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Association of cardiovascular-kidney-metabolic multimorbidity with clinical outcomes and guideline-directed medical therapy response in patients with heart failure: a multicentre prospective study

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Research Article

Keywords: Cardiovascular-Kidney-Metabolic multimorbidity, Heart failure, Guideline-directed medical therapy, Clinical outcomes, Risk gradient

Posted Date: November 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10605590/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Cardiovascular-kidney-metabolic (CKM) multimorbidity is common in patients with heart failure (HF), but its clinical impact on the Chinese population remains poorly characterized. This study aimed to evaluate the association of CKM multimorbidity with clinical outcomes and the response to guideline-directed medical therapy (GDMT).

Methods

Based on the GREAT study, this study included 7,339 HF patients from 32 hospitals in an underdeveloped region of China. CKM conditions included atherosclerotic cardiovascular disease, chronic kidney disease, and type 2 diabetes. The primary outcome was a composite of 1-yeah cardiovascular death and HF hospitalizations. Secondary outcomes included the individual components of the primary outcome and all-cause death. Competing-risk and Cox models were used to evaluate the association between CKM multimorbidity and clinical outcomes. We also assessed the efficacy of GDMT and the heterogeneity of its benefit across CKM burden strata.

Results

Overall, 72.1% had ≥ 1 CKM condition and 9.2% had all three. Higher CKM burden was associated with stepwise increased risks of the primary composite endpoint (3 vs. 0 CKM: adjusted Hazard Ratio [aHR] 1.73, 95% CI 1.45–2.07), cardiovascular death (aHR 1.66, 1.26–2.18), HF hospitalization (aHR 1.67, 1.33–2.09), and all-cause death (aHR 2.06, 1.63–2.61) (all p for trend < 0.05). The CKM-associated risk gradient for 1-year outcomes was attenuated by quadruple GDMT (p for trend ≥ 0.05). Although GDMT benefit exhibited no significant heterogeneity across CKM strata, the strongest signal was seen in patients with two CKM conditions (aHR 0.69, 95% CI 0.52–0.91).

Conclusions

CKM multimorbidity is highly prevalent in this underdeveloped Chinese region and predicts a graded increase in adverse outcomes. Quadruple GDMT attenuated the CKM-related prognostic risk gradient, with the greatest relative benefit in patients with two CKM conditions.

1. Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome is a recently proposed systemic disease characterized by pathophysiological interplay among cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic risk factors such as type 2 diabetes (T2D)[1]. This interplay leads to multiorgan dysfunction and a high incidence of adverse cardiovascular outcomes[2, 3]. Recent analyses have confirmed that CKM

multimorbidity is common in HF and is positively correlated with hospitalization, mortality, and impaired quality of life[4–7].

Despite these insights, large-scale studies on CKM syndrome in HF remain limited, with existing populations predominantly from the United States and Western Europe[4, 6]. This geographic selectivity limits generalizability to low- and middle-income countries (LMICs). Although a domestic study has been conducted, it focused on Northeast China[5]. In fact, HF incidence varies significantly within China: the north has a higher incidence and a greater burden of coronary heart disease, while patients in the southwest have higher rates of hypertension, chronic obstructive pulmonary disease (COPD), and CKD[8]. Furthermore, HF mortality varies by region according to underlying etiology[9]. As an economically underdeveloped border region in southwestern China with a large ethnic minority population, Guangxi offers a representative setting for exploring the coexistence of CKM syndrome and HF. Furthermore, current studies have partially focused on HF with preserved ejection fraction (HFpEF) or mildly reduced EF (HFmrEF), whereas the impact of cumulative CKM multimorbidity burden across the full spectrum of left ventricular ejection fraction (LVEF) has not been fully evaluated[6, 7]. Moreover, no study has yet assessed interaction between CKM burden and GDMT on clinical outcomes.

Accordingly, we conducted statistical analyses based on data from the conGestive heaRt failurE registry of diAgnosis and Therapy in Guangxi (GREAT) study. Our objectives were to: (i) supplement and extend the multimorbidity characteristics of CKM syndrome in patients with HF in the real-world setting in China; (ii) evaluate its prognostic impact across LVEF-stratified HF subtypes; and (iii) determine the influence of CKM multimorbidity on the response to GDMT.

2. Methods

2.1 Study population

- The GREAT study was a multicenter, prospective cohort study involving patients with HF across 32 hospitals of Guangxi, China. The diagnosis of HF was based on the European HF guidelines applicable at the time of the study[10]. A total of 8,755 patients were hospitalized due to confirmed HF between January 2021 and December 2021. Patients were excluded from the study if any of the following conditions were present: (1) age < 18 years old; (2) without echocardiology data; and (3) patients whose medical records could not be acquired or who decline to participate. The baseline data were collected during the index hospitalization. Only the first hospitalization was tallied if the patient had several hospitalizations during the study period. Among these, 69 non-first hospitalizations were excluded. Surviving patients were followed up at 1 year post-discharge via electronic medical record review or telephone interview. Follow-up data were missing in 5.9% of patients. The final analysis included 7,339 patients (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the People's Hospital of Guangxi Zhuang Autonomous Region as well as the ethics committees of all participating hospitals (in October 2020; approval number KY-DZX-202006). Written informed consent was obtained from all participants.

2.2 Data collection

- Patient data were obtained from the electronic medical records of the 32 hospitals included in the cohort. Demographic characteristics and medical history were collected through face-to-face interviews conducted by the first-attending physicians. Patients' individual measurement parameters, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and body mass index (BMI), were measured by experienced physicians. Laboratory tests (hemoglobin (Hb), N-terminal pro-brain natriuretic peptide (NT-proBNP), glycated hemoglobin (HbA1c), creatinine, estimated glomerular filtration rate (eGFR), and echocardiography were performed by trained laboratory technicians and sonographers, respectively. Comorbidities were diagnosed and confirmed by experienced cardiologists during hospitalization. Information on specific treatments during hospitalization (including revascularization and hemodialysis) and discharge medications was extracted from the electronic medical records. HF phenotypes were categorized into HF with reduced EF (HFrEF, LVEF < 40%), HF with mildly reduced EF (HFmrEF, 40% ≤ LVEF < 50%), and HF with preserved EF (HFpEF, LVEF ≥ 50%). The New York Heart Association (NYHA) functional classification was assessed by trained cardiovascular specialists.

2.3 Assessment of CKM conditions

- Patients were classified according to the overlap categories of CKM conditions based on the presence or absence of comorbid CKM conditions at baseline. CKM conditions included atherosclerotic cardiovascular disease (ASCVD), CKD and T2D[1]. ASCVD was defined as a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, stroke, or peripheral artery disease[11]. CKD was defined as a history of CKD or baseline eGFR < 60 mL/min/1.73 m². The eGFR was calculated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[12]. T2D was defined as a history of T2D, or a baseline HbA1c level of 6.5%, or a positive glucose tolerance test. To avoid the potential introduction of misclassification due to alternative indications, the use of glucose-lowering medications was not included in the criteria for T2D. Patients were categorized according to the number of CKM conditions (0, 1, 2, or 3 conditions) or the combination of CKM conditions (none, ASCVD only, CKD only, T2D only, ASCVD + CKD, CKD + T2D, ASCVD + T2D, ASCVD + CKD + T2D).

