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Determination and distribution of left ventricular size as measured by noncontrast CT in the Multi-Ethnic Study of Atherosclerosis

Permalink

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Journal

Journal of Cardiovascular Computed Tomography, 9(2)

ISSN

1934-5925

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Publication Date

2015-03-01

DOI

10.1016/j.jcct.2015.01.001

Peer reviewed

Impact of Mild-to-moderate Renal Disease on Left Ventricular Size in Individuals without Known Cardiovascular Disease:
Multi-Ethnic Study of Atherosclerosis (MESA)

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Running Title: Renal Function and Left Ventricular Size

Word Count: Abstract: 246 words **Manuscript:** 2368 words; **Figure** 3; **Tables** 3

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ABSTRACT

Background: Effects of mild–to–moderate renal impairment on cardiac structure in individuals free of coronary artery disease are not well-studied.

Methods: Computed tomography and magnetic resonance imaging-based-left ventricular (MRLV and CTLV) sizes were calculated in Whites, Blacks, Hispanics and Asians free of coronary artery disease (n = 6753) in the Multi-ethnic Study of Atherosclerosis Cohort. The relationships of glomerular filtration rate (GFR, calculated by modification of diet in renal-disease; MDRD equation) with CTLV and MRLV sizes were assessed in multivariable logistic and linear regression models adjusted for demographics and potential confounders.

Results: The mean CTLV of 6753 (mean age 62±10, women 53%) individuals was 188±57 cm^3, MRLV size was 221±56 cm^3 and mean GFR was 81±18ml/min. The 4th quartile of CTLV size was 225 cm^3 and MRLV size was 256 cm^3. Mild–to–moderate CKD was associated inversely with 4th quartile of CTLV (OR 0.83; 95% CI 0.71 – 0.98, p = 0.02) and MRLV (OR 0.81; 95% CI 0.65 – 0.99, p = 0.04) in adjusted logistic regression model. GFR was positively associated LV mass (ß 0.06, p = 0.01), but not with averaged LV volume (ß 0.004, p = 0.78). There were no interactions with GFR by age, sex or race/ethnicity.

Conclusions: Mild–to–moderate renal disease was associated with reduced LV size as measured by CT and MR in individuals without known coronary artery disease. It was linearly positively associated with LV mass but not LV volume suggesting this relationship is mainly driven by changes in myocardium.

Key Words: Left ventricular size, chronic kidney disease, glomerular filtration rate, traditional cardiovascular risk factors

INTRODUCTION

Coronary artery disease (CAD) is the main cause of mortality and morbidity among patients with impaired renal function. Their mortality is 15 to 30 times higher than the age-adjusted cardiovascular (CV) mortality in the general population. Left ventricular size is also a known risk factor of CV mortality.[5] The prevalence of mild–to–moderate chronic kidney disease (CKD) in US is 42 – 60%.

There is evidence in pediatric population that cardiac changes may begin during mild–to–moderate CKD.[8] Changes in cardiac structure are well-established in individuals with coronary artery disease. Thus, it has been speculated that cardiac remodeling in renal disease patients is a result of atherosclerotic disease.[11] A knowledge gap exists regarding establishing these changes in mild–to–moderate CKD individuals without known CAD.

The relationship between mild–to–moderate CKD and cardiac structure can be elucidated by using non-contrast computed tomography (CT) and magnetic resonance imaging derived left ventricular (LV) volume and LV mass. We have previously showed that non – contrast CT used for obtaining for coronary calcium score may provide reliable estimate of LV size.[12] Understanding the relationship of cardiac structure and mild–to–moderate CKD may provide us insight into underlying mechanisms leading to cardiac remodeling. We investigated association of mild–to–moderate CKD and changes in CT derived LV (CTLV) size.

METHODS

Study population and design

The Multi-Ethnic Study of Atherosclerosis (MESA) investigated the prevalence, correlates, and progression of subclinical cardiovascular disease (CVD) in a population-based sample of 6,814 men and women aged 45–84 years from 4 racial/ethnic backgrounds (Whites, Asians, Blacks and Hispanics) that were free of known cardiovascular disease at baseline. The study objectives and design have been published before.[13] Briefly, this prospective cohort study recruited individuals from six U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). In this analysis, we included all individuals who had baseline LV size assessment on non-contrast computed tomography. We used baseline data from MESA (Jul 2000

– Jul 2002). A total of 6,753 individuals formed the study cohort in whom CTLV sizes were available. Institutional Review Board approval was obtained at all MESA sites, and written informed consent obtained from all individuals. Individuals with eGFR <30 ml/min (n = 33) were excluded.

