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ORIGINAL ARTICLE

Associations between eGFR and albuminuria with right ventricular measures: the MESA-Right Ventricle study

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ABSTRACT

Background. Chronic kidney disease (CKD) is associated with an increased risk of pulmonary hypertension, which may lead to right ventricular (RV) pressure overload and RV dysfunction. However, the presence of subclinical changes in RV structure or function in early CKD and the influence of these changes on mortality are not well studied. We hypothesized that early CKD, as indicated by elevated albuminuria or mild reductions in estimated glomerular filtration rate (eGFR), is associated with greater RV dilation and RV mass.

Methods. We included 4063 participants (age 45–84 years) without baseline clinical cardiovascular disease from the Multi-Ethnic Study of Atherosclerosis. The associations of baseline creatinine–cystatin C-based eGFR and albuminuria with cardiac magnetic resonance–derived RV measures (2000–02) were examined cross-sectionally with linear regression models. Cox regression models were used to examine whether RV parameters modified the associations of eGFR and albuminuria with all-cause mortality.

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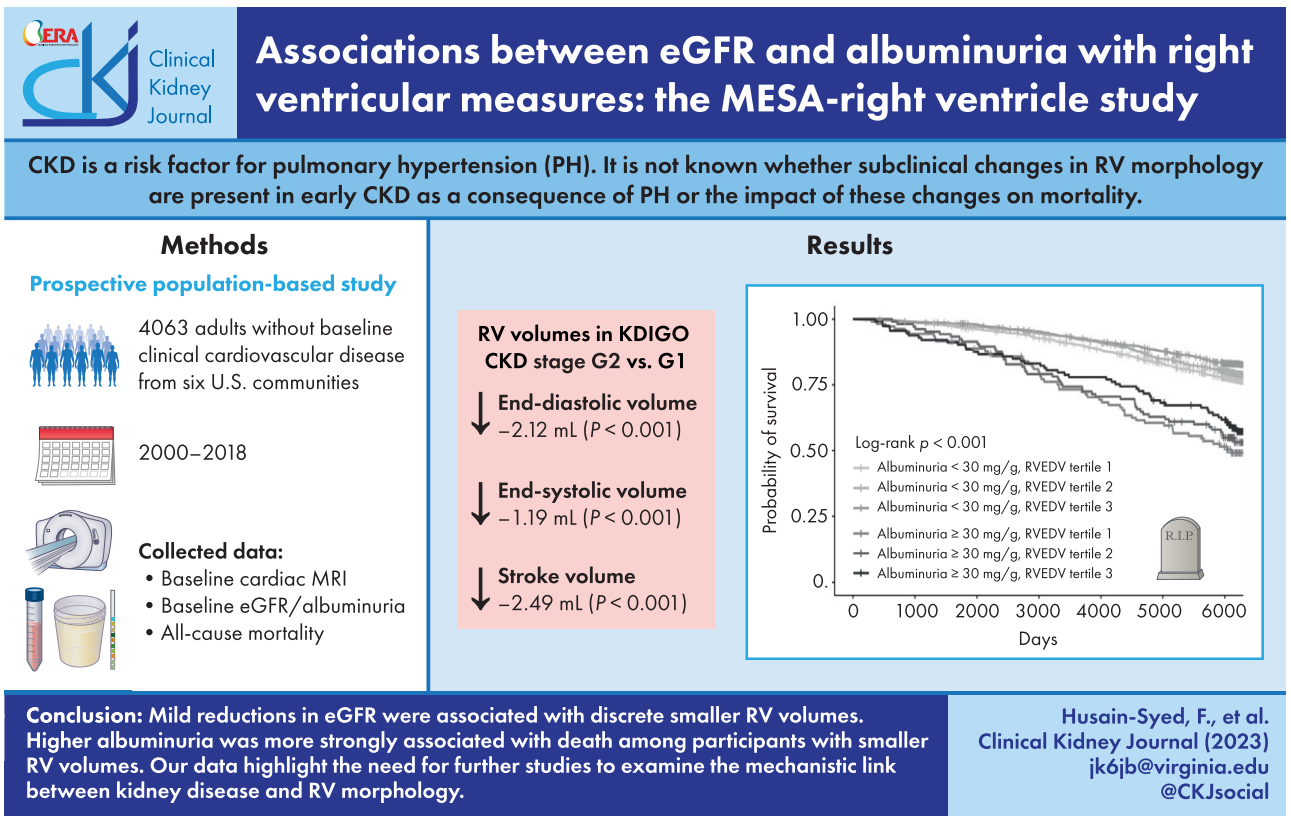
Results. Participants with reductions in eGFR primarily within the 60–89 mL/min/1.73 m^2 category had smaller RV end-diastolic and end-systolic volumes and stroke volume (all adjusted P-trends <.001) than those with eGFR ≥90 mL/min/1.73 m^2, an association that was predominantly seen in participants with albuminuria below 30 mg/g creatinine. Albuminuria was more strongly associated with death among those with lower RV volumes (P-values for interaction <.03).

Conclusions. Among community-dwelling adults, reductions in eGFR primarily within the normal range were associated with smaller RV volumes and the association of albuminuria with worse survival was stronger among those with smaller RV volumes. Further studies are needed to elucidate the underlying mechanistic pathways that link kidney measures and RV morphology.

LAY SUMMARY

Low glomerular filtration rate (GFR) and increased albuminuria are well-known risk factors associated with all-cause and cardiovascular mortality. However, limited data are available on the independent associations of GFR and albuminuria with cardiac morphology, and prior studies largely focused on the left ventricle and patients with advanced CKD. Furthermore, it is not known whether subclinical changes in right ventricular (RV) morphology are present in early CKD or the impact of these changes on mortality. In a large, diverse population-based cohort without cardiovascular disease and predominantly no CKD at baseline, reductions in eGFR primarily within the normal range were associated with discrete smaller RV volumes. Higher albuminuria and smaller RV volumes were associated with increased all-cause mortality risk independent of eGFR, traditional risk factors and left ventricular parameters. Our data highlight the need for further studies to examine the mechanistic link between kidney disease and RV morphology.

GRAPHICAL ABSTRACT



Keywords: cardiac magnetic resonance, cardiorenal syndromes, chronic kidney disease, kidney function, pulmonary hypertension

INTRODUCTION

Chronic kidney disease (CKD) is a recognized risk factor for the development of pulmonary hypertension (PH) [1–3], and it may be related to pressure/volume overload or vascular dysfunction due to alterations in vasoactive factors (e.g. nitric oxide, prostacyclin, endothelin-1), vascular calcification and inflammation [3, 4]. The prevalence of CKD is approximately 35% in patients with PH [5], and its presence is associated with an enhanced risk for adverse outcomes, with the risk increasing incrementally with declining kidney function [2, 6]. The main consequence of PH is increased right ventricular (RV) afterload and, ultimately, right-sided heart failure (HF), which contribute to increased morbidity and mortality [2, 7, 8]. Poor RV function may increase venous congestion, alter ventricular interdependence, decrease effective cardiac output and activate the renin–angiotensin–aldosterone system, thereby aggravating kidney disease [8, 9].