2.4 Clinical outcomes

- The follow-up duration of this study was 12 months. The primary endpoint was a composite of cardiovascular death or HF hospitalization. Secondary endpoints included the individual components of this composite endpoint and all-cause death. Cardiovascular death was defined as death resulting from acute myocardial infarction, sudden cardiac death, HF, stroke, or other cardiovascular etiologies. Causes of death were obtained from the electronic medical records of each participating hospital and were further adjudicated by experienced clinicians.

2.5 Evaluation of GDMT effectiveness

- We also evaluated the effectiveness of GDMT for HF, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium–glucose cotransporter 2 inhibitors (SGLT2is). GDMT use was defined as medications prescribed at discharge, and the endpoints for evaluating treatment effectiveness were identical to those described above.

2.6 Statistical analysis

- Normally distributed continuous variables were presented as mean ± standard deviation and compared using analysis of variance (ANOVA). Non-normally distributed continuous variables were presented as median (interquartile range, IQR) and assessed using the Mann-Whitney U or Kruskal-Wallis H test. Categorical variables were presented as counts and percentages [n (%)] and compared using the chi-square test or the Cochran-Mantel-Haenszel chi-square test. For laboratory indices, samples with missing data were excluded, and only cases with complete data were used for analysis.
- The Cumulative Incidence Functions were estimated for the primary composite outcome, cardiovascular death, and heart failure hospitalization to account for competing risks, with between-group comparisons performed using Fine–Gray tests. Cumulative all-cause mortality was estimated by the Kaplan–Meier method and compared using the log-rank test.
- Cox proportional hazards models were used for all-cause mortality, Fine-Gray competing risk regression models were applied for cardiovascular death, heart failure hospitalization, and the cardiovascular composite endpoint. Non-cardiovascular death treated as the competing event for the composite endpoint and cardiovascular death, and all-cause death as the competing event for HF hospitalization.
- Variable selection for multivariable regression considered both statistical significance and clinical relevance, given the large sample size from univariate analyses. The association of CKM conditions with each outcome was evaluated separately within LVEF subgroups (HFrEF, HFmrEF, and HFpEF), and the effect of GDMT was assessed separately within subgroups defined by the number of CKM (0, 1, 2, and 3). Trends across CKM count categories were evaluated using trend tests.
- All statistical analyses were performed using R software version 4.5.0. All reported *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1 Baseline characteristics

- This study enrolled 7,739 patients. Their mean age was 66 ± 14 years. Male patients made up 65% of the cohort (n = 5,010). Table 1 summarizes the baseline characteristics according to the number of CKM diseases. Among these patients, 72.1% (n = 5,582) had at least one CKM disease, and 9.2% (n = 390) had three CKM diseases. Compared with patients without CKM diseases, those with a higher number of CKM diseases tended to be older, had a higher proportion of Han ethnicity, presented with higher SBP and more severe HF (a higher proportion of patients with NYHA functional class III or IV), and exhibited a higher prevalence of hypertension and anemia. Regarding discharge medications, this group had a higher prescription rate of SGLT2 inhibitors and lower prescription rates of MRAs and digoxin.

- Grouping by CKM comorbidity overlap types revealed the following: ASCVD alone occurred in 9.7% (n = 753) of patients, CKD alone in 20% (n = 1,552), T2D alone in 7.0% (n = 541), both ASCVD and CKD in 11.2% (n = 864), both CKD and T2D in 9.6% (n = 742), and both ASCVD and T2D in 5.4% (n = 421). Baseline characteristics stratified by CKM disease combinations are summarized in Supplemental Table S1. Patients with CKD as part of combination tended to be older, have more severe HF and higher NT-proBNP levels, have a higher prevalence of atrial fibrillation and infections, and have more prescriptions for diuretics and MRA at discharge. Patients with T2D as part of combination tended to be younger, with a higher BMI and a lower prevalence of COPD and anaemia. Patients with ASCVD as part of combination tended to have slower heart rates and a higher proportion of HFpEF.

Table 1
Baseline characteristics according to numbers of CKM conditions

Characteristic	Number of additional CKM conditions					
	Total	0	1	2	3	p-value
	N = 7,739	n = 2,157	n = 2,846	n = 2,027	n = 709	
Male, n(%)	5,010 (65%)	1,360 (63%)	1,802 (63%)	1,370 (68%)	478 (67%)	0.002
Age(years), mean (SD)	66.02 (14.00)	59.77 (14.65)	66.45 (13.84)	70.06 (11.98)	71.76 (10.42)	< 0.001
Age > 65, n(%)	4,340 (56%)	832 (39%)	1,636 (57%)	1,362 (67%)	510 (72%)	< 0.001
Ethnicity, n(%)						< 0.001
Han	4,848 (63%)	1,201 (56%)	1,763 (62%)	1,362 (67%)	522 (74%)	
other	2,891 (37%)	956 (44%)	1,083 (38%)	665 (33%)	187 (26%)	
sbp, mmHg	133.58 (26.34)	128.35 (23.05)	133.88 (26.74)	136.97 (27.38)	138.52 (28.44)	< 0.001
dbp, mmHg	80.67 (16.51)	80.64 (15.80)	81.33 (17.21)	80.65 (16.24)	78.22 (16.32)	< 0.001
Heart rate, bpm	87.36 (21.02)	88.74 (21.24)	87.40 (21.47)	86.55 (20.07)	85.33 (20.97)	< 0.001
BMI	23.85 (4.10)	23.55 (4.24)	23.72 (4.07)	24.26 (4.13)	24.41 (3.39)	< 0.001
LVEF phenotypes, n (%)						0.245
HFrEF	2,522 (33%)	720 (33%)	930 (33%)	647 (32%)	225 (32%)	
HFmrEF	1,454 (19%)	379 (18%)	534 (19%)	417 (21%)	124 (17%)	
HFpEF	3,763 (49%)	1,058 (49%)	1,382 (49%)	963 (48%)	360 (51%)	

Abbreviations: IQR=interquartile range; SD=standard deviation; SMD=standardised mean difference. CKM, cardiovascular-kidney-metabolic disease; PCI: Percutaneous coronary intervention; CABG: Coronary Artery bypass grafting; MI: Myocardial infarction; AF, atrial flutter; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker and neprilysin inhibitor; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; CRT-D, cardiac resynchronization therapy with defibrillator.

