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Association of left ventricular hypertrophy and functional impairment with cardiovascular outcomes and mortality among patients with chronic kidney disease, results from the C-STRIDE study

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Abstract

Aim: Left ventricular hypertrophy and impaired systolic and diastolic function are commonly seen in patients with chronic kidney disease (CKD), but relationships between the disorders and cardiovascular outcomes are not well established among the patients.

Methods: Totally, 2020 patients with CKD Stages 1–4 were used in the analysis. Left ventricular hypertrophy was defined by left ventricular mass index >49.2 g/m$^{2.7}$ in men and > 46.7 g/m$^{2.7}$ in women. Incident heart failure, non-heart failure cardiovascular events, and all-cause mortality were recorded longitudinally. Cox proportional hazards regression model was used to evaluate the association between the echo parameters and the outcomes, with death treated as the competing risk event for the cardiovascular events.

Results: After a median follow-up of 4.5 years, 53 heart failure, 76 non-heart failure cardiovascular events and 82 deaths occurred. No overall association was found between left ventricular hypertrophy and subsequent heart failure, but the relationship was significant among patients with no diabetes with the multivariable adjusted hazard ratio of 3.66 (95% confidence interval: 1.42–9.46). Ejection fraction<55% was associated with both heart failure and non-heart failure cardiovascular events with hazard ratios of 3.16 (1.28–7.77) and 2.76 (1.08–7.04), respectively. E/A ratio ≤ 0.75 was associated with non-heart failure cardiovascular events [hazard ratio = 2.03 (1.09–3.80)], compared with E/A ratio of 0.76–1.49.

Conclusion: Associations of reduced left ventricular ejection fraction with both heart failure and non-heart failure cardiovascular events and of impaired left ventricular diastolic function with non-heart failure cardiovascular events were validated in a Chinese cohort of CKD.

KEYWORDS

all-cause mortality, cardiovascular disease, chronic kidney disease, cohort, echocardiography

The Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE) collaborators are listed in the Supplementary file.

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SUMMARY AT A GLANCE

This is a multi-centre cohort from China on the association of left ventricular hypertrophy and functional impairment with cardiovascular outcomes and mortality in CKD patients. Ejection fraction <55% was associated with both heart failure and non-heart failure cardiovascular events.

1 | INTRODUCTION

Patients with chronic kidney disease (CKD) are predisposed to cardiovascular complications.[1–3] Several pathophysiologic pathways are involved in the process. Anaemia and sodium and water retention due to reduced kidney function can increase volume overload. Hypertension and calcification of cardiac vessels and valves, which are commonly seen among patients with CKD, can lead to pressure overload. Volume and pressure overload are direct causes of left ventricular (LV) hypertrophy and impairment.[4] Some other disorders inherent or related to CKD, such as chronic inflammation, hyperphosphatemia and impairment of electrolyte homeostasis, can also contribute to cardiovascular disorders.[5–7] Mechanically, the close relationship between CKD and cardiovascular disease (CVD) are summarized as chronic renocardiac syndrome.[8]

Patients with end-stage kidney disease (ESKD) and predialysis CKD have high prevalence of disordered LV structure and function, which can be detected by echocardiographic examinations.[9,10] The association of LV hypertrophy (LVH) and impaired systolic and diastolic functions with CVD events and death has been confirmed among patients with ESKD.[9,11] However, evidence regarding patients with predialysis CKD is still limited. In the African American Study of Kidney Disease and Hypertension (AASK) cohort, LVH was shown to be significantly associated with composite CVD events and heart failure (HF). Diastolic function reflecting a less compliant LV was also associated with HF in the study.[12] In the Chronic Kidney Insufficiency Cohort (CRIC) study, patients with CKD from several clinical centres in North America were recruited. LV mass index (LVMI) was found to increase the risk of HF and death, which was independent of important heart injury makers of B–type natriuretic peptide and troponin T. Reduced systolic function was detected as a risk factor for HF.[13] Among Asians, only a single-centre study conducted in Taiwan documented significantly increased risk for CVD outcomes among those with increased LVMI and LV ejection fraction (EF) < 55%.[14] Comprehensive evaluations for the relationship between echocardiographic parameters and adverse events are still lacking among East Asians, who may represent different characteristics in genetic background, etiologies and comorbidities of CKD.

Based on the longitudinal Chinese Cohort Study of CKD (C-STRIDE), we investigated the relationship between conventional echocardiographic parameters and risk of CVD and mortality.

