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Echocardiographic features of left ventricular dysfunction and outcomes in chronic kidney disease

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ABSTRACT

Objective Heart failure (HF) imposes a substantial burden and the prevalence of HF is high in patients with chronic kidney disease (CKD). HF results in multiple hospital admissions, but whether HF subtypes worsen long-term outcomes and renal function in patients with CKD remains inconclusive.

Methods The study comprised 10 904 patients with CKD aged ≥20 years who underwent echocardiography between 1 January 2011 and 31 December 2018. The patients were stratified into four groups: non-HF, HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF). The primary end points were all-cause mortality, major adverse cardiovascular events (MACEs) and adverse renal outcomes.

Results In inverse probability of treatment weighting-adjusted method, the risk of all-cause mortality and MACEs relative to the non-HF group was greatest in the HFrEF group (HR 3.18 (95% CI 2.57 to 3.93) and HR 3.83 (95% CI 3.20 to 4.59)), followed by the HFmrEF (HR 2.75 (95% CI 2.22 to 3.42) and HR 3.08 (95% CI 2.57 to 3.69)) and HFpEF (HR 1.85 (95% CI 1.59 to 2.15) and HR 2.43 (95% CI 2.16 to 2.73) groups. In addition, the HFrEF group had the greatest risks of end-stage renal disease (HR 2.58 (95% CI 1.94 to 3.44)) compared with other groups.

Conclusions HF is associated with subsequent worse clinical outcomes, which may be more pronounced in patients with HFrEF, followed by those with HFmrEF and those with HFpEF relative to non-HF group.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Heart failure (HF) is highly prevalent in patients with chronic kidney disease (CKD), and it is strongly associated with adverse outcomes.
⇒ Although differences exist among different HF subtypes in cardiac remodelling and associated outcomes, the relationship between HF subtypes, diastolic dysfunction and the risks of long-term outcomes has never been explored.

WHAT THIS STUDY ADDS?

⇒ Our study included 10 904 patients with CKD who had undergone transthoracic echocardiography.
⇒ The risks of all-cause mortality, major adverse cardiovascular events (MACEs) and end-stage renal disease (ESRD) were 3.18-fold, 3.83-fold and 2.58-fold higher in HF with reduced ejection fraction group compared with non-HF group.
⇒ Furthermore, risks of all-cause mortality, MACEs and ESRD were 3.33-fold, 3.21-fold and 2.76-fold higher in grade 3 diastolic dysfunction compared with non-HF group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ Based on the results from our study, implementation of HF screening coupled with early diagnosis are crucial for these patients.

INTRODUCTION

Chronic kidney disease (CKD) is recognised as a worldwide health burden, causing an estimated 850 000 deaths per year and affecting an estimated 17% of the adult population in the USA.[1] Left ventricular (LV) structural and functional abnormalities are common in patients with CKD, and 30%–60% of patients with CKD experience heart failure (HF) with preserved or reduced ejection fractions.[2] The associations between CKD and HF are often complicated by bidirectional causal relationships.

Myocardial hypertrophy caused by hypertension and underlying comorbidities in patients with CKD leads to a mismatch between the myocardial oxygen supply and demand, resulting in myocardial ischaemia.[3] Myocardial ischaemia has a detrimental effect on myocardial cell survival, promoting the accumulation of extracellular matrix and collagen and myocardial fibrosis, which, in turn, increases the LV filling pressure, impairs diastolic filling and causes heart dysfunction in patients with CKD.[4] HF reduces the renal blood flow and causes renal hypoperfusion, leading to an ineffective circulating volume and the activation of the renin-angiotensin system, which, in turn, increases sodium retention and decreases the effects of endogenous vasodilators, mainly nitric oxide and natriuretic peptides.[5] In addition, coexisting comorbidities and renal dysfunction may share traditional cardiovascular risk factors, such as diabetes mellitus, hypertension and smoking, and multiple comorbidities may cause major adverse cardiovascular events (MACEs) and adverse renal outcomes in patients with CKD and HF.[6] Cross-sectional studies have shown that

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Table 1 The characteristic of patients with CKD with different HF subtypes