Characteristic	Number of additional CKM conditions					
	Total	0	1	2	3	p-value
NYHA class, n(%)						< 0.001
□- □	2,709 (35%)	828 (38%)	1,019 (36%)	652 (32%)	210 (30%)	
□-□	5,030 (65%)	1,329 (62%)	1,827 (64%)	1,375 (68%)	499 (70%)	
Etiologies, n(%)						< 0.001
Non-Ischemic	3,829 (49%)	1,382 (64%)	1,498 (53%)	785 (39%)	164 (23%)	
Ischemic	3,162 (41%)	546 (25%)	1,070 (38%)	1,057 (52%)	489 (69%)	
undefined	748 (9.7%)	229 (11%)	278 (9.8%)	185 (9.1%)	56 (7.9%)	
History of PCI, n(%)	1,146 (15%)	0 (0%)	308 (11%)	500 (25%)	338 (48%)	< 0.001
History of CABG, n(%)	79 (1.0%)	0 (0%)	24 (0.8%)	28 (1.4%)	27 (3.8%)	< 0.001
History of MI, n(%)	1,991 (26%)	0 (0%)	525 (18%)	950 (47%)	516 (73%)	< 0.001
History of Stroke, n(%)	1,055 (14%)	0 (0%)	288 (10%)	464 (23%)	303 (43%)	< 0.001
Hypertension, n(%)	4,559 (59%)	783 (36%)	1,662 (58%)	1,513 (75%)	601 (85%)	< 0.001
Diabetes, n(%)	1,787 (23%)	0 (0%)	349 (12%)	860 (42%)	578 (82%)	< 0.001
AF, n(%)	1,309 (17%)	410 (19%)	494 (17%)	313 (15%)	92 (13%)	< 0.001
Malignancies, n(%)	219 (2.8%)	45 (2.1%)	81 (2.8%)	76 (3.7%)	17 (2.4%)	0.011
COPD, n(%)	326 (4.2%)	75 (3.5%)	118 (4.1%)	95 (4.7%)	38 (5.4%)	0.095

Abbreviations: IQR=interquartile range; SD=standard deviation; SMD=standardised mean difference. CKM, cardiovascular-kidney-metabolic disease; PCI: Percutaneous coronary intervention; CABG: Coronary Artery bypass grafting; MI: Myocardial infarction; AF, atrial flutter; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker and neprilysin inhibitor; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; CRT-D, cardiac resynchronization therapy with defibrillator.

Characteristic	Number of additional CKM conditions					
	Total	0	1	2	3	p-value
Infections, n(%)	2,581 (33%)	646 (30%)	964 (34%)	698 (34%)	273 (39%)	< 0.001
Anemia, n(%)	2,720 (35%)	518 (24%)	980 (34%)	862 (43%)	360 (51%)	< 0.001
Hb, g/L	122.44 (28.29)	128.98 (24.06)	122.99 (31.04)	118.10 (27.13)	112.81 (27.00)	< 0.001
NT-pro BNP, pg/mL	2,768.74 (810.75, 7,910.40)	1,775.00 (554.80, 4,278.00)	2,897.40 (855.25, 8,385.00)	3,844.00 (1,073.00, 10,395.00)	5,112.50 (1,490.00, 16,746.00)	< 0.001
HbA1c, %	6.65 (3.58)	5.64 (0.57)	6.41 (3.24)	7.34 (4.75)	7.76 (4.07)	< 0.001
Creatinine, µmol/L	100.00 (79.00, 136.00)	80.00 (68.00, 93.00)	101.00 (80.00, 137.00)	122.00 (96.00, 176.00)	152.00 (117.00, 251.00)	< 0.001
eGFR, mL/min/1.73 m2						< 0.001
>=90	1,158 (15%)	694 (32%)	340 (12%)	121 (6.0%)	3 (0.4%)	
60–89	2,764 (36%)	1,461 (68%)	970 (34%)	323 (16%)	10 (1.4%)	
30–59	2,475 (32%)	2 (< 0.1%)	1,034 (36%)	1,042 (51%)	397 (56%)	
15–29	662 (8.6%)	0 (0%)	234 (8.2%)	270 (13%)	158 (22%)	
<15	680 (8.8%)	0 (0%)	268 (9.4%)	271 (13%)	141 (20%)	
Diuretics, n(%)	5,441 (70%)	1,534 (71%)	1,963 (69%)	1,423 (70%)	521 (73%)	0.088
ACEI/ARB/ARNI, n(%)	5,013 (65%)	1,307 (61%)	1,877 (66%)	1,380 (68%)	449 (63%)	< 0.001
Beta-blockers, n(%)	5,189 (67%)	1,398 (65%)	1,907 (67%)	1,385 (68%)	499 (70%)	0.019

Abbreviations: IQR=interquartile range; SD=standard deviation; SMD=standardised mean difference. CKM, cardiovascular-kidney-metabolic disease; PCI: Percutaneous coronary intervention; CABG: Coronary Artery bypass grafting; MI: Myocardial infarction; AF, atrial flutter; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker and neprilysin inhibitor; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; CRT-D, cardiac resynchronization therapy with defibrillator.

Characteristic	Number of additional CKM conditions					
	Total	0	1	2	3	p-value
MRA, n(%)	5,500 (71%)	1,598 (74%)	2,028 (71%)	1,403 (69%)	471 (66%)	< 0.001
SGLT2i, n(%)	1,600 (21%)	342 (16%)	521 (18%)	498 (25%)	239 (34%)	< 0.001
No. of GDMT						
≥ 3	3,352 (43%)	891 (41%)	1,205 (42%)	928 (46%)	328 (46%)	0.007
4	1,091 (14%)	286 (13%)	368 (13%)	306 (15%)	131 (18%)	< 0.001
Digoxin, n(%)	2,015 (26%)	606 (28%)	779 (27%)	483 (24%)	147 (21%)	< 0.001
Revascularization, n(%)	835 (11%)	215 (10.0%)	320 (11%)	222 (11%)	78 (11%)	0.529
Dialysis, n(%)	218 (2.8%)	8 (0.4%)	90 (3.2%)	74 (3.7%)	46 (6.5%)	< 0.001

Abbreviations: IQR=interquartile range; SD=standard deviation; SMD=standardised mean difference. CKM, cardiovascular-kidney-metabolic disease; PCI: Percutaneous coronary intervention; CABG: Coronary Artery bypass grafting; MI: Myocardial infarction; AF, atrial flutter; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker and neprilysin inhibitor; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; CRT-D, cardiac resynchronization therapy with defibrillator.

3.2 Associations of CKM with clinical outcomes

3.2.1 Association between the number of CKM overlap and clinical outcomes

- At the 1-year follow-up, 1,864 patients (24.1%) reached the primary endpoint. Death occurred in 1,066 patients (13.8%) of whom 784 (73.5%) died from cardiovascular causes. A total of 1,184 patients (15.3%) were hospitalised for HF. Unadjusted and adjusted analyses both showed that a higher burden of CKM conditions was linked to a progressively greater risk of 1-year clinical outcomes (all p for trend < 0.05) (Fig. 2 and Table 2). After adjustment for confounding factors, patients with three overlapping CKM conditions had significantly increased risks of the 1-year primary composite outcome (aHR 1.73, 95% CI: 1.45–2.07), cardiovascular death (aHR 1.66, 95% CI: 1.26–2.18), HF hospitalization (aHR 1.67, 95% CI: 1.33–2.09), and all-cause death (aHR 2.06, 95% CI: 1.63–2.61), compared with those without any CKM condition.

