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ORIGINAL RESEARCH

Impact of Comorbidity Clusters on Quality of Life in Chronic Heart Failure

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Purpose: Grouping comorbidities can better reflect the intrinsic relationships among complications. We aimed to explore the relationships between comorbidity groups and dynamic changes in health-related quality of life (HRQoL) in patients with chronic heart failure (CHF).

Patients and Methods: A total of 1533 patients with CHF were included. Demographic and clinical variables were recorded during hospitalization. HRQoL was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline and at 3 and 12 months. Latent class analysis was used to identify comorbidity groups among patients with CHF. This method identifies latent subgroups by analyzing patterns in their comorbidities. Repeated-measures analysis of variance (ANOVA) was used to assess the relationships between comorbidity groups and dynamic changes in KCCQ scores.

Results: Three comorbidity clusters were identified: the young/valvular heart disease (VHD) group, the elderly/coronary heart disease (CHD) group, and the high-comorbidity burden group. The young group had a relatively lower comorbidity burden and the best HRQoL, followed by the elderly/CHD group, while the high-comorbidity burden group showed the worst HRQoL. The overall summary scores, clinical summary scores, social limitations, physical limitations, and self-efficacy were significantly highest in the high-comorbidity burden group. In addition, at 3 months the symptom scores had decreased in all three groups. Repeated-measures ANOVA showed that the comorbidity groups were significantly associated with dynamic changes in HRQoL through time and group effects.

Conclusion: There were significant differences in the baseline characteristics and dynamic changes of HRQoL among different comorbidity clusters. Patients in the high-comorbidity burden group performed the worst in terms of quality of life, but the improvement was the most significant.

Keywords: chronic heart failure, comorbidities, latent class analysis, health-related quality of life, Kansas City Cardiomyopathy Questionnaire

Introduction

Chronic heart failure (CHF) is often considered a final, serious stage in the progression of cardiovascular disease. It imposes a substantial socioeconomic burden and is associated with complex clinical presentations, high readmission and mortality rates,[1,2] all of which seriously affect patients' health-related quality of life (HRQoL).[3,4] Studies have shown that the HRQoL is poorer in patients with CHF than in those with other chronic diseases.[5,6] In recent years, therapeutic advances have led to declining rates of readmission and mortality in patients with CHF; however, the HRQoL in these patients remains poor.[7] Therefore, adequate evaluation and further improvement of the HRQoL status are crucial for the management of patients with CHF.[8]

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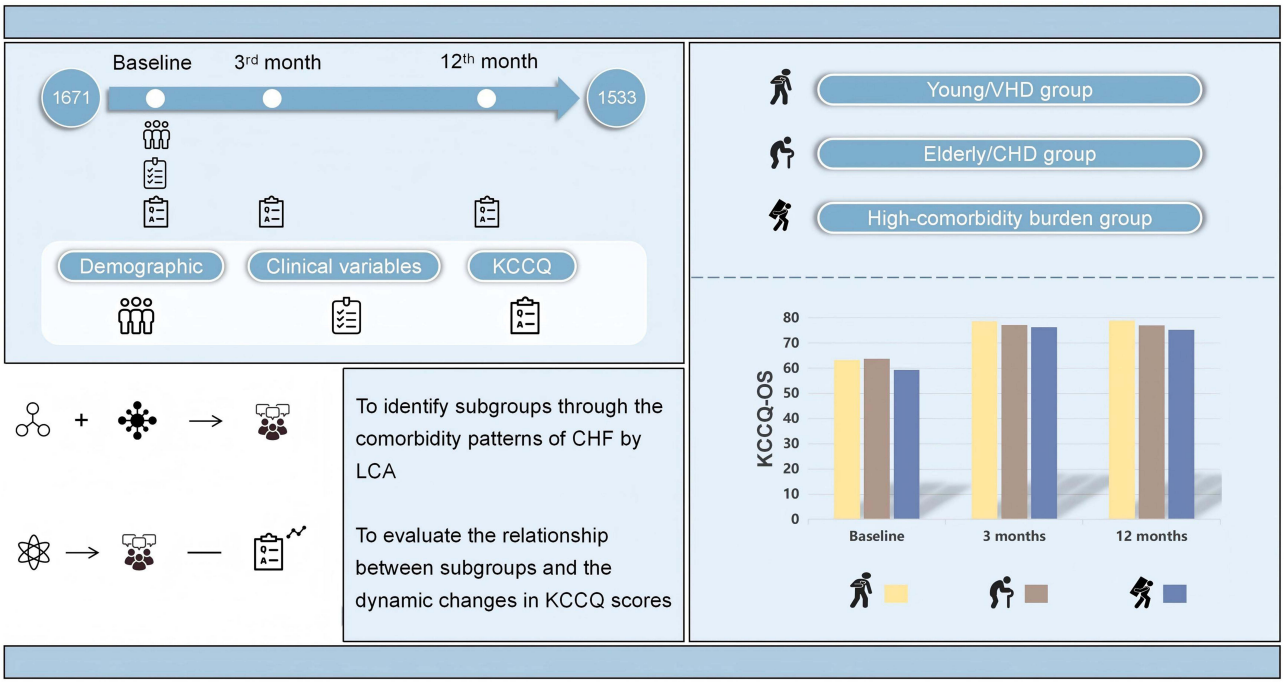
Graphical Abstract