	Before IPTW						After IPTW				
	All patients	Non-HF	HFpEF	HFmrEF	HFrEF	SMD	Non-HF	HFpEF	HFmrEF	HFrEF	SMD
No. of patients	N=10904	N=5414	N=3773	N=780	N=937		N=5414	N=3773	N=780	N=937	
Age, years	75.1 (62.6, 84.6)	67.3 (58.2, 78.6)	81.5 (71.6, 87.3)	81.6 (70.3, 87.0)	81.1 (68.6, 86.8)	0.423	74.5 (62.2, 84.2)	75.9 (63.5, 84.9)	76.5 (63.3, 84.6)	78.0 (65.2, 85.3)	0.084
Male sex	54.3%	49.1%	53.7%	69.5%	74.0%	0.318	54.5%	54.1%	57.8%	61.0%	0.080
HbA1c, % (n=)	6.8 (6.0, 8.5)	6.7 (6.0, 8.2)	6.7 (6.0, 8.7)	6.8 (5.9, 8.4)	7.0 (6.1, 9.0)	0.057	6.8 (6.0, 8.3)	6.7 (6.0, 8.4)	6.7 (5.9, 8.2)	7.0 (6.1, 8.9)	0.050
eGFR, mL/min/1.73 m^2	58.7 (39.3, 80.5)	66.1 (44.6, 85.8)	56.0 (37.5, 76.6)	48.5 (30.7, 69.4)	47.5(31.0, 69.0)	0.298	59.6 (40.8, 81.3)	58.9 (39.9, 80.2)	57.7 (39.4, 77.8)	54.7 (37.0, 75.9)	0.097
≥90	13.4%	18.9%	8.9%	7.1%	5.9%		14.0%	13.7%	11.6%	8.5%	
60–89	34.8%	37.1%	35.2%	26.5%	27.1%		35.4%	34.6%	35.6%	35.3%	
30–59	35.5%	31.0%	38.6%	42.3%	43.0%		35.4%	36.1%	37.3%	38.0%	
15–29	9.6%	7.2%	10.5%	13.8%	16.2%		8.8%	9.2%	9.4%	11.2%	
<15	6.7%	5.9%	6.9%	10.3%	7.8%		6.4%	6.4%	6.2%	6.9%	
UPCR, mg/mg	0.31 (0.13, 0.95)	0.30 (0.13, 0.84)	0.31 (0.13, 1.06)	0.36 (0.15, 1.30)	0.34 (0.14, 1.13)	0.025	0.31 (0.13, 0.91)	0.30 (0.14, 0.89)	0.31 (0.14, 0.94)	0.31 (0.13, 0.84)	0.041
UACR, mg/mg	0.04 (0.01, 0.24)	0.03 (0.01, 0.17)	0.05 (0.01, 0.29)	0.05 (0.01, 0.38)	0.07 (0.01, 0.42)	0.083	0.04 (0.01, 0.24)	0.04 (0.01, 0.22)	0.04 (0.01, 0.23)	0.04 (0.01, 0.23)	0.025
Comorbidities											
Hypertension	64.5%	57.6%	71.7%	73.2%	68.1%	0.179	63.8%	65.8%	65.6%	66.6%	0.030
DM	38.9%	38.7%	38.8%	40.5%	38.7%	0.019	39.1%	38.1%	38.8%	37.8%	0.016
CAD	43.7%	38.2%	44.0%	56.8%	63.0%	0.297	42.6%	43.4%	46.6%	48.8%	0.073
Malignancy	30.5%	27.2%	35.2%	31.8%	28.9%	0.097	30.1%	31.5%	29.2%	28.8%	0.032
Medications											
CCBs	44.5%	42.0%	50.5%	45.0%	34.2%	0.177	45.1%	45.1%	43.1%	43.6%	0.024
Beta-blockers	46.7%	42.6%	44.8%	58.8%	67.4%	0.304	45.6%	46.3%	49.0%	52.4%	0.077
RAASi	52.2%	46.3%	54.1%	61.5%	71.0%	0.281	52.0%	52.1%	55.1%	58.4%	0.074
Statins	36.3%	39.4%	31.0%	37.3%	38.2%	0.091	36.8%	35.2%	33.7%	36.3%	0.036
OHAs	17.9%	16.5%	17.8%	22.9%	21.7%	0.097	17.3%	17.7%	17.9%	19.9%	0.034
Insulins	10.2%	6.7%	13.0%	14.9%	14.9%	0.143	9.2%	10.5%	10.9%	11.6%	0.042

*Values are median and IQR or %.
CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IPTW, inverse probability of treatment weighting; OHA, oral hypoglycaemic agents; RAASi, renin-angiotensin-aldosterone system inhibitor; SMD, standardised mean difference; UACR, spot urine albumin-to-creatinine ratio; UPCR, spot urine protein-to-creatinine ratio.

Table 2 Risks of all-cause mortality, major adverse cardiovascular events and adverse renal outcomes among patients with CKD with different HF subtypes

