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ORIGINAL RESEARCH

Dynamic Trajectory of a Patient-Reported Outcome and Its Associated Factors for Patients with Chronic Heart Failure: A Growth Mixture Model Approach

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Purpose: This study aimed to identify subgroups of chronic heart failure (CHF) patients with distinct trajectories of quality of life (QOL) and to identify baseline characteristics associated with the trajectories.

Patients and methods: Two-year, prospective, cohort study including 315 patients with CHF was conducted from July 2017. Information on QOL assessed by CHF-patient-reported outcomes measure (CHF-PROM) was collected at baseline, 6, 12, 18, and 24 months. Demographic and clinical variables were recorded at baseline. Growth mixture model was used to identify distinct trajectories of CHF-PROM and its physical, psychological, social, and therapeutic domains. Single factor analysis was employed to assess the factors associated with development of CHF-PROM over time.

Results: Two classes of overall score of CHF-PROM were identified: poorer (14.0%) and better (86.0%). Poorer class tended to be aged, have low diastolic blood pressure, have concomitant atrial fibrillation, diabetes, chronic obstructive pulmonary disease, cancers, and central nervous system diseases, and used nitrates. Three classes of physical scores were identified: unstable-poorer (5.2%), stable-poorer (29.4%) and better (65.4%). Age, NYHA grade, chronic obstructive pulmonary disease, combined with cancers and central nervous system diseases were related to the grouping. Poorer (8.6%) and better (91.4%) classes of psychological scores were identified. Poorer class tended to be female and had concomitant atrial fibrillation. Degenerate class (34.6%) and meliorate class (65.4%) of therapeutic scores were identified. Degenerate class tended to have concomitant chronic obstructive pulmonary disease and use less angiotensin converting enzyme inhibitors.

Conclusion: We identified different classes with distinct trajectories of QOL that may help proper evaluate QOL and further improve its status for patients CHF.

Keywords: patient-reported outcome, chronic heart failure, growth mixture model, dynamic trajectory

Introduction

Chronic heart failure (CHF) is the serious stage of various cardiovascular diseases. The morbidity rates of CHF increase up to about 1–2% in adults, and 10% in individuals over the age of 70 years.[1] The prognosis of CHF is poor; its 1-year and 5-year mortality rates are 20% and 53%, respectively, and each CHF patient has an average number of 1.3 hospitalizations per year.[1] Quality of life (QOL) is an important outcome measure of CHF. Owing to the severity of CHF, long disease duration, and the high cost of treatment, the QOL of patients with CHF is worse than that of other chronic diseases.[2] Recently, with the improvement of therapy, the rates of mortality and rehospitalization for CHF have declined, while the QOL remains poor.[1] Therefore, QOL has become one of the most pressing aims for the treatment of CHF and has attracted more attention. Proper evaluation of QOL and further improvements to its status based on

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evaluations are, therefore, necessary for CHF patients. For evaluating QOL correctly, we should focus on both the evaluation instruments and analysis methods.

Patient-reported outcomes (PROs) are derived from health-related quality of life and directly reflect the patient's health and function status, behavioural psychology, treatment satisfaction, and social environment.[3] The patient-reported outcome measures (PROMs) are evaluated using self-administered questionnaires that serve as ideal tools for measuring QOL. Based on Chinese social and cultural characteristics, we developed CHF-PROM, which is more suited for the Chinese population.[4] We applied CHF-PROM to measure QOL in this study.

PROs of CHF change dynamically over time. Compared to horizontal data (extracted from a cross-sectional study design), longitudinal data (from a longitudinal cohort study design) can better assess QOL of patients. In follow-up studies recently, the data of PROM scores at several different time points was simply extracted and collated, without subjecting it to dynamic trend analysis.[5,6] Growth models can be used to analyse the change of repeated measurement data at multiple nodes. In this study, given that the influences on PROs may vary between individuals and within individuals over time, much heterogeneity of PROs trajectories in patients with CHF can be expected. However, the traditional growth models assume that the overall development trend is homogenous and ignore the heterogeneity among individuals. Researchers proposed the growth mixture modelling (GMM) that can handle this problem through the latent variables.[7] Using GMM, we can categorize the observed population into several subgroups and describe the dynamic trajectories of the subgroups and the changes of individual status. Therefore, the aim of our approach was to identify subgroups of CHF patients with distinct trajectories of CHF-PROM using GMM and explore predictors of subgroup membership, so as to provide evidence to improve the QOL for patients with CHF.

Methods

Participants

This study was designed as a multi-center, prospective cohort study. Patients from three medical centers in Shanxi Province of People's Republic of China were enrolled between July 1, 2017 and June 30, 2019. Inclusion criteria were patients who were diagnosed with CHF according to the guideline of European Society of Cardiology[1] and classified as functional class II–IV according to the New York Heart Association (NYHA). Patients who had suffered acute cardiovascular events two months prior to enrolment or were not able to complete the questionnaire owing to intellectual disabilities were excluded. All patients provided written informed consent for participation before the initiation of the study. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by Institutional Review Board of Shanxi Medical University.

Procedure

Information regarding CHF-PROM scores were collected during hospitalization, and at 6, 12, 18, and 24 months after discharge by face-to-face consultations or over the phone. Demographic and clinical variables were assessed at baseline during hospitalization. To ensure quality, all the data was entered into the system by professionally trained individuals.

Measures

Demographic and Clinical Variables

Demographic information was collected through questionnaires, which included age, sex, body mass index (BMI), occupation, marital status, family income, level of education, and health insurance. We formulated a case history form to record the clinical indicators during hospitalization, which included blood pressure, heart rate, NYHA class, left ventricular ejection fraction (LVEF), severe comorbidities, and orally administered medications prescribed at discharge. Among these variables, comorbidities included coronary heart disease, hypertension, atrial fibrillation, valvular heart disease, hyperlipidaemia, diabetes mellitus, chronic obstructive pulmonary disease (COPD), renal insufficiency, cancers, and central nervous system diseases;[1] orally administered medications were nitrates, diuretics, digoxin, beta blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and aldosterone receptor antagonists.