Patients with CHF often present with multiple comorbidities.[9] Further studies have confirmed that patients with CHF and with a higher burden of comorbidities have worse HRQoL.[10–12] Moreover, effective management of comorbidities can improve HRQoL in patients with CHF.[5] Therefore, clarifying the relationship between comorbidities and HRQoL is essential for determining and applying individualized treatments at discharge approaches in patients with CHF.[11] Recent studies on multiple comorbidities have used the Charlson Comorbidity Index and self-reported comorbidities for assessment.[13] However, the multiple comorbidities in the above studies were contingent and did not reflect the internal connection of comorbidities caused by a certain disease or aetiology.[14] Grouping methods can solve this problem by automatically identifying patient comorbidities and classifying them into meaningful subgroups.[15] Moreover, a few studies using comorbidity groups only assessed the baseline HRQoL in patients with CHF without analyzing its changes.[12,16] However, HRQoL changes dynamically with the course of CHF, and longitudinal data can better reflect the actual state of patients[17] and provide a more accurate assessment of HRQoL than cross-sectional data.[18]

Latent Class Analysis (LCA) is a technique used to explore the latent categorical variables behind observed categorical variables that exhibit statistical associations. LCA can handle multiple indicators simultaneously and can be used to analyse the data by integrating information from all indicators.[19] In this study, we used the grouping methods of LCA to identify comorbidity groups among patients with CHF, collected data through the Kansas City Cardiomyopathy Questionnaire (KCCQ) to reflect dynamic changes in HRQoL, and analysed the relationships between the comorbidity groups and dynamic changes in HRQoL. This study aimed to identify distinct comorbidity clusters, which may inform personalized management strategies to improve HRQoL in patients with CHF. This study aimed to identify distinct comorbidity clusters, which may inform personalized management strategies to improve HRQoL in patients with CHF.

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Materials and Methods

Participants

This was a longitudinal study reported in accordance with the STROBE statement [see Supplementary file STROBE]. Patients diagnosed with CHF at three medical centres in the Shanxi Province of the People's Republic of China were enrolled between November 2017 and October 2021. The inclusion criteria were 1) patients diagnosed with CHF according to the guidelines of the European Society of Cardiology,[20] and 2) classified as functional classes II–IV according to the New York Heart Association (NYHA).[20] Patients who had suffered acute cardiovascular events 2 months before enrolment or who were unable to complete the questionnaire due to intellectual disabilities were excluded. The study was conducted following the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Shanxi Medical University. All patients provided informed consent before enrolment.

Procedure

Demographic information and clinical variables were assessed during hospitalization to provide baseline data. Data on KCCQ scores were collected during hospitalization and at 3 and 12 months after discharge through face-to-face consultations or over the phone. To ensure quality, professionally trained individuals entered all the data into the EpiData system.

Measures

Demographic and Clinical Variables

Demographic information, including age, sex, body mass index (BMI), occupation, smoking history, alcohol history, and health insurance status, was collected through questionnaires. We devised a case history form to record the clinical variables, which included blood pressure, heart rate, NYHA class, left ventricular ejection fraction, laboratory findings, severe comorbidities, and patients' medication and surgical treatments at discharge.

Patients' medications included platelet aggregation inhibitors, statins, nitrates, beta-blockers, aldosterone blockers, cardiotonics, diuretics, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Surgical treatments at discharges included percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Comorbidity Definitions

According to the 2021 ESC of Cardiology guidelines for the diagnosis and treatment at discharge of acute and chronic heart failure,[7] this study included 11 comorbidities, namely atrial fibrillation (AF), coronary heart disease (CHD), hypertension, valvular heart disease (VHD), diabetes, stroke, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), hyperlipidemia, obesity, and cancer.

The definitions of comorbidities in the Asian Sudden Cardiac Death in Heart Failure registry have been previously described.[16,21,22] AF was defined as a medical history of AF or the observation of AF on electrocardiogram. CHD was defined as the angiographically documented presence of significant coronary obstruction, history of myocardial infarction, or previous revascularization. Hypertension was defined as having a clinical diagnosis (blood pressure ≥140/90 mmHg) or being treated for hypertension. Diabetes was defined as a clinical diagnosis (fasting plasma glucose ≥7 mmol/L or random plasma glucose ≥11.1 mmol/L or glycated haemoglobin ≥6.5%) or being treated for diabetes. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation,[23] and CKD was defined as eGFR <60 mL/min/1.73 m^2. Obesity was defined based on the standard BMI cut-off defined by the World Health Organization (≥30 kg/m^2). The occurrence of VHD, stroke, COPD, hyperlipidemia, and cancer were identified based on medical record data.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ-23 is a patient-reported outcome scale that measures HRQoL in patients with CHF.[24] The questionnaire used in this study covered six domains, namely physical limitations, symptom stability, symptom scores, self-efficacy scores,

quality of life scores, and social limitations. Two summary scores were calculated from these domains, namely a clinical summary score (KCCQ-CS) of physical limitations and symptom scores and an overall summary score (KCCQ-OS) of the sum of physical limitations, symptom scores, quality of life, and social limitations. The scores for each domain and the summary scores of the KCCQ were transformed to a range of 0–100, with higher scores reflecting better HRQoL. The mean score difference (MD) was used to calculate the change in scores for each group at baseline and 3 and 12 months.

Statistical Analysis

The Epidata 3.1 software was used to input data from the electronic medical records of patients with CHF. Quantitative data are expressed as mean (standard deviation, SD) when normally distributed and were compared using one-way analysis of variance (ANOVA); when not normally distributed, they are presented as median (interquartile range, IQR) and compared using the Kruskal–Wallis *H*-test. Qualitative data are expressed as numbers (percentages), and comparisons between groups were performed using the chi-square test or the Wilcoxon signed-rank test. A value of $P<0.05$ was considered statistically significant.

