	19 ± 8	19 ± 9	0.75
(ml/m ²)							
LVSV				79 ± 16	82 ± 16	78 ± 17	0.09
(ml)							
LVEF				69 ± 9	68 ± 10	69 ± 8	0.56
(%)							
LVMI				64 ± 14	66 ± 14	63 ± 14	0.28
(g/m ²)							
RVEDV				68 ± 14	67 ± 14	68 ± 14	0.62
(ml/m ²)							
RVESV				30 ± 11	28 ± 11	31 ± 10	0.05
(ml/m ²)							
RVSV				75 ± 16	78 ± 17	74 ± 16	0.22
(ml)							
RVEF				61 ± 7	62 ± 9	61 ± 7	0.39
(%)							
LVH				9 (5.6)	4 (7.3)	5 (4.7)	0.49
Systolic BP				125 ± 16	130 ± 16	133 ± 26	128 ± 8
(mmHg)							
Diastolic BP				76 ± 11	82 ± 10	76 ± 13	76 ± 11
(mmHg)							
Haemoglobin (g/L)				135 ± 14	140 ± 13	150 ± 20	138 ± 16
Total cholesterol				5.1 ± 1	5 ± 1	4 ± 1.5	5.1 ± 0.7
(mmol/L)							

Immunosuppression usage <i>n</i> (%)	8 (30)	6 (35)	1 (20)	1 (25)
Anti-hypertensives usage <i>n</i> (%)	21 (78)	15 (88)	5 (100)	4 (100)
Statin usage <i>n</i> (%)	15 (53)	6 (40)	3 (60)	1 (25)
ECG <i>n</i> (%)				
Q wave	2 (7)	0 (0)	1 (20)	0 (0)
T wave inversion	3 (11)	1 (6)	1 (20)	0 (0)
CMR data				
LVEDV (ml/m ²)	61 ±11	59 ± 11	74 ± 14	54 ± 13
LVESV (ml/m ²)	18 ± 6	18 ± 5	37 ± 12	16 ± 5
LVSV (ml)	85 ± 15	78 ± 17	78 ± 16	80 ± 11
LVEF (%)	71 ± 7	68 ± 10	51 ± 8	72 ± 7
LVMI (g/m ²)	62 ± 13	67 ± 14	79 ± 16	67 ± 8
RVEDV (ml/m ²)	68 ± 14	67 ± 16	63 ± 7	64 ± 4
RVESV (ml/m ²)	27 ± 10	29 ± 15	29 ± 5	24 ± 3.
RVSV (ml)	80 ± 17	74 ± 16	73 ± 23	77 ± 10
RVEF (%)	62 ± 7	61 ± 11	60 ± 9	59 ± 10
LVH <i>n</i> (%)	1 (3.6)	2 (11)	1 (20)	0 (0)

Continuous variables are presented as mean \pm SD if normally distributed or medians and [25th-75th percentile] for skewed variables. Categorical variables are presented as *n* (valid %). Significant p values are bold. BMI: Body mass index. BP: blood pressure, CMR; Cardiovascular magnetic resonance. eGFR: estimated glomerular filtration rate, KDIGO: Kidney Disease Improving Global Outcomes. LVEDVI: Left ventricular end-diastolic ventricular volume index. LVESVI: Left ventricular end systolic ventricular volume index. LSV: Left ventricular stroke volume. LVEF: Left ventricular ejection fraction. LVMI: Left ventricular mass index. LVH: Left ventricular hypertrophy. RVEDVI: Right ventricular end diastolic volume index. RVESVI: Right ventricular end systolic volume index. RVSV: Right ventricular systolic volume. RVEF: Right ventricular ejection fraction.

There was no significant differences between groups.

References

1. Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townend JN: **Effect of Spironolactone on Left Ventricular Mass and Aortic Stiffness in Early-Stage Chronic Kidney Disease: A Randomized Controlled Trial.** *Journal of the American College of Cardiology* 2009, **54**(6):505-512.
2. Edwards NC, Moody WE, Yuan M, Hayer MK, Ferro CJ, Townend JN, Steeds RP: **Diffuse Interstitial Fibrosis and Myocardial Dysfunction in Early Chronic Kidney Disease.** *American Journal of Cardiology* 2015, **115**(9):1311-1317.