CHF-PROM

CHF-PROM used in this study consists of 57 items, 12 subdomains, and 4 domains (physical domain, psychological domain, social domain, and therapeutic domain).[4] Each of the items is measured on a five-level Likert scale from 0 to 4 to reflect the frequency of occurrence of each issue during the past two weeks (where score 0: never, 1: occasionally, 2: about half of the time, 3: often, and 4: almost every day). All responses were transformed into scores based on the following principle: positively scored items were recorded as the original score plus 1, while negatively scored items were recorded as 5 minus the original score. Next, overall scores (OS), physical scores (PHYS), psychological scores (PSYS), social scores (SOCS), and therapeutic scores (TRES) of CHF-PROM were calculated by adding scores of the corresponding items. The structure and scoring principles of CHF-PROM are presented in Table S1.

Statistics

Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range). The categorical variables were expressed as n (%). The variables with ≥15% of missing observations were deleted. Furthermore, for variables with <15% of missing observations, the missing data were filled by running it through the MissForest algorithm. Cronbach's α coefficient was applied to assess the quality of CHF-PROM data.

The GMM approach was applied to identify distinct subgroups according to the OS of CHF-PROM and scores in four domains over two years and to model CHF-PROM trajectories of subgroups and individuals within the subgroups. The GMM approach contains continuous and classified latent variables. The continuous latent variables include intercept and slope of growth characteristic parameters, and the classified latent variables could divide patients into subgroups to describe the heterogeneity.[8]

In this study, we established 2, 3, or 4 subgroups in patients with CHF using GMM in a three-stage procedure. In the first step, we used linear, quadratic function, and undefined curve GMM to identify subgroups for OS, PHYS, PSYS, SOCS, and TRES of CHF-PROM. Then, we used the following indicators to assess the models. Log-likelihood (LL) were applied to evaluate model fitting effect. Model with the minimum chi-square Akaike information criterion (AIC), Bayesian information criterion (BIC), or adjusted BIC (aBIC) was considered the proper latent group with significant goodness-of-fit. Entropy ranging from 0 to 1 was applied to indicate the accuracy of the models. The closer the entropy was to 1, the more accurate was the model classification.[9] Moreover, Lo-Mendell-Rubin test (LMR-test) and bootstrapped likelihood ratio test (BLRT) were used to compare the goodness-of-fit between the n-class model and n-1 class model. $P<0.05$ indicated the n-class model had better goodness-of-fit.[9] The parameter estimation using maximum likelihood (ML) and Bayesian method of the selected model was the third step. The data were iterated many times to obtain the estimated values of parameters and posterior probabilities.

Specifically, patients' demographic and clinical characteristics at baseline were analysed with single-factor analysis to identify predictors of subgroups. The Sankey diagram completed by Microsoft Excel was used to indicate the flow relationship between variables and subgroups of CHF-PROM.

Univariate analysis of variables was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). The MissForest algorithm was completed using R version 4.0.5 (Lucent Technologies, Murray Hill, NJ, USA). The GMM approach was conducted using Mplus version 8.3 (Muthén and Muthén, Los Angeles, CA, USA).

Results

Descriptive Analysis

A total of 408 patients participated at baseline. During the two-year period, 93 patients were lost to follow-up because of death (n=48) and individual reasons (n=45), resulting in a sample size of 315 patients. The individual reasons included refusal for follow-up visits (n=13) and inability to reach the patients on phone resulting in partial loss of follow-up data (n=32).

During the follow-up period, 88 (27.9%) patients were re-hospitalized due to exacerbated HFand 32 (10.2%) patients were deteriorated without re-hospitalization. Participant demographic and clinical characteristics are presented in Table 1. The mean age of the patients was 66.1±15.0 years and 43.8% were women. Most of the patients were married (82.2%)

and had a low level of education (below secondary high school [70.5%]); 41.9% and 56.5% had a low and medium annual income, respectively. The proportion of patients with NYHA stages II, III, and IV were 17.1%, 46.0%, and 36.8%, respectively. The average LVEF of the patients was 43.8%. Regarding comorbidities, 49.5% patients had coronary heart disease, 60.3% had hypertension, 37.1% had atrial fibrillation, and 35.2% had diabetes. Regarding medications, most of the patients took diuretics (70.8%) and aldosterone receptor antagonists (66.3%), followed by ACEI/ARBs (48.9%), beta blockers (47.6%), nitrates (46.0%), and digoxin (24.4%). Moreover, there were no significant differences at baseline between the participants who completed the follow-up and those who dropped out for all of the indicators, except for taking ACEI/ARBs and aldosterone antagonists (see Table S2).

Cronbach's α coefficients for the OS, PHYS, PSYS, SOCS, and TRES were 0.914, 0.921, 0.916, 0.868, and 0.873, respectively. The mean CHF-PROM scores at baseline for OS, PSYS, PHYS, SOCS and TRES were 221.1±20.8, 59.7 ±10.1, 89.3±12.1, 46.9±6.4, and 25.0±6.0, respectively. The scores were lowest at baseline and improved significantly after discharge until one year later. Additionally, the OS, SOCS, and TRES remained high, but the PHYS demonstrated a gradual decline from then on. The scores are shown in Table 2 and the percentages of them are shown Figure 1.