Table 2
Risk of outcomes according to numbers of CKM conditions

Outcome	Events(%)	HR(95%CI)	Uni.P	aHR(95%CI)	Multi.P	p for trend
Primary composite endpoint						< 0.001
0 CKM (HF only)	394 (18%)	Ref	Ref	Ref	Ref	
1 CKM	671 (24%)	1.33 (1.18–1.51)	< 0.001	1.22 (1.07–1.38)	0.003	
2 CKM	557 (27%)	1.60 (1.40–1.82)	< 0.001	1.39 (1.21–1.60)	< 0.001	
3 CKM	242 (34%)	2.06 (1.76–2.42)	< 0.001	1.73 (1.45–2.07)	< 0.001	
CV death						0.004
0 CKM (HF only)	148 (6.9%)	Ref	Ref	Ref	Ref	
1 CKM	295 (10%)	1.54 (1.26–1.88)	< 0.001	1.27 (1.04–1.56)	0.02	
2 CKM	235 (12%)	1.73 (1.41–2.13)	< 0.001	1.32 (1.06–1.66)	0.015	
3 CKM	106 (15%)	2.26 (1.77–2.90)	< 0.001	1.66 (1.26–2.18)	< 0.001	
HF Hospitalization						< 0.001
0 CKM (HF only)	261 (12%)	Ref	Ref	Ref	Ref	
1 CKM	414 (15%)	1.22 (1.04–1.42)	0.013	1.17 (1.00-1.38)	0.048	
2 CKM	362 (18%)	1.53 (1.30–1.79)	< 0.001	1.44 (1.21–1.71)	< 0.001	
3 CKM	147 (21%)	1.81 (1.48–2.22)	< 0.001	1.67 (1.33–2.09)	< 0.001	
All-cause death						< 0.001
0 CKM (HF only)	175 (8.1%)	Ref	Ref	Ref	Ref	

Univariable and multivariable analysis of outcomes according to numbers of CKM conditions. The reference (Ref) is no CKM. Multivariable analysis was adjusted for age, sex, ethnicity, NYHA class, hypertension, AF, malignancies, COPD, infections, anemia, revascularization, dialysis, and medications prescribed at discharge (diuretics, ACEI/ARB/ARNI, beta-receptor blocker, MRA, SGLT2i, digoxin). Cox regression models were used to assess all-cause mortality, while competing risks models were employed for the primary composite outcome, cardiovascular death, and heart failure hospitalization.

Abbreviations: CV: cardiovascular; HF: heart failure; CI, confidence interval; HR, Hazard Ratio; aHR, adjusted Hazard Ratio.

Outcome	Events(%)	HR(95%CI)	Uni.P	aHR(95%CI)	Multi.P	p for trend
1 CKM	372 (13%)	1.66 (1.38–1.98)	< 0.001	1.30 (1.08–1.57)	0.005	
2 CKM	355 (18%)	2.26 (1.89–2.71)	< 0.001	1.60 (1.32–1.95)	< 0.001	
3 CKM	164 (23%)	3.07 (2.48–3.80)	< 0.001	2.06 (1.63–2.61)	< 0.001	

Univariable and multivariable analysis of outcomes according to numbers of CKM conditions. The reference (Ref) is no CKM. Multivariable analysis was adjusted for age, sex, ethnicity, NYHA class, hypertension, AF, malignancies, COPD, infections, anemia, revascularization, dialysis, and medications prescribed at discharge (diuretics, ACEI/ARB/ARNI, beta-receptor blocker, MRA, SGLT2i, digoxin). Cox regression models were used to assess all-cause mortality, while competing risks models were employed for the primary composite outcome, cardiovascular death, and heart failure hospitalization.

Abbreviations: CV: cardiovascular; HF: heart failure; CI, confidence interval; HR, Hazard Ratio; aHR, adjusted Hazard Ratio.

3.2.2 Association between the type of CKM overlap and clinical outcomes

- When grouped by the type of CKM overlap, significant differences in the risk of clinical outcomes were observed across groups. Among patients with only one CKM condition, those with CKD had the highest risk of 1-year primary composite endpoint events (aHR: 1.34, 95% CI: 1.16–1.54). This risk exceeded that in patients with ASCVD alone or T2D alone. Among patients with two CKM conditions, those with CKD + T2D had a higher risk of 1-year primary composite endpoint events (aHR: 1.45, 95% CI: 1.21–1.74) than those with ASCVD + CKD (aHR: 1.40, 95% CI: 1.18–1.66) or ASCVD + T2D (aHR: 1.27, 95% CI: 1.00–1.61) (Table 3). Similar patterns were observed for 1-year cardiovascular death, all-cause death, and HF hospitalization.

Table 3
Rate of outcome stratified by type of CKM overlap

Outcome	None (HF only) (n = 2157)	ASCVD only (n = 753)	CKD only (n = 1552)	T2D only (n = 541)	ASCVD + CKD (n = 864)	ASCVD+T2D (n = 421)	CKD+T2D (n = 742)	ASCVD+ CKD+T2D (n = 709)
Primary composite endpoint								
Events(%)	394 (18%)	142 (19%)	434 (28%)	95 (18%)	261 (30%)	87 (21%)	209 (28%)	242 (34%)
HR(95%CI)	Ref	1.04 (0.86–1.26)	1.63 (1.42–1.86)	0.96 (0.77–1.2)	1.78 (1.52–2.08)	1.15 (0.91–1.45)	1.66 (1.4–1.96)	2.06 (1.76–2.42)
Uni.P	Ref	0.7	< 0.001	0.72	< 0.001	0.24	< 0.001	< 0.001
aHR(95%CI)	Ref	1.05 (0.86–1.28)	1.34 (1.16–1.54)	1.07 (0.85–1.34)	1.40 (1.18–1.66)	1.27 (1-1.61)	1.45 (1.21–1.74)	1.75 (1.46–2.09)
Multi.P	Ref	0.65	< 0.001	0.57	< 0.001	0.05	< 0.001	< 0.001
CV death								
Events(%)	148 (6.9%)	53 (7.0%)	209 (13%)	33 (6.1%)	118 (14%)	29 (6.9%)	88 (12%)	106 (15%)
HR(95%CI)	Ref	1.02 (0.75–1.4)	2.04 (1.65–2.52)	0.88 (0.61–1.29)	2.06 (1.62–2.62)	1 (0.67–1.5)	1.78 (1.37–2.32)	2.26 (1.77–2.9)
Uni.P	Ref	0.88	< 0.001	0.52	< 0.001	0.98	< 0.001	< 0.001
aHR(95%CI)	Ref	0.95 (0.69–1.3)	1.45 (1.17–1.81)	1.08 (0.73–1.58)	1.33 (1.02–1.73)	1.14 (0.76–1.71)	1.42 (1.07–1.89)	1.67 (1.27–2.2)
Multi.P	Ref	0.75	< 0.001	0.7	0.037	0.51	0.016	< 0.001
HF Hospitalization								
Events(%)	261 (12%)	101 (13%)	248 (16%)	65 (12%)	164 (19%)	63 (15%)	135 (18%)	147 (21%)

Univariable and multivariable analysis of outcomes according to numbers of CKM conditions. The reference (Ref) is no CKM. Multivariable analysis was adjusted for age, sex, ethnicity, NYHA class, hypertension, AF, malignancies, COPD, infections, anemia, revascularization, dialysis, and medications prescribed at discharge (diuretics, ACEI/ARB/ARNI, beta-receptor blocker, MRA, SGLT2i, digoxin). Cox regression models were used to assess all-cause mortality, while competing risks models were employed for the primary composite outcome, cardiovascular death, and heart failure hospitalization.