The comorbidity variables AF, CHD, hypertension, VHD, diabetes, stroke, CKD, COPD, hyperlipidaemia, obesity, and cancer were analysed using LCA. LCA is a robust probabilistic modelling algorithm that allows for data grouping and statistical inference.[25,26] This algorithm can simultaneously process multiple indicators and classify patients into groups.[22] The main information criteria for evaluating the LCA model were the Akaike information criterion (AIC), Bayesian information criterion (BIC), sample size-adjusted Bayes information criterion (aBIC), entropy, Lo-Mendell-Rubin test (LMRT), and bootstrapped likelihood ratio test (BLRT). Smaller AIC, BIC, and aBIC estimates indicate a better fit of the model.[26] The entropy ranged from 0 to 1. In general, entropy was above 0.7, indicating a sufficiently good model fit.[10] The LMRT and BLRT compare the latent class model (k) to a model with one less class (k - 1), and a $P < 0.05$ indicates that the current model works better than the model with one less class. This study determined the optimal number of groups based on the statistical fit criteria and clinical interpretability of the results. Moreover, we drew a group using petal maps to visually depict the complications in each group.

In this study, clinical characteristics at baseline and KCCQ scores were compared between comorbidity groups of patients with CHF using the chi-square test, the Student-Newman-Keuls test, and the Kruskal–Wallis *H*-test. $P < 0.05$ was considered statistically significant.

A repeated-measures ANOVA model was used to analyse KCCQ score changes at each time point during the patient follow-up. The KCCQ data at baseline and at 3 and 12 months of follow-up were included. A repeated-measures ANOVA model was used to assess the differences in comorbidity groups, six domains, and two total KCCQ scores at the three time points.

All statistical analyses and comparisons between groups were performed using R 4.5.1 software (www.r-project.org). Missing data were filled in using the missForest package in R software, version 4.5.1, a multiple scheme based on a random forest model.[27] The LCA models were constructed using Mplus version 8.3.[10] Tableau software was used to construct the petal maps.

Latent Class Analysis and Group Descriptions

To identify clinically meaningful subgroups, we employed latent class analysis (LCA). This model-based technique classifies individuals based on their model-derived posterior membership probabilities. The optimal number of classes was selected by jointly evaluating statistical fit indices and clinical interpretability, after which each patient was assigned to their most probable latent class.[28] Unlike crude classifications based solely on disease counts, LCA simultaneously analyzes patterns across all comorbidities to identify subgroups defined by holistic clinical profiles. This approach seeks to uncover latent subgroups that reflect shared underlying pathophysiology, thereby enhancing the clinical relevance of the derived clusters.[29] The final classes were interpreted and named according to their unique comorbidity probability profiles and distinguishing clinical characteristics.

Results

Baseline Characteristics

A total of 1671 patients were included at baseline. During follow-up, 138 patients were lost to follow-up owing to death (n=82) and for individual reasons (n=56), which included refusal of follow-up visits and the inability to reach the patients on the phone, resulting in a partial loss of follow-up data. A total of 1533 patients were included in this study. The flow diagram is shown in Figure 1. Patients' mean age was 69.2 (SD = 14.8) years; among them, 882 (57.5%) were men. Hypertension (70.5%) and hyperlipidaemia (63.8%) were the most common comorbidities, followed by valvular heart disease (VHD)(52.8%) and AF (40.3%).

Comorbidity Groups Analysis

The fitting statistics of the LCA models for Categories 1–6 are shown in Supplementary Table S1. The results showed that the AIC, BIC, and aBIC of the three classifications were small, with entropy closest to 1. Combined with clinical interpretability, these were identified as the best comorbidity groups.

Table 1 shows the characteristics of patients in each cluster, and the comorbidity variables used in the LCA showed high discrimination between clusters ($P<0.01$). According to the characteristics of the patients in each group, they could be divided into the young/VHD, elderly/coronary heart disease (CHD), and high-comorbidity burden groups. In the young/VHD group (Group 1, Figure 2A), patients were the youngest (63.9 years, SD = 15.9) and had the highest prevalence of VHD (70.3%). In the elderly/CHD group (Group 2, Figure 2B), patients were the oldest (74.2 years, SD = 11.8) and had the highest prevalence of CHD (94.3%). Most of these patients were men and underwent PCI/CABG (32.5%). In the high-comorbidity burden group (Group 3, Figure 2C), patients had the highest mean BMI (27.1 kg/m^2) and the highest prevalence of comorbidities, such as hypertension (100.0%), hyperlipidemia (91.6%), obesity (85.5%), diabetes (59.0%), and CKD (56.6%).