GMM for Overall Scores of CHF-PROM

Table S3 presents model fitting indices for the OS of CHF-PROM. The four classes of linear GMM and three classes of quadratic function presented significant differences in LMR-test and BLRT, but there were classes with low probability in these two kinds of classification (0.010 and 0.014). In undefined curve GMM for OS, the significant differences were observed by LMR-test and BLRT of the two-class model. Significant differences existed when comparing the three-class

Table 1 Characteristics of Patients with Chronic Heart Failure Included in the Study

Variable	No Event	Variable	No Event
Age (years)	66.1±15.0	**Occupation, n (%)**	
Women, n (%)	138 (43.8%)	Nonmanual workers,	98 (31.1%)
Body Mass Index (kg/m^2)	24.3±4.1	Manual workers	217 (68.9%)
Heart rate (beats/minute)	77.9±15.7	**NYHA, n (%)**	
Systolic pressure (mmHg)	127.7±19.6	II	54 (17.1%)
Diastolic pressure(mmHg)	77.4±12.6	III	145 (46.0%)
		IV	116 (36.8%)
Marital status, n (%)		**Comorbidities, n (%)**	
Single	6 (1.9%)	Coronary heart disease	156 (49.5%)
Married	259 (82.2%)	Hypertension	190 (60.3%)
Divorced	1 (0.3%)	Atrial fibrillation	117 (37.1%)
Widowed	49 (15.6%)	Valvular heart disease,	77 (24.4%)
Education, n (%)		Hyperlipidaemia	99 (31.4%)
Illiterate	27 (8.6%)	Diabetes	111 (35.2%)
Low level	195 (61.9%)	COPD	73 (23.2%)
Secondary school and higher level	93 (29.5%)	Chronic renal insufficiency	83 (26.3%)
LVEF (%)	43.8±14.3	Cancers	24 (7.6%)
Income, n (%)		Central nervous system disease	69 (21.9%)
Low	132 (41.9%)	**Drugs, n (%)**	
Medium	178 (56.5%)	Nitrates	145 (46.0%)
High	5 (1.6%)	Diuretic	223 (70.8%)
Health care, n (%)		Digoxin	77 (24.4%)
City health insurance	214 (67.9%)	Beta-blocker	150 (47.6%)
Rural health insurance	98 (31.1%)	ACEI/ARB	154 (48.9%)
Self-paying	3 (1.0%)	Aldosterone antagonist	209 (66.3%)

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor antagonist; COPD, Chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

Table 2 Scores of CHF-PROM in Different Times for Patients with Chronic Heart Failure

	Baseline	Six Months	One Year	Eighteen Months	Two Years
Overall score	221.0±20.8	243.0±14.6	245.5±11.7	249.5±15.5	251.8±15.5
PHYS	59.7±10.1	70.9±7.6	72.4±6.8	71.5±8.1	71.4±7.7
PSYS	89.3±12.1	97.9±9.4	98.7±8.5	99.7±8.7	98.5±9.9
SOCS	46.9±6.4	46.9±4.3	46.8±4.2	50.3±5.6	51.9±5.3
TRES	25.0±6.0	25.3±3.9	25.5±3.5	26.1±3.3	27.5±4.2

Abbreviations: CHF-PROM, chronic heart failure - patient reported outcome measures; PHYS, physical scores; PSYS, psychological scores; SOCS, social scores; TRES, therapeutic scores.

model to the two-class model. However, the probability of one subgroup of the three-class model was too low (0.014). Taking all the indicators comprehensively, the two-class model was identified as the best one.

Figure 2A presents the subgroups and the trajectory curves of OS of CHF-PROM. The poorer class (14.0%) and better class (86.0%) displayed almost the same growth trends, and the growth rate was faster in the first six months than that after. The poorer class reported worse CHF-PRO than the better class at baseline and two years later. The parameter estimates for two classes with corresponding standard errors and *P*-values and descriptive statistics of OS are shown in Table 3. Patients in the poorer class were significantly more likely to be older, have lower diastolic blood pressure, have concomitant atrial fibrillation, diabetes, COPD, cancers, and central nervous system diseases, have higher LVEF, and higher intake of nitrates. The result of single factor analysis is presented in Table 4. As shown in Figure 3A, patients were with advanced age (17.9% vs 8.2%), with diastolic pressure <90mmHg (15.5% vs 5.8%), and combined with atrial fibrillation (20.9% vs 9.5%) and other diseases mentioned above were more likely to be in poorer class.

GMM for Physical Scores of CHF-PROM

Table S4 presents model fitting indices for PHYS of CHF-PROM. The three-class model of quadratic function GMM for PHYS presented significant differences in LMR-test and BLRT and the highest entropy (0.921). According to the same analysis process, we identified this three-class model for PHYS.

As shown in Figure 2B, the subgroups of this model were named unstable-poorer class (5.2%), stable-poorer class (29.4%), and better class (65.4%). The PHYS at baseline and at two-years later of the unstable-poorer class and the