Covariate assessment

Medical history, anthropometric measurements, and laboratory data for the present study were taken from the first examination of the MESA cohort (July 2000 to August 2002). Information about age, sex, race/ethnicity, and medical history were obtained by questionnaires. Years of tobacco smoking were obtained by self-report. Diabetes mellitus (DM) was defined as a fasting glucose ≥126 mg/dL or use of hypoglycemic medications. Resting blood pressure was measured 3 times in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of medication prescribed for hypertension. Body mass index (BMI) was calculated from the equation weight (kg)/ height (m2). Low-density lipoprotein cholesterol (LDL) was estimated by the Friedewald equation[14]. Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based four-variable Modification of Diet in Renal Disease (MDRD) equation[15]:

$$GFR = 175 \text{ x } SerumCr^{-1.154} * age^{-0.203} * 1.212 \text{ (if patient is black)} * 0.742 \text{ (if female)}$$

Mild-to-moderate CKD was defined as eGFR from 30 – 90 ml/min. Details for feasibility, development of methodology and determination of LVS have been described previously. Briefly, LVS was defined as total LV volume which is actually the sum of LV mass and LV intracavitary volume. This can be calculated from trigonometry formula for volume of a cone. Thus, LVS is simply LV area (**A**) multiplied with LV height (**H**). LV height is obtained by multiplying the number of slices required to cover the whole LV myocardium with thickness of each slice. LV area was calculated using a single slice obtained at the level containing the coronary sinus or the first level below the left atrium during mid-diastole.

Left ventricular size by non-contrast computed tomography (CTLV)

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For measuring LV area, a straight line was drawn from anterior interventricular groove to the posterior interventricular groove. The anterior interventricular groove was determined by natural markers such as an abrupt dip between both ventricles anteriorly which represents fat tissue or a high density circular image which represents cross-section of left anterior descending artery. The posterior interventricular groove was determined by groove present in the area where coronary sinus enters right atrium. The next step was to trace the outer border of left ventricle to obtain LV area. LVS was then calculated by the following formula described by Mao et al. [16] This formula was obtained from linear regression model that used A and H calculated from contrast enhanced cardiac CT. This formula has shown excellent correlation with LVS obtained from NCCT [16] and measures obtained from cardiac magnetic resonance imaging[17]:

$$\textbf{LVS = 0.051 x A + 3.92 x H} - \textbf{277}\text{ (LVS in cc, A in mm}^2\text{, H in mm).}$$

Left ventricular size by magnetic resonance imaging (MRLV)

Magnetic resonance images were acquired by 1.5T MR scanners (SIGNA [LX and CVi], General Electric Medical Systems, Waukesha, WI, and Siemens Medical Solutions [Vision and Sonata], Erlangen, Germany). These images were interpreted at Johns Hopkins University. These images were obtained by electrocardiogram-triggered segmented *k*-space fast-spoiled gradient-echo (SPGR or FLASH) pulse sequence during breathholds (12–18 s). Six- millimeter-thick slices were acquired from the base of the ventricles to the heart apex at end-expiration. Each slice was 4 mm thick. Imaging parameters included the following: repetition time 8 –10 ms, echo time 3–5 ms, flip angle 20 degrees and effective temporal resolution ≤50 ms. In-plane spatial resolution was 1.25 x 2.0 mm^2. LV volume and LV mass were calculated by tracing endocardial and epicardial borders were traced semi automatically (with manual correction) in the short – axis plane using MASS version 4.2 (Medis, Leiden, the Netherlands). LV volumes were calculated based on Simpson's rule (summation of areas on each separate slice is multiplied with slice thickness and image gap). LV mass was determined by the sum of myocardial area (the difference between endo- and epi-cardial contours) multiplied by slice thickness plus image gap in the end-diastolic phase multiplied by myocardial gravity (1.05 gram/cm^3). The magnetic resonance LV (MRLV) size will be calculated by averaging the LV end-diastolic and end-systolic volumes plus LV mass. This was determined at mid-ventricular level. MRLV size was available in a subsample of cohort (n = 4982).