Outcome	None (HF only) (n = 2157)	ASCVD only (n = 753)	CKD only (n = 1552)	T2D only (n = 541)	ASCVD + CKD (n = 864)	ASCVD+T2D (n = 421)	CKD+T2D (n = 742)	ASCVD+ CKD+T2D (n = 709)
HR(95%CI)	Ref	1.12 (0.89–1.41)	1.34 (1.13–1.6)	0.99 (0.76–1.31)	1.63 (1.34–1.98)	1.26 (0.96–1.66)	1.57 (1.27–1.93)	1.81 (1.48–2.22)
Uni.P	Ref	0.33	< 0.001	0.97	< 0.001	0.1	< 0.001	< 0.001
aHR(95%CI)	Ref	1.19 (0.94–1.5)	1.22 (1.02–1.46)	1.03 (0.78–1.35)	1.5 (1.21–1.84)	1.32 (1-1.75)	1.46 (1.17–1.82)	1.68 (1.34–2.1)
Multi.P	Ref	0.16	0.027	0.86	< 0.001	0.053	< 0.001	< 0.001
All-cause death								
Events(%)	175 (8.1%)	70 (9.3%)	257 (17%)	45 (8.3%)	178 (21%)	41 (9.7%)	136 (18%)	164 (23%)
HR(95%CI)	Ref	1.15 (0.87–1.52)	2.14 (1.77–2.6)	1.02 (0.74–1.42)	2.69 (2.19–3.32)	1.21 (0.86–1.7)	2.39 (1.91–2.99)	3.07 (2.48–3.8)
Uni.P	Ref	0.319	< 0.001	0.893	< 0.001	0.279	< 0.001	< 0.001
aHR(95%CI)	Ref	1.03 (0.77–1.36)	1.44 (1.18–1.76)	1.21 (0.87–1.69)	1.62 (1.3–2.03)	1.3 (0.92–1.84)	1.73 (1.36–2.2)	2.09 (1.65–2.64)
Multi.P	Ref	0.853	< 0.001	0.259	< 0.001	0.14	< 0.001	< 0.001

Univariable and multivariable analysis of outcomes according to numbers of CKM conditions. The reference (Ref) is no CKM. Multivariable analysis was adjusted for age, sex, ethnicity, NYHA class, hypertension, AF, malignancies, COPD, infections, anemia, revascularization, dialysis, and medications prescribed at discharge (diuretics, ACEI/ARB/ARNI, beta-receptor blocker, MRA, SGLT2i, digoxin). Cox regression models were used to assess all-cause mortality, while competing risks models were employed for the primary composite outcome, cardiovascular death, and heart failure hospitalization.

3.3 Outcomes of LVEF phenotypes across CKM conditions

- In patients with HFrEF/HFmrEF, a higher CKM condition count was associated with progressively worse outcomes (p for trend < 0.05). In HFpEF patients, the trends for most endpoints paralleled those in HFrEF/HFmrEF, except for HF hospitalisation (p for trend = 0.920). Subgroup analyses suggested that the link between three overlapping CKM conditions and 1-year cardiovascular death was stronger in HFrEF patients (aHR: 2.08, 95% CI: 1.36–3.18) and HFmrEF patients (aHR: 2.14, 95% CI: 1.16–3.97), compared with patients with HFpEF (p for interaction = 0.028). However, no significant differences were observed across HF phenotype subgroups regarding the strength of associations between CKM conditions and the primary endpoint, HF hospitalisation, and all-cause death (Supplemental Figure S1).

3.4 Correlation between CKM burden and GDMT response

3.4.1 CKM burden and clinical outcomes: a comparison of quadruple versus non-quadruple GDMT

- Among patients not receiving quadruple GDMT, a significant association was observed between cumulative CKM burden and the risk of 1-year primary composite outcome, cardiovascular death, and HF hospitalization (all p for trend < 0.05). However, the risk gradients for the primary composite endpoint, cardiovascular death and HF hospitalization were attenuated among those on optimal quadruple therapy (all p for trend > 0.05). Nevertheless, even in the setting of quadruple GDMT, the presence of three CKM conditions was associated with a 1.76-fold increased risk of all-cause death compared with baseline. The interaction between CKM burden and quadruple therapy status on the primary composite endpoint was of borderline statistical significance (p for interaction = 0.075) (Fig. 3).

3.4.2 The magnitude of GDMT benefit across different levels of CKM burden

- As shown in Table 4, intensified GDMT provided prognostic protection across multiple CKM burden. Among patients with two CKM conditions, treatment with ≥ 3 GDMT classes was associated with a 19% reduction in the primary composite endpoint (aHR 0.81, 95% CI 0.68–0.98), driven by a 41% lower risk of cardiovascular death and a 33% lower risk of all-cause death. The survival benefit was further amplified with quadruple GDMT, yielding a 31% risk reduction for the primary endpoint (aHR 0.69, 95% CI 0.52–0.91), along with 62% and 51% reductions in cardiovascular and all-cause death, respectively. However, the benefit of quadruple therapy did not reach statistical significance in patients with three coexisting CKM conditions. Incremental GDMT intensification conferred only modest risk reduction in patients with none or one CKM condition. For HF hospitalization, neither triple nor quadruple GDMT demonstrated significant benefit. Interaction analyses indicated no significant heterogeneity in the treatment effects of GDMT across CKM burden for any clinical endpoint.