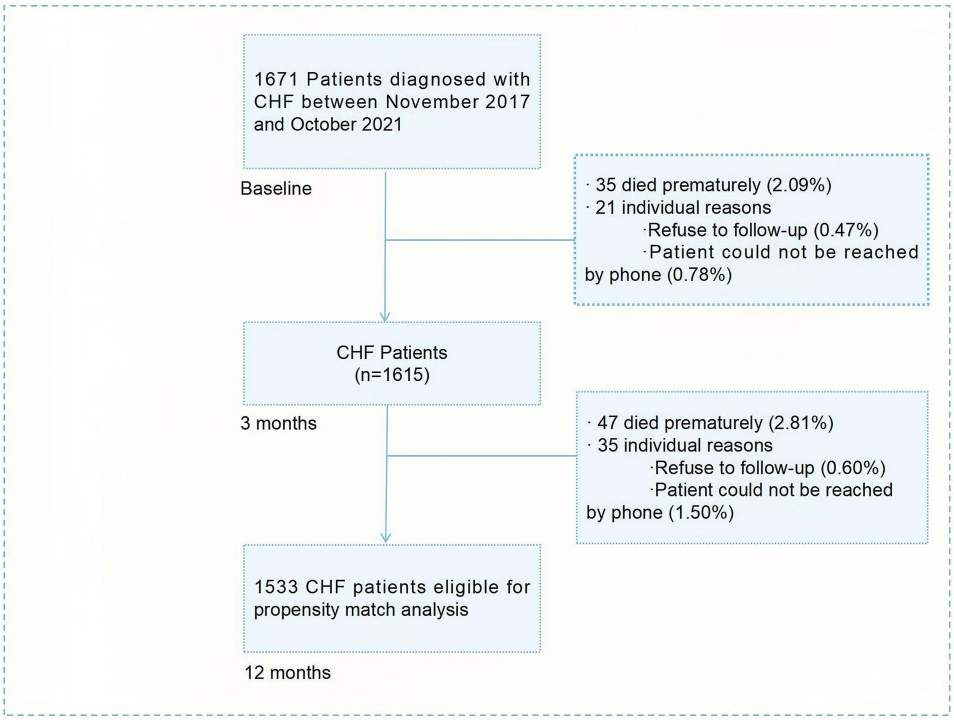

Figure 1 Enrollment process. This figure outlines the screening process for study participants, detailing the timing of initial screening, follow-up visits, and reasons for any loss to follow-up. It also indicates the final number of participants who were successfully included in the study.

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Table 1 Characteristics of the Patients in Each Group

	Total (n=1533)	Young/VHD Group (n=546)	Elderly/CHD Group (n=738)	High-Comorbidity Burden Group (n=249)	$\chi^2/F/Z$	*P*
Age (years)	69.2±14.8	63.9±15.9	74.2±11.8 [a]	65.8±15.7 [b]	30.711	<0.001
Sex					2.357	0.308
Male	882 (57.5%)	294 (53.8%)	450 (61.0%)	138 (55.4%)		
Female	651 (42.5%)	252 (46.2%)	288 (39.0%)	111 (44.6%)		
NYHA					23.665	<0.001
II	270 (17.6%)	51 (9.3%)	174 (23.6%)[a]	45 (18.1%)		
III	852 (55.6%)	294 (53.8%)	402 (54.5%)	156 (62.7%)		
IV	411 (26.8%)	201 (36.8%)	162 (22.0%)[a]	48 (19.3%)[a]		
BMI (kg/m^2)	24.6±3.8	24.0±4.0	24.2±3.3	27.1±4.3[a b]	22.699	<0.001
Heart rate (times/min)	78.8±18.5	83.6±20.5	76.5±16.6 [a]	75.0±16.9[a]	10.283	<0.001
SBP (mmHg)	131.4±22.1	128.7±22.5	129.8±20.7	142.2±22.3[a b]	12.139	<0.001
DBP (mmHg)	78.0±14.7	77.9±15.4	76.9±12.6	81.3±17.9	2.754	0.065
HDL-C (mmol/L)	1.0±0.3	1.0±0.4	1.0±0.3	1.0±0.4	0.161	0.852
LDL-C (mmol/L)	2.5±0.8	2.5±0.8	2.3±0.7 [a]	2.7±1.2[b]	6.585	0.002
eGFR (mL/min/1.73 m^2)	85.3±33.8	90.4±30.8	85.6±30.5	73.1±45.2[a]	7.658	<0.001
NT-proBNP (ng/L)	3.2±0.6	3.3±0.5	3.2±0.6 [a]	3.2±0.7	2.740	0.019
LVEF	44.7±13.9	42.8±14.7	45.5±13.4	46.7±13.1[a]	2.963	0.053
Occupation					9.194	0.010
Manual workers	471 (30.7%)	210 (38.5%)	183 (24.8%)[a]	78 (31.3%)		
Nonmanual workers	1062 (69.3%)	336 (61.5%)	555 (75.2%)[a]	171 (68.7%)		
Smoking history					2.552	0.635
Never	937 (61.1%)	339 (62.1%)	456 (61.8%)	141 (56.6%)		
Quitting smoking	176 (11.5%)	51 (9.3%)	96 (13.0%)	30 (12.0%)		
Smoking	420 (27.4%)	156 (28.6%)	186 (25.2%)	78 (31.3%)		
Drinking	363 (23.7%)	141 (25.8%)	156 (21.1%)	66 (26.5%)	1.709	0.425
Health care					9.623	0.037
City health insurance	1265 (82.5%)	435 (79.7%)	636 (86.2%)	195 (78.3%)		
Rural health insurance	238 (15.5%)	102 (18.7%)	81 (11.0%)	54 (21.7%)[b]		
Self-paying	30 (2.0%)	9 (1.6%)	21 (2.8%)	0 (0.0%)		
Medication						
Platelet aggregation inhibitors	981 (64.0%)	198 (36.3%)	585 (79.3%)[a]	198 (79.5%)[a]	94.326	<0.001
Statins	1023 (66.7%)	198 (36.3%)	618 (83.7%)[a]	207 (83.1%)[a]	118.213	<0.001
Nitrates	520 (33.9%)	93 (17.0%)	354 (48.0%)[a]	72 (28.9%)[b]	45.782	<0.001
β-blocker	1119 (73.0%)	384 (70.3%)	552 (74.8%)	183 (73.5%)	1.071	0.585
Aldosterone blockers	944 (61.6%)	387 (70.9%)	435 (58.9%)[a]	123 (49.4%)[a]	12.589	0.002
Diuretics	1110 (72.4%)	429 (78.6%)	516 (69.9%)	165 (66.3%)	5.791	0.055
Cardiotonic	327 (21.3%)	189 (34.6%)	111 (15.0%)[a]	27 (10.8%)[a]	30.381	<0.001
ACEI/ARB	543 (35.4%)	165 (30.2%)	264 (35.8%)	114 (45.8%)[a]	6.062	0.048
PCI/CABG	310 (20.2%)	12 (2.2%)	240 (32.5%) [a]	57 (22.9%)[a]	60.224	<0.001
Comorbidities						
AF	618 (40.3%)	306 (56.0%)	297 (40.2%)[a]	15 (6.0%)[a b]	59.275	<0.001
CHD	875 (57.1%)	0 (0.0%)	696 (94.3%)[a]	180 (72.3%)[a b]	389.195	<0.001
Hypertension	1081 (70.5%)	225 (41.2%)	606 (82.1%)[a]	249 (100.0%)[a b]	125.642	<0.001
VHD	809 (52.8%)	384 (70.3%)	366 (49.6%)[a]	60 (24.1%)[a b]	50.899	<0.001
Stroke	300 (19.6%)	33 (6.0%)	207 (28.0%)[a]	60 (24.1%)[a]	33.471	<0.001
Diabetes	480 (31.3%)	51 (9.3%)	282 (38.2%)[a]	147 (59.0%)[a b]	75.958	<0.001