Outcome	No. of events	Person-years	Incidence rate*	Before IPTW		IPTW		IPTW-adjusted†	
				HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality									
HFpHF	633	10119	6.26	3.61 (3.15 to 4.14)	<0.001	1.90 (1.64 to 2.21)	<0.001	1.85 (1.59 to 2.15)	<0.001
HFmrHF	189	2452	7.71	4.78 (3.99 to 5.73)	<0.001	2.66 (2.14 to 3.31)	<0.001	2.75 (2.22 to 3.42)	<0.001
HFrHF	237	2674	8.86	5.29 (4.47 to 6.27)	<0.001	3.18 (2.58 to 3.93)	<0.001	3.18 (2.57 to 3.93)	<0.001
Non-HF	311	19802	1.57	Reference		Reference		Reference	
Major adverse cardiovascular events									
HFpHF	946	7708	12.27	3.68 (3.31 to 4.11)	<0.001	2.48 (2.20 to 2.80)	<0.001	2.43 (2.16 to 2.73)	<0.001
HFmrHF	243	1791	13.57	4.38 (3.76 to 5.10)	<0.001	3.11 (2.59 to 3.73)	<0.001	3.08 (2.57 to 3.69)	<0.001
HFrHF	347	1836	18.90	5.81 (5.07 to 6.67)	<0.001	3.97 (3.32 to 4.74)	<0.001	3.83 (3.20 to 4.59)	<0.001
Non-HF	510	18476	2.76	Reference		Reference		Reference	
Ischaemic stroke									
HFpHF	160	9742	1.64	1.38 (1.12 to 1.69)	0.002	0.96 (0.77 to 1.21)	0.751	0.97 (0.77 to 1.22)	0.806
HFmrHF	43	2347	1.83	1.59 (1.15 to 2.21)	0.005	1.15 (0.79 to 1.69)	0.459	1.21 (0.83 to 1.78)	0.323
HFrHF	48	2573	1.87	1.60 (1.17 to 2.19)	0.003	1.06 (0.71 to 1.57)	0.775	1.06 (0.72 to 1.58)	0.766
Non-HF	218	19204	1.14	Reference		Reference		Reference	
Myocardial infarction									
HFpHF	100	9927	1.01	2.31 (1.71 to 3.11)	<0.001	1.55 (1.11 to 2.14)	0.009	1.53 (1.10 to 2.13)	0.013
HFmrHF	38	2345	1.62	4.01 (2.71 to 5.91)	<0.001	2.18 (1.32 to 3.59)	0.002	2.09 (1.26 to 3.46)	0.004
HFrHF	73	2508	2.91	6.84 (4.96 to 9.44)	<0.001	3.64 (2.45 to 5.41)	<0.001	3.12 (2.08 to 4.69)	<0.001
Non-HF	76	19609	0.39	Reference		Reference		Reference	
Hospitalisation for HF									
HFpHF	787	8100	9.72	5.52 (4.80 to 6.33)	<0.001	3.53 (3.02 to 4.12)	<0.001	3.44 (2.94 to 4.01)	<0.001
HFmrHF	199	1928	10.32	6.44 (5.36 to 7.73)	<0.001	4.34 (3.49 to 5.39)	<0.001	4.31 (3.46 to 5.36)	<0.001
HFrHF	280	1995	14.04	8.28 (7.00 to 9.78)	<0.001	5.72 (4.65 to 7.05)	<0.001	5.56 (4.48 to 6.90)	<0.001
Non-HF	273	19157	1.43	Reference		Reference		Reference	
Estimated glomerular filtration rate decline ≥30%									
HFpHF	235	9558	2.46	2.46 (2.01 to 3.02)	<0.001	1.67 (1.32 to 2.10)	<0.001	1.62 (1.28 to 2.04)	<0.001
HFmrHF	55	2313	2.38	2.74 (2.01 to 3.73)	<0.001	2.04 (1.40 to 2.99)	<0.001	2.03 (1.38 to 3.00)	<0.001
HFrHF	88	2453	3.59	3.79 (2.92 to 4.93)	<0.001	2.61 (1.90 to 3.59)	<0.001	2.56 (1.85 to 3.56)	<0.001
Non-HF	152	19276	0.79	Reference		Reference		Reference	
End-stage renal disease									
HFpHF	342	9408	3.64	2.91 (2.44 to 3.48)	<0.001	1.82 (1.48 to 2.23)	<0.001	1.86 (1.52 to 2.27)	<0.001
HFmrHF	101	2262	4.47	4.07 (3.20 to 5.18)	<0.001	2.02 (1.49 to 2.75)	<0.001	2.23 (1.63 to 3.05)	<0.001
HFrHF	130	2404	5.41	4.50 (3.60 to 5.62)	<0.001	2.62 (1.98 to 3.49)	<0.001	2.58 (1.94 to 3.44)	<0.001
Non-HF	191	19268	0.99	Reference		Reference		Reference	

*Per 10^2 person-years.
†Adjusted for age, sex, haemoglobin A1c, estimated glomerular filtration rate, spot urine protein-to-creatinine ratio, spot urine albumin-to-creatinine ratio, hypertension, diabetes mellitus, coronary artery disease, malignancy, uses of calcium channel blockers, beta-blockers, renin-angiotensin-aldosterone system inhibitors, statins, oral hypoglycaemic agents and insulin.
CKD, chronic kidney disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IPTW, inverse probability of treatment weighting.

patients with HF have impaired renal function, but long-term follow-up data are still limited.[7]

According to 2021 Universal Definition and Classification of Heart Failure,[8] HF is reclassified into three subgroups: HF with reduced EF (HFrEF; left ventricular ejection fraction (LVEF) ≤40%), HF with mildly reduced ejection fraction EF (HFmrEF; LVEF 41%–49%) and HF with preserved EF (HFpEF; LVEF ≥50%). The HFmrEF subtype was described as an intermediate group between patients with HFrEF and patients with HFpEF. The clinical presentations of HFmrEF are more like those of HFrEF, but HFmrEF may have a better clinical prognosis than those with HFrEF. HFmrEF and HFpEF are also heterogeneous in their presentation and pathophysiology, which influence their prognosis and treatment.[9] However, long-term clinical outcomes in patients with CKD based on the HF subtypes according to the echocardiographic findings remain unknown.

To fill this gap in knowledge, we explored the risks of all-cause mortality, MACEs, renal adverse outcomes and kidney function decline by using a large-scale CKD cohort study. This study used the echocardiography data to discuss the potential different prognoses between HFrEF, HFmrEF, HFpEF and non-HF in patients with CKD.

METHOD

Study population

This comprehensive patient data were extracted from the Big Data Center of Taipei Veterans General Hospital, which includes medical records, prescription order, pharmacy use, laboratory tests and examination echocardiogram parameters from all inpatient, outpatient and emergency services.[10] The study cohort consisted of patients who were diagnosed with CKD between 1 January 2011 and 31 December 2018, according to International