Abnormalities in RV structure and function may be early subclinical indicators of developing PH. Despite the frequency of kidney disease in PH, the presence of subclinical changes in RV structure or function in early CKD and the impact of these changes on mortality are currently unknown. Notably, albuminuria, a putative marker of systemic endothelial dysfunction, is associated with early structural changes in the myocardium and may therefore precede the onset of cardiac dysfunction and remodeling, including remodeling of the right ventricle [10–12]. In the present study, we examined cross-sectional associations of the baseline estimated glomerular filtration rate (eGFR) and albuminuria with baseline RV structure and function assessed by cardiac magnetic resonance (CMR) imaging among community-dwelling adults in the Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that reduced eGFR values and/or higher levels of albuminuria would be associated with greater RV end-diastolic mass (RVEDM), larger RV end-diastolic and end-systolic volumes (RVEDV and RVESV, respectively), smaller RV stroke volume (RVSV) and lower RV ejection fraction (RVEF). Subsequently, we examined whether RV measures influenced the relationships of kidney measures with mortality and incident HF.

MATERIALS AND METHODS

Study sample

The MESA design has been detailed previously [13]. Briefly, it is a multicenter, National Heart, Lung, and Blood Institute (NHLBI)-sponsored prospective cohort study with the original objective of investigating the progression of subclinical cardiovascular disease (ClinicalTrials.gov: NCT00005487). The study enrolled 6814 participants aged 45–84 years from six US communities at Examination 1 (2000–02). The Institutional Review Boards of all collaborating institutions and the NHLBI approved the protocols of MESA and all studies described herein.

For the present study, we included MESA-Right Ventricle participants who underwent CMR imaging at Examination 1 and had no missing covariate data of interest. The MESA-Right Ventricle study is an ancillary study focused on measuring the RV morphology in MESA participants eligible for CMR imaging (without metal implants, devices or fragments) with interpretable studies at baseline [14].

RV structure and function assessment

The CMR protocol and the interpretation methods for the left ventricular (LV) and RV measures have been previously reported [15, 16] and are detailed in Supplementary Methods. RVSV was calculated by subtracting the RVESV from the RVEDV. RVEF was calculated by dividing the RVSV by the RVEDV, and then multiplying by 100. In the present work, non-indexed RV parameters constituted the main outcome measures to allow comparability to previous MESA-Right Ventricle studies [17–19]. Adjustment for height and weight avoids the assumptions made in indexing the RV measures to body habitus [e.g. body surface area (BSA)], while achieving the same end of accounting for inter-participant body size differences [17]. In a sensitivity analysis, we evaluated whether the association between kidney measures and RV volumes/RV mass differed when using RV measures indexed to BSA using the Du Bois formula [20].

eGFR and albuminuria

Urine and blood were collected in the fasting state at Examination 1 prior to CMR imaging. The eGFR was calculated using the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine–cystatin C equation [21]. In a sensitivity analysis, we evaluated whether the association of kidney measures and RV measures differed when using the 2021 creatinine–cystatin C equation, which does not include adjustment for race [22]. Participants were grouped into four eGFR categories (mL/min/1.73 m^2): $<$45, 45–59, 60–89 and $\geq$90 [23]. Albuminuria was measured on a single fasting spot sample collected at Examination 1 and normalized to the urinary creatinine concentration. Participants were categorized as normal to mildly increased albuminuria ($<$30 mg/g) or moderately to severely increased albuminuria ($\geq$30 mg/g). The laboratory methods and covariates of interest are described in detail in Supplementary Methods.

Mortality and HF

Interviewers telephoned participants or a family member at 9- to 12-month intervals to inquire about hospital admissions, outpatient diagnoses of cardiovascular disease and death. HF outcomes were adjudicated by a central committee composed of two physicians blinded to study data outside of medical records. HF was diagnosed according to standardized criteria that consisted of physician-based diagnosis with appropriate treatment with or without objective findings (e.g. pulmonary edema/congestion on chest radiography, LV dilation or decreased systolic function, or evidence of diastolic dysfunction; see Supplementary Methods for detailed description). Deaths were ascertained using the National Death Index. Event ascertainment of death and incident HF for the present work extended through the calendar year of 2018.

Statistical analysis

Continuous variables were expressed as the mean ($\pm$ standard deviation) or median (interquartile range). Categorical variables were expressed as the number of participants (%). Patient characteristics were compared within subgroups using ANOVA, Kruskal–Wallis test or pairwise Chi-squared test, as appropriate. The relationships between eGFR and albuminuria with RV parameters were assessed with multivariable ordinary least squares linear regression. Models were performed using eGFR/albuminuria categories and eGFR/natural log-transformed albuminuria as continuous predictors, respectively. We selected covariates identified as potentially related to either kidney function or RV morphology [16, 24]. The adjusted models included

age, sex, race/ethnicity, educational attainment (marker of socioeconomic status), study site, weight, height, waist circumference, smoking (history and cigarette pack-years), hypertension, diabetes, total cholesterol, high density lipoprotein levels, triglycerides, C-reactive protein (CRP), use of renin–angiotensin system blockers, diuretic medication use, Agatston calcium score and total intentional exercise. We omitted the covariates weight and height in regression models with indexed RV parameters as outcome measures except for RVEF, since it is not indexed to BSA. Linear regression models investigating the relationship of eGFR with RV parameters were adjusted for albuminuria, and models investigating the relationship of albuminuria with RV parameters were adjusted for eGFR. Finally, the respective LV measures were added to the adjusted models to account for the contribution of LV abnormalities to RV changes (e.g. increased LV mass causing pulmonary venous hypertension leading to increased RV mass), to better account for body size differences, and to examine RV-specific associations. Considering the significant interdependence of these measures, RVSV was not adjusted for LV stroke volume. We addressed risks of an inflated false-positive rate in cases with multiple contrasts by performing a joint hypothesis F-test adjusted for the number of contrasts and reporting the *P*-values and F-statistics for each group of contrasts. Contrasts and joint hypothesis tests were produced using the emmeans package for R [25]. We used generalized additive models adjusted for the covariates mentioned above to assess the associations of eGFR and natural log-transformed albuminuria, modeled as continuous variables, with RV measures and to test for non-linearity.