(*Continued*)

Table 1 (Continued).

	Total (n=1533)	Young/VHD Group (n=546)	Elderly/CHD Group (n=738)	High-Comorbidity Burden Group (n=249)	$\chi^2/F/Z$	*P*
Obesity	399 (26.0%)	102 (18.7%)	84 (11.4%)	213 (85.5%)[a] [b]	185.202	<0.001
CKD	411 (26.8%)	96 (17.6%)	174 (23.6%)	141 (56.6%)[a] [b]	46.812	<0.001
COPD	323 (21.1%)	120 (22.0%)	195 (26.4%)	9 (3.6%)[a] [b]	19.490	<0.001
Hyperlipidemia	978 (63.8%)	330 (60.4%)	420 (56.9%)	228 (91.6%)[a] [b]	33.651	<0.001
Cancer	31 (2.0%)	3 (0.5%)	27 (3.7%)	0 (0.0%)	6.077	0.043

Notes: [a]Statistical differences from Young/VHD group; [b]Statistical differences from Elderly/CHD group; *P* value represents the statistical difference among the three groups.
Abbreviations: SBP, systolic blood pressure; DBP, Diastolic blood pressure; BMI, body mass index; NYHA, New York Heart Association; HDL–C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic brain natriuretic peptide; AF, atrial fibrillation; CHD, coronary heart disease, hypertension; VHD valvular heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEI, angiotensin converting enzyme inhibitors; ARB, Angiotensin Receptor Blocker.

Relationship Between Comorbidity Groups and HRQoL

Table 2 shows the KCCQ scores of the three groups at baseline. The elderly/CHD group had the highest KCCQ-OS score (mean: 56.77, 95% CI: 55.38–58.15), followed by the young/VHD group (mean: 55.84, 95% CI: 53.96–57.73), and the high-comorbidity group had the lowest KCCQ-OS score (mean: 52.27, 95% CI: 49.22–55.32). There was a significant difference in KCCQ-OS scores among the three groups (*P*=0.035). Similarly, there were significant differences among the three groups in terms of physical limitations (*P*=0.030), symptom scores (*P*=0.020), and KCCQ-CS scores (*P*=0.043). However, patients in the young/VHD group had the highest scores for physical limitations.

