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ORIGINAL RESEARCH

Long-Term Trajectories of High-Sensitivity C-Reactive Protein Level Among Patients with Acute Heart Failure

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Background: Inflammation contributes to the progression of heart failure (HF). However, long-term inflammatory trajectories and their associations with outcomes in patients with acute HF remain unclear.

Methods: Data was obtained from the China Patient-Centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study, and high-sensitivity C-reactive protein (hsCRP) was used to reflect the inflammatory level. Only patients who survived over 12-month and had hsCRP data at admission, 1-, and 12-month after discharge were included. The latent class trajectory modeling was used to characterize hsCRP trajectories. Multivariable Cox regression models were used to explore the association between hsCRP trajectories and following mortality.

Results: Totally, 1281 patients with a median 4.77 (interquartile range [IQR]: 4.24–5.07) years follow-up were included. The median age was 64 years (IQR: 54–73 years); 453 (35.4%) were female. Four distinct inflammatory trajectories were characterized: persistently low (n = 419, 32.7%), very high-marked decrease (n = 99, 7.7%), persistently high (n = 649, 50.7%), and persistently very high (n = 114, 8.9%). Compared with the persistently low trajectory, the all-cause mortality was increased in a graded pattern in the persistently high (hazard ratio [HR]: 1.59, 95% confidence interval [CI]: 1.23–2.07) and persistently very high (HR: 2.56, 95% CI: 1.83–3.70) trajectories; nevertheless, the mortality was not significantly increased in very high-marked decrease trajectory (HR: 0.94, 95% CI: 0.57–1.54).

Conclusion: Four distinct inflammatory trajectories were identified among patients with acute HF who survived over 12-month. Patients with persistently high and very high trajectories had significantly higher mortality than those with the persistently low trajectory.

Keywords: heart failure, high-sensitivity C-reactive protein, trajectory, latent class trajectory modeling, mortality

Introduction

Heart failure (HF) is a life-threatening syndrome causing substantial morbidity and mortality, with an estimated 64.3 million people affected worldwide.[1,2] In recent decades, it has been widely recognized that systemic inflammation could contribute to the pathogenesis and progression of HF via multiple mechanisms, including atherosclerosis, reducing energy production and myocardial contractility, extracellular matrix remodeling, cardiomyocyte stiffness, and

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hypertrophy.[3–7] Meanwhile, elevated levels of inflammation are common among patients with HF, which also indicated an increased risk of death.[8,9] High-sensitivity C-reactive protein (hsCRP) is a biomarker reflecting systemic inflammation level which is simple to assay, and has also emerged as a potential prognostic factor in HF.[9,10] Understanding patterns of hsCRP and inflammation level over time may provide novel insights in the association between inflammation and HF.

However, little is known about the long-term hsCRP trajectories among patients hospitalized for HF, and their associations with following outcomes. Prior studies merely reported the hsCRP change within short-term periods, such as changes from index hospitalization to 1-month after discharge,[11–14] which could not reflect the long-term hsCRP trajectory. In addition, they only directly calculated the hsCRP changes based on the overall cohorts, this classic analytic approach, however, could not capture the interindividual variability of hsCRP and inflammatory trajectory subgroups.[11,13,14] Recent studies have introduced the latent class trajectory modeling (LCTM), a group-based approach to identify and characterize the trajectories of a given parameter, and has been used for the analyses of fatigue, mental health, and blood pressure,[15–17] which provides a novel approach to study the long-term hsCRP trajectories. Furthermore, the association between long-term hsCRP trajectory and following mortality also remains to be elucidated. Given the complex association between inflammation and HF, a more nuanced picture of hsCRP trajectory patterns over time may help to understand the pathophysiology of HF and guide clinical management.

To address the knowledge gaps, using the data from a national prospective cohort of patients hospitalized for HF, we aimed to: i) identify and characterize the hsCRP trajectories from admission to 12-month after discharge, and ii) explore the association of hsCRP trajectories with following all-cause and cardiovascular mortality.