Table 4
Benefit of combination GDMT stratified by CKM burden

Outcome	0 CKM (HF only)	1 CKM	2 CKM	3 CKM	p for interaction
	HR or SHR (95%CI)	HR or SHR (95%CI)	HR or SHR (95%CI)	HR or SHR (95%CI)	
Primary composite endpoint					
GDMT ≥ 3 (yes vs. no)	0.89 (0.71–1.12)	0.86 (0.72–1.02)	0.81 (0.68–0.98)	0.82 (0.62–1.08)	0.630
GDMT = 4 (yes vs. no)	0.97 (0.72–1.32)	0.93 (0.73–1.20)	0.69 (0.52–0.91)	0.71 (0.49–1.03)	0.075
CV death					
GDMT ≥ 3 (yes vs. no)	0.82 (0.56–1.19)	0.59 (0.45–0.78)	0.59 (0.44–0.79)	0.68 (0.45–1.05)	0.330
GDMT = 4 (yes vs. no)	0.52 (0.27–1.01)	0.68 (0.44–1.06)	0.38 (0.22–0.65)	0.81 (0.47–1.40)	0.150
HF Hospitalization					
GDMT ≥ 3 (yes vs. no)	0.85 (0.65–1.12)	1.15 (0.93–1.42)	1.07 (0.85–1.34)	1.00 (0.69–1.44)	0.930
GDMT = 4 (yes vs. no)	1.13 (0.80–1.61)	1.06 (0.79–1.43)	1.06 (0.78–1.45)	0.76 (0.47–1.21)	0.120
All-cause death					
GDMT ≥ 3 (yes vs. no)	0.80 (0.57–1.11)	0.64 (0.50–0.81)	0.67 (0.53–0.85)	0.64 (0.45–0.90)	0.743
GDMT = 4 (yes vs. no)	0.55 (0.30–1.01)	0.75 (0.51–1.10)	0.49 (0.33–0.74)	0.87 (0.57–1.34)	0.170
Adjusted for age, sex, ethnicity, NYHA class, hypertension, AF, malignancies, COPD, infections, anemia, revascularization, dialysis, and medications prescribed at discharge (diuretics, ACEI/ARB/ARNI, beta-receptor blocker, MRA, SGLT2i, digoxin).					
Abbreviations: SHR, Subdistribution Hazard Ratio.					

4. Discussion

Based on the GREAT study, this investigation represents a real-world analysis of HF patients from an economically underdeveloped, multi-ethnic border region in China. CKM multimorbidity was highly prevalent in HF patients, and a higher CKM burden was associated with a stepwise increase in the 1-year risks of adverse clinical outcomes. The association between CKM burden and cardiovascular death was significantly stronger in patients with HFrEF or HFmrEF than in those with HFpEF. Notably, the CKM-associated risk gradient for 1-year outcomes was attenuated by optimal quadruple GDMT. Although GDMT benefit did not show significant heterogeneity across CKM strata, the strongest signal was seen in patients with two CKM conditions.

Driven by a series of shared risk factors and pathogenic pathways, patients with HF frequently present with overlapping CKM conditions[13]. The prevalence of CKM multimorbidity in our cohort (72.1%) was similar to that reported in the PEACE 5p-HF study from Fuwai Hospital in China, but slightly lower than post-hoc analyses of several European and US HF studies[4, 5, 7].A previous global cohort study (REPORT-HF) similarly found that multimorbidity in acute HF was less common in low-income than in high-income countries[14]. Limited healthcare access, lower physician exposure, and resource-poor environments likely contribute to this disparity[15]. In our study, as the number of overlapping CKM conditions increased, the risks of 1-year cardiovascular death, HF hospitalization, and all-cause death progressively increased. Compared with patients with HF alone, those with the quadruple combination of HF, ASCVD, CKD, and T2D had a nearly 2-fold higher risk of cardiovascular death and a more than 2-fold higher risk of all-cause mortality. This finding further supports the predictive stratification capability of the number of CKM conditions for adverse outcomes, as observed in previous studies[16, 17]. Our findings provide complementary evidence to predominantly urban or northern Chinese data and extend the important geographic scope of global CKM literature. For LMICs facing similar resource constraints, our data offer a more relevant benchmark than studies from high-income settings.

In our analysis, CKD alone or with T2D conferred the highest risk at equivalent CKM burden. This finding is consistent with the PEACE 5p-HF study[5] and highlights kidney-heart crosstalk in HF progression[18]. Moderate-to-severe renal impairment is an independent predictor of mortality in HF patients[19]. CKD accelerates HF deterioration through volume overload, uremic toxins, and neurohormonal activation[20]. Conversely, HF can induce cardiorenal syndrome, thereby creating a vicious cycle[21]. Overlapping T2D further amplifies risk via multiple pathways[22]. Importantly, CKD patients often cannot tolerate full GDMT due to hyperkalemia or low eGFR[23] and are less likely to receive SGLT2 inhibitors despite clear indications[22]. These observations suggest that the kidney lies at the core of CKM syndrome, and preserving renal function may improve outcomes. Additionally, we observed that the association between CKM burden and cardiovascular death was stronger in HFrEF/HFmrEF than in HFpEF. This may reflect greater neurohormonal activation in HFrEF. Coexisting CKM conditions further amplify this effect[24]. Alternatively, HFpEF patients often have a higher burden of non-cardiovascular comorbidities, and the competing risk of non-cardiovascular death dilutes the occurrence of cardiovascular events[25]. Our results align with previous studies and imply that HFrEF/HFmrEF patients with high CKM burden may require more aggressive multi-targeted therapy[26].

To our knowledge, this is the first study to use prospective cohort data to assess the interaction of CKM burden and GDMT intensity on clinical outcomes in HF. Prior studies have shown that HF patients with metabolic derangements gain the most survival benefit from optimised quadruple GDMT[27]. In our cohort, quadruple GDMT attenuated the adverse prognostic gradient imposed by CKM burden. Quadruple GDMT confers synergistic cardioprotection through neurohormonal suppression, metabolic optimisation, and anti-inflammatory[28]. However, residual excess mortality remained in patients with three CKM components despite quadruple therapy. Stratified analyses revealed the largest benefit in patients with two CKM comorbidities. Patients with none or three components showed no significant benefit. These findings suggest that moderate CKM burden may be the optimal therapeutic window. Multi-domain metabolic disturbances induce polypharmacological resistance, limiting GDMT efficacy in high-burden patients, consistent with prior

real-world cohort study that higher comorbidity burden attenuates GDMT's survival advantage[23, 29]. Our findings align with the 2026 ACC CKM Guideline, which prioritises quadruple GDMT for intermediate-burden patients and recommends adjunctive metabolic modulators for high-burden cases[30]. Notably, the interaction between CKM burden and GDMT did not reach statistical significance for any endpoint. Therefore, subgroup differences require validation in larger cohorts. Our findings provide real-world evidence for individualised HF pharmacotherapy under the CKM staging framework.

Limitations

Our study has several limitations. First, T2D was diagnosed without fasting or random glucose levels, and a single HbA1c measurement may overestimate prevalence. Second, ASCVD was defined as a composite of several conditions, which may obscure the differential impact of individual vascular diseases. Third, the prospective design precludes causal inference, and unmeasured confounding may remain despite extensive adjustment. Fourth, patients who declined participation had more severe illness, potentially leading to underestimation of adverse outcomes. Fifth, the small sample size in the three-CKM subgroup (n = 709) warrants cautious interpretation of null findings. Sixth, our sample was drawn exclusively from Guangxi, an underdeveloped border region in southwestern China; geographic specificity may limit generalizability to other HF populations, although it provides valuable data for LMICs with similar demographic and economic profiles.

5. Conclusions

In this real-world cohort of > 7,000 HF patients from an underdeveloped Chinese region, CKM multimorbidity was common and associated with a stepwise increase in adverse outcomes. Quadruple GDMT attenuated the CKM-related prognostic risk gradient, with the greatest relative benefit in patients with two CKM conditions. These findings support routine CKM assessment, burden-stratified GDMT strategies, and the need for implementation of individualized treatment strategies.