Death incidence rates are reported as the number of events per 1000 person-years and stratified by eGFR and albuminuria categories. Cox regression models were used to examine the association of baseline eGFR and albuminuria with overall death stratified by RV measurement in tertiles. The models were adjusted for baseline age, sex, self-reported race/ethnicity, smoking history, cigarette pack-years, height, weight, statin and hypertension medication use, systolic and diastolic blood pressure, history of diabetes, total intentional exercise, Agatston calcium score, history of cancer and study site. eGFR categories and natural log-transformed albuminuria were adjusted for in the Cox regression models that examined albuminuria and eGFR as the primary exposure variable of interest, respectively. We used the log-likelihood ratio test with and without the interaction term between kidney measures (eGFR or albuminuria) and RV measures to determine whether a RV measure modified the association between kidney measure and death. We also examined whether RV measures influenced the relationship between kidney measures and risk of incident HF using a similar approach as in the mortality analysis. Due to fewer HF events compared with deaths and many subgroups using the eGFR categories, we used log-transformed eGFR as our primary independent variable in the Cox regression analysis for HF. $P < .05$ was considered statistically significant for main and interactive effects. Analyses were performed using SAS 9.4 (SAS Institute) and R Foundation for Statistical Computing version 4.0.4 (Vienna, Austria).

RESULTS

Study population characteristics

Of the 6814 MESA participants from Examination 1, 5098 underwent CMR imaging and showed scans interpretable for LV measures (Supplementary data, Fig. S1). A total of 4063 (97%) participants had complete covariate data and constituted the study sample. The majority (92.6%) of the participants had a normal-to-mildly reduced eGFR (i.e. ≥60 mL/min/1.73 m^2) (Table 1). CKD as defined by eGFR <60 mL/min/1.73 m^2 or albuminuria ≥30 mg/g was present in 561 (13.8%) participants (see Supplementary data, Table S1 for distribution based on the KDIGO CKD categories). Lower RVEDM and smaller RV volumes were related to older age, female sex, smaller body size, hypertension, diuretic medication use, higher CRP levels, lower total intentional exercise and lower LV end-diastolic mass and smaller LV volumes (Supplementary data, Tables S2–S6).

Association of baseline eGFR and albuminuria with RV structure and function

Compared with participants with eGFR values ≥90 mL/min/1.73 m^2 (reference category), those with an eGFR of 60–89 mL/min/1.73 m^2 had smaller RVEDV {−2.12 mL [95% confidence interval (CI) −3.25, −0.99]}, RVESV [−1.19 mL (95% CI −1.88, −0.49)] and RVSV [−2.49 mL (95% CI −3.62, −1.37)] after adjustment for all covariates, including the respective LV measures (Model 3, Table 2). A global F-test indicated that these contrasts by eGFR groups were significant. No association was observed between eGFR categories, RVEDM and RVEF. Furthermore, no statistical evidence of nonlinearity was observed in the association of eGFR with non-indexed RV volumes or RVEF ($P \geq .05$ for nonlinearity), except for RVEDM ($P = .008$ for nonlinearity; Supplementary data, Fig S2A–E). Models using eGFR as continuous predictor were similar to eGFR category models (Supplementary data, Table S7).

Three hundred and forty participants (8.4%) showed moderately-to-severely increased albuminuria (Supplementary data, Table S8). Participants with moderately-to-severely increased albuminuria had greater RVEDM [0.45 g (95% CI 0.07, 0.82)] than those with albuminuria levels <30 mg/g after adjustment for covariates (Model 2, Table 3); however, this association was attenuated after adjustment for LV mass (Model 3). No associations were observed between albuminuria categories and non-indexed RV volumes or RVEF. In addition, no evidence of nonlinearity was observed in the association between albuminuria and the non-indexed RV measures ($P \geq .05$ for nonlinearity; Supplementary data, Fig. S2F–J). In contrast, a 1-unit increment in log-transformed albuminuria was associated with a −0.64 mL (95% CI −1.21, −0.07) difference in RVEDV and a −0.44 mL (95% CI −0.79, −0.09) difference in RVESV (Supplementary data, Table S9).

Considering a subgroup of MESA participants with eGFR values ≥60 mL/min/1.73 m^2 ($n = 3763$), those with CKD as defined by elevated albuminuria ≥30 mg/g were more likely to have hypertension, diabetes, higher CRP levels and greater LV mass (Supplementary data, Table S10). No association was observed for any of the non-indexed RV parameters between participants with mild CKD (i.e. eGFR ≥60 mL/min/1.73 m^2 and albuminuria ≥30 mg/g) and those with both eGFR ≥90 mL/min/1.73 m^2 and albuminuria <30 mg/g in the fully adjusted model (Fig. 1). In contrast, participants with no CKD but mildly reduced eGFR (i.e. eGFR 60–89 mL/min/1.73 m^2 and albuminuria <30 mg/g) had smaller RVEDV [−2.27 mL (95% CI −3.44, −1.11)], RVESV [−1.30 mL (95% CI −2.02, −0.59)] and RVSV [−2.50 mL (95% CI −3.67, −1.34)] in the fully adjusted models. The differences across non-indexed RV volumes remained significant after accounting for multiple testing.

Overall, the observed associations of kidney measures with RV structure and function were comparable when using indexed

Table 1: Baseline characteristics of the cohort by eGFR category.