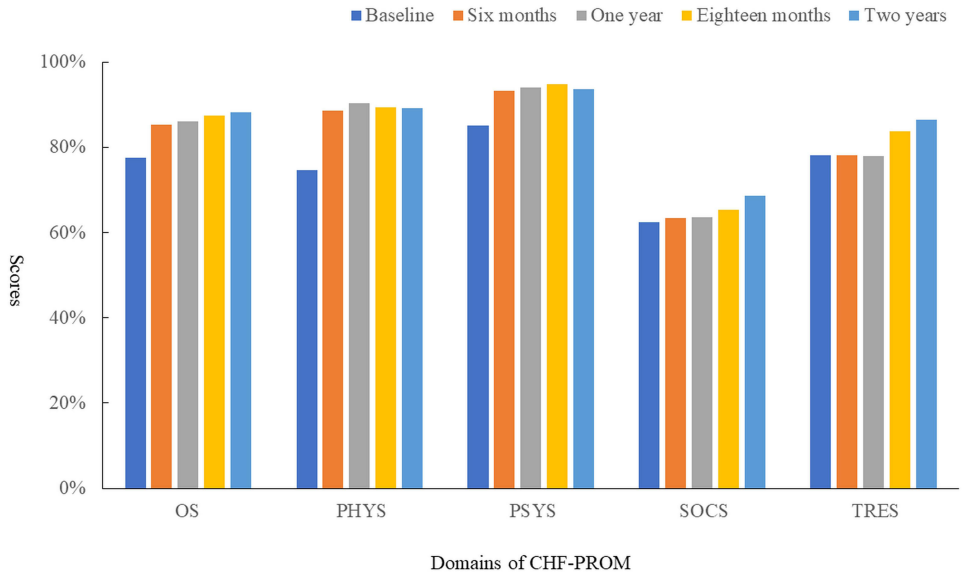

Figure 1 Changes in percentages of CHF-PROM scores across two years. The horizontal axis represents follow-up time and the vertical axis represents percentages of CHF-PROM scores. Percentage was calculated as the average score divided by the total score in the corresponding domain.
Abbreviations: CHF-PROM, chronic heart failure – patient reported outcome measures; OS, overall scores; PHYS, physical scores; PSYS, psychological scores; SOCS, social scores; TRES, therapeutic scores.

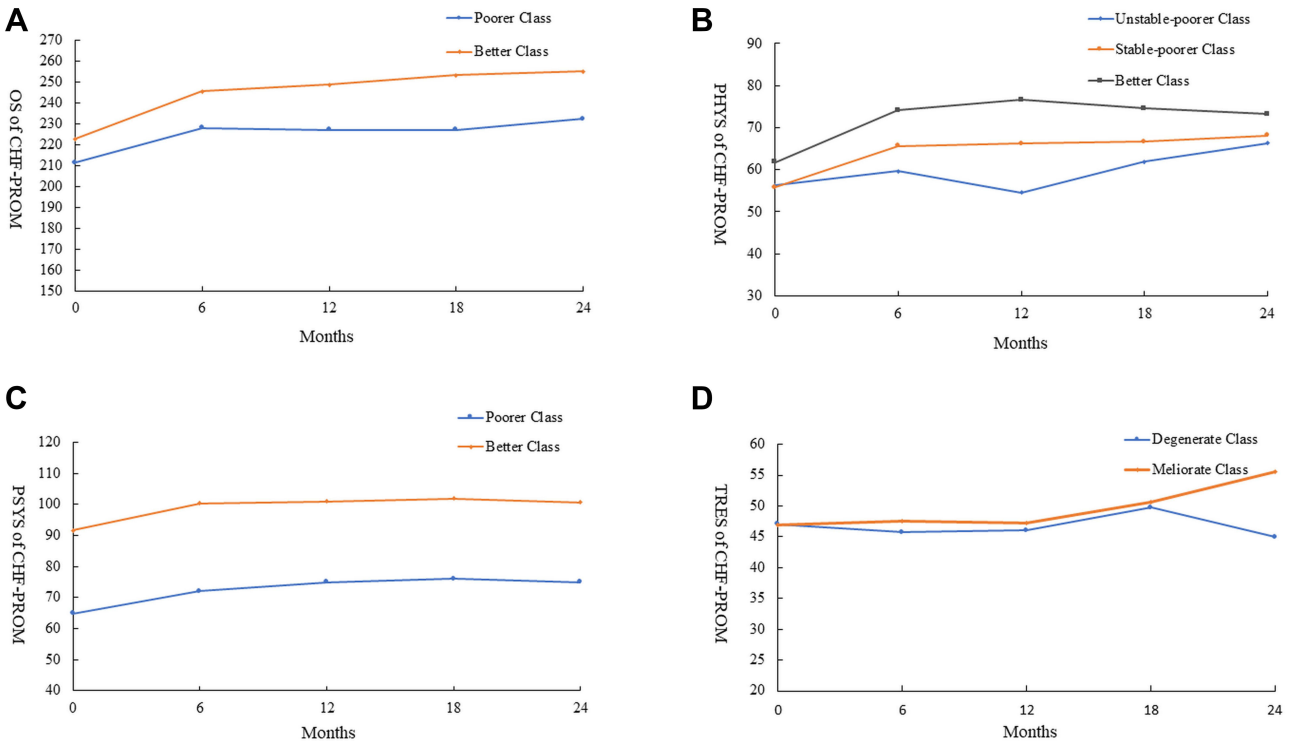

Figure 2 Subgroups and trajectory curves of CHF-PROM identified by the growth mixture model. The figure shows the subgroups and the trajectory curves for OS (**A**), PHYS (**B**), PSYS (**C**) and TRES (**D**) of CHF-PROM.

Abbreviations: CHF-PROM, patient-reported outcome measures of chronic heart failure; OS, overall scores; PHYS, physical scores; PSYS, psychological scores; SOCS, social scores; TRES, therapeutic scores.

stable-poorer class were almost similar and lower than that of the better class, while the PHYS of the stable-poorer class grew steadily during the two years and the unstable-poorer class fluctuated greatly. The better class had the highest PHYS and demonstrated an increase in the first year and a slight decrease after that. The parameter estimates for this model with corresponding standard errors and *P*-values and descriptive statistics of PHYS are shown in Table 3. Compared with the better class, both the unstable-poorer class and the stable-poorer class were significantly more likely to have terrible baseline features. These included old age, high-level NYHA, comorbidities, such as COPD, cancers, and central nervous system diseases (all $P<0.05$). The profiles of the unstable-poorer class and the stable-poorer class were similar to each other, although the unstable-poorer class showed worse trends for these indicators (see Table 4). Figure 3B shows the distribution of patients with different characteristics in the three subgroups of PHYS.