2 | METHODS

2.1 | Study population

C-STRIDE is a multi-centre prospective cohort study of CKD. The participants were recruited from 39 clinical centres across different geographic regions of China. The study design, inclusion and exclusion criteria have been published previously.[15] Briefly, 3700 individuals aged 18–74 years with CKD Stages 1–4 were enrolled from November 2011 to December 2016. The estimated glomerular filtration rate (eGFR) of patients was requested to be between specific range according to different etiologies of CKD. For glomerulonephritis, eGFR was ≥15 ml/min/1.73m^2. For diabetic nephropathy, eGFR was either between 15 and 59 ml/min/1.73m^2 or ≥ 60 ml/min/1.73m^2 with 24-h urinary protein≥3.5 g or urinary albumin to creatinine ratio (ACR) ≥2000 mg/g or equivalent levels of other proteinuria measurements. For the aetiology other than glomerulonephritis and diabetic nephropathy, eGFR was between 15 and 59 mL/min/1.73m^2. The exclusion criteria included CKD caused by systemic inflammatory illness or autoimmune disease, isolated hematuria, hereditary kidney disease, kidney or other transplantation, treatment with immunosuppressive agents in the preceding 6 months to treat kidney or immune disease, HIV infection and/or diagnosis of AIDS, chronic heart failure with New York Heart Association Class III or IV, known diagnosis of cirrhosis, pregnancy or breast-feeding, malignancy treated with chemotherapy within last 2 years, and current participation in clinical trial. Totally, 2646 participants finished the echocardiographic examination. LVMI was set a priori as the key exposure of the study, so participants with missing data of echocardiographic parameters (end-diastolic and end-systolic LV internal diameters, interventricular septal thickness, and the posterior wall thickness) ($n = 89$) or height to calculate LVMI ($n = 525$) were excluded. In addition, those with baseline HF history ($n = 12$) were also excluded. A total of 2020 individuals were included in the analysis. Participants who were excluded from the study were older (51.2 ± 14.6 years vs. 48.7 ± 13.8 years); had higher proportion of male (59.5% vs. 57.2%); and had a slightly higher proportion of baseline CVD history (10.8% vs. 10.1%), but a lower proportion of diabetes (22.4% vs. 25.7%), lower albumin to creatinine ratio (ACR) [319.7(64.2, 818.8) mg/g vs. 381.5(84.0, 947.3) mg/g] and lower eGFR (46.9 ± 29.3 vs. 53.1 ± 30.9 ml/min/1.73m^2) than those included in the analysis. All participants provided written informed consent and the study was approved by the institutional review board of Peking University First

Hospital [2011(043)]. The C-STRIDE study has been registered at ClinicalTrials.gov (ID: NCT03041987).

2.2 | Echocardiography

An Echocardiogram was performed within 1 month of enrollment. M-mode, two-dimensional, and Doppler echocardiography examinations were performed by registered sonographers at participating centres using commercially available equipment. The reading of the echocardiograms was conducted at each participating centre and the sonographers were blinded to the baseline eGFR of participants. To ensure the quality and consistency between centres, a protocol was developed for training of technologists according to the guideline of standardized operation of echocardiography issued by the Chinese Society of Medical Imaging Technology, which adapted the American

TABLE 1 Characteristics of the population in total and stratified by status of left ventricular hypertrophy (LVH)

Parameters	Total ($n = 2020$)	non-LVH ($n = 1649$)	LVH ($n = 371$)	*p* value
Male (*n*%)	1156 (57.23%)	971 (58.88%)	186 (50.13%)	.002
High school and above (*n*%)	1099 (54.95%)	937 (57.38%)	162 (44.14%)	<.001
Smoking status (*n*%)	723 (36.72%)	589 (36.67%)	134 (36.91%)	.93
Body mass index (kg/m^2)	24.61 ± 3.81	24.35 ± 3.73	25.80 ± 3.93	<.001
Systolic BP (mmHg)	128.83 ± 17.62	126.54 ± 16.22	139.00 ± 19.88	<.001
Diastolic BP (mmHg)	80.73 ± 10.73	79.99 ± 10	84.03 ± 13.03	<.001
Using anti-hypertensive medication in last 2 weeks (*n*%)	1331 (71.21%)	1032 (67.72%)	299 (86.67%)	<.001
Diabetes (*n*%)	467 (25.73%)	334 (22.55%)	133 (39.82%)	<.001
History of CVD (*n*%)	203 (10.13%)	150 (9.17%)	53 (14.36%)	.003
Triglyceride (mmol/L)	1.80 (1.23, 2.57)	1.79 (1.22, 2.55)	1.81 (1.29, 2.62)	.56
LDL-C (mmol/L)	2.56 (2.07, 3.21)	2.56 (2.08, 3.20)	2.61 (2.06, 3.23)	.78
UACR (mg/g)	381.45 (84.00, 947.33)	351.14 (77.80, 843.59)	608.10 (130.10, 1486.03)	<.001
UACR group (mg/g)				.001
<30	257 (14.46%)	221 (15.24%)	36 (11.01%)	
30–299	540 (30.39%)	459 (31.66%)	81 (24.77%)	
≥300	980 (55.15%)	770 (53.10%)	210 (64.22%)	
Creatinine (μmol/L)	139 (95, 200.1)	135 (91.5, 192)	168 (116, 219.4)	<.001
eGFR (ml/min per 1.73m^2)	53.10 ± 30.92	55.66 ± 31.66	41.74 ± 24.4	<.001
eGFR group (ml/min per 1.73m^2)				<.001
≥90	331 (16.39%)	307 (18.62%)	24 (6.47%)	
60–89	371 (18.37%)	326 (19.77%)	45 (12.13%)	
45–59	296 (14.65%)	240 (14.55%)	56 (15.09%)	
30–44	460 (22.77%)	361 (21.89%)	99 (26.68%)	
15–29	562 (27.82%)	415 (25.17%)	147 (39.62%)	
LVMI (g/m$^{2.7}$)	39.79 ± 12.06	35.41 ± 6.74	59.29 ± 11.17	<.001
EF (%)	65.51 ± 6.25	66.12 ± 5.59	62.89 ± 8.06	<.001
EF < 55% (*n*%)	69 (3.71%)	30 (1.98%)	39 (11.17%)	<.001
E/A ratio	1.05 ± 0.39	1.07 ± 0.39	0.97 ± 0.39	<.001
E/A ratio group				.005
≤0.75	396 (26.24%)	308 (25.00%)	88 (31.77%)	
0.76–1.49	938 (62.16%)	768 (62.34%)	170 (61.37%)	
≥1.5	175 (11.60%)	156 (12.66%)	19 (6.86%)	