Variable	eGFR categories (mL/min/1.73 m^2)				P-value
	≥90 (n = 1755)	60–89 (n = 2008)	45–59 (n = 238)	<45 (n = 62)	
Serum creatinine, mg/dL	0.8 (0.7–1.0)	1.0 (0.9–1.1)	1.2 (1.0–1.4)	1.6 (1.3–1.9)	<.001
Cystatin C, mg/L	0.8 (0.7–0.8)	0.9 (0.9–1.0)	1.2 (1.2–1.3)	1.6 (1.4–1.8)	<.001
eGFR, mL/min/1.73 m^2	101.3 ± 8.2	77.7 ± 8.2	54.6 ± 3.9	36.3 ± 9.1	<.001
Albuminuria, mg/g creatinine	5.0 (3.3–8.9)	5.2 (3.3–10.1)	6.7 (3.9–18.2)	29.0 (7.4–303.2)	<.001
Age, years	56.1 ± 8.4	64.6 ± 9.1	71.4 ± 8.6	73.7 ± 8.1	<.001
Male, n (%)	872 (49.7)	928 (46.2)	102 (42.9)	28 (45.2)	.08
Race/ethnicity, n (%)					<.001
White	547 (31.2)	899 (44.8)	133 (55.9)	17 (27.4)	
Chinese	268 (15.3)	212 (10.6)	25 (10.5)	10 (16.1)	
African–American	525 (29.9)	474 (23.6)	44 (18.5)	16 (25.8)	
Hispanic	415 (23.6)	423 (21.1)	36 (15.1)	19 (30.6)	
Education status, n (%)					<.001
Lower than high school	279 (15.9)	325 (16.2)	40 (16.8)	21 (33.9)	
High school	290 (16.5)	388 (19.3)	55 (23.1)	13 (21.0)	
Some college	298 (17.0)	303 (15.1)	48 (20.2)	7 (11.3)	
Bachelor degree	348 (19.8)	351 (17.5)	33 (13.9)	7 (11.3)	
Graduate degree	323 (18.4)	394 (19.6)	29 (12.2)	8 (12.9)	
Height, cm	166.9 ± 9.8	166.2 ± 10.0	164.8 ± 9.8	163.3 ± 10.0	.001
Weight, kg	76.7 ± 16.1	78.0 ± 16.3	77.7 ± 16.1	77.3 ± 15.8	.12
Body mass index, kg/m^2	27.4 ± 4.9	28.1 ± 5.0	28.5 ± 5.0	28.9 ± 4.6	<.001
Hypertension, n (%)	559 (31.9)	954 (47.5)	174 (73.1)	55 (88.7)	<.001
Systolic blood pressure, mmHg	122 ± 20	127 ± 21	136 ± 24	143 ± 28	<.001
Diastolic blood pressure, mmHg	72 ± 10	72 ± 10	71 ± 11	71 ± 12	.038
Fasting glucose, mg/dL	88 (82–98)	89 (83–98)	92 (84–102)	98 (88–115)	<.001
Diabetes mellitus, n (%)					<.001
Normal	1 335 (76.1)	1 531 (76.2)	160 (67.2)	30 (48.4)	
Impaired fasting glucose	206 (11.7)	274 (13.6)	48 (20.2)	11 (17.7)	
Untreated diabetes	52 (3.0)	35 (1.7)	6 (2.5)	5 (8.1)	
Treated diabetes	162 (9.2)	168 (8.4)	24 (10.1)	16 (25.8)	
Smoking status, n (%)					.004
Never smoker	940 (53.6)	1 027 (51.1)	126 (52.9)	34 (54.8)	
Former smoker	564 (32.1)	751 (37.4)	92 (38.7)	21 (33.9)	
Current smoker	251 (14.3)	230 (11.5)	20 (8.4)	7 (11.3)	
Pack-years (among ever smokers)	0 (0–13)	0 (0–15)	0 (0–16)	0 (0–11)	.25
ACE inhibitor, n (%)	147 (8.4)	222 (11.1)	59 (24.8)	17 (27.4)	<.001
Angiotensin receptor blocker, n (%)	36 (2.1)	74 (3.7)	15 (6.3)	11 (17.7)	<.001
Diuretics, n (%)[a]	115 (6.6)	279 (13.9)	77 (32.4)	30 (48.4)	<.001
Total cholesterol, mg/dL	194.4 ± 35.0	194.0 ± 34.7	197.0 ± 32.7	191.2 ± 50.2	.20
HDL cholesterol, mg/dL	51.6 ± 15.2	50.8 ± 14.6	50.3 ± 14.5	48.6 ± 17.8	.10
LDL cholesterol, mg/dL	117.9 ± 31.5	117.1 ± 30.6	117.5 ± 28.1	108.5 ± 29.7	.12
Triglycerides, mg/dL	105 (73–154)	115 (80–162)	131 (88–182)	138 (93–192)	<.001
CRP, mg/L	1.5 (3.3–8.9)	2.0 (0.9–4.3)	2.4 (1.2–4.8)	2.4 (1.3–4.6)	<.001
RV measures					
End-diastolic mass, g	21.6 ± 4.5	20.7 ± 4.3	19.9 ± 4.5	20.2 ± 4.1	<.001
End-diastolic volume, mL	128.5 ± 31.4	121.6 ± 30.2	116.4 ± 31.3	114.0 ± 28.5	<.001
End-systolic volume, mL	39.3 ± 14.8	36.2 ± 13.7	33.5 ± 14.1	32.5 ± 11.7	<.001
Stroke volume, mL	89.2 ± 20.8	85.4 ± 20.3	82.8 ± 20.8	81.5 ± 19.7	<.001
Ejection fraction, %	69.9 ± 6.6	70.7 ± 6.4	71.7 ± 6.7	71.8 ± 5.7	<.001
Stroke volume/end-systolic volume ratio	2.5 ± 0.8	2.6 ± 0.8	2.8 ± 1.1	2.7 ± 0.7	<.001
LV measures					
End-diastolic mass, g	146.8 ± 39.2	144.3 ± 38.5	146.7 ± 43.8	156.6 ± 44.5	.05
End-diastolic volume, mL	130.6 ± 31.8	124.1 ± 30.6	119.9 ± 34.2	121.2 ± 33.0	<.001
End-systolic volume, mL	42.0 ± 17.2	38.9 ± 16.3	37.1 ± 19.0	39.1 ± 24.5	<.001
Ejection fraction, %	68.5 ± 7.2	69.3 ± 7.3	69.8 ± 8.8	69.3 ± 10.1	<.001

Values are the mean ± standard deviation, median (interquartile range) or n (%). RV and LV measures are non-indexed.

[a]Diuretics include loop diuretics or thiazide diuretics with/without potassium-sparing agents.

ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2: Associations of eGFR categories with RV measures.

Outcome measure	eGFR categories (mL/min/1.73 m^2) ≥90 (n = 1755)	60–89 (n = 2008)	45–59 (n = 238)	<45 (n = 62)	Omnibus P-value
RV end-diastolic mass (g)					
Model 1	REF	0.21 (−0.09, 0.51)	0.33 (−0.30, 0.95)	0.96 (−0.16, 2.07)	
Model 2	REF	−0.37 (−0.60, −0.13)**	−0.34 (−0.83, 0.14)	0.02 (−0.87, 0.92)	
Model 3	REF	−0.21 (−0.43, 0.01)	−0.30 (−0.76, 0.16)	0.05 (−0.80, 0.89)	.24
RV end-diastolic volume (mL)					
Model 1	REF	−0.27 (−2.38, 1.85)	−0.10 (−4.47, 4.26)	−0.77 (−8.58, 7.05)	
Model 2	REF	−4.17 (−5.67, −2.67)**	−3.84 (−6.93, −0.75)*	−5.42 (−11.15, −0.31)	
Model 3	REF	−2.12 (−3.25, −0.99)**	−2.39 (−4.71, −0.07)*	−3.59 (−7.90, 0.71)	.002
RV end-systolic volume (mL)					
Model 1	REF	−0.46 (−1.44, 0.52)	−0.90 (−2.92, 1.13)	−1.24 (−4.87, 2.38)	
Model 2	REF	−1.68 (−2.44, −0.91)**	−1.90 (−3.48, −0.32)*	−2.21 (−5.14, 0.72)	
Model 3	REF	−1.19 (−1.88, −0.49)**	−1.68 (−3.10, −0.25)*	−2.43 (−5.07, 0.22)	.004
RV stroke volume (mL)					
Model 1	REF	0.20 (−1.22, 1.61)	0.79 (−2.14, 3.72)	0.48 (−4.76, 5.72)	
Model 2	REF	−2.49 (−3.62, −1.37)**	−1.94 (−4.25, 0.37)	−3.21 (−7.51, 1.08)	<.001
RV ejection fraction (%)					
Model 1	REF	0.22 (−0.23, 0.67)	0.72 (−0.21, 1.66)	0.63 (−1.05, 2.30)	
Model 2	REF	0.29 (−0.15, 0.73)	0.69 (−0.21, 1.59)	0.44 (−1.23, 2.11)	
Model 3	REF	0.23 (−0.18, 0.63)	0.73 (−0.09, 1.56)	0.71 (−0.82, 2.25)	.32

Quantitative variables are presented as the median and 95% CI (in brackets).