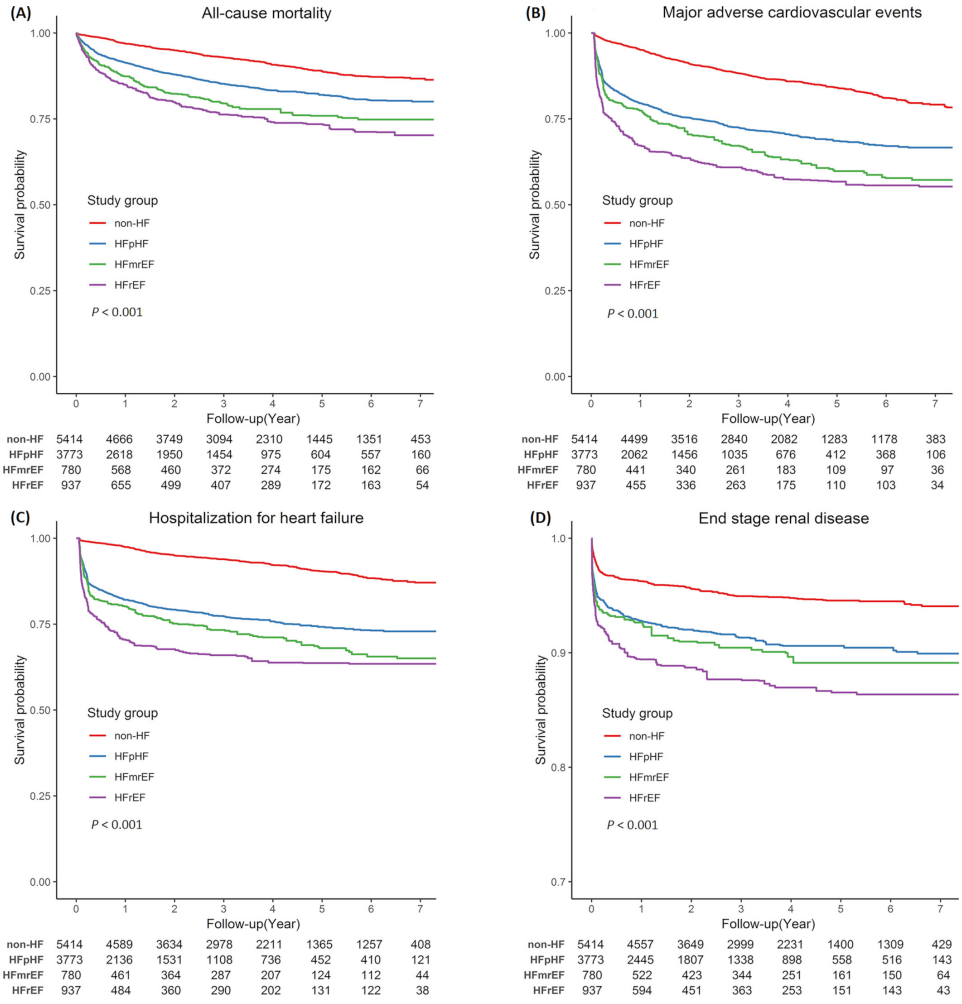

Figure 1 Kaplan-Meier curves for the risks of (A) all-cause mortality, (B) major adverse cardiovascular events, (C) hospitalisation for HF and (D) end-stage renal disease in HFpEF, HFmrEF, HFrEF and non-HF groups. HF, heart failure; HFmrEF, heart failure with mildly reduced ejection; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Classification of Diseases diagnostic codes (ICD codes) 581–583, 585–589, N00–N08, N18–N19 and N25–N27. In our study, CKD stage 1 and 2 were identified by the ICD codes, urine albumin-to-creatinine ratio >30 mg/g and/or urine protein-to-creatinine ratio >150 mg/g. CKD categories 3–5 were identified based on estimated glomerular filtration rate (eGFR) and/or ICD codes.[11] We excluded patients aged <20 years, those who had received renal replacement therapy (haemodialysis, peritoneal dialysis or kidney transplantation) prior to enrolment and patients who did not undergo echocardiography.

Clinical variables

The demographic characteristics included in the analysis were age and sex. The presence of underlying comorbidities, such as hypertension, diabetes mellitus, coronary artery disease and malignancy, medications prescribed, such as calcium channel blockers, beta-blockers, renin-angiotensin-aldosterone system inhibitors, statins, oral hypoglycaemic agents and insulin, were recorded. Laboratory data extracted from the patients' medical records were the glycated haemoglobin concentrations, eGFR, the spot urine protein-to-creatinine ratio, spot urine albumin-to-creatinine ratio and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. eGFRs were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[12]

The transthoracic echocardiographic parameters in M-mode, two-dimensional and Doppler images were analysed and read by two sonographers. The LV volumes and LVEF were traced manually at end-diastole and end-systole at four-chamber and two-chamber view using the modified biplane Simpson's method.[13] Other echocardiographic variables included aortic root diameter, left atrial diameter, left atrial volume, end-systolic and end-diastolic LV internal diameter, interventricular septal diameter end-diastolic LV posterior wall thickness, end-systolic and end-diastolic volume, mitral E-wave velocity, mitral A-wave velocity, mitral E/A ratio, medial and lateral E/e′ ratio and average E/e′ ratio (online supplemental table 1).

Different HF subtypes based on the parameters of echocardiography

The HF subtype in patients with CKD were divided into four groups based on the LVEF and evidence of increased LV filling pressure: non-HF, HFrEF (LVEF ≤40%), HFmrEF (LVEF 41%–49%) and HFpEF groups (LVEF ≥50%). The evidence of increased LV filling pressure included elevated natriuretic peptide (NT-proBNP ≥125 pg/mL in ambulatory patients and ≥300 pg/mL in hospitalised/decompensated patients), non-invasive echocardiographic measurements (average E/e′ >14, septal e′ <7, lateral e′ <10, tricuspid regurgitation velocity

Table 3 Risks of all-cause mortality, major adverse cardiovascular events and adverse renal outcomes among patients with CKD with diastolic dysfunction