Figures

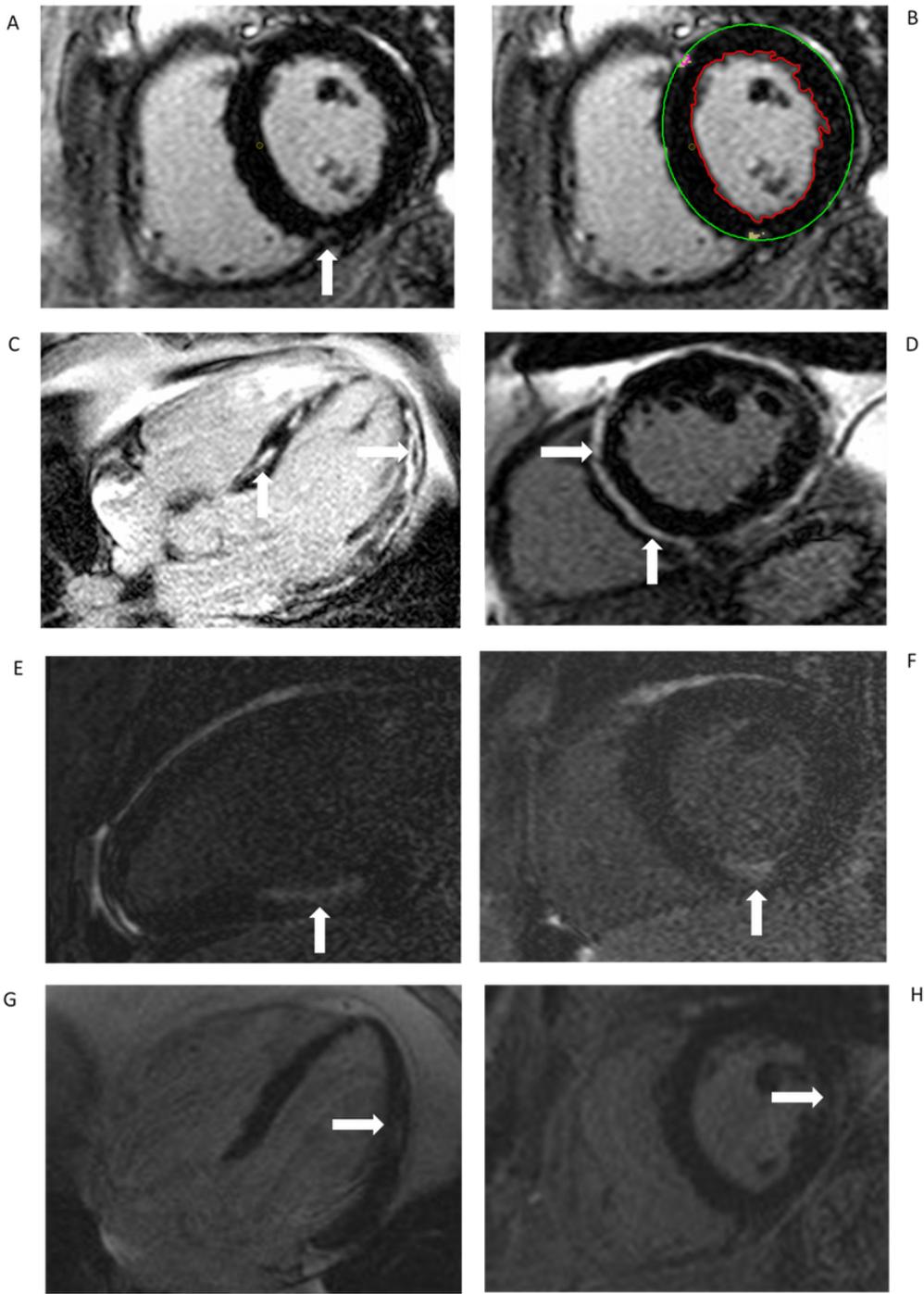


Figure 1

Examples of LGEpos patterns and quantification methods: A&B) A mid-ventricular LGE image with inferior and superior RVIP LGE (A). Endocardial and epicardial contours are drawn using cvi42 (B) and the maximum area of hyper enhancement selected. Areas of LGE are quantified using full-width-half maximum methodology and appear pixelated. LGE is given as grams and represented as percentage of total left ventricular mass. This patient had membranous nephropathy, stage 2 CKD and was in remission at the time of CMR. C & D) Mid-wall LGE; C & D Horizontal long axis 4-chamber view and corresponding mid short axis view showing extensive septal and lateral mid wall LGE in a patient with CKD secondary to Adult Polycystic Kidney Disease. The patient initially underwent a CMR as part of a research study and was asymptomatic. Coronary angiogram was normal. Ambulatory ECG monitoring demonstrated sinus rhythm with no arrhythmias. He later had a successful renal transplant with no

arrhythmias or deterioration in LV function. Follow up CMRs have confirmed fixed appearances of LGE. E & F) Sub-endocardial; E & F Vertical long axis 2-chamber and corresponding short axis view demonstrating focal inferior sub-endocardial infarction.* The patient had focal segmental glomerular sclerosis with stable CKD stage 3 disease. The patient was asymptomatic. He underwent a CT coronary angiogram and calcium score which demonstrated moderate coronary calcification above the 90th centile for age and gender but no evidence of coronary artery stenosis. G & H) Sub-epicardial LGE; G & H Horizontal long axis 4-chamber view and corresponding basal short axis view with sub-epicardial LGE in the basal-mid inferior wall. The patient was a 59 year old with Adult Polycystic Kidney Disease and stable CKD stage 3a. He was asymptomatic. There has been no clinical history suggestive of either sarcoidosis or myocarditis. *Images originally published in QJM: An International Journal of Medicine. [30]