Statistical analysis

For descriptive analysis continuous variables were presented as mean ± standard deviations and were compared using Student's t – test. Categorical data was presented as percentages, which were compared by using chi – square test or non-parametric Mann Whitney U test depending upon the normality of variable's distribution. CTLV and MRLV sizes were dichotomized into 4th quartile and 1-3rd quartile groups. Estimated GFR was analyzed both as dichotomous variable with cut off as 90 ml/min. We assessed relationship of 4th quartile of CTLV size with CKD eGFR ≤90 ml/min vs. non-CKD eGFR >90 ml/min in univariate and multivariable logistic regression models. We constructed two models, model 1 adjusted for demographics (age, sex, race/ethnicity) and model 2 adjusted in addition to demographics, body mass index, hypertension, diabetes, cigarette pack years of smoking, LDL cholesterol levels, and cholesterol lowering medications. We evaluated similar univariate and multivariable models for MRLV size. We also constructed univariate and multivariable linear regression models to assess relationship of eGFR with LV mass and averaged LV volume. Multivariable regression models were adjusted for model 1 and model 2 (given above). Averaged LV volume was calculated by averaging LV end-systolic and end-diastolic volumes. Correlation between CTLV size and MRLV size was assessed. Scatter plots with correlation coefficient were also constructed. Interactions of eGFR with age, sex and race/ethnicity were tested. Statistical analyses were performed using JMP v. 10.0 (SAS Inc, Cary, NC).

RESULTS

A total of 6,753 individuals in whom CTLV size was available were included in the primary analysis. MRLV size was available 4982 individuals. The correlation between CTLV size and MRLV size was 0.79, p <0.001. There were 83% individuals with mild–to–moderate CKD. The individuals with CKD were more likely to be older, hypertensive, diabetic, and smokers compared to non CKD participants (**Table 1**). The mean CTLV size was 188±57 cm^3, MRLV size was 221±56 cm^3 and mean eGFR was 81±18ml/min. The 4th quartile of CTLV size was 225 cm^3 and MRLV size was 256 cm^3.

In univariate logistic regression model, mild–to–moderate CKD group was directly associated with 4th quartiles of CTLV size (OR 0.60, 95% CI 0.52 – 0.68, p <0.001) and MRLV sizes (OR 0.60, 95% CI 0.51 – 0.71, p <0.001), respectively. These associations attenuated with

adjustment of model 1 and model 2 variables, however; retained significant associations (**Table 2**). Individuals with eGFR ≤90 ml/min had lower proportion of highest quartile of CTLV size (**Figure 1**). There were no significant interactions for age, sex and race/ethnicity observed.

In univariate linear regression model, eGFR was directly associated with averaged LV volume and LV mass (**Table 3**). However, when linear regression model was adjusted for demographics and potential confounders, the significant association of eGFR with averaged LV volume disappeared but the association with LV mass remained significant (p = 0.01). There was a linear association of eGFR with CTLV size and MRLV size is shown in scatter plots (**Figure 3**). There were no significant interactions for age, sex and race/ethnicity observed.

DISCUSSION

In this study, we evaluated the independent relationship of mild–to–moderate renal dysfunction (CKD stage 2 and 3) with non-contrast CT based LV size and MRI based LV size. We demonstrated that eGFR was significantly positively associated with LV size irrespective of modality of measurement. On further exploratory analysis, this association was mainly determined by LV mass rather than LV volumes.

To the best of our knowledge, this is the first study showing association of renal function with left ventricular size using a single section of non-contrast CT. We have also extended previous findings by demonstrating an effect on left ventricle size among individuals with milder renal impairment. Previous literature has shown similar association among moderate to severe forms of CKD (CKD stage >3).[18-20] Prior literature suggests coronary artery disease as a possible causative factor in development of these changes in renal disease patients. The participants of this cohort were rigorously screened for coronary artery disease prior to enrollment and represent individuals without known coronary artery disease. Thus, suggesting that there are mechanisms other than coronary artery disease at play in renal disease patients that lead to cardiac changes.