*P-value <.05 and **P-value <.001 when compared with REF group (eGFR ≥90 mL/min/1.73 m^2). The omnibus statistics were calculated using a joint hypothesis F-test for the three contrasts of interest. The corresponding F-statistics for the omnibus tests are: 1.40 (RVEDM), 4.80 (RVEDV), 4.43 (RVESV), 6.40 (RVSV) and 1.16 (RVEF). REF, reference.

Model 1 is adjusted for age. Model 2 is adjusted for age, sex, ethnicity, education level, weight, height, waist circumference, diabetes, triglycerides, hypertension, angiotensin receptor blockers, ACE inhibitors, smoking (history and pack-years), total cholesterol, HDL levels, CRP, diuretic medication use, Agatston calcium score, total intentional exercise, study site and albuminuria. Model 3 includes all covariates used in Model 2 and is also adjusted for the analogous LV measure. RV stroke volume was not adjusted for LV stroke volume, considering the significant inter-dependence of these measures.

RV measures are non-indexed.

ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein.

instead of non-indexed RV parameters as outcome measures (Supplementary data, Tables S11–S15).

The 2021 race-free CKD-EPI eGFR equation reclassified 437 (10.8%) and 38 (0.9%) of participants to higher and lower eGFR categories, respectively (Supplementary data, Fig. S3). Overall, the associations of kidney measures with non-indexed RV parameters were comparable between both 2012 and 2021 CKD-EPI equations (Supplementary data, Tables S16–S18). Results between both eGFR equations were comparable when using indexed RV measures instead of non-indexed RV parameters as outcome variables (Supplementary data, Tables S19–S21).

Baseline kidney measures, RV structure and function, and mortality and incident HF events

Over 62 508 person-years, a total of 917 deaths (22.6%) occurred in the 18-year follow-up period. The annualized all-cause mortality rate showed an incremental increase with increasing kidney disease severity at baseline (Table 4).

A significant association was observed between lower eGFR categories and death among participants with greater RVEDM and RVEF after adjustment for covariates, including albuminuria (P-values for interaction <.01) (Supplementary data, Table S22). The association of eGFR with death was not modified by RVESV, RVEDV or RVSV. Associations between albuminuria and death were stronger among those in the lowest tertiles of RVESV, RVEDV and RVSV after adjustment for covariates, including eGFR (P-values for interaction <.03) (Fig. 2 and Table 5). RVEDM and RVEF did not modify the association between albuminuria and death. The associations between albuminuria and death were comparable when stratified by indexed RV measures, except that a significant association was observed between lower eGFR categories and death among participants in the lowest tertiles of indexed RVEDM/RV volumes (Supplementary data, Tables S23 and S24).

Over 59 956 person-years, a total of 226 incident HF events (5.6%) occurred in the 18-year follow-up period (Supplementary data, Table S25). No associations were observed between kidney measures and incident HF stratified by non-indexed RV measures (Supplementary data, Tables S26 and S27). Results were comparable when stratified by indexed RV parameters, except that the associations between kidney measures and HF events were significant among participants within the second tertile of indexed RVEDM/RVSV (Supplementary data, Tables S28 and S29).

DISCUSSION

Contrary to our hypothesis, we found that reductions in eGFR primarily within the normal range were associated with discrete smaller RV volumes even after adjustment for the respective LV parameters. Albuminuria categories, on the other hand, were not associated with RV measures when adjusted for the analogous LV measure. No differences were observed in RVEF in relation to both kidney markers. Furthermore, higher albuminuria was more strongly associated with death in those with smaller RV volumes.

The current KDIGO consensus guideline [23] suggests defining and staging CKD severity based on kidney functional (i.e. GFR) and damage (i.e. albuminuria) markers, since both markers are likely to reflect different biologic processes and are based