GMM for Psychological Scores of CHF-PROM

Table S5 presents model fitting indices for PSYS of CHF-PROM. Two-class of linear, quadratic function, and undefined curve GMM all showed significant differences in LMR-test and BLRT. Among these two-class models, undefined curve GMM had the minimum LL, AIC, BIC and aBIC and the highest entropy, so we identified it as the optimal model for PSYS.

Figure 2C showed the subgroups and the trajectory curves of PSYS. The PSYS of better class (91.4%) was higher than that of the poorer class (8.6%). Both subgroups maintained almost the same growth trend over the two years. The parameter estimates for two classes with corresponding standard errors and *P*-values and descriptive statistics of OS are shown in Table 3. Compared with the better class, patients in the poorer class were significantly more likely to be female and have concomitant coronary heart disease and atrial fibrillation (see Table 4). Figure 3C shows the distribution of patients with different characteristics in the two subgroups of PSYS.

Table 3 Parameter Estimates for Classes of CHF-PROM

		Estimated Value	$S_{\bar{X}}$	*t*	*P*
Overall Scores					
Poorer Class	Mean intercept	217.566	4.556	47.756	<0.001
	Mean slope	5.803	1.728	3.359	0.001
Better Class	Mean intercept	229.640	1.520	151.031	<0.001
	Mean slope	10.206	0.796	12.826	<0.001
	Covariance	−25.829	17.130	−1.508	0.132
	Intercept variance	96.673	39.449	2.451	0.014
	Slope variance	6.015	8.023	0.750	0.453
Physical Scores					
Unstable-Poorer Class	Mean intercept	58.321	2.854	20.437	<0.001
	Mean slope	−4.608	1.978	−2.329	0.020
	Mean Q	1.663	0.442	3.762	<0.001
Stable-Poorer Class	Mean intercept	57.376	1.230	46.636	<0.001
	Mean slope	6.841	1.059	6.463	<0.001
	Mean Q	−1.081	0.223	−4.840	<0.001
Better Class	Mean intercept	63.169	0.899	70.275	<0.001
	Mean slope	11.157	0.602	18.542	<0.001
	Mean Q	−2.204	0.115	−19.128	<0.001
	Covariance	−33.127	9.782	−3.386	0.001
	Intercept variance	53.751	13.097	4.104	<0.001
	Slope variance	19.766	8.775	2.253	0.024
	Q variance	0.585	0.391	1.497	0.135
Psychological Scores					
Poorer Class	Mean intercept	64.029	2.426	26.391	<0.001
	Mean slope	5.376	1.128	4.766	<0.001
Better Class	Mean intercept	91.716	0.598	153.497	<0.001
	Mean slope	4.554	0.282	16.158	<0.001
	Covariance	−10.867	2.525	−4.304	<0.001
	Intercept variance	33.173	6.653	4.986	<0.001
	Slope variance	5.665	1.379	4.107	<0.001
Therapeutic Scores					
Degenerate Class	Mean intercept	46.826	0.436	107.362	<0.001
	Mean slope	−0.378	0.112	−3.369	0.001
Meliorate Class	Mean intercept	45.019	0.328	137.397	<0.001
	Mean slope	2.085	0.069	30.394	<0.001
	Covariance	−1.513	0.380	−3.978	<0.001
	Intercept variance	7.865	1.768	4.449	<0.001
	Slope variance	0.351	0.116	3.032	0.002

Abbreviation: CHF-PROM, chronic heart failure - patient reported outcome measures.

GMM for Social Scores of CHF-PROM

As for the GMM for SOCS, there were no significant differences in LMR-test and BLRT, therefore, we could not divide it into different subgroups.

GMM for Therapeutic Scores of CHF-PROM

Table S6 presents model fitting indices for TRES of CHF-PROM. The two-class model of quadratic function GMM for TRES presented significant differences in LMR-test and BLRT, and no low probability among the classes, therefore, we identified this model for TRES.

Table 4 Basic Characteristics Between Subgroups of Patients with Chronic Heart Failure