Note: Missing counts: Education-20, Smoking status-51, Haemoglobin-133, Systolic BP-95, Diastolic BP-95, Using anti-hypertensive medication-151, Diabetes mellitus-205, Triglyceride-350, LDL-C-418, History of CVD-16, Serum calcium-69, Serum phospharus-126, Intact parathyroid hormone-372, UACR-243, EF-158, E/A ratio-511.

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; E/A, peak velocity flow in early to late diastole; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; UACR, urine albumin to creatinine ratio.

Society of Echocardiography guidelines.[16] Empirically, LVMI, EF and mitral E wave to A wave (E/A) ratio were determined to represent cardiac structure, and systolic and diastolic function, respectively. LVMI was calculated using an anatomically validated formula and indexed to height$^{2.7}$.[17,18] LVH was defined according to sex-specific threshold as LVMI >49.2 g/m$^{2.7}$ in men and > 46.7 g/m$^{2.7}$ in women.[18] EF < 55% was defined as abnormal.[14] E/A ratio was divided into three clinically relevant categories based on prior studies as: ≤0.75, >0.75 and < 1.5 or ≥ 1.5.[19]

2.3 | Measurement of covariates

The trained staff in each clinical centre conducted the questionnaire and physical examinations. All blood and urine biomarkers used in the current study were analysed in the Central Laboratory of Peking University First Hospital. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Blood pressure (BP) was measured three times at 5-min intervals by a sphygmomanometer. The mean value of the three readings was calculated. Either abnormal BP (systolic BP≥140 mmHg or diastolic BP≥90 mmHg) or using anti-hypertensive medications in the past 2 weeks was defined as hypertension. Diabetes was defined as fasting plasma glucose≥7.0 mmol/L, haemoglobin A1c ≥ 6.5%, or self-reported diagnosis of diabetes with current use of hypoglycemic agents. History of cardiovascular diseases included a self-reported history or reviewing of medical records at baseline for myocardial infarction, hospitalization for congestive heart failure, serious cardiac arrhythmia, peripheral arterial disease (PAD) or cerebrovascular events. The measurements of serum and urine creatinine were traceable to the isotope dilution mass spectrometry. eGFR was determined with the CKD-EPI creatinine equation.[20] The urine ACR (mg/g creatinine) was calculated.

2.4 | Outcomes

The outcomes in the current study included new occurrence of hospitalization for congestive HF, non-HF CVD events and all-cause mortality. The non-HF CVD events included non-fatal acute myocardial infarction, unstable angina, cerebrovascular events (intraparenchymal haemorrhage, subarachnoid haemorrhage, cerebral infarction, etc.), and PAD. Outcomes were investigated at a 3 to 6-month interval through phone calls or routine outpatient clinical follow-up. The patients who cannot be contacted for more than half a year were considered loss of follow-up, with the date of last follow-up used for censoring. Medical records or death certificates were asked for or copied by the study staff in order to verify suspected outcomes. An independent committee consisting of specialist physicians in Peking University First Hospital adjudicated the outcomes. If several non-HF CVD events occurred, the first event was used as the index event. As occurrence of ESKD (initiation of haemodialysis or peritoneal dialysis or kidney transplantation) leads to a termination of follow-up in the current study, CVD outcomes were censored at the occurrence of ESKD, loss of follow-up or administrative end of follow-up (December 31, 2017), while death was treated as a competing risk event. Death was censored at the occurrence of ESKD, loss of follow-up or the administrative end of follow-up.

2.5 | Statistical analysis

Continuous variables were described as mean ± *SD* or median (interquartile range [IQR]) and compared between groups of LVH by *t* test or Wilcoxon rank sum test, as appropriate. Categorical variables were described as frequency (proportion) and compared by chi-square test. Incidence rates of the outcomes were calculated by number of events

TABLE 2 Proportion and crude event rate stratified by status of LVH, EF categories and E/A ratio groups