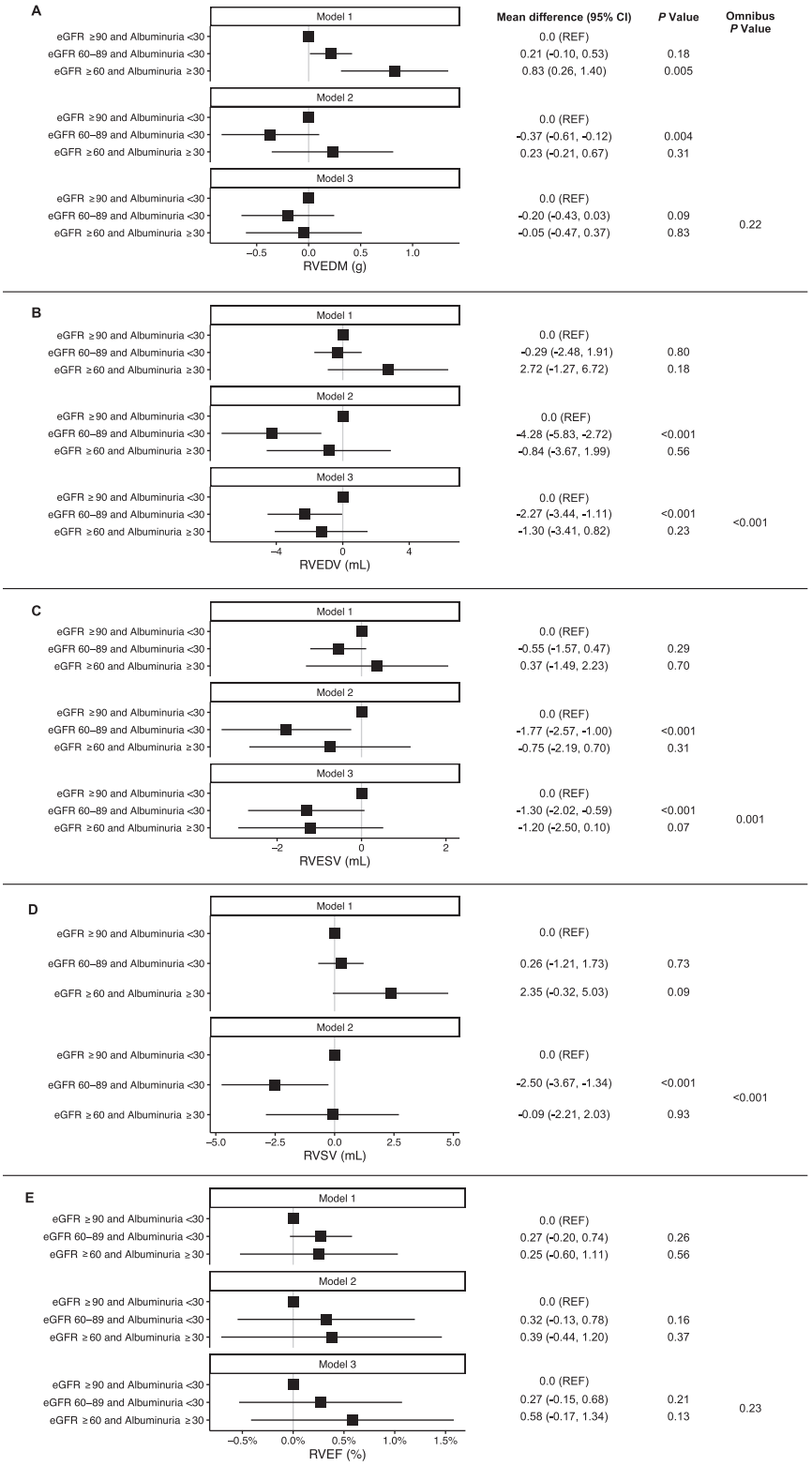


Figure 1: Forest plots showing the associations of eGFR and albuminuria in KDIGO CKD categories G1–2/A1–3 with RV measures. Boxes represent effect estimates and horizontal lines represent 95% CI. Analysis includes 3763 MESA participants with a eGFR ≥60 mL/min/1.73 m^2. The omnibus statistics were calculated using a joint hypothesis F-test for the two contrasts of interest. The corresponding F-statistics for the omnibus tests are: 1.50 (RVEDM), 7.34 (RVEDV), 6.61 (RVESV), 9.88 (RVSV) and 1.47 (RVEF). REF = reference group (eGFR ≥90 mL/min/1.73 m^2 and albuminuria <30 mg/g creatinine). Model 1 is adjusted for age. Model 2 is adjusted for age, sex, ethnicity, education level, weight, height, waist circumference, diabetes, triglycerides, hypertension, angiotensin receptor blockers, ACE inhibitors, smoking (history and pack-years), total cholesterol, HDL levels, CRP, diuretic medication use, Agatston calcium score, total intentional exercise and study site. Model 3 includes all covariates used in Model 2 and is also adjusted for the analogous LV measure. RVSV was not adjusted for LV stroke volume, considering the significant inter-dependence of these measures. RV measures are non-indexed. ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein.

Table 3: Associations of albuminuria categories with RV measures.

	Albuminuria categories (mg/g creatinine)			
Outcome measure	<30 (n = 3 723)	≥30 (n = 340)	Difference between ≥30 and <30	P-value
RVEDM (g)				
Model 1	21.00 (20.86, 21.14)	21.73 (21.27, 22.19)	0.73 (0.25, 1.21)	.003
Model 2	21.06 (20.64, 21.48)	21.51 (20.99, 22.02)	0.45 (0.07, 0.82)	.020
Model 3	20.85 (20.45, 21.24)	20.85 (20.36, 21.35)	0.01 (−0.35, 0.36)	.98
RVEDV (mL)				
Model 1	123.88 (122.91, 124.84)	127.30 (124.08, 130.51)	3.42 (0.06, 6.78)	.046
Model 2	124.26 (121.60, 126.93)	126.45 (123.13, 129.76)	2.18 (−0.22, 4.58)	.08
Model 3	124.73 (122.72, 126.73)	124.46 (121.96, 126.95)	−0.27 (−2.07, 1.53)	.78
RVSV (mL)				
Model 1	86.62 (85.97, 87.26)	89.22 (87.07, 91.38)	2.60 (0.35, 4.86)	.024
Model 2	86.83 (84.84, 88.83)	88.54 (86.05, 91.02)	1.70 (−0.09, 3.50)	.06
RVESV (mL)				
Model 1	37.26 (36.81, 37.70)	38.07 (36.58, 39.56)	0.82 (−0.74, 2.37)	.31
Model 2	37.43 (36.07, 38.79)	37.91 (36.22, 39.61)	0.48 (−0.75, 1.70)	.44
Model 3	37.51 (36.28, 38.79)	37.26 (35.73, 38.79)	−0.25 (−1.35, 0.86)	.66
RVEF (%)				
Model 1	70.44 (70.23, 70.64)	70.55 (69.87, 71.24)	0.12 (−0.60, 0.84)	.75
Model 2	70.48 (69.71, 71.26)	70.63 (69.66, 71.60)	0.15 (−0.55, 0.85)	.68
Model 3	70.48 (69.77, 71.20)	70.72 (69.83, 71.61)	0.24 (−0.40, 0.88)	.47

Quantitative variables are presented as median and 95% CI (in brackets).
Model 1 is adjusted for age. Model 2 is adjusted for age, sex, ethnicity, education level, weight, height, waist circumference, diabetes, triglycerides, hypertension, angiotensin receptor blockers, ACE inhibitors, smoking (history and pack-years), total cholesterol, HDL levels, CRP, diuretic medication use, Agatston calcium score, total intentional exercise, study site and eGFR. Model 3 includes all covariates used in Model 2 and is also adjusted for the analogous LV measure. RV stroke volume was not adjusted for LV stroke volume, considering the significant inter-dependence of these measures.
RV measures are non-indexed.
ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein.

Table 4: Overall death rates by kidney measures.

Kidney measure	No. participants	Total person-years	Deaths	Death rate per 1000 person-years (95% CI)
eGFR				
>90 mL/min/1.73 m^2	525	8018	121	15.1 (12.4, 17.8)
60–89 mL/min/1.73 m^2	2867	45 197	556	12.3 (11.3, 13.3)
45–59 mL/min/1.73 m^2	570	8420	193	22.9 (19.7, 26.2)
<45 mL/min/1.73 m^2	72	873	47	53.8 (38.4, 69.2)
Albuminuria				
<30 mg/g creatinine	3697	57 989	763	13.2 (12.2, 14.1)
≥30 mg/g creatinine	337	4519	154	34.1 (28.7, 39.5)

on the heterogeneous nature of CKD [26]. Although patients with kidney failure are at the greatest mortality risk, the risk increases incrementally with decreasing eGFR levels below approximately 85 mL/min/1.73 m^2 when using the creatinine–cystatin C equation [27]. Accordingly, impaired LV diastolic relaxation and hypertrophy, and diffuse myocardial fibrosis are present in individuals with an eGFR of 60–89 mL/min/1.73 m^2 [28, 29]. For patients with PH and right-sided HF, evidence has shown the prognostic value of mild decreases in eGFR within the normal range for mortality [6, 30]. However, RV changes associated with milder forms of kidney disease remain largely unexplored and were the focus of this study. In contrast to the nonlinear risk relationship for eGFR, there is no threshold effect for the association of albuminuria with cardiovascular and mortality risk [31, 32]. The associations between albuminuria and adverse changes in LV morphology and function have been well-described and are observed even when eGFR is normal or mildly decreased [12, 33]. These findings suggest that the relationship between mortality and CKD is not entirely due to decreased kidney function, and may reflect other mechanisms such as myocardial strain, endothelial impairment and subendocardial myocardial dysfunction affecting the heart globally in individuals with increased albuminuria [12, 34].