	OS		PHYS			PSYS		TRES	
	Poorer Class (n=44)	**Better Class (n=271)**	**Unstable Poorer Class (n=16)**	**Stable Poorer Class (n=93)**	**Better Class (n=206)**	**Poorer Class (n=27)**	**Better Class (n=288)**	**Degenerate Class (n=109)**	**Meliorate Class (n=206)**
Age	72.0±13.6*	65.1±15.0*	74.6±11.9[c]	71.3±13.9[c]	63.0±14.9	68.3±14.3	65.9±15.1	68.5±15.4	64.8±14.7
Women	23(52.3%)	115(42.4%)	7(43.8%)	52 (55.9%)[c]	79(38.3%)[b]	20(74.1%)*	118(41.0%)*	50 (45.9%)	88(42.7%)
Body mass index (kg/m^2)	24.3±4.5	24.2±4.1	24.2±11.9	23.9±4.5	24.4±4.0	23.9±3.5	24.3±4.2	23.8±3.6	24.5±4.3
Heart rate (beats/ minute)	75.7±13.9	78.3±15.9	79.7±15.5	77.5±14.9	78.0±16.1	74.7±12.3	78.2±15.9	77.3±15.3	78.2±15.9
Systolic pressure (mmHg)	124.9±17.3	128.1±19.9	124.1±14.8	127.5±20.5	128.0±19.5	122.7±17.2	128.1±19.8	128.7±20.4	127.1±19.2
Diastolic pressure (mmHg)	72.8±9.8*	78.1±12.8*	72.0±11.3	76.9±13.2	78.1±12.3	73.3±9.3	77.8±12.8	76.4±12.7	77.9±12.5
Marital state									
Single	1(2.3%)	4(1.5%)	0	2(2.2%)	3(1.5%)	0	5(1.7%)	1(0.9%)	5(2.4%)
Married	34(77.3%)	225(83.0%)	12(75.0%)	73(78.5%)	175(85.0%)	22(81.5%)	237(82.3%)	91(83.5%)	168(81.6%)
Divorced	0	1(0.4%)	0	0	1(0.5%)	0	1(0.3%)	0	1(0.5%)
Widowed	9(20.5%)	40(14.8%)	6(37.5%)	18(19.4%)	27(13.1%)	5(18.5%)	44(15.3%)	17(15.6%)	32(15.5%)
Education									
Illiteracy	7(15.9%)	18(6.6%)	3(18.8%)	11(11.8%)[a]	10(4.9%)[a]	3(11.1%)	21(7.3%)	10(9.2%)	14(6.8%)
Low level	24(54.5%)	173(63.8%)	6(37.5%)	62(66.7%)[a]	129(62.6%)[a]	18(66.7%)	178(61.8%)	70(64.2%)	126(61.2%)
Secondary school and high level	14(31.8%)	81(29.9%)	6(37.5%)	20(21.5)%[a]	68(33.0%)[a]	6(22.2%)	89(30.9%)	29(26.6%)	65(31.6%)
Occupation									
Nonmanual workers	12(27.3%)	85(31.4%)	3(18.8%)	27(29.0%)	68(33.0%)	7(25.9%)	91(31.6%)	27(24.8%)	71(34.5%)
Manual workers	32(72.7%)	186(68.6%)	13(81.3%)	66(71.0%)	138(67.0%)	20(74.1%)	197(68.4%)	82(75.2%)	135(65.5%)
Income									
Low	19(43.2%)	113(41.7%)	5(31.3%)	43(46.2%)	84(40.8%)	15(55.6%)	118(41.0%)	46(42.2%)	86(41.7%)
Medium	24(54.5%)	155(57.2%)	10(62.5%)	49(52.7%)	120(58.3%)	12(44.4%)	166(57.6%)	61(56.0%)	117(56.8%)
High	1(2.3%)	5(1.8%)	1 (6.3%)	1(1.1%)	2(1.0%)	0	4(1.4%)	2(1.8%)	2(1.0%)
Health care									
City health insurance	34(77.3%)	180(66.4%)	14(87.5%)	61(65.6%)	139(67.5%)	18(66.7%)	196(68.1%)	69(63.3%)	145(70.4%)
Rural health insurance	9(20.5%)	89(32.8%)	2(12.5%)	31(33.3%)	64(31.1%)	9(33.3%)	89(30.9%)	39(35.8%)	59(28.6%)
Self-paying	1(2.3%)	2(0.7%)	0	1(1.1%)	2(1.0%)	0	3(1.0%)	1(0.9%)	2(1.0%)

NYHA									
II	7(15.9%)	48(17.7%)	2(12.5%)	10(10.8%)[c]	42(20.4%)[b]	2(7.4%)	52(18.1%)	14(12.8%)	40(19.4%)
III	18(40.9%)	127(46.8%)	5(31.3%)	38(40.9%)[c]	102(49.5%)[b]	12(44.4%)	133(46.2%)	49(45.0%)	96(46.6%)
IV	19(43.2%)	96(35.4%)	8(50.0%)	45(48.4%)[c]	62(30.1%)[b]	12(44.4%)	103(35.8%)	46(42.2%)	70(34.0%)
Complications									
Coronary heart disease	24(54.5%)	133(49.1%)	10(62.5%)	46(49.5%)	100(48.5%)	8(29.6%)*	148(51.4%)*	50(45.9%)	106(51.5%)
Hypertension	30(68.2%)	159(58.7%)	10(62.5%)	58(62.4%)	121(58.7%)	11(40.7%)	178(61.8%)	60(55.0%)	130(63.1%)
Atrial fibrillation	25(56.8%)*	92(33.9%)*	8(50.0%)	38(40.9%)	70(34.0%)	18(66.7%)*	98(34.0%)*	41(37.6%)	75(36.4%)
Valvular heart disease	15(34.1%)	63(23.2%)	5(31.3%)	24(25.8%)	49(23.8%)	9(33.3%)	69(24.0%)	28(25.7%)	50(24.3%)
Hyperlipidemia	17(38.6%)	82(30.3%)	8(50.0%)	27(29.0%)	63(30.6%)	10(37.0%)	89(30.9%)	27(24.8%)	72(35.0%)
Diabetes	25(56.8%)*	86(31.7%)*	8(50.0%)	36(38.7%)	67(32.5%)	10(37.0%)	101(35.1%)	70(64.2%)	74(35.9%)
COPD	19(43.2%)*	54(19.9%)*	10(62.5%)[c]	35(37.6%)[c]	29(14.1%)	7(25.9%)	67(23.3%)	33(30.3%)*	40(19.4%)*
Chronic renal insufficiency	17(38.6%)	66(24.4%)	6(37.5%)	21(22.6%)	55(26.7%)	9(33.3%)	74(25.7%)	29(26.6%)	54(26.2%)
Cancers	11(25.0%)*	13(4.8%)*	4(25.0%)[c]	8(8.6%)	12(5.8%)[a]	1(3.7%)	23(8.0%)	9(8.3%)	15(7.3%)
Central nervous system disease	21(47.7%)*	48(17.7%)*	10(62.5%)[c]	32(34.4%)[c]	27(13.1%)	8(29.6%)	61(21.2%)	29(26.6%)	40(19.4%)
LVEF (%)	49.1±13.8*	42.9±14.2*	44.9±12.9	44.9±11.5	44.4±12.6	46.7±17.3	43.5±13.9	44.7±15.5	43.3±13.6
Drugs									
Nitrates	29(65.9%)*	116(42.8%)*	12(75.0%)	44(47.3%)	90(43.7%)	9(33.3%)	136(47.2%)	49(45.0%)	96(46.6%)
Diuretics	35(79.5%)	188(69.4%)	11(68.8%)	71(76.3%)	142(68.9%)	15(55.6%)	208(72.2%)	75(68.8%)	148(71.8%)
Digoxins	14(31.8%)	63(23.2%)	5(31.3%)	21(22.6%)	50(24.3%)	8(29.6%)	69(24.0%)	28(25.7%)	49(23.8%)
Beta-blockers	24(54.5%)	126(46.5%)	8(50.0%)	43(46.2%)	98(47.6%)	10(37.0%)	140(48.6%)	49(45.0%)	101(49.0%)
ACEI/ARBs	24(54.5%)	130(48.0%)	11(68.8%)	37(39.8%)	106(51.5%)	11(40.7%)	143(49.7%)	44(40.4%)*	110(53.4%)*
Aldosterone antagonists	28(63.6%)	181(66.8%)	9(56.3%)	61(65.6%)	141(68.4%)	15(55.6%)	195(67.7%)	66(60.6%)	144(69.9%)