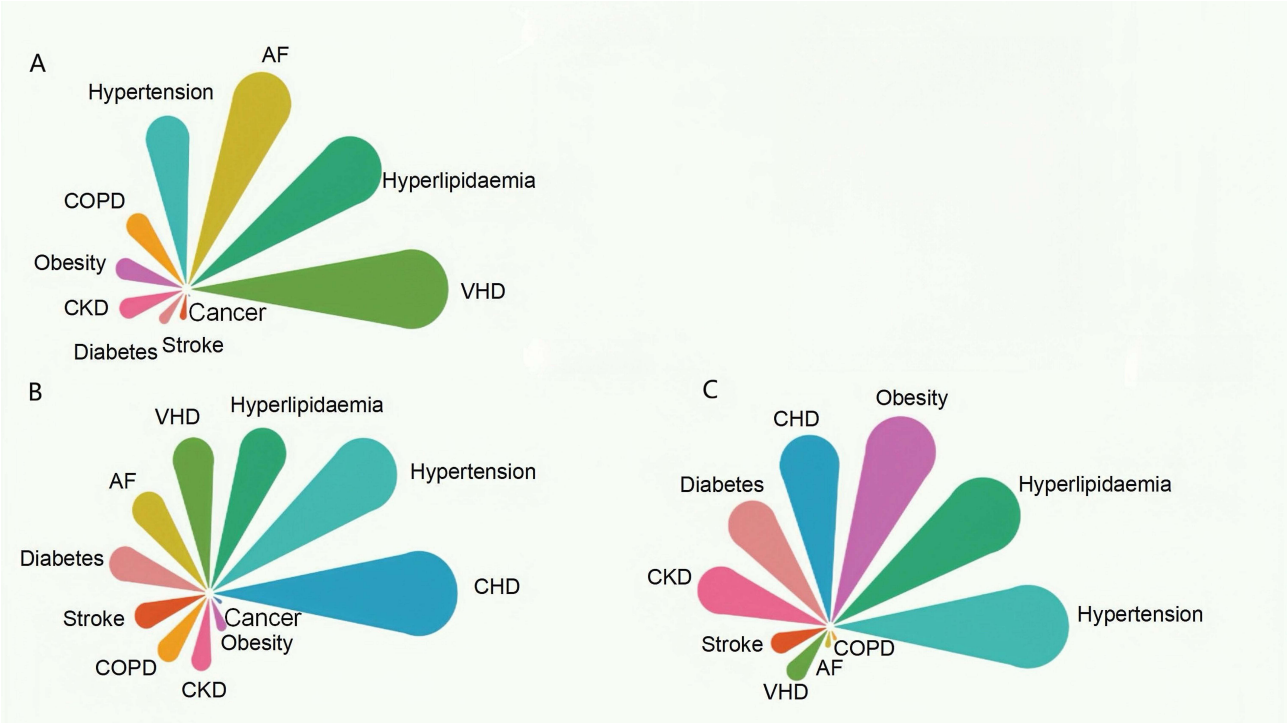

Figure 2 Patient comorbidity profiles in each group. The colour of the petals represents the comorbidity variable, and the area represents the constituent ratio of each comorbidity in the group, arranged in descending order. The figure shows the comorbidities aggregation in the (**A**) young/valvular heart disease (VHD) group, (**B**) elderly/coronary heart disease (CHD) group, and (**C**) high-comorbidity burden group.
Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; VHD, valvular heart disease.

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Table 2 Baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) Scores of the Three Comorbidity Clusters

	Young/VHD Group (n=546)	Elderly/CHD Group (n=738)	High-Comorbidity Burden Group (n=249)	*F*	*P*
Physical Limitations	63.5±23.8	60.0±23.6	55.0±27.7*	3.518	0.030
Symptom Stability	81.3±20.9	80.8±19.9	81.3±19.5	0.044	0.957
Symptom	63.3±19.5	67.2±18.1*	61.1±22.6	3.964	0.020
Self-Efficacy	65.3±19.7	65.7±17.9	62.7±20.7	0.800	0.450
Quality of Life	61.7±14.6	63.2±15.9	62.2±17.5	0.534	0.587
Social Limitations	62.8±17.1	62.0±17.8	59.0±20.7	1.346	0.261
KCCQ Clinical Summary	63.4±17.7	63.9±16.7	58.3±21.3*†	3.155	0.043
KCCQ Overall Summary	63.3±13.9	63.8±12.7	59.3±16.4*†	3.365	0.035

Notes: * statistical comparison with the young/VHD group; †, statistical comparison with the elderly/CHD group.
Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.

Figure 3 shows the KCCQ scores during follow-up. Overall, the KCCQ scores were the highest in the young/VHD group, followed by the elderly/CHD group and the high-comorbidity burden group. The three groups showed improvement in most KCCQ domains at 3 and 12 months after discharge compared with that at the baseline, with the most significant changes being observed at 3 months. The QoL score of the young/VHD group significantly improved compared with that of the other groups (MD=19.1). KCCQ-OS scores (MD=17), KCCQ-CS scores (MD=18.4), social limitations (MD=15.6), physical limitations (MD=14.4), and self-efficacy (MD=10.9) significantly improved in the high-comorbidity burden group compared with those in the other groups. Additionally, at 3 and 12 months, the symptom scores had decreased in all three groups.

The results of the repeated-measures ANOVA are presented in Table 3. The time effect significantly affected changes in patients' QoL ($P < 0.001$), social limitations ($P < 0.001$), self-efficacy ($P < 0.001$), physical limitations ($P < 0.001$), KCCQ-OS ($P < 0.001$), and KCCQ-CS ($P < 0.001$) scores. Meanwhile, the intergroup effect significantly affected the changes in patients' physical limitations ($P = 0.013$), social limitations ($P = 0.044$), and KCCQ-OS ($P = 0.041$) scores. Further pairwise comparisons showed that the physical limitation score was 4.1 points higher in the young/VHD group than that in the elderly/CHD group ($P = 0.018$). The young/VHD group also had higher scores for physical limitations (MD = 6.0, $P = 0.010$), social limitations (MD = 3.9, $P = 0.013$), and KCCQ-OS (MD = 3.4, $P = 0.012$) than did the high-comorbidity burden group. Overall, the HRQoL of the young/VHD group was better. Further details are presented in Supplementary Table S2.

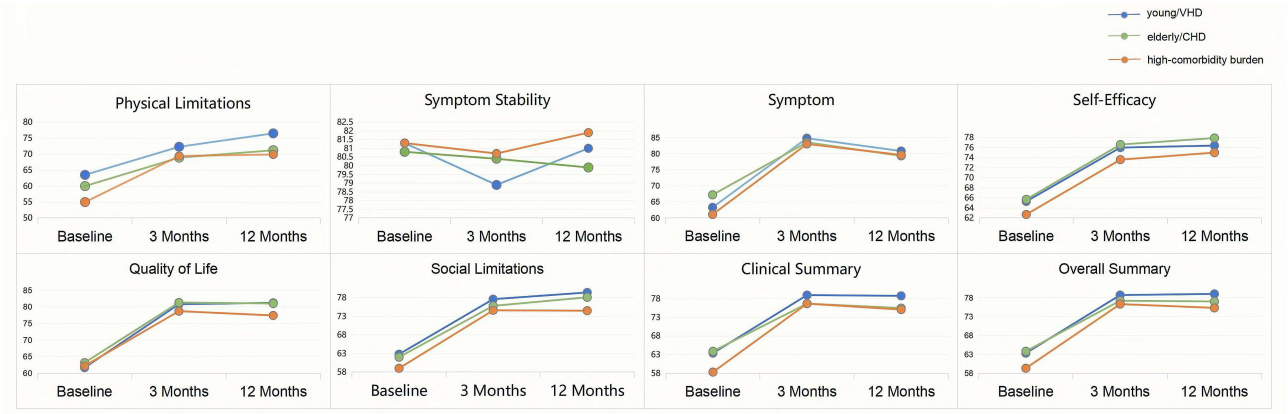

Figure 3 Line chart of KCCQ scores distribution in the three groups at baseline and 3 and 12 months.