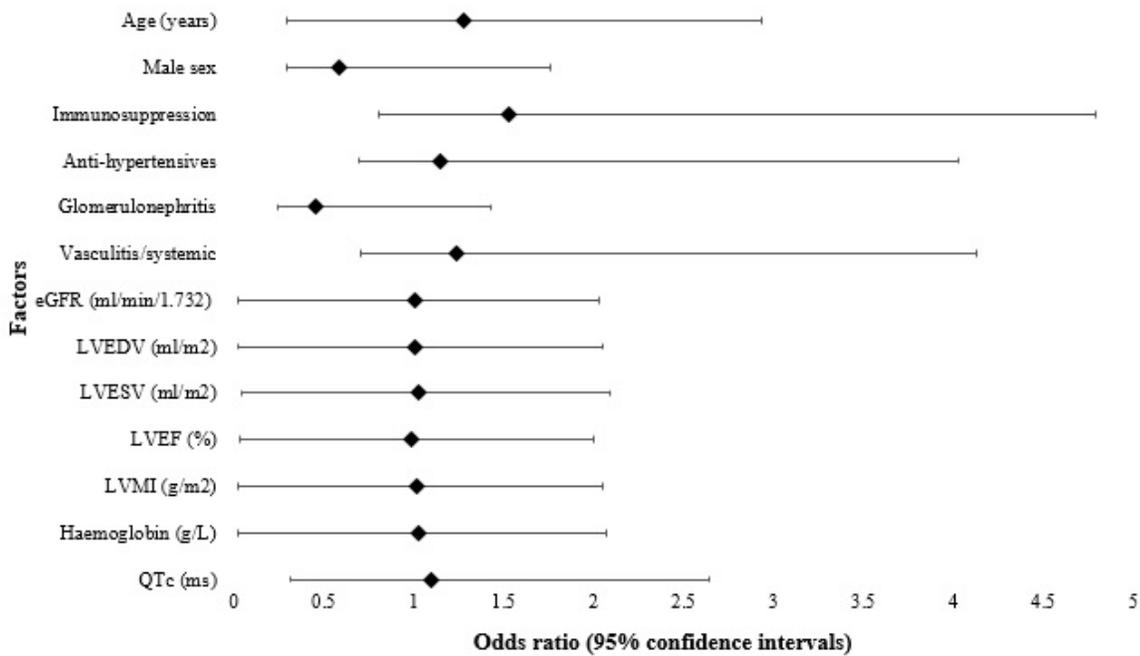


Figure 2

Predictors of LGE in CKD: Forest plot demonstrating the odds ratio (diamond marker) and 95% confidence intervals of all the factors which may influence the presence of late gadolinium enhancement on univariate analysis. The odds ratio (OR) is defined per 10 unit change. I.e. for age, OR given for per 10 years. Binary logistic regression was used for analysis with the dependent variable as the presence of LGE. All p values were more than 0.05 indicating there was no significant factor which predicts the presence of LGE on CMR. Abbreviations: eGFR: Estimated glomerular