	HF event			non-HF CVD events			All-cause mortality		
Characteristics	Number of events	Events per 100 person-years	*p* for log-rank	Number of events	Events per 100 person-years	*p* for log-rank	Number of events	Events per 100 person-years	*p* for log-rank
LVH			<.001			.003			.02
No	31(1.88%)	0.45		53(3.21%)	0.78		59(3.58%)	0.78	
Yes	22(5.93%)	1.56		23(6.20%)	1.63		23(6.20%)	1.36	
EF category[a]			<.001			.01			.002
≥55%	39(2.18%)	0.52		60(3.35%)	0.81		70(3.90%)	0.85	
<55%	10(14.49%)	3.77		6(8.70%)	2.23		8(11.59%)	2.59	
E/A ratio group[a]			.01			<.001			.79
≤0.75	15(3.79%)	0.90		27(6.82%)	1.66		14(3.54%)	0.76	
0.76–1.49	13(1.39%)	0.34		20(2.13%)	0.52		35(3.73%)	0.82	
≥1.5	2(1.14%)	0.26		1(0.57%)	0.13		5(2.86%)	0.60	
Total	53(2.62%)	0.64		76(3.76%)	0.93		82(4.06%)	0.89	

Abbreviation: CVD, cardiovascular disease; E/A, peak velocity flow in early to late diastole; EF, ejection fraction; HF, heart failure; LVH, left ventricular hypertrophy.

[a]Missing counts: EF category-158, E/A ratio group-511.

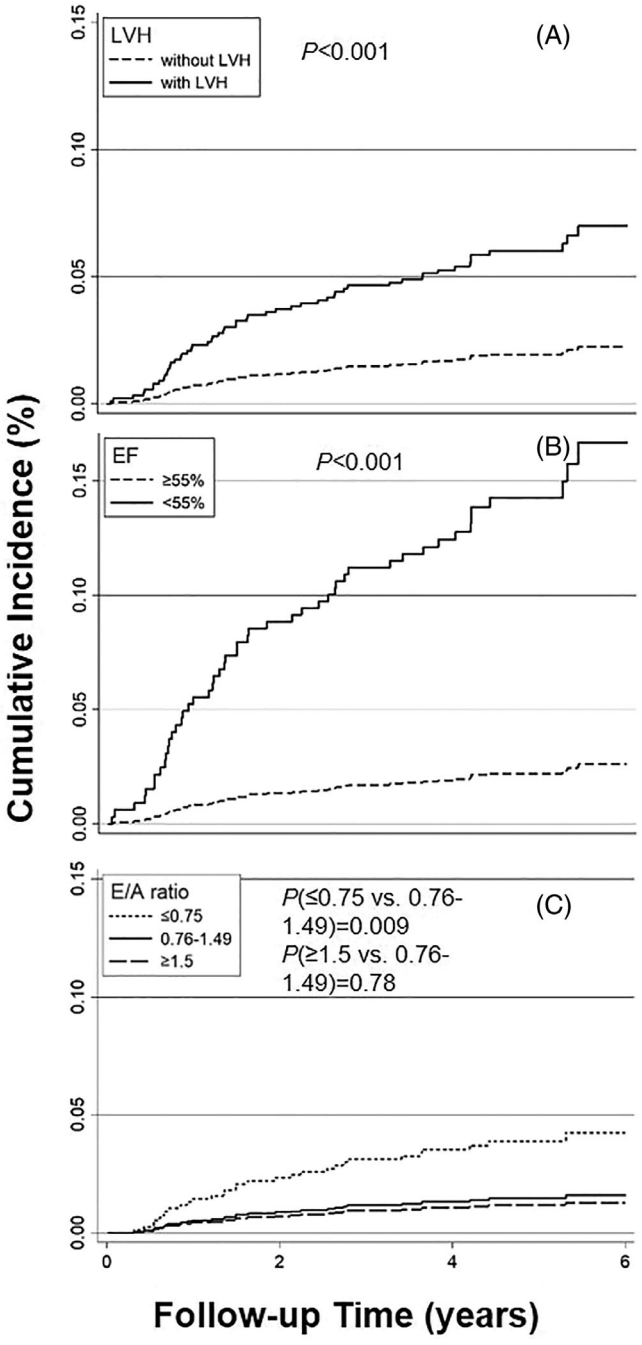

FIGURE 1 Cumulative incidence of HF stratified by parameters of left ventricular structure and function. Cumulative incidence of HF stratified (A) by LVH status; (B) by EF categories; (C) by E/A ratio categories. *p*-values of Gray's test are indicated for difference among the curves. HF, heart failure; LVH, left ventricular hypertrophy; EF, ejection fraction; E/A, peak velocity flow in early to late diastole