Abbreviations

HF
Heart failure
CKM
Cardiovascular-kidney-metabolic
GDMT
Guideline-directed medical therapy
ASCVD
Atherosclerotic cardiovascular disease
CKD
Chronic kidney disease
T2D
Type 2 diabetes
LMICs
Low- and middle-income countries

LVEF
Left ventricular ejection fraction
HFpEF/HFmrEF/HFrEF
Heart failure with preserved/mildly reduced/reduced ejection fraction

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the People's Hospital of Guangxi Zhuang Autonomous Region as well as the ethics committees of all participating hospitals (in October 2020; approval number KY-DZX-202006). Written informed consent was obtained from all participants.

Consent for publication

All patient data were anonymized, and no personally identifiable information was accessible or shared. Therefore, informed consent was not required.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to institutional data use agreements, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Natural Science Foundation of China (82260060, 82370439,and 82560060) and Guangxi Science and Technology Base and Special Talents' Project (GK AD17129026).

Authors' contributions

HL, WC, and HS designed and conducted the study, performed data analysis, Writing – original draft, and obtained the funding. ML, HZ, YS, and QL performed data analysis and visualization. YZ, HL, CG, YL, DW, ST, QG, CZ, CL, and CL collected the data. QJ and YZ were responsible for project administration, supervision, and writing – review & editing. All authors read and approved the final version of the manuscript.

Acknowledgments

We thank all the patients and researchers who contributed to every stage of this study.

Clinical trial number: not applicable.

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Figures

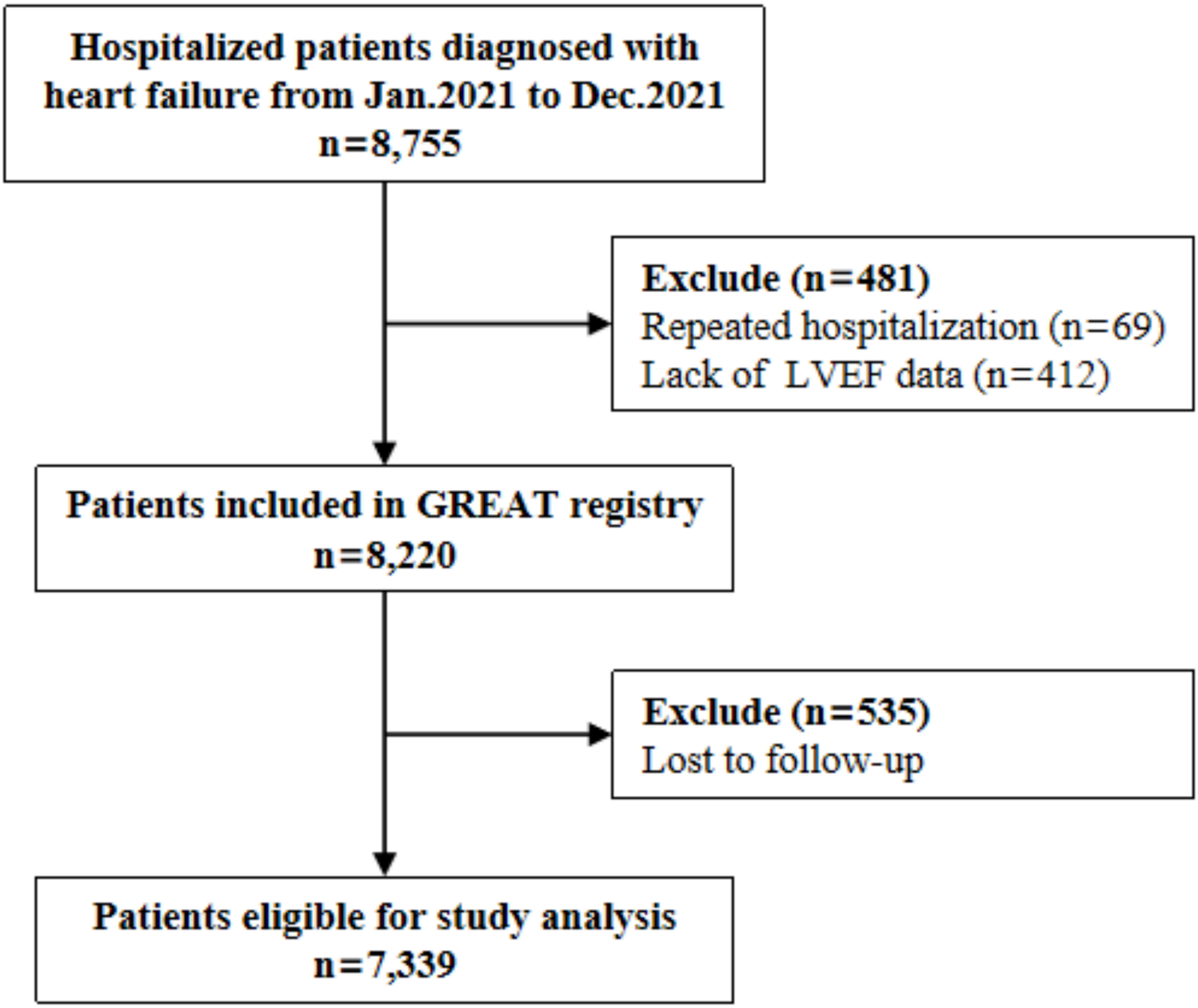


Figure 1

Flow chart of study population inclusion and exclusion.

Abbreviations: GREAT, conGestive heaRt failurE registry of diAgnosis and Therapy in Guangxi, China; LVEF: left ventricular ejection fraction.