Table 3 Repeated-Measures ANOVA for KCCQ Scores

	Young/VHD Group			Elderly/CHD Group			High-Comorbidity Burden Group			*P*		
	Baseline	**3 Months**	**12 Months**	**Baseline**	**3 Months**	**12 Months**	**Baseline**	**3 Months**	**12 Months**	**Group**	**Time**	**Interaction**
Physical Limitations	63.5±23.8	72.3±22.5	76.5±20.9	60.0±23.6	68.9±24.2	71.2±22.6	55.0±27.7	69.4±23.9	69.9±24.4	0.013	<0.001	0.494
Symptom Stability	81.3±20.9	78.9±13.4	81.0±12.2	80.8±19.9	80.4±13.5	79.9±14.2	81.3±19.5	80.7±11.9	81.9±16.7	0.754	0.386	0.540
Symptom	63.3±19.5	84.8±13.3	80.8±18.7	67.2±18.1	83.5±13.4	79.3±20.2	61.1±22.6	83.0±16.4	79.6±21.0	0.336	<0.001	0.059
Self-Efficacy	65.3±19.7	76.0±13.6	76.4±17.0	65.7±17.9	76.6±14.7	77.9±16.3	62.7±20.7	73.6±15.4	75.0±21.0	0.070	<0.001	0.987
Quality of Life	61.7±14.6	80.8±11.0	81.2±15.2	63.2±15.9	81.3±9.2	81.0±14.4	62.2±17.5	78.7±11.6	77.4±16.8	0.106	<0.001	0.657
Social Limitations	62.8±17.1	77.6±15.1	79.4±18.5	62.0±17.8	75.8±14.0	78.1±17.4	59.0±20.7	74.6±17.8	74.5±19.9	0.044	<0.001	0.881
KCCQ Clinical Summary	63.4±17.7	79.0±15.0	78.8±17.1	63.9±16.7	76.7±15.8	75.5±18.3	58.3±21.3	76.7±18.2	75.1±18.9	0.068	<0.001	0.143
KCCQ Overall Summary	63.3±13.9	78.7±12.9	79.0±15.5	63.8±12.7	77.2±12.9	77.0±15.7	59.3±16.4	76.3±15.5	75.3±17.4	0.041	<0.001	0.360

Abbreviation: KCCQ, Kansas City Cardiomyopathy Questionnaire.

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Discussion

This is one of few prospective studies investigating the relationships between comorbidity grouping patterns and HRQoL in patients with CHF. In this study, patients with CHF were classified into the young/valvular heart disease (VHD), elderly/coronary heart disease (CHD), and high-comorbidity burden groups based on their comorbidities. There were differences in the HRQoL and its improvement among the three groups. At follow-up, patients in the young/VHD group had the best HRQoL, while patients in the high-comorbidity burden group had the worst HRQoL but showed the most significant improvement. This may be related to several factors: younger patients may have limited scope for improvement in HRQoL owing to better physiological reserve and milder symptoms (reflected by lower NYHA classification).[30] Furthermore, suboptimal long-term medication adherence among younger patients could be another factor limiting their HRQoL gains.[31] In contrast, the high-comorbidity burden group, despite facing similar or greater challenges in medication adherence, started with the poorest health status, thus having the greatest potential for measurable improvement. The results of this study confirm the effect of comorbidities on HRQoL and provide new avenues for clinicians to improve patients' HRQoL.

Previous studies used group analysis to identify groups with CHF comorbidities. David et al[32] performed a group analysis of patients with ejection fraction-preserved heart failure (HFpEF) in the I-PRESERVE trial and divided them into six subgroups based on demographic information, laboratory findings, and comorbidity variables. The characteristics of subgroup C were similar to those of the high-comorbidity burden group in our study. However, this previous study only included patients with HFpEF in a specific clinical trial, which might not extend to all patients with CHF. Additionally, the comorbidities in that study were limited to AF, coronary artery disease, diabetes, hyperlipidemia, and VHD, whereas our study more comprehensively identified comorbidities based on the heart failure guidelines.[33] In a prospective cohort study of Asian patients with CHF, five comorbidity groups were identified based on 16 comorbidities, namely elderly/AF, metabolic, young, ischemic, and lean diabetic group.[16] Some groups were similar in characteristics to the comorbidity groups identified in the present study. However, the prospective cohort study only analysed the effect of CHF comorbidity groups on HRQoL at baseline and did not further explore their effect on dynamic changes. However, managing CHF patients with multiple comorbidities is extremely challenging owing to potential interactions between comorbidities.[21] Comorbidities may interfere with the diagnosis and treatment of heart failure, exacerbate symptoms, and further compromise quality of life. Future studies should focus on optimising the management of comorbidities and assessing their impact on heart failure outcomes.

The results of this study showed that patients in the elderly/CHD group had higher KCCQ scores and better HRQoL at baseline. However, the results of the aforementioned study showed that younger groups had the best HRQoL.[16] There are several possible reasons for this. First, the mean age of our study population was high. Second, the elderly/CHD group of patients had a relatively better NYHA classification. Previous studies have shown that HRQoL scores deteriorate with an increase in NYHA grade.[34] Our study also showed that patients in the high-comorbidity burden group had poorer HRQoL, consistent with previous studies.[9,35] This finding suggests that clinicians should pay more attention to the HRQoL of patients with a higher comorbidity burden.