				Before IPTW		IPTW		IPTW-adjusted†	
Outcome	**No. of events**	**Person-years**	Incidence rate*	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
All-cause mortality									
Grade 1 diastolic dysfunction	148	2065	7.17	4.02 (3.30 to 4.89)	<0.001	2.29 (1.78 to 2.94)	<0.001	1.94 (1.51 to 2.49)	<0.001
Grade 2 diastolic dysfunction	177	3291	5.38	3.17 (2.63 to 3.81)	<0.001	1.92 (1.47 to 2.50)	<0.001	2.24 (1.72 to 2.94)	<0.001
Grade 3 diastolic dysfunction	28	399	7.02	4.12 (2.80 to 6.07)	<0.001	2.71 (1.56 to 4.70)	<0.001	3.33 (1.92 to 5.77)	<0.001
Non-HF	311	19802	1.57	Reference		Reference			
Major adverse cardiovascular events									
Grade 1 diastolic dysfunction	193	1688	11.43	3.36 (2.85 to 3.97)	<0.001	2.23 (1.75 to 2.83)	<0.001	1.96 (1.53 to 2.51)	<0.001
Grade 2 diastolic dysfunction	290	2668	10.87	3.47 (3.00 to 4.01)	<0.001	2.60 (2.13 to 3.18)	<0.001	2.75 (2.27 to 3.34)	<0.001
Grade 3 diastolic dysfunction	47	294	15.99	4.93 (3.65 to 6.64)	<0.001	3.11 (1.98 to 4.88)	<0.001	3.21 (2.07 to 4.98)	<0.001
Non-HF	510	18476	2.76	Reference		Reference		Reference	
Ischaemic stroke									
Grade 1 diastolic dysfunction	34	1996	1.70	1.37 (0.95 to 1.97)	0.090	0.98 (0.60 to 1.60)	0.939	0.80 (0.50 to 1.30)	0.375
Grade 2 diastolic dysfunction	45	3169	1.42	1.18 (0.86 to 1.63)	0.313	0.77 (0.50 to 1.18)	0.229	0.82 (0.54 to 1.23)	0.331
Grade 3 diastolic dysfunction	5	394	1.27	1.06 (0.44 to 2.57)	0.901	0.93 (0.32 to 2.69)	0.899	1.08 (0.38 to 3.05)	0.889
Non-HF	218	19204	1.14	Reference		Reference		Reference	
Myocardial infarction									
Grade 1 diastolic dysfunction	30	2015	1.49	3.14 (2.05 to 4.80)	<0.001	1.80 (1.12 to 2.88)	0.015	1.51 (0.93 to 2.46)	0.096
Grade 2 diastolic dysfunction	48	3192	1.50	3.42 (2.38 to 4.92)	<0.001	2.61 (1.55 to 4.37)	<0.001	2.25 (1.36 to 3.73)	0.002
Grade 3 diastolic dysfunction	8	386	2.07	4.66 (2.25 to 9.65)	<0.001	3.92 (1.63 to 9.41)	0.002	3.29 (1.37 to 7.91)	0.008
Non-HF	76	19609	0.39	Reference		Reference		Reference	
Hospitalisation for HF									
Grade 1 diastolic dysfunction	155	1769	8.76	4.91 (4.02 to 5.99)	<0.001	3.03 (2.28 to 4.03)	<0.001	2.73 (2.03 to 3.67)	<0.001
Grade 2 diastolic dysfunction	230	2826	8.14	4.98 (4.17 to 5.94)	<0.001	3.70 (2.92 to 4.68)	<0.001	4.02 (3.21 to 5.03)	<0.001
Grade 3 diastolic dysfunction	42	307	13.68	8.00 (5.78 to 11.08)	<0.001	4.62 (2.87 to 7.43)	<0.001	4.74 (2.94 to 7.65)	<0.001
Non-HF	273	19157	1.43	Reference		Reference		Reference	
Estimated glomerular filtration rate decline ≥30%									
Grade 1 diastolic dysfunction	53	1964	2.70	2.30 (1.68 to 3.14)	<0.001	1.79 (1.09 to 2.93)	0.021	1.54 (0.92 to 2.58)	0.097
Grade 2 diastolic dysfunction	65	3128	2.08	2.05 (1.53 to 2.74)	<0.001	1.45 (0.97 to 2.17)	0.071	1.48 (0.99 to 2.20)	0.055
Grade 3 diastolic dysfunction	13	360	3.61	3.37 (1.91 to 5.95)	<0.001	3.29 (1.60 to 6.77)	0.001	3.22 (1.57 to 6.63)	0.001
Non-HF	152	19276	0.79	Reference		Reference		Reference	
End-stage renal disease†									
Grade 1 diastolic dysfunction	90	1917	4.69	3.18 (2.47 to 4.09)	<0.001	2.01 (1.39 to 2.90)	<0.001	1.61 (1.14 to 2.28)	0.007
Grade 2 diastolic dysfunction	138	3018	4.57	3.58 (2.87 to 4.46)	<0.001	2.18 (1.63 to 2.91)	<0.001	1.99 (1.48 to 2.67)	<0.001
Grade 3 diastolic dysfunction	20	374	5.35	4.17 (2.63 to 6.61)	<0.001	2.59 (1.33 to 5.03)	0.005	2.76 (1.40 to 5.43)	0.003
Non-HF	191	19268	0.99	Reference		Reference		Reference	

*Per 10^2 person-years.
†Adjusted for age, sex, haemoglobin A1c, estimated glomerular filtration rate, spot urine protein-to-creatinine ratio, spot urine albumin-to-creatinine ratio, hypertension, diabetes mellitus, coronary artery disease, malignancy, uses of calcium channel blockers, beta-blockers, renin-angiotensin-aldosterone system inhibitors, statins, oral hypoglycaemic agents and insulin.
CKD, chronic kidney disease; HF, heart failure; IPTW, inverse probability of treatment weighting.

>2.8 m/s or left atrial volume index >34 mL/m^2) and/or invasive haemodynamic parameters (pulmonary capillary wedge pressure or LV end-diastolic pressure >15 mm Hg).[14] Diastolic dysfunction was further examined based on the 2016 American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines.[15] The grade of diastolic dysfunction was further classified into grade 1 (E/A <0.8), grade 2 (E/A 0.8–2) and grade 3 (E/A >2).

Outcomes of interest

The outcomes of interest were all-cause mortality, MACEs (defined as a composite of non-fatal stroke, non-fatal myocardial infarction and hospitalisation for HF), ischaemic stroke, myocardial infarction and hospitalisation for HF. The adverse renal outcomes examined were eGFR decline ≥30% and end-stage renal disease (ESRD, defined as eGFR <15 mL/min/1.73 m^2, chronic dialysis or renal transplantation).