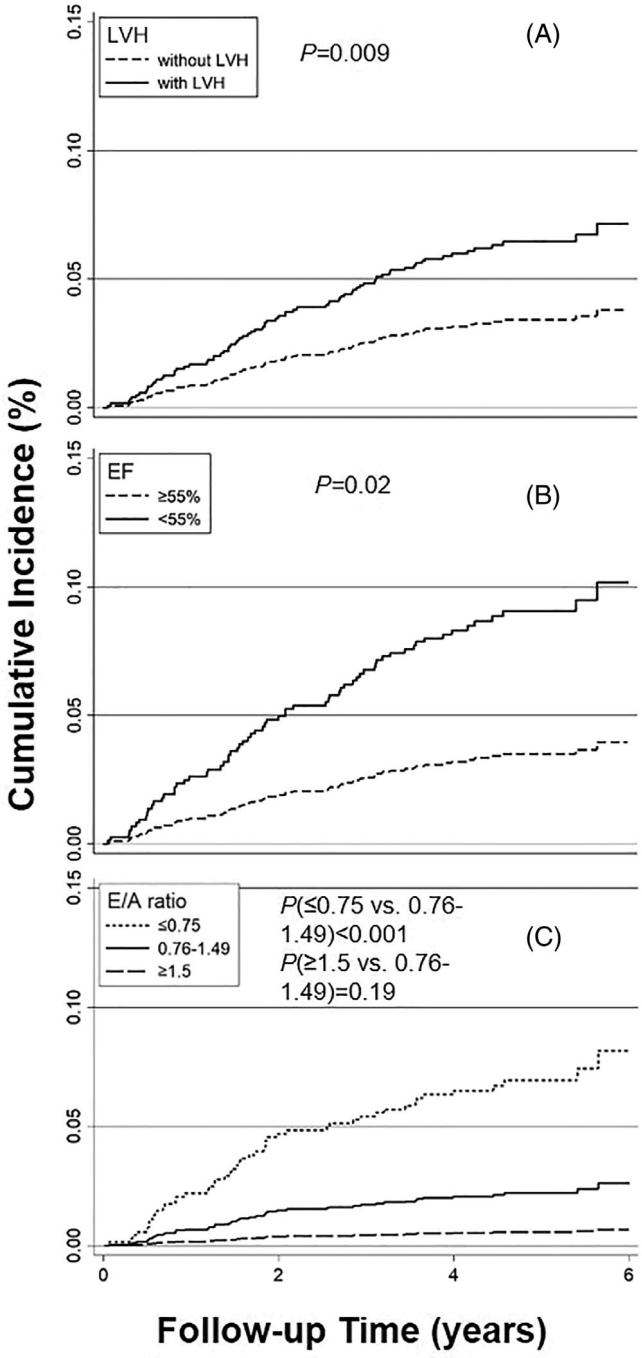

FIGURE 2 Cumulative incidence of non-HF CVD stratified by parameters of left ventricular structure and function. Cumulative incidence of HF stratified (A) by LVH status; (B) by EF categories; (C) by E/A ratio categories. *p*-values of Gray's test are indicated for difference among the curves. HF, heart failure; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; EF, ejection fraction; E/A, peak velocity flow in early to late diastole

divided by the sum of follow-up time (per 100-person years) and compared through levels of the echocardiographic parameters by log-rank test. Cumulative incidence curves of HF and non-HF CVD were depicted stratified by LVH, EF abnormality and E/A ratio categories accounting for the competing risk of death. Grey's test was given for the comparisons of cumulative incidence curves.[21] Subdistribution Cox proportional hazards regression model was used to evaluate the association between echocardiographic parameters and cardiovascular events, while a cause-specific model was used for death.[22] A series of adjusted models were performed. Model 1 adjusted for age, sex and eGFR. Model

TABLE 3 Association of LVMI, EF and E/A with HF event, non-HF CVD events and all-cause mortality

Exposure		HR (95% CI)		
		Model 1	Model 2	Model 3
HF event				
LVMI ($n = 2020$)	non-LVH	Reference	Reference	Reference
	LVH	**2.19(1.27, 3.76)**	1.66(0.90, 3.08)	1.38(0.67, 2.84)
	LVMI (per 1 *SD* increase)	**1.37(1.09, 1.71)**	1.25(0.96, 1.62)	1.17(0.85, 1.62)
EF ($n = 1862$)[a]	≥55%	Reference	Reference	Reference
	<55%	**4.87(2.41, 9.84)**	**3.78(1.62, 8.78)**	**3.16(1.29, 7.77)**
	EF (per 1 *SD* decrease)	**1.49(1.27, 1.75)**	**1.41(1.14, 1.74)**	**1.32(1.07, 1.63)**
E/A ratio ($n = 1509$)[a]	≤0.75	1.49(0.72, 3.06)	1.28(0.60, 2.74)	1.41(0.66, 2.97)
	0.76–1.49	Reference	Reference	Reference
	≥1.5	1.93(0.41, 8.95)	2.15(0.45, 10.28)	2.12(0.44, 10.20)
non-HF CVD events				
LVMI ($n = 2020$)	non-LVH	Reference	Reference	Reference
	LVH	1.43(0.87, 2.35)	1.37(0.82, 2.29)	1.33(0.79, 2.23)
	LVMI (per 1 *SD* increase)	1.20(0.96, 1.49)	1.20(0.95, 1.52)	1.19(0.94, 1.51)
EF ($n = 1862$)[a]	≥55%	Reference	Reference	Reference
	<55%	2.35(0.99, 5.58)	**2.66(1.05, 6.74)**	**2.76(1.08, 7.04)**
	EF (per 1 *SD* decrease)	1.12(0.88, 1.42)	1.13(0.88, 1.46)	1.12(0.87, 1.45)
E/A ratio ($n = 1509$)[a]	≤0.75	**2.01(1.12, 3.61)**	**1.98(1.07, 3.69)**	**2.03(1.09, 3.80)**
	0.76–1.49	Reference	Reference	Reference
	≥1.5	0.47(0.06, 3.84)	0.47(0.06, 3.67)	0.51(0.06, 3.90)
All-cause mortality				
LVMI ($n = 2020$)	non-LVH	Reference	Reference	Reference
	LVH	1.44(0.89, 2.35)	1.26(0.75, 2.13)	1.34(0.80, 2.26)
	LVMI (per 1 *SD* increase)	1.09(0.89, 1.32)	1.02(0.79, 1.31)	1.06(0.86, 1.31)
EF ($n = 1862$)[a]	≥55%	Reference	Reference	Reference
	<55%	**2.25(1.08, 4.72)**	1.77(0.76, 4.16)	1.73(0.80, 3.73)
	EF (per 1 *SD* decrease)	**1.33(1.12, 1.57)**	**1.29(1.04, 1.58)**	**1.28(1.07, 1.54)**
E/A ratio ($n = 1509$)[a]	≤0.75	0.65(0.34, 1.24)	0.63(0.33, 1.21)	0.64(0.33, 1.23)
	0.76–1.49	Reference	Reference	Reference
	≥1.5	1.14(0.44, 2.97)	1.09(0.42, 2.87)	1.10(0.41, 2.90)