Methods

Study Design and Participants

The China Patient-Centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study (China PEACE 5p-HF Study) is a nationwide, prospective, multicenter observational cohort study. The protocol of the China PEACE 5p-HF Study has been published.[18] In brief, the study consecutively screened patients hospitalized for HF within 48 hours of admission between August 2016 and May 2018 from 52 hospitals throughout 20 provinces, covering all economic-geographic regions in China. The eligibility criteria included patients aged 18 years or older and hospitalized for new-onset HF or acute decompensated chronic HF. All enrolled patients had signed the informed consent. Patients were followed up at 1-, 6-, and 12-month after discharge, and annually thereafter. The diagnosis criteria of HF were based on the Chinese guidelines of HF,[19] which is consistent with those of the American College of Cardiology/American Heart Association and the European Society of Cardiology.[20,21] Patients were excluded if they died during the index hospitalization or within 12-month after discharge (n = 890), or lacked hsCRP data at baseline (48-hour of admission), 1-, or 12-month after discharge (n = 2736). Only patients who survived within 12-month and had hsCRP data at admission, 1-, and 12-month were included in the analyses.

The China PEACE 5p-HF Study was approved by the Ethics Committees of Fuwai Hospital and all collaborating hospitals, and the investigation conforms with the principles outlined in the Declaration of Helsinki. The study was registered on www.clinicaltrials.gov (NCT02878811).

Data Collection and Definition

Demographics (age and sex) were collected by physicians using a standardized questionnaire through in-person interviews during the index hospitalization. Comorbidities, clinical characteristics at admission (including systolic blood pressure, diastolic blood pressure, and heart rate), and New York Heart Association (NYHA) class were obtained from medical charts. Left ventricular ejection fraction (LVEF) was measured according to the standard echocardiogram protocol by trained local physicians. Blood samples were taken within 48-hour of admission, and biomarkers at admission (hsCRP, N-terminal pro-B type natriuretic peptide [NT-proBNP], glycosylated hemoglobin A1c [HbA_{1c}], and creatinine) were analyzed at the central laboratory. Other biomarkers at admission (hemoglobin and albumin) were analyzed in the local laboratories.

LVEF subtypes were categorized as HF with reduced ejection fraction (HFrEF, LVEF ≤ 40%), HF with mildly reduced ejection fraction (HFmrEF, LVEF 41–49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥ 50%).[20] New-onset HF was defined as patients without a medical history of previous HF, and decompensated chronic HF as patients with previous HF at baseline. Comorbidities, including hypertension, pneumonia, coronary heart disease, myocardial infarction, atrial fibrillation, valvular heart disease, anemia, diabetes, hypoalbuminemia, reduced renal function, chronic obstructive pulmonary disease (COPD), and stroke, were defined according to medical history, discharge diagnosis, and laboratory results. Anemia was defined as hemoglobin <120 g/L in men, or <110 g/L in women;[22] diabetes as a history of diabetes or HbA_{1c} ≥6.5%; and hypoalbuminemia as albumin <35 g/L. We calculated the estimated glomerular filtration rate (eGFR) with an equation developed by adaptation of the Modification of Diet in Renal Disease equation based on data from Chinese chronic kidney disease patients, and reduced renal function was defined as an eGFR <60 mL/min/1.73m^2.[23,24] Self-report use of medication was recorded at each follow-up.

High-Sensitivity C-Reactive Protein Assay

Serum hsCRP levels were centrally analyzed by a clinical chemistry analyzer (Beckman Coulter AU680); the limit of detection was 0.02mg/L. The intra-assay coefficient of variation was ≤6.21%, and the inter-assay coefficient of variation was ≤8.28%.

Outcomes

The primary clinical outcome was all-cause death, and the secondary clinical outcome was cardiovascular death. Cardiovascular death included sudden cardiac death, death due to HF, cerebrovascular events, acute coronary syndrome, aortic vascular disease, peripheral arterial disease, and pulmonary hypertension.

Deaths were collected, adjudicated, and recorded by the internationally recognized practice employed in multicenter clinical trials.[25] Deaths were collected from death certificates, interviews of patients' relatives, or the national database of death causes. The clinical outcome data was confirmed by clinic staff at the national coordinating center.[26]

Statistical Analysis

Median (interquartile range, IQR) and frequency (percent) were reported for continuous and categorical variables, respectively. Kruskal–Wallis test and Pearson's chi-square test were used to compare continuous and categorical variables, respectively. Given the skewed distribution, the data of hsCRP levels were log-transformed (log_2).