Our findings that reduced eGFR primarily within the normal range and higher albuminuria were associated with smaller RV volumes and higher risk of death, respectively, appear counterintuitive. We hypothesized that incremental increases in RV volumes would be expected across the kidney disease severity spectrum [35]. Notably, similar relationships have been reported between smaller RV size and other markers of chronic inflammatory, fibrosing diseases [36–38]. In addition, early diabetes mellitus and lower cardiorespiratory fitness were also associated with smaller cardiac chambers in a general population cohort [39, 40].

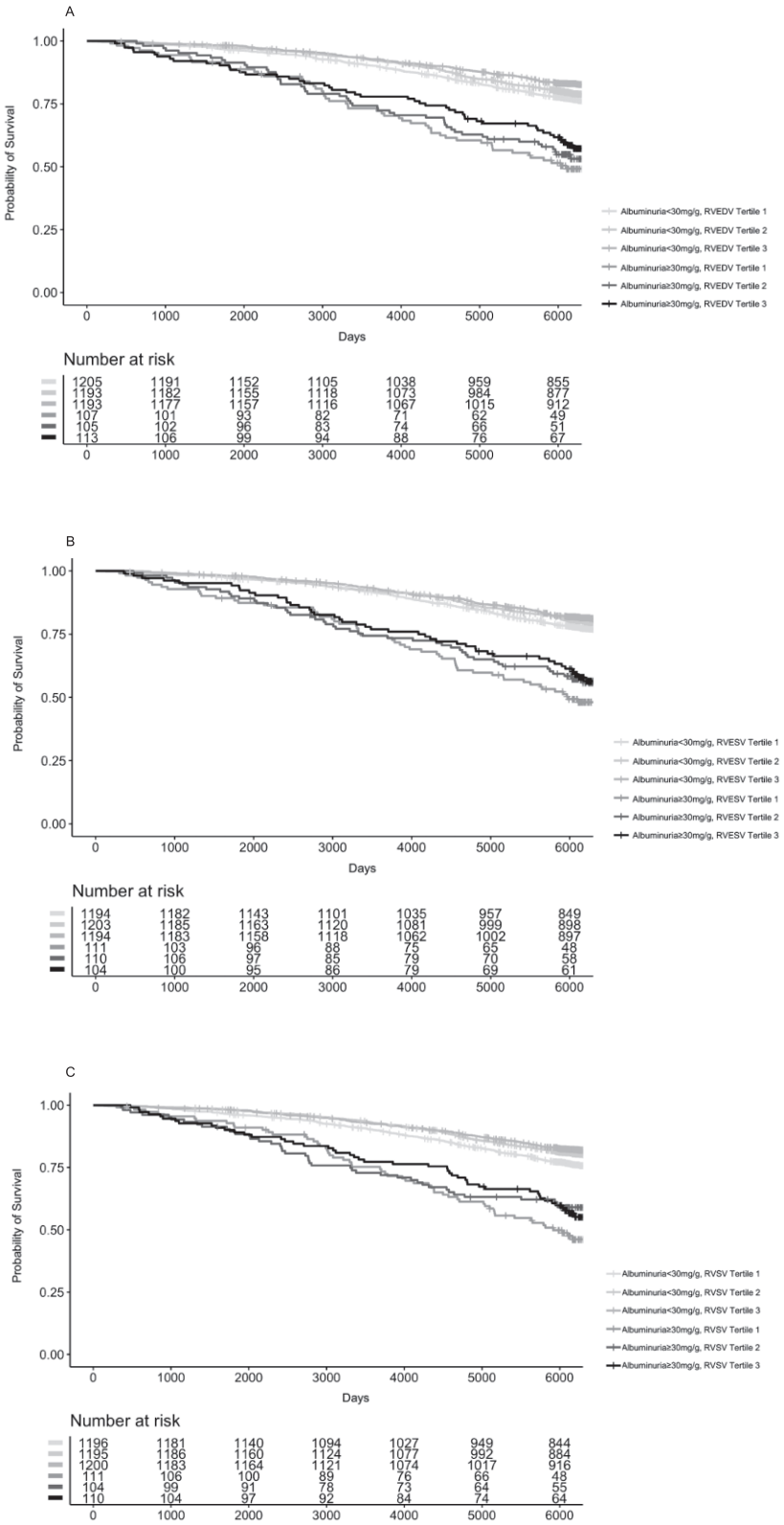


Figure 2: Kaplan–Meier survival curves according to albuminuria categories and non-indexed RV volumes tertiles. Kaplan–Meier survival curves show the associations of albuminuria (<30 mg/g versus ≥30 mg/g creatinine) by (**A**) RVEDV tertiles (log-rank $P < .001$), (**B**) RVESV tertiles (log-rank $P < .001$) and (**C**) RVSV tertiles (log-rank $P < .001$). RV measures are non-indexed.

Table 5: Associations of albuminuria with mortality stratified by RV measures.

Outcome measure	No. participants	Hazard ratio per doubling of albuminuria (95% CI)	*P*-value for interaction
RVEDM			.70
1st tertile	1302	1.20 (1.12, 1.28)	
2nd tertile	1305	1.17 (1.09, 1.27)	
3rd tertile	1309	1.16 (1.09, 1.24)	
RVEDV			.006
1st tertile	1312	1.25 (1.17, 1.33)	
2nd tertile	1298	1.16 (1.08, 1.25)	
3rd tertile	1306	1.12 (1.05, 1.20)	
RVESV			.02
1st tertile	1305	1.24 (1.15, 1.32)	
2nd tertile	1313	1.18 (1.09, 1.27)	
3rd tertile	1298	1.13 (1.05, 1.21)	
RVSV			.03
1st tertile	1307	1.23 (1.16, 1.31)	
2nd tertile	1299	1.16 (1.07, 1.25)	
3rd tertile	1310	1.13 (1.06, 1.21)	
RVEF			.44
1st tertile	1293	1.17 (1.09, 1.25)	
2nd tertile	1303	1.16 (1.08, 1.25)	
3rd tertile	1320	1.21 (1.13, 1.29)	

Model is adjusted for baseline age, sex, self-reported race/ethnicity, smoking history, cigarette pack-years, height, weight, statin and hypertension medication use, systolic and diastolic blood pressure, history of diabetes, total intentional exercise, Agatston calcium score, history of cancer, study site and eGFR. The Model was also adjusted for the respective RV measurement and its interaction with albuminuria. Albuminuria was normalized to the urinary creatinine concentration.
RV measures are non-indexed.