Note: Model 1 adjusted for age, sex and estimated glomerular filtration rate. Model 2 adjusted for covariates in Model 1 plus high school education and above, smoking, systolic blood pressure, using anti-hypertensive medication in last 2 weeks, diabetes, history of cardiovascular disease. Model 3 adjusted for covariates in model 1 and model 2 plus body mass index, log(triglyceride), log(low-density lipoprotein cholesterol), and log(urine albumin to creatinine ratio). Bold values in the table indicate significant association ($p < 0.05$).

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; E/A, peak velocity flow in early to late diastole; EF, ejection fraction; HF, heart failure; HR, hazard ratio; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; *SD*, standard deviation.

[a]Missing counts: EF-158, E/A ratio-511.

2 adjusted for covariates in Model 1 plus education, smoking status, history of CVD, systolic BP, anti-hypertensive medication use, and diabetes mellitus. Model 3 further added BMI, log(serum triglyceride), log(low-density lipoprotein cholesterol), and log(urine ACR) into the covariates in Model 2. Missing values were filled with mean or median for continuous variables and with a separate category for categorical variables before the variables were included in the regression models. The results were expressed as hazard ratios (HR) with 95% confidence interval. We also investigated effect modification a priori for age, diabetes mellitus and eGFR. The interaction term between each LVMI or EF as a continuous variable and a potential effect modifier was included in the fully adjusted regression model (Model 3). If statistical significance for the interaction term was detected, stratified analysis was performed through levels of the effect modifier. The proportional-hazards assumption was tested by assessing the log–log plot of survival and using Schoenfeld residuals. No violations were found for each of the covariates. A p value less than .05 was considered as statistically significant. All analyses were conducted using SAS software (version 9.4, SAS Institute Inc, Cary, NC).

3 | RESULTS

The mean age of the patients was 48.68 ± 13.82 years, with 57.23% male. The majority had reduced eGFR (<60 ml/min/1.73m^2) (65.24%) and increased ACR (≥30 mg/g) (85.54%). The mean of LVMI was 39.79 ± 12.06 g/m$^{2.7}$, with 18.4% of LVH. The proportion of EF < 55% was 3.71% and those of E/A ≤ 0.75, 0.76–1.49 and ≥ 1.5 accounted for 26.24%, 62.16% and 11.60% of the population, respectively. The patients with LVH were older, had higher level of BMI, systolic and diastolic BP, and ACR, and lower level of eGFR than those without LVH (all *p* values<.05). In addition, patients with LVH were less likely to be male and to have high school and above education, but more likely to be under anti-hypertensive treatment, with diabetes and with history of CVD (all *p* values<.05) (Table 1).

Totally, 61 (3.02%) patients were lost of follow-up. The median follow-up time for HF event, non-HF CVD events and all-cause mortality were 4.55 years (IQR: 3.55–5.37 years), 4.52 years (IQR: 3.45–5.36 years) and 4.82 years (IQR: 4.12–5.51 years), respectively. LVH and EF < 55% were associated with increased incidence of all three outcomes, while increased categories of E/A were associated with decreased incidence of HF or non-HF CVD events (*p* value for log-rank<.05). The incidence of all-cause mortality was not significantly different across levels of E/A (*p* value for log-rank = .79) (Table 2). The non-HF CVD events consisted of 14 cases of non-fatal acute myocardial infarction, 19 unstable angina, 45 cerebrovascular events and 2 PAD. The comparison of incidence rates of the components was listed in Table S1. Regarding cumulative incidence of HF and non-HF CVD event, similar patterns across the LVH, EF and E/A ratio categories were observed as in the survival analysis (Figures 1 and 2).