Statistical analysis

Baseline characteristics were presented as medians with IQRs for continuous variables, and percentages for categorical variables. Inverse probability of treatment weighting (IPTW) was used to minimise covariate imbalance among the non-HF, HFpEF, HFmrEF and HFrEF groups.[16 17] The detailed description of the missing values handling and IPTW methods are shown in online supplemental methods. We evaluated the balance among non-HF and HF subtypes by comparing standardised mean differences of baseline covariates, and a baseline characteristic was considered balanced if the maximum standardised mean difference was <0.1. All analyses were performed using SAS (V.9.4; SAS Institute, Cary, North Carolina, USA) and R (V.3.5.2 for Windows; R Foundation for Statistical Computing, Vienna, Austria). P values <0.05 were considered statistically significant.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Study population and baseline characteristics

We identified 10 904 patients with CKD who had undergone echocardiography during the study period. The median age was 75.1 (IQR 62.6–84.6) years and male predominant. Table 1 shows the baseline characteristics of all patients, non-HF, HFpEF, HFmrEF and HFrEF groups before and after IPTW matching. The detailed NT-proBNP levels, New York Heart Association Functional Classification and parameters of echocardiography among patients with CKD with different HF subtype groups are shown in online supplemental table 1. After IPTW matching, the study groups had more balanced characteristics (online supplemental figure 1).

Risks of all-cause mortality and MACEs among patients with CKD with different HF subtypes

During the study period, there were 633 (16.8%) patients in the HFpEF group, 189 (24.2%) patients in the HFmrEF group and 237 (25.3%) patients in the HFrEF group who died. In IPTW-adjusted methods, compared with the non-HF group, the risk of all-cause mortality was greatest in the HFrEF group (HR 3.18; 95% CI 2.57 to 3.93; p<0.001), followed by the HFmrEF group (HR 2.75; 95% CI 2.22 to 3.42; p<0.001) and the HFpEF group (HR 1.85; 95% CI 1.59 to 2.15; p<0.001; table 2). The risk of MACEs was also highest in the HFrEF group (HR 3.83; 95% CI 3.20 to 4.59; p<0.001), followed by the HFmrEF group (HR 3.08; 95% CI 2.57 to 3.69; p<0.001) and the HFpEF group (HR 2.43; 95% CI 2.16 to 2.73; p<0.001), compared with the non-HF group. The risks of myocardial infarction and hospitalisation for HF were significantly highest in the HFrEF (HR 3.12; 95% CI 2.08 to 4.69; p<0.001 and HR 5.56; 95% CI 4.48 to 6.90; p<0.001) followed by the HFmrEF group (HR 2.09; 95% CI 1.26 to 3.46; p=0.004 and HR 4.31; 95% CI 3.46 to 5.36; p<0.001) and the HFpEF group (HR 1.53; 95% CI 1.10 to 2.13; p=0.013 and HR 3.44; 95% CI 2.94 to 4.01; p<0.001) compared with the non-HF group. However, the risks of ischaemic stroke showed no significant difference between four groups.

Risks of eGFR decline ≥30% and ESRD among patients with CKD with different HF subtypes

Compared with the non-HF group, the risk of eGFR decline ≥30% was greatest in the HFrEF group (HR 2.56; 95% CI 1.85 to 3.56; p<0.001), followed by the HFmrEF group (HR 2.03; 95% CI 1.38 to 3.00; p<0.001) and the HFpEF group (HR 1.62; 95% CI 1.28 to 2.04; p<0.001) compared with the non-HF group (table 2). The risk of ESRD was also greatest in the HFrEF group (HR 2.58; 95% CI 1.94 to 3.44; p<0.001), followed by HFmrEF group (HR 2.23; 95% CI 1.63 to 3.05; p<0.001) and the HFpEF group (HR 1.86; 95% CI 1.52 to 2.27; p<0.001), compared with the non-HF group. The HFrEF had higher rates of eGFR decline compared with those with HFmrEF and HFpEF. The annual eGFR declines were −5.54 mL/min/1.73 m^2/year in HFrEF group, −5.02 mL/min/1.73 m^2/year in HFmrEF group, −4.47 mL/min/1.73 m^2/year in HFpEF group and −3.83 mL/min/1.73 m^2/year in non-HF CKD group.

Kaplan-Meier curves for all-cause mortality, MACEs, hospitalisation for HF and ESRD for the four study groups are provided in figure 1. Subgroup analyses produced results similar to those of the main analyses in HFrEF versus non-HF group (online supplemental figures 2–5), HFmrEF versus non-HF group (online supplemental figures 6–9) and HFpEF versus non-HF group (online supplemental figures 10–13).

Risk factors for all-cause mortality, MACEs and adverse renal outcomes in HFpEF

In HFpEF group, older age, male gender, higher CKD stages and hypertension were associated with higher risks of all-cause mortality, MACEs and ESRD (online supplemental table 2). However, diabetes mellitus, use of RAASi or beta-blockers had no significant effects on long-term clinical outcomes in HFpEF.

Grade of diastolic dysfunction among patients with CKD

Grade 3 diastolic dysfunction group was associated with highest risks of all-cause mortality (HR 3.33; 95% CI 1.92 to 5.77; p<0.001), MACEs (HR 3.21; 95% CI 2.07 to 4.98; p<0.001), hospitalisation for HF (HR 4.74; 95% CI 2.94 to 7.65; p<0.001) and myocardial infarction (HR 3.29; 95% CI 1.37 to 7.91; p=0.008) when compared with grade 1 and 2 diastolic dysfunction groups and non-HF group (table 3). Grade 3 diastolic dysfunction group was still at greatest risks of eGFR decline ≥30% (HR 3.22; 95% CI 1.57 to 6.63; p=0.001) and ESRD (HR 2.76; 95% CI 1.40 to 5.43; p=0.003) when compared with grade 1 and 2 diastolic dysfunction groups and non-HF groups.