Notes: *Statistical difference between the two groups; [a]Statistical differences from unstable poorer class of PHYS; [b]Statistical differences from stable poorer class of PHYS; [c]Statistical differences from better class of PHYS.
Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor antagonist; COPD, Chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; OS, overall score; PHYS, physical scores; PSYS, psychological scores; TRES, therapeutic scores.

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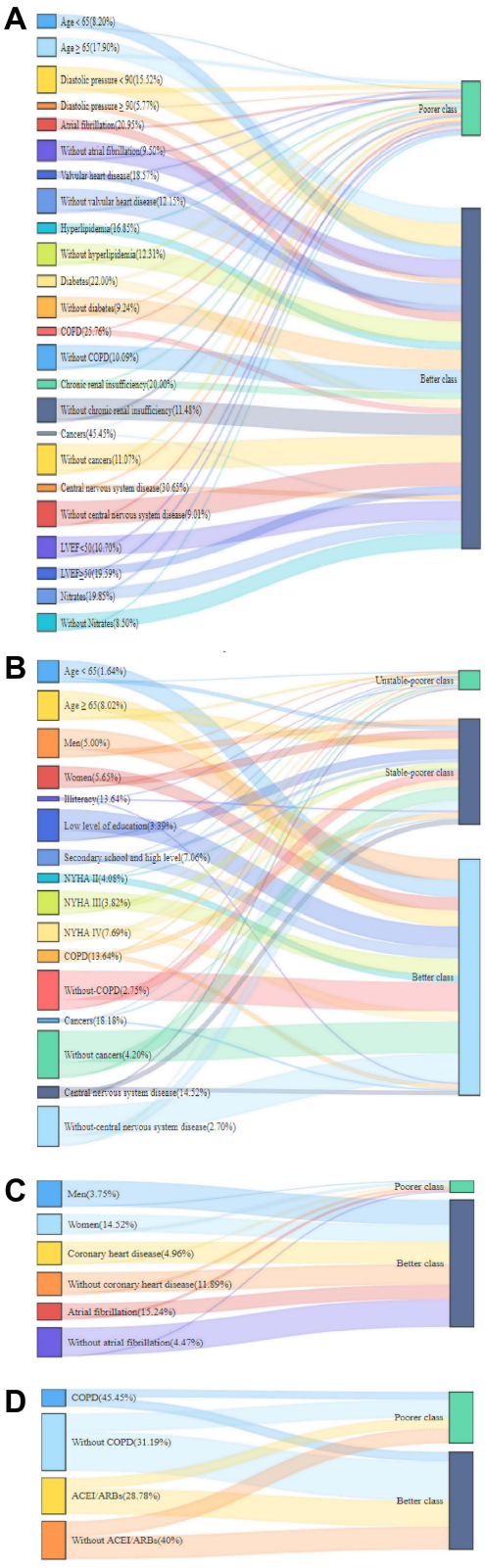

Figure 3 Sankey diagram between baseline characteristics and subgroups of CHF-PROM. (**A**) OS, (**B**) PHYS, (**C**) PSYS and (**D**) TRES. The left of the figure presents baseline characteristics and the corresponding percentage that fall into the different subgroups. The right of the figure presents different subgroups of CHF-PROM.
Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor antagonist; COPD, Chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

Figure 2D shows the subgroups and the trajectory curves of TRES. Regarding TRES of CHF-PROM, the degenerate class (34.6%) and the meliorate class (65.4%) had almost the same baseline and curve of slope till 18 months. The TRES of degenerate class decreased quickly, while that of the meliorate class increased from then on. The parameter estimates for two classes with corresponding standard errors and *P*-values and descriptive statistics of OS are shown in Table 3. Compared with the meliorate class, patients in the degenerate class were significantly more likely to have concomitant COPD and take less ACEI/ARBs (see Table 4). Figure 3D shows the distribution of patients with different characteristics in the two subgroups of TRES.

Discussion

Chronic heart failure greatly affects patients' QOL, and the PROs are important tools for measuring QOL. In this study, we used CHF-PROM to measure QOL of patients with CHF. To the best of our knowledge, this is the first study to identify subgroup trajectories of PROM using a longitudinal prospective study design. Moreover, the baseline characteristics associated with the trajectories were also examined to help identify different subgroups.