Both LVH and continuous LVMI value were significantly associated with risk of HF after adjustment for age, sex and eGFR, but the association lost statistical significance after more covariates were added into the model. However, both EF < 55% and continuous EF value were associated with increased risk of HF event. The HR was 3.16 (95% CI: 1.29, 7.77) for EF < 55% compared with EF≥55% and was 1.32 (95% CI: 1.07, 1.63) per one *SD* decrease of EF in the fully adjusted model. Regarding non-HF CVD events, reduced EF (EF≥55% vs. <55%) was associated with increased risk of the outcome with fully adjusted HR of 2.76 (95% CI: 1.08, 7.04). At the same time, reduced E/A ratio (E/A ratio ≤ 0.75 vs. 0.76–1.49) was also linked with increased risk of non-HF CVD events with fully adjusted HR of 2.03 (95% CI: 1.09, 3.80). When each component of the non-HF CVD events was analysed separately, reduced EF and reduced E/A ratio were associated with incident coronary artery disease (acute myocardial infarction or unstable angina), while LVMI as a continuous variable was marginally related to incident cerebrovascular events (Table S2). Solely the decreased EF as a continuous value was found associated with increased risk of all-cause mortality [fully adjusted HR = 1.28 (95% CI: 1.07, 1.54)], rather than any other echocardiographic parameters (Table 3).

TABLE 4 Association of left ventricular mass index with heart failure event and all-cause mortality stratified by status of diabetes or age

Exposure[a]		HR (95% CI)[b]	*p* value for interaction
HF event			
Non-diabetes (*n* = 1348)	non-LVH	Reference	.02
	LVH	**3.66(1.42, 9.46)**	
	LVMI (per 1 *SD* increase)	**2.12(1.35, 3.33)**	
Diabetes (*n* = 467)	non-LVH	Reference	
	LVH	0.91(0.36, 2.29)	
	LVMI (per 1 *SD* increase)	0.83(0.53, 1.30)	
All-cause mortality			
Aged<60 years (*n* = 1516)	non-LVH	Reference	.002
	LVH	0.89(0.40, 2.03)	
	LVMI (per 1 *SD* increase)	0.76(0.53, 1.07)	
Aged≥60 years (*n* = 504)	non-LVH	Reference	
	LVH	**2.07(1.00, 4.27)**	
	LVMI (per 1 *SD* increase)	**1.42(1.06, 1.92)**	

Note: Bold values in the table indicate significant association ($p < 0.05$).
Abbreviations: CI, confidence interval; EF, ejection fraction; HR, hazard ratio; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; *SD*, standard deviation.
[a]Missing counts: Diabetes-205.
[b]Adjusted for age, sex, estimated glomerular filtration rate, high school education and above, smoking, systolic blood pressure, using anti-hypertensive medication in last 2 weeks, diabetes, history of cardiovascular disease, body mass index, log(triglyceride), log(low-density lipoprotein cholesterol), and log(urine albumin to creatinine ratio). In case diabetes or age was used to stratify population, they were not included in the multivariable adjusted model.

Significant interactions were detected between LVMI and diabetes for HF and between the parameter and age for all-cause mortality in the fully adjusted model. Hence, we conducted stratified analysis to show the effect of the echocardiographic parameters through the levels of the risk factors. Increased LVMI was associated with increased risk of HF events among the patients without diabetes rather than those with diabetes. In contrast, increased LVMI was associated with increased risk of all-cause mortality only among older adults instead of the younger adults (Table 4).

4 | DISCUSSION

In the present study, we validated the association between decreased level of EF and HF event, non-HF CVD event and death. Furthermore, a less compliant heart, indicated by E/A ratio ≤ 0.75, was shown to increase the risk of non-HF CVD events, compared to E/A ratio of 0.76 to 1.49.

LVH and impaired LV systolic and diastolic function are precursors of heart failure, which are commonly seen among patients with CKD. In the CRIC cohort of patients with CKD in the United States, the prevalence of LVH, EF < 50% and diastolic dysfunction were 61.6%, 21.4% and 76.5% in non-Hispanic Blacks and 38.7%, 18.8% and 65.9% in non-Hispanic Whites.[23] Among Asians, LVH was detected in 23.4% of the patients participating in the CKD Japan Cohort.[24] A slightly higher prevalence (30.3%) was observed among participants in the Korean Cohort study for outcomes in patients with CKD study.[25] In our study, the prevalence of LVH, systolic and diastolic dysfunction were much lower (18.4%, 3.71% and 26.24%, respectively), which may be partly explained by the considerable proportion of patients with glomerulonephritis and with preserved kidney function. There are complex links between cardiac disorders and CKD with the involvement of several CKD specific pathways.[8] For example, recent studies have shown that increase in FGF-23, which indicates hyperphosphatemia, plays an important role in the development of clinical and subclinical HF.[26,27]