Although the observed differences in RV volumes among individuals with an eGFR of 60–89 mL/min/1.73 m^2 in our study were consistent across analyses, the magnitude of differences was small and warrants further prospective research. However, it should be noted that for RV volumes within the eGFR of 60–89 mL/min/1.73 m^2 category, the mean difference from the ≥90 mL/min/1.73 m^2 category represented ∼10% of the standard deviation in RV volumes among all study participants. Thus, given that these were individuals without known cardiovascular disease, the minimal clinically important difference is likely to be smaller than that expected in patients with cardiac disease.

While we did not see an association between clinically defined albuminuria categories with RV measures, our analysis with albuminuria as a continuous predictor indicated that incremental increases in albuminuria were significantly associated with smaller RV measures. The pathophysiology of the observed association between albuminuria and RV size is unclear. A possible contributing mechanism to the smaller RV volumes could be impaired RV relaxation and increased fibrosis. Endothelial inflammation in the coronary microvasculature plays a prominent role in abnormal ventricular relaxation [41]. CKD is considered a systemic inflammatory disease even at its earlier stages [42]. The levels of proinflammatory circulatory mediators progressively increase as GFR declines and albuminuria increases [43]. Therefore, the observed associations may be related to the inflammation and endothelial dysfunction that may underlie both albuminuria and smaller RV volumes. We speculate that the thin-walled right ventricle is susceptible to reductions in myocardial compliance induced by inflammation and fibrosis. Given the low pressure generated by the normal right ventricle, even small decrements in compliance may lead to reduced size. Notably, the relationship between albuminuria, RV volumes and death did not change after accounting for CRP levels, suggesting that if inflammation is important in the relationship between albuminuria and RV morphology, it involves an inflammatory pathway that is not reflected by CRP. Furthermore, endothelial microvascular dysfunction may contribute to impaired myocardial blood supply and limit RV adaptation to an increased cardiac workload [44–46]. Alternatively, a mechanical explanation may clarify the mechanism by which RV volumes are decreased to maintain ejection/emptying fraction [47].

Whether smaller RV volumes represent very early RV changes associated with inflammation and myocardial fibrosis, which may inhibit RV volume changes during remodeling, remains unknown. Further studies using CMR imaging gadolinium late enhancement would be important to assess the contribution of RV wall interstitial fibrosis to reduced RV volumes and potential clinical implications in early CKD. Future investigations with larger cohort sizes and larger HF event rates will be important for further evaluation of this relationship.

In rodent models, partial nephrectomy increased LV size, while the RV mass was only slightly increased and even demonstrated increased contractility [48]. In contrast, in patients with HF with preserved ejection fraction, albuminuria has been independently linked to greater RV wall thickness and worse RV systolic function [11]. These findings suggest that CKD may exert differential effects on the left and right ventricles depending on whether clinical HF is present. Our findings highlight the gaps in extrapolating preclinical and clinical information and the importance of investigating potentially distinct pathophysiological processes in population-based cohorts.

Contrary to our original hypothesis, eGFR categories <60 mL/min/1.73 m^2 were not associated with RV structural and functional changes despite prior studies demonstrating a strong relationship between PH and eGFR categories G3–5 [2, 4, 5]. A potential explanation may be the smaller number of participants within the lower eGFR categories, which may have limited the power to detect statistically significant differences. We did, however, observe a graded association across the full range of eGFR with RV measures when analyzing eGFR as a continuous predictor. Future investigations involving patients with advanced CKD will be important to further evaluate this relationship.

The principal strength of this study is that it is, to our knowledge, the largest cohort study in the literature to examine the association between kidney measures and RV size in a diverse, population-based cohort of community-dwelling adults with a prevalence of CKD comparable to the US general population at that time [49]. Another strength of the study is the consistency of the results between the 2012 CKD-EPI equation and the contemporary race-free CKD-EPI equation. Our study had several limitations. First, the observational design limited inferences about causal relationships. Second, given the exclusion of clinical cardiovascular disease at baseline, the MESA cohort by design had a limited number of participants with CKD. Therefore, we were unable to describe the full spectrum of the association between kidney markers and RV function and structure. As described above, it is difficult to determine whether the lack of significant differences across the lower eGFR categories is secondary to the small sample size in this group or to other causes. Third, decreased eGFR or elevated albuminuria were defined at one timepoint, excluding the ability to examine the full KDIGO definition

of chronicity, which includes persistence for at least 3 months [23]. Fourth, albuminuria was quantified by the results of a single spot urine test, which may have resulted in misclassification error. We did not have timed urine collections for comparison of albuminuria with spot urine samples, and urine specimens were not always first morning voids [50]. Fifth, this study adjusted for potential confounding variables, but we lacked details related to other CKD-associated factors that may have potentially contributed to altered RV structure and function, including bone mineral disorder and uremic toxins [51, 52]. Sixth, the number of incident HF cases were small in MESA, and reported HF events were adjudicated hospitalized HF cases, so milder HF cases identified and treated as outpatients were missed. Seventh, echocardiography was not performed at the baseline visit, thus, we could not evaluate the role of PH. Eighth, right heart catheterizations were not feasible or ethical in a large population-based cohort.

CONCLUSIONS

Among community-dwelling adults without cardiovascular disease, reductions in eGFR primarily within the normal range were associated with discrete smaller RV volumes. Higher baseline albuminuria and smaller RV volumes were associated with worse survival that was independent of eGFR, traditional risk factors and LV parameters. Our data highlight the need for further studies to examine the mechanistic link between kidney disease and RV morphology and clarify the changes in RV structure and function across the CKD severity spectrum.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

M.F.DiF. and S.M.K. contributed to the concept and design of this study. All authors (F.H.-S., M.F.DiF., R.D., R.G.B., J.J.S., D.A.B., R.A.K., J.A.C.L., A.P., R.P.T., M.S., S.M.K. and J.S.K.) provided literature research and clinical advice, and were involved in acquisition, analyses or interpretation of data. F.H.-S., M.F.D.iF., S.M.K. and J.S.K. contributed to manuscript drafting. All authors (F.H.-S., M.F.DiF., R.D., R.G.B., J.J.S., D.A.B., R.A.K., J.A.C.L., A.P., R.P.T., M.S., S.M.K. and J.S.K.) provided intellectual feedback to the manuscript and approved the final version. S.M.K. provided study supervision. F.H.-S. and J.S.K. take responsibility for the content of the manuscript, including the data and analysis. S.M.K. and J.S.K. are the senior authors of the work.

DATA AVAILABILITY STATEMENT

The data used for the work are available from MESA upon approval by the MESA Committee.

CONFLICT OF INTEREST STATEMENT

J.S.K. receives grant support from the National Heart, Lung, and Blood Institute (NHLBI). All other authors have declared that no conflict of interests exists. The results presented in this paper have not been presented or published previously in whole or part nor in abstract form.

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