When we investigated the relationship of renal disease with MR derived LV mass and LV volumes, we found that the association of GFR was stronger for LV mass than LV volumes. Prior studies have studied LV mass and LV volumes in isolation [18-20] and have suggested that left ventricular function decreases with progression of renal disease and there is progressive dilatation of LV.[21-23] We observed that this may not be true in individuals with mild–to–moderate CKD. We also observed that LV mass was directly associated with eGFR rather than inversely as observed

in studies with moderate to severe CKD. Thus, there is a likely possibility of J shaped nonlinear association of eGFR with LV structural changes which further remains to be investigated in future studies.

There are many possible mechanisms that may explain this observation. It is possible that loss of functioning myocardium in mild – moderate CKD and replacement fibrosis may lead to reduction in LV mass and size.[26] In a rodent model of mild renal insufficiency, dUTP nick-end labeling (TUNEL) staining revealed increased apoptosis and loss of myocardium.[26] There is an early increase in intravascular volume of mild–to–moderate CKD in the presence of activated renin-angiotensin-aldosterone system.[27] This may lead to remodeling in the early phase of CKD. However, much remains to be still investigated in the realm of mild CKD.

There are several implications of this study. This study documents strong association of non-contrast CT measured LV size with mild–to–moderate CKD which may provide a non-diagnostic test to detect early cardiac changes in these patients. Also, the study suggests that mild–to–moderate CKD might not be benign since this might be the time when reversibility of many of these cardiac changes can occur. However, currently these patients are cared by general internists where management of risk factors of cardiovascular disease is the main choice of treatment. The individuals in this study were relatively at lower risk of cardiovascular disease but still had cardiac structural changes. A rigorous approach towards detection of cardiac structural changes is not currently considered in these patients however, data from other studies have shown that early treatment of reversible causes of cardiac structural changes results in improved survival. [28-30]

There are several strengths of the study such as large sample size, uniform and robust methods used to obtain NCCTs, no missing values, multi-ethnic and adequately powered study to analyze the small effect of mild – to – moderate renal disease on LV size. There are several limitations worth mentioning. We calculated LV size from a single slice of NCCT. Individuals with cardiomyopathy have severely deformed left ventricles, and this might lead to a systematic error. However, MESA cohort individuals were screened at the baseline for cardiomyopathies and none of the individuals suffered from a known cardiomyopathy detectable by MRI at baseline. CTLV size also ignores delineation between LV volumes and LV mass thus, causing difficulty to assess separate effects. However, we included data from calculated MRLV size to explain the

associations of renal disease with measures of cardiac structure. Also, prognosis of CTLV size is not included in this study and will be subject of a future study.

In conclusion, this study shows direct association of renal function with LV size in individuals free of cardiovascular disease. This association was consistent for LV size measured by non-contrast CT as well as cardiac MRI. We also found that association of renal function was stronger for LV mass than LV volumes. Further studies are required to delineate the causal pathway and directionality of this cross-sectional association.

FINANCIAL DISCLOSURES

M Budoff is a member of the speakers' bureau of GE, Milwaukee, Wisconsin.

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Table 1: Baseline characteristics of the study cohort

Characteristic	Mild-to-moderate renal disease	No renal disease	p-value
n	5594	1159	
Age (years)	63±10	58±10	<0.0001
Women	525 (45%)	3047 (54%)	0.01
Race/ethnicity			<0.0001
White	2413 (43%)	192 (17%)	
Asian	671 (12%)	127(11%)	
Black	1341 (24%)	532(46%)	
Hispanic	1169 (21%)	308 (27%)	
Hypertension	2535 (45%)	480 (41%)	0.02
Diabetes mellitus	446 (8%)	204 (18%)	0.007
Cigarette pack years (years)	11±23	12±20	0.37
Body Mass Index (kg/m^2)	28±5	29±6	0.69
Low-Density Lipoprotein Cholesterol (mg/dL)	118±31	115±32	0.003
Cholesterol medication use	956 (17%)	135 (12%)	<0.0001

N (%) expressed for categorical variables and mean ± standard deviation for continuous variables. Mild – to – moderate renal disease means eGFR from 30 – 90 ml/min

Table 2: Association of mild – to – moderate renal disease with 4th quartile of computed tomography (CT) and magnetic resonance imaging (MRI) based left ventricular size, Odds ratio (95% confidence intervals)