Of note, we found that the highest scores for physical limitations were in the young/VHD group. Beyond younger age and milder symptoms, this defines a distinct phenotypic subgroup characterized by valvular etiology and a unique disease trajectory. However, their better self-reported health may foster therapeutic complacency and suboptimal adherence, limiting further gains.[36] Therefore, particular attention should be paid to this subgroup to mitigate adherence risks and improve their long-term quality of life.

Our study further assessed the effects of comorbidity groups on short-and long-term changes in HRQoL. The results of this study showed that short-term HRQoL improved significantly in patients with CHF, with the changes stabilizing over the subsequent follow-ups. We found that the QoL scores of patients in the young/VHD group improved more significantly within 3 months than did those of patients in the other groups. This rapid early gain in the young/VHD group might be attributed to their better physiological responsiveness to initial treatment.[36] Furthermore, suboptimal long-term medication adherence among younger patients could be another factor limiting their overall HRQoL gains.[31] In contrast, the high-comorbidity burden group demonstrated the greatest overall gain. This likely reflects their greater perceived treatment need, the integrated benefit of comprehensive pharmacotherapy, and closer clinical

attention. Consequently, management should focus not only on severe cases but also on patients with milder conditions, to improve the quality of life for all. However, it has also been shown that improving patient medication adherence improves the health of patients with comorbidities.[37] Additionally, compared with the other groups, the high-comorbidity burden group showed significant improvements in KCCQ-OS, KCCQ-CS, social limitations, physical limitations, and self-efficacy scores over 3 months. The higher administration of beta-blockers, ACEIs/ARBs, and aldosterone antagonists in this group may have improved HRQoL, as reported in previous studies.[38,39] The application of guideline-directed medical therapy (GDMT) without contraindications is crucial to improve patients' HRQoL. However, Chinese registration studies have shown that the use of such drugs is significantly lower than that in European countries,[40,41] and the application of GDMT should be enhanced in the future. Our study also found that symptom scores in the young/VHD and elderly/CHD groups showed a significant downward trend at the 3- and 12-month follow-ups. The main reason for this decline may be related to poor treatments at discharge compliance during long-term follow-ups.[42–44] Especially for elderly patients with CHD, there may be adherence issues owing to cognitive decline, the complexity of polypharmacy, and socioeconomic difficulties.[45] The ESC 2024 guidelines have recommended proactive measures, such as simplifying medication and involving family members, to address the problem of poor adherence in older patients.[46] These results suggest that more attention should be paid to the follow-up of patients with CHF at 3 and 12 months to improve their HRQoL.

Limitations

This study had some limitations. First, this study only included patients with CHF in the Shanxi Province, which may have led to insufficient extrapolation power and failed to adequately reflect regional differences. We will verify the obtained results in other regional populations. Second, 138 patients were lost to follow-up. If the lost patients had unobserved characteristics, such as more severe comorbidities, it may have led to an overestimation of the improvement in health-related quality of life (HRQoL), which may have affected the internal validity of our results. Third, the current bias in HRQoL obtained by relying on a self-report scale cannot be avoided, and future research could further reduce the bias or variability that may be introduced by combining symptomatic, psychological, and social support factors through the scale, thus improving the quality of HRQoL. Fourth, imbalances in baseline characteristics across clusters and the lack of systematic assessment for psychiatric comorbidities constitute residual confounding, which may affect estimates of the independent association between clusters and quality of life. Future studies should collect more comprehensive data and employ advanced methods to control for such confounding. Further, as patients were not stratified by left ventricular ejection fraction subtype (eg, HFrEF, HFpEF, HFmrEF), the observed relationships may vary across these pathophysiologically distinct groups. Future research validating these phenotypes within specific HF subtypes is therefore warranted. Finally, we collected KCCQ data only on surviving patients during the follow-up. More suitable statistical analysis methods should be explored in further studies.

Conclusion

This study identified three clinically distinct clusters among patients with CHF based on their comorbidity profiles. Significant differences were observed in both the baseline levels and trajectories of health-related quality of life (HRQoL) across these clusters. These findings are of direct relevance to clinicians, as they facilitate the early identification of patient subgroups at high risk for symptom deterioration and those with the greatest potential for improvement. This provides a rationale for developing targeted management strategies and supports the advancement of more personalized and effective care in CHF.

Clinical Trial Registration

Trial registration: URL: http://www.chictr.org.cn/index.aspx; Unique identifier: ChiCTR2100043337. Date: 2021-02-11.

Abbreviations

aBIC, adjusted Bayesian Information Criterion; ACEI, Angiotensin-Converting Enzyme Inhibitors; AF, Atrial Fibrillation; AIC, Akaike Information Criterion; ARB, Angiotensin Receptor Blockers; BIC, Bayesian Information

Criterion; BLRT, Bootstrapped Likelihood Ratio Test; BMI, Body Mass Index; CABG, Coronary Artery Bypass Grafting; CCI, Charlson Comorbidity Index; CHD, Coronary Heart Disease; CHF, Chronic Heart Failure; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; eGFR, estimated Glomerular Filtration Rate; GDMT, Guideline-Directed Medical Therapy; HRQoL, Health-Related Quality of Life; HFpEF, Heart Failure with preserved Ejection Fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; KCCQ-CS, Kansas City Cardiomyopathy Questionnaire Clinical Summary; LCA, Latent Class Analysis; LMRT, Lo-Mendell-Rubin Test; MD, Mean score Difference; NYHA, New York Heart Association; PCI, Percutaneous Coronary Intervention; VHD, Valvular Heart Disease; WHO, World Health Organization.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author (Yanbo Zhang) on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Shanxi Medical University (approval reference No. 2021GLL103; date of approval: 4 March 2021). All procedures were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants, who received compensation for their time and effort.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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