The relationship between LVH and LV dysfunction and CVD outcomes has been established in ESKD, while still not conclusive among patients with CKD, perhaps due to heterogeneity in settings of ethnicity, aetiology, comorbidities and disease severity of CKD.[9,11] One community-based study among older adults (≥65 years) determined LVH as the top traditional risk factor contributing to the largest increase of absolute risk for CVD mortality among patients with CKD.[28] In the Rochester Epidemiology Project recruiting a community-living population with preserved EF, Jain and colleagues reported that diastolic function, measured by E/e′ (e′ is the early myocardial diastolic velocity), was associated with HF and all-cause mortality among those with reduced kidney function (eGFR<60 ml/min/1.73m^2).[29] More evidence came from studies conducted in the settings of clinical centres. In the AASK study, LVH was found to be associated with CVD events (including cardiac death, myocardial infarction, stroke and HF), and an abnormal E/A ratio was specifically associated with HF.[12] In the CRIC cohort with CKD patients without baseline HF, LVMI was determined to be associated with HF and mortality, EF < 50% with HF, while no significant associations were detected for diastolic dysfunction.[13] A study conducted in Taiwan reported LVMI and EF < 55% were independent risk factors for composite CVD events (including CVD death, hospitalization for HF and atherosclerosis CVD events). However, the study was based on a single clinical centre.[14] Based on a meta-analysis involving 73 trials evaluating efficacy of several commonly-used therapies on reducing LVMI among patients with CKD, evidence is still lacking regarding the effect of regression of LVH on reducing the risk of all-cause and CVD specific mortality.[30] Our study extended the previous findings by recruiting CKD population with a broad spectrum of eGFR and various etiologies. We demonstrated the association of reduced EF with CVD outcomes and death. What's more, compared with the null findings of previous studies regarding relaxation impairment reflected by reduced E/A ratio, we detected significant associations of E/A ratio ≤ 0.75 with non-HF CVD events, even independent of known traditional CVD and kidney-related risk factors. The result suggests a severe relaxation abnormality among patients with CKD may require further evaluation and intervention.

Diabetes is a well-established risk factor for adverse CVD outcomes and death.[31] In the present study, increased risk of HF relating to LVMI was only identified in persons without diabetes. The findings were consistent with that reported in CRIC cohort, where the associations of LVMI with both HF and mortality were more pronounced in patients with CKD without diabetes compared with those in patients with diabetes.[13] Due to the high burden of metabolic abnormalities coexisting with diabetes, the effect of LVH on incident HF may be less important than some other risk factors, although we have adjusted for well-recognized traditional and CKD-specific risk factors in our study.

In the current study, EF < 55% or an incremental decrease of EF was demonstrated to be associated with CVD events and all-cause mortality, which was consistent with findings from the aforementioned CRIC study and the study of Chinese in Taiwan.[13,14] Recent studies prompted the use of strain echocardiography with the parameter of global longitudinal strain. This technology grades systolic function among patients with normal ejection fraction. Several studies have reported that global longitudinal strain was associated with adverse CVD outcomes and mortality among CKD patients with preserved EF.[32,33] Given the limited number of patients with reduced EF in our study, further analysis using the up-to-date parameter for measuring systolic function is warranted. Regarding diastolic dysfunction, only a relationship between the reduced E/A ratio and non-HF CVD events was found in our study. The lack of association regarding other outcomes in the current study and the null findings by others may be due to the use of pulse wave Doppler, which may lack of sensitivity for detecting abnormal diastolic function. Instead, tissue Doppler imaging of the septal and lateral mitral valve with the measurements of s' (peak systolic myocardial velocity) and e′ may be more suitable to reflect diastolic function. Several studies have employed E/e′ as the parameter for measurement of diastolic function with some significant associations regarding increased risk of CVD outcomes reported.[12,29,34]

The present study has several advantages including a large sample of patients with CKD with various etiologies and severity of disease, thorough characterization of many traditional cardiovascular and CKD-specific risk factors and a modestly long term of follow-up. However, there are some limitations of the study. First, the measurement of echocardiography and reading of image were implemented individually in every participating centre. Although some restrictive quality control measures were taken, variation of standards across centres cannot be entirely avoided. Second, echocardiograms were not available for some participants, which might have introduced selection bias. The participants excluded were older, with more male and with lower eGFR, among whom, the association between the echocardiographic parameters and the outcomes may be more pronounced. Therefore, we may miss some significant findings due to exclusion of such a population. Third, as we have discussed, tissue Doppler imaging and strain echocardiogram were not conducted. This might have compromised the ability to detect more subtle changes of LV diastolic and systolic function. Fourth, HF with or without preserved EF was not distinguished, which could have reduced the ability to detect the association between LV structural and functional parameters and the outcomes. Fifth, the longitudinal BP control and use of anti-hypertensive treatments during follow-up were not considered in the current study, which may lead to residual confounding in estimating the effect of exposure variables.

In conclusion, we replicated some of the significant associations between echocardiographic parameters and adverse cardiac outcomes and death among patients with CKD Stages 1–4. Further studies are needed to validate the association, especially by using the new technologies of echocardiogram.

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DISCLOSURE OF INTEREST

The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Jinwei Wang, Jicheng Lv and Luxia Zhang designed the study; Jinwei Wang, Fang Wang, Bixia Gao, Ming-Hui Zhao and Luxia Zhang collected the data; Jinwei Wang, Jicheng Lv and Kevin He analysed the data; Jinwei Wang, Kevin He, Fang Wang, Bixia Gao, Ming-Hui Zhao and Luxia Zhang drafted and revised the paper; all authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data sets generated and analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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