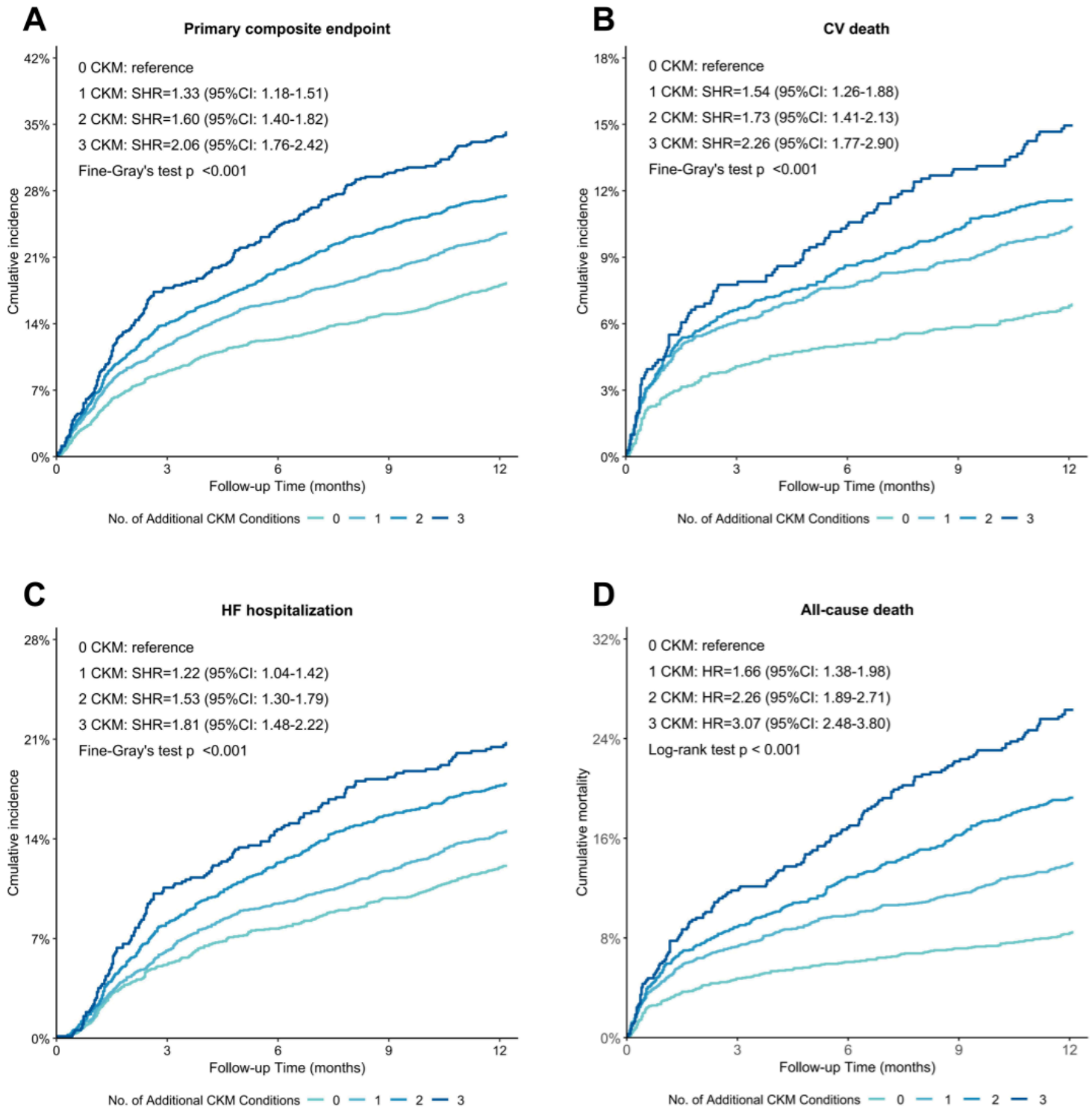


Figure 2

1-year outcomes according to numbers of CKM conditions.

(A) Primary composite endpoint, (B) CV death, (C) HF hospitalization, (D) all-cause death.

Abbreviations: CKM, cardiovascular-kidney-metabolic disease; CV, cardiovascular; HF: heart failure.

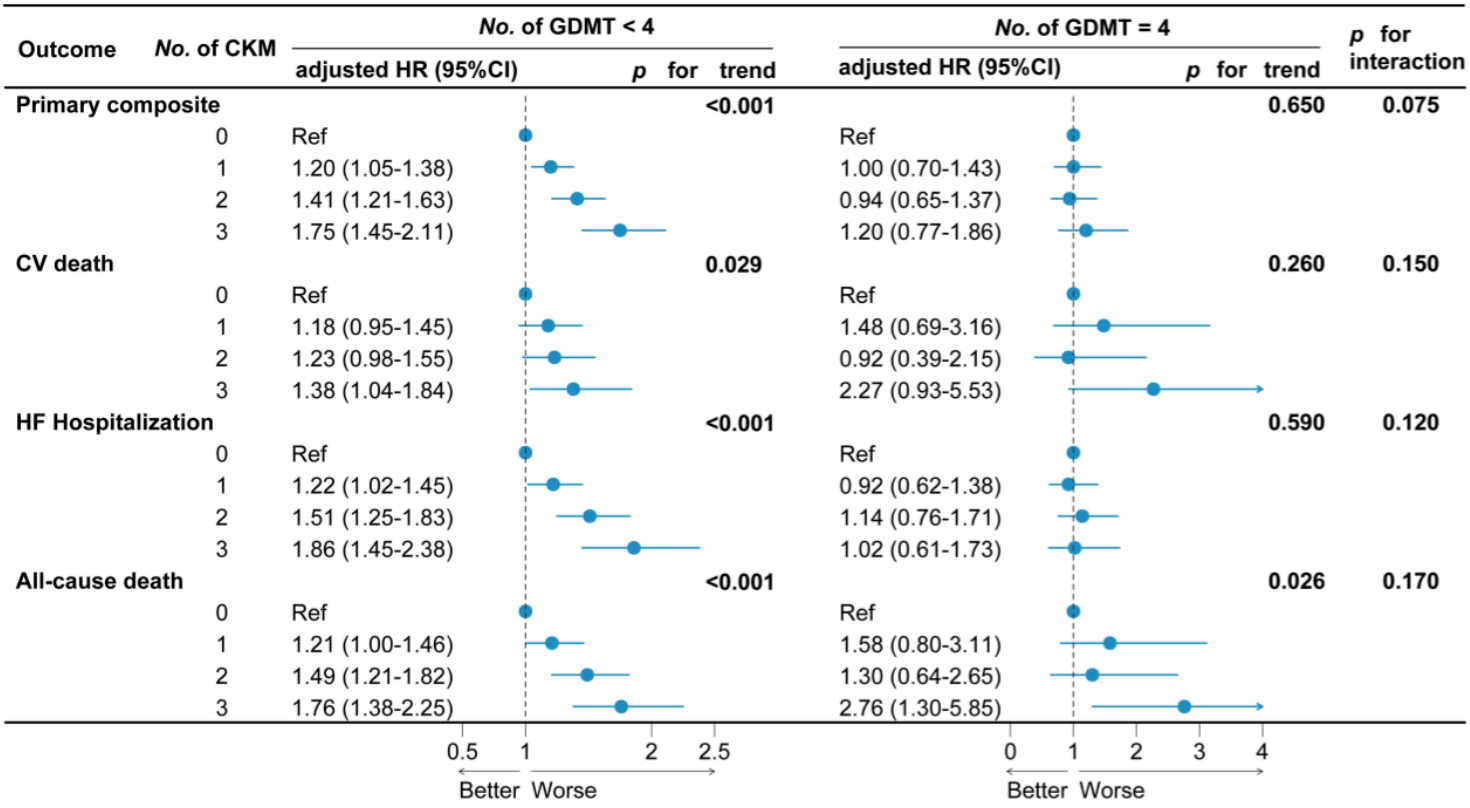


Figure 3

Association of CKM burden with clinical outcomes on quadruple GDMT.

Models were adjusted for age, sex, ethnicity, NYHA class, hypertension, AF, malignancies, COPD, infections, anemia, revascularization, dialysis, and medications prescribed at discharge (diuretics, ACEI/ARB/ARNI, beta-receptor blocker, MRA, SGLT2i, digoxin).

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