Models	4th quartile CT based LV size	p	4th quartile MRI based LV size	p
n	1688/6752		1239/3730	
Unadjusted	0.60 (0.52 – 0.68)	<0.0001	0.61 (0.51 – 0.71)	<0.0001
Model 1	0.82 (0.70 – 0.96)	0.01	0.80 (0.66 – 0.97)	0.02
Model 2	0.83 (0.71 – 0.98)	0.02	0.81 (0.65 – 0.99)	0.04

LV, left ventricular; MRI, magnetic resonance imaging; 4th quartile for CT based left ventricular size is >225 cm^3 and MRI based left ventricular size >256 cm^3

Model 1: Adjusted for age, race/ethnicity and sex

Model 2: Adjusted for Model 1 and body mass index, hypertension, diabetes, cigarette pack years of smoking, LDL cholesterol, and cholesterol lowering medications

Table 3: Association of glomerular filtration rate (independent variable) and averaged left ventricular volume and left ventricular mass

Models	Averaged left ventricular volume, ß	p	Left ventricular mass, ß	p
Unadjusted	0.15	<0.0001	0.24	<0.0001
Model 1	0.001	0.97	0.05	0.10
Model 2	0.004	0.78	0.06	0.0097

Averaged left ventricular volume is the average of left ventricular end-diastolic volume and left ventricular end-systolic volume.

Model 1: Adjusted for age, race/ethnicity and sex

Model 2: Adjusted for Model 1 and body mass index, hypertension, diabetes, cigarette pack years of smoking, LDL cholesterol, and cholesterol lowering medications

FIGURE LEGENDS

Figure 1: Prevalence of 4th quartile of computed tomography derived left ventricular (CTLV) size and magnetic resonance imaging derived left ventricular (MRLV) size for normal and mild – to – moderate chronic kidney disease

Figure 2: Scatter plot showing linear relationship of glomerular filtration rate and computed tomography based left ventricular (LV) size and magnetic resonance imaging based left ventricular size

Figure 3: Scatter plot showing linear relationship of glomerular filtration rate and magnetic resonance imaging based averaged left ventricular (LV) volume and left ventricular mass