Risk matrices for all-cause mortality, MACEs and ESRD demonstrate HRs in different CKD stage stratified by LVEF and diastolic dysfunction

The risk matrices demonstrated the risks of all-cause mortality, MACEs and ESRD combining CKD stage and LVEF stratification

		CKD stage			CKD stage			CKD stage		
		Stage 1-2	Stage 3	Stage 4-5	Stage 1-2	Stage 3	Stage 4-5	Stage 1-2	Stage 3	Stage 4-5
(A)	LVEF stratification	All-cause mortality			MACEs			ESRD		
	LVEF ≥ 50%	1 (Reference)	**1.39 (1.26-1.53)**	**2.19 (1.97-2.44)**	1 (Reference)	**1.16 (1.08-1.24)**	**1.14 (1.04-1.25)**	1 (Reference)	**1.84 (1.47-2.31)**	**4.81 (3.86-6.03)**
	40% ≤ LVEF < 50%	**1.71 (1.53-1.90)**	**2.99 (2.71-3.30)**	**4.04 (3.57-4.56)**	**1.92 (1.78-2.06)**	**2.39 (2.22-2.58)**	**1.64 (1.45-1.85)**	0.98 (0.71-1.34)	**2.99 (2.32-3.84)**	**7.66 (5.93-9.87)**
	LVEF < 40%	**2.33 (2.10-2.58)**	**3.10 (2.80-3.41)**	**4.45 (3.97-4.98)**	**2.49 (2.31-2.68)**	**2.61 (2.42-2.81)**	**2.93 (2.66-3.23)**	**3.16 (2.49-4.02)**	**4.33 (3.43-5.46)**	**4.13 (3.05-5.52)**
(B)	Diastolic dysfunction									
	Normal	1 (Reference)	**1.67 (1.43-1.94)**	**2.46 (2.06-2.93)**	1 (Reference)	**1.20 (1.07-1.35)**	**1.20 (1.02-1.40)**	1 (Reference)	1.55 (0.93-2.57)	**3.91 (2.36-6.47)**
	Grade 1	**2.25 (1.82-2.77)**	**3.40 (2.82-4.08)**	**4.43 (3.54-5.51)**	**2.26 (1.94-2.62)**	**2.20 (1.89-2.56)**	**2.66 (2.18-3.22)**	0.35 (0.02-1.63)	**2.63 (1.13-5.43)**	**8.95 (4.42-16.93)**
	Grade 2	**1.93 (1.64-2.27)**	**3.24 (2.76-3.80)**	**4.08 (3.40-4.88)**	**2.72 (2.44-3.03)**	**2.76 (2.44-3.11)**	**2.96 (2.55-3.41)**	1.63 (0.70-3.36)	**4.83 (2.66-8.51)**	**7.43 (3.91-13.49)**
	Grade 3	**3.67 (3.18-4.24)**	**5.33 (4.64-6.13)**	**7.40 (6.36-8.64)**	**4.05 (3.65-4.49)**	**4.80 (4.33-5.33)**	**5.13 (4.52-5.82)**	**5.29 (2.62-9.99)**	**6.75 (3.71-11.88)**	**8.68 (4.18-16.68)**

Figure 2 The risk matrices for all-cause mortality, MACEs and ESRD demonstrate HRs in different CKD stage stratified by LVEF and diastolic dysfunction. On the basis of the range of HRs, cells are coloured from light (close to 1.0) to dark (towards risk). The numbers in bold numbers indicate statistical significance (p<0.05). The white colour indicates the reference (risk estimate of 1.0) or non-statistically significant cells. CKD, chronic kidney disease; ESRD, end-stage renal disease; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events.

using patients with CKD stages 1 and 2 and LVEFs ≥50% as the reference groups (figure 2A). In all stages of CKD, patients with LVEFs <40% had the highest risks for all-cause mortality, MACEs and ESRD compared with those with LVEFs between 40% and 50% and LVEFs ≥50%. Moreover, the risks of all-cause mortality, MACEs and ESRD were highest in patients with grade 3 diastolic dysfunction compared with those with other grades of diastolic dysfunction in all CKD stages (figure 2B). The risks associated with CKD and diastolic dysfunction on long-term outcomes appeared to be higher than those associated with CKD and LVEF stratification.

DISCUSSION

The detailed study design and key findings are summarised in figure 3. In our study, HFrEF group has the highest risk of MACE when compared with non-HF group (HR 3.83), followed by HFmrEF (HR 3.08) and then HFpEF (HR 2.43). In addition, the HFrEF group has the highest risk of decline in eGFR ≥30% and ESRD compared with the non-HF group (HR 2.56 and 2.58), followed by HFmrEF (HR 2.03 and 2.23) and then HFpEF (HR 1.62 and 1.86). Furthermore, diastolic dysfunction, which occurs during the diastolic phase, increased these risks of MACEs and ESRD, but to a greatest extent in diastolic dysfunction grade 3 (HR 3.21 and 2.76) compared with those without HF.

In the Framingham Heart Study,[18] the mortality rate ranged from 20% to 60% after diagnosis of HF in the US population, and the Rotterdam study[19] reported that the mortality rate ranged from 11% to 40% in the European population. The Third National Health and Nutrition Examination Study including the US general population aged 18–64 years found that 27.58% of participants with renal dysfunction had HF,[20] and other study suggested that about 30%–60% of patients with CKD have HF.[2 21] Consistent with previous studies, our study found about 50.3% of patients with CKD had HF, and the mortality rate among patients with CKD with HF ranged from 16.8% in HFpEF group to 25.3% in HFrEF group.