filtration rate. LVEDVI: Left ventricular end diastolic volume, indexed. LVESVI: Left ventricular systolic volume, indexed. LVEF: Left ventricular ejection fraction. LVMI: Left ventricular mass index. LVH: left ventricular hypertrophy. QTc: Corrected QT interval.

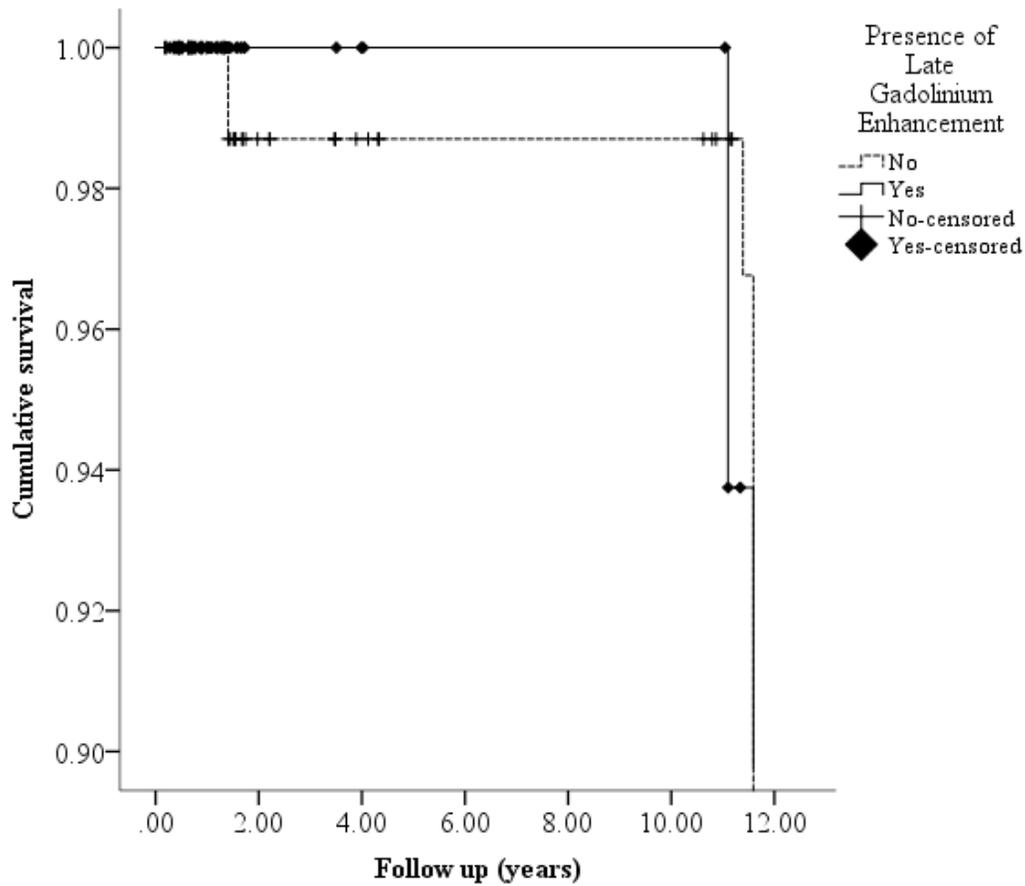


Figure 3

Kaplan- Meier curve of survival comparisons: A Kaplan-Meier curve demonstrates that there were very few events within those with and without LGE. There was no significant difference in survival between the two groups (Log Rank Mantel Cox and Breslow tests were non-significant at $p=0.154$ and $p=0.209$ respectively).