Figure 1: Prevalence of 4th quartile of computed tomography derived left ventricular (CTLV) size and magnetic resonance imaging derived left ventricular (MRLV) size for normal and mild – to – moderate chronic kidney disease (CKD)
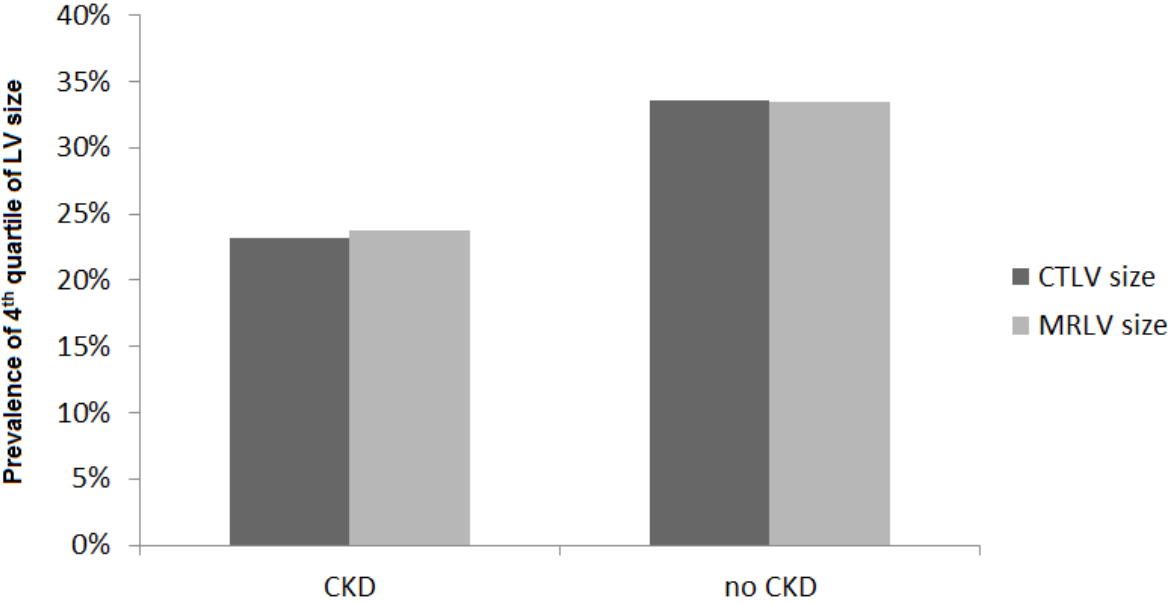
Figure 2: Scatter plot showing linear relationship of glomerular filtration rate and computed tomography based left ventricular (LV) size and magnetic resonance imaging based left ventricular size
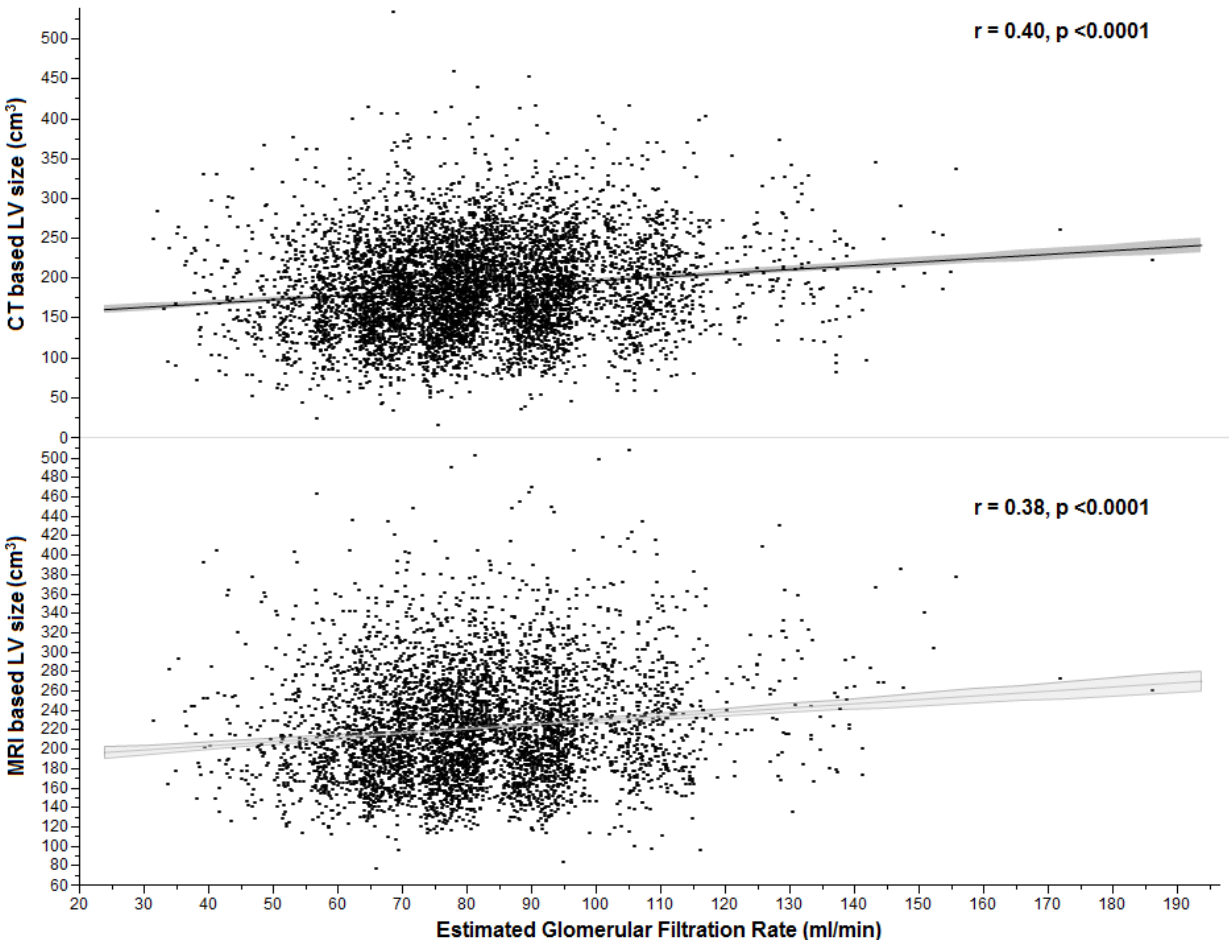
Figure 3: Scatter plot showing linear relationship of glomerular filtration rate and magnetic resonance imaging based averaged left ventricular (LV) volume and left ventricular mass