Clinical-epidemiological studies have shown that patients with HFmrEF had different clinical characteristics and may be intermediate between the those with HFrEF or HFpEF.[22] In the meta-analysis of 12 observational studies with 109 257 patients, all-cause mortality and hospitalisation for HF were lower in patients with HFmrEF than in those with HFrEF and HFpEF.[23] However, the study population was heterogeneous, and only five

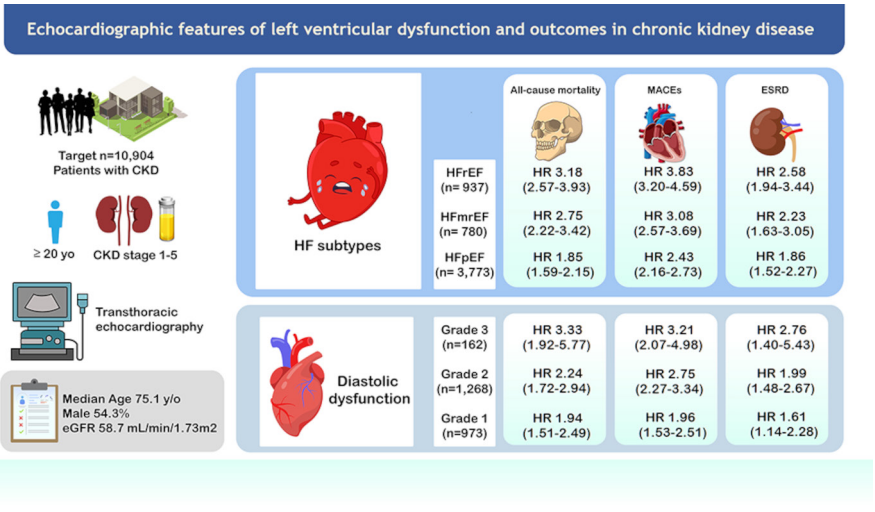

Figure 3 The numbered visual graph summarises the study design and key findings. Patients with CKD with HFrEF have worse outcomes than do those with other systolic dysfunction, but outcomes in those with HFmrEF and HFpEF remain worse than those with non-HF. In addition, the diastolic dysfunction in patients with CKD may still have worse prognostic value for patients with CKD. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular events.

studies provided outcomes of cardiovascular death or hospitalisation for HF. Therefore, the results may be inconclusive and should be interpreted cautiously. In contrast, a cohort study of 42 987 patients with ischaemic heart disease from the Swedish Heart Failure Registry found that ischaemic heart disease was associated with an increased risk of all other outcomes except non-significant changes in all-cause mortality in HFpEF.[24] Our study focusing on the long-term clinical outcomes in CKD populations, who are well known cardiovascular risk populations, found that the risks of all-cause mortality and MACEs still increased as LVEF decreased. The risk of all-cause mortality was 3.18 times higher in the HFrEF group, followed by 2.75 times greater risks in HFmrEF and 1.85 times greater risks in the HFpEF group compared with non-HF group.

Animal models of renal congestion found HF with reduced ejection fraction leads to volume overload and increased intra-abdominal pressure may cause venous congestion and subsequent tubular injury.[25] In addition, excessive reactive oxygen species production and endothelial dysfunction in HF promote profibrotic pathways, interstitial fibrosis and renal function decline.[26] Previous clinical studies found that CKD is common in patients with HF, and a large meta-analysis from 57 studies including 1 076 104 patients found that about 32% of patients with HF suffered from CKD.[27] However, most previous studies were limited by cross-sectional design, preventing the thorough investigation of clinically important long-term renal outcomes. In the present study, HFrEF, HFmrEF and HFpEF groups were associated with eGFR decline $\geq$30% and ESRD, but HFrEF group carried the greatest risk.

Diastolic dysfunction is characterised by reduced ventricular compliance and elevated filling pressure of the left ventricle during diastole, and the risk of diastolic dysfunction increases with the presence of comorbid conditions such as hypertension and diabetes.[28 29] Since the diseases associated with diastolic dysfunction are risk factors for CKD, and therefore diastolic dysfunction are still common in patients with CKD.[30] In spite of a better prognosis than systolic dysfunction, diastolic dysfunction has an annual mortality rate of about 10%.[30] Limited data exist on diastolic dysfunction and long-term renal dysfunction. In the present study, we found that diastolic dysfunction was also associated with future risks of MACEs and renal function decline in patients with CKD, and these risks are greatest in patients with CKD with grade 3 diastolic dysfunction relative to other groups. Our findings suggest the existence of detrimental the interplay between worsening HF and worsening renal function in patients with either HF subtypes or diastolic dysfunction.

The primary strength of this study is the evaluation of cardiac function and associated longitudinal risks of a large cohort of patients with CKD who underwent echocardiography. However, this study has some limitations. First, we cannot rule out the possibility of variable imbalance among study groups. To minimise such bias, we performed IPTW-based analyses to balance the distribution of clinical variables. Second, patients who did not undergo echocardiography were excluded from this study, meaning that our findings may be generalisable only to patients with CKD for whom measures of cardiac function are available. In addition, the study only included patients with CKD who underwent echocardiography, and therefore, selection bias may have been present. Finally, although we analysed consecutive eGFR measurements, these measurements were not performed at the same intervals in all patients. However, this situation may be representative of real-world practice.

In conclusion, our data suggest that patients with CKD with HFrEF have worse outcomes than do those with other systolic dysfunction, but outcomes in those with HFmrEF and HFpEF remain worse than those with non-HF. In addition, the diastolic dysfunction in patients with CKD may still have worse prognostic value for patients with CKD.

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