We have identified two subgroups with distinct trajectories of OS of CHF-PROM. The OS increased linearly in both subgroups during six months after discharge. After that, it plateaued. This trend indicated that the first six months are extremely significant, as it is a critical period for the improvement of QOL. Another important finding was that in the poorer class, the OS remained lower during two years compared with the better class, and decreased slightly from six to eighteen months after discharge. Thus, more attention should be paid to patients in the poorer class, especially after six months. For the predictors of class membership, we found age, diastolic pressure, LVEF, several kinds of comorbidities, and use of nitrates to be vital. Previous studies have confirmed that advanced age was an important risk factor for the decline of PROs in CHF,[6,10,11] which is consistent with the result of our study. A study further confirmed the relationship between age and trajectories of PROs.[6] Meanwhile, studies reported that lower systolic blood pressure was associated with poorer Kansas City Cardiomyopathy Questionnaire (KCCQ) and its change.[12,13] It is interesting to note that the poorer class presented with higher LVEF. This may be because the patients of heart failure with preserved ejection fraction had similar QOL as that of patients having heart failure with reduced ejection fraction,[14] which affected the result. Our study showed that diastolic blood pressure, but not systolic blood pressure was important for the dynamic change. Recently, comorbidities have attracted the attention of researchers; they have connected comorbidities to poor prognosis of CHF, including PROs. A Dutch prospective, multicenter study confirmed that patients with comorbidities had lower scores on the physical limitation scale and clinical summary score of the KCCQ.[12] Our study found that atrial fibrillation, diabetes, COPD, cancers, and central nervous system diseases were all related to the subgroup with poorer CHF-PRO. Consequently, QOL of patients with comorbidities should be given due consideration throughout the course of CHF.

For the physical domain of CHF-PROM, we divided patients into three classes based on GMM of PHYS. The scores of better class decreased at one year after discharge, indicating the need to focus on even those patients with comparatively good PHYS, especially after a long time out of the hospital. The curves also indicated the condition of patients in the unstable-poorer class greatly deteriorated between six months to one year after discharge and fluctuated greatly during the follow-up; thus, special attentions should be paid to these patients, especially those of oldest age, highest NYHA grade, and patients with concomitant COPD, cancers, and central nervous system diseases. It is interesting to note that as these factors got worse, so did the physical condition of the patients reflected by PHYS. Age affects the physical condition and NYHA is graded according to physical condition, thus, they were reported to be factors influencing physical limitation.[6,15] Moreover, the results of PHYS emphasized the importance of comorbidities with CHF, because they could further exacerbate physical domain of patients with CHF.[12] Among comorbidities of CHF, COPD, cancers, and central nervous system diseases were statistically significant between groups, which may be due to the greater impairment of physical function in these comorbidities.

The curves showed that PSYS increased modestly throughout the follow-up period. This trend hints at the fact that the psychological states of patients are often overlooked in therapy and need more attention. The curves also present that some patients (poorer class) maintained poorer psychological states. Mental health is seriously affected by CHF; depression and anxiety rates were higher in patients with CHF than that with other diseases.[16] Our results further

highlighted that sex, combined with atrial fibrillation and coronary heart disease, can help to characterize the subgroup with poorer PSYS. Previous study also showed that women had poorer psychological states compared to men.[17] Meanwhile, atrial fibrillation affects patients' PROs as well as psychological domain,[18] and patients with coronary heart disease have higher incidences of anxiety.[19] There was a great difference in the number of patients between two subgroups divided on the basis of psychological domain (better vs poorer: 91.5% vs 8.5%). Despite the poorer PSYS subgroup being in the minority, there is still an urgent need for intervention.

The GMM results for therapeutic domain have clinical significance. The TRES remained mostly stable in the two subgroups until eighteen months after discharge. From then onwards, there was a distinctly opposite trend shown by the two groups, highlighting two points. First, the initial eighteen months may be critical for therapeutic condition. Therapy experience and compliance should be given due focus. Second, CHF concomitant with COPD and use of ACEI/ARBs could help to identify the subgroups of TRES. The percentages of patients took drugs, such as ACEIs/ARBs, in our study were similar to other studies in China and lower than in the United States and Europe.[20,21] We should do more efforts to promote Guideline Determined Medication Therapy for suitable patients with CHF in China. Patients whose TRES decreased (degenerate class) were significantly more likely to have concomitant COPD and use less ACEI/ARBs. Previous study about patient-reported compliance confirmed treatment with ACEI/ARBs was one of the factors positively affecting compliance.[18,22] Patients believed ACEI/ARBs to be an important and necessary part of their treatment and tended to think that compliance with pharmacological treatment can prevent health deterioration and negative outcomes.[23,24] Polypharmacy is common in CHF concomitant with other diseases, which may cause increased side effects and decreased adherence.[23] There are some drug–drug interactions between CHF and COPD treatment regimens.[25] COPD therapy relies heavily on long-acting inhaled β2 agonists, which may precipitate CHF.[26] Contrastingly, use of ACEIs and aspirin for CHF treatment may lead to bronchial hyperresponsiveness.[27]

Although we have carefully designed the analyses, there are several limitations to this study. First, the data of our study were mainly from the Shanxi Province of China, which limits generalizability and requires further validation in other populations. Second, 93 patients were lost to follow-up; this may have affected the internal validity of results. Finally, the patients who died during the follow-up were not included in the final data set of our analysis. More suitable statistical analysis method should be explored in further studies.

Conclusion

In conclusion, this study provides novel insights into the longitudinal changes in QOL of patients with CHF as reflected by CHF-PROM over a period of two years. Different classes were identified with distinct trajectories in the evolution of CHF-PROM using GMM to help provide a perspective on QOL during the disease progression. We identified certain demographic and clinical risk factors that will aid clinicians in formulating necessary interventions to improve QOL for patients with CHF.

Data Sharing Statement

Please contact the corresponding author Yanbo Zhang for the study data, which will be granted upon reasonable request.

Ethics Approval and Consent to Participate

The study protocol received medical and ethical approval from Shanxi Medical University. All participants provided written informed consent and received compensation for their time and effort.

Consent for Publication

All authors have approved the manuscript for publication.

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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 declare that they have no competing interests.

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