We first used a group-based trajectory model to identify the distinct hsCRP trajectories from admission to 12-month after discharge. The group-based trajectory modeling (latent class trajectory modeling, LCTM) is a statistical approach that combines finite mixture modeling and growth curve modeling into a unified model to identify the latent classes of individuals with similar patterns of change over time.[27] To determine the optimal number of groups, we fitted several models ranging from 1 to 6 latent classes and chose the best model based on the Bayes factor, which compared the Bayesian Information Criterion for each model.[28–30] We also considered the resulting group sizes when selecting the best fit model. Model parameters were estimated by the maximum likelihood. Each patient was then assigned to the trajectory group that best reflected their hsCRP fluctuation using a maximum probability assignment rule for the posterior probabilities for subclass membership obtained from the model. The trajectory class modeling was conducted in SAS using PROC TRAJ. Then, we displayed the spaghetti plots for each hsCRP trajectory group. To test the robustness of the findings, we performed subgroup analyses. In specific, using the same approach, we identified distinct hsCRP trajectories in age, sex, HF presentation (new-onset HF/decompensated chronic HF), LVEF subtype (HFrEF/HFmrEF/HFpEF), and low or high baseline NT-proBNP level subgroups.

We plotted and compared the cumulative incidences of death across hsCRP trajectories using Kaplan–Meier curves and Log-rank tests. Multi-variable Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of clinical outcomes, using the trajectory with the lowest hsCRP level as the reference. Candidate covariates included age, sex, NYHA class, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, anemia, hypoalbuminemia, diabetes, reduced renal function, COPD, stroke, pneumonia at admission, HF presentation, LVEF subtypes, 12-month NT-proBNP levels, self-reported 12-month medication

(angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs] or angiotensin receptor neprilysin inhibitors [ARNIs], β-blockers, and aldosterone receptor antagonists). When analyzing cardiovascular death, non-cardiovascular death was considered as a competing risk.[31] Moreover, using a multi-variable logistic regression model, we also evaluated the factors associated with hsCRP trajectories.

To test the robustness of our findings, three sensitivity analyses were conducted. First, we excluded patients with pneumonia at admission. Second, we excluded patients rehospitalized for HF, myocardial infarction, stroke, or infection within 12-month after discharge. Third, we included patients with at least 2 hsCRP data at admission, 1-, and 12-month.

Rates of the missing value ranged from 0% to 5.0% (HbA_{1c}). Baseline missing data were imputed using multiple imputations. Tests for statistical significance were 2-sided with a level of 0.05. All analyses were performed using SAS software (Version 9.4 SAS Institute, Cary, NC) and R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics by High-Sensitivity C-Reactive Protein Trajectories

A total of 1281 patients hospitalized for HF who survived within 12-month after discharge were included in the analyses. The median follow-up duration was 4.77 years (IQR: 4.24–5.07 years). The median age was 64 years (IQR: 54–73 years), and women accounted for 453 (35.4%) patients. The mean hsCRP level decreased steeply from admission (log_2-hsCRP: 1.99, 95% CI: 1.88–2.11) to 1-month (log_2-hsCRP: 0.67, 95% CI: 0.58–0.76), then slightly increased at 12-month (log_2-hsCRP: 0.87, 95% CI: 0.78–0.97) after discharge (Supplement Figure S1).

After fitting models with 1 to 6 latent classes, a 4-class model was considered the best fit (Supplement Table S1). There were 419 (32.7%) in the persistently low, 99 (7.7%) in the very high-marked decrease, 649 (50.7%) in the persistently high, and 114 (8.9%) in the persistently very high hsCRP trajectories. The four distinct trajectories are shown in Figure 1, and the spaghetti plots of hsCRP levels by trajectories were displayed in Supplement Figure S2. The hsCRP trajectories were similar in important subgroups, including age, sex, HF presentation, LVEF subtypes, with low or high NT-proBNP levels at baseline (Supplement Figures S3–S7).

The baseline characteristics by hsCRP trajectories are presented in Table 1. Patients in the persistently very high trajectory were older, with higher NYHA class, more frequently to be complicated with hypertension, reduced renal function, and hypoalbuminemia, and with higher levels of NT-proBNP, creatinine, and hsCRP at admission, 1-, and 12-month after discharge. Moreover, patients in the very high-marked decrease trajectory were more likely to have pneumonia at admission.

Association of High-Sensitivity C-Reactive Protein Trajectories with All-Cause Mortality

During the follow-up, all-cause death occurred in 374 (29.2%) patients. The unadjusted Kaplan–Meier curves of all-cause death are displayed in Figure 2A. The all-cause mortality was the highest in the persistently very high trajectory (53.5%), followed by the persistently high (32.1%), and similar in the very high-marked decrease (20.2%) and the persistently low (20.3%) trajectories (Log-rank $P < 0.001$). In the multi-variable analyses, taking the persistently low trajectory as a reference, patients in the persistently high (HR: 1.59, 95% CI: 1.23–2.07) and very high (HR: 2.56, 95% CI: 1.83–3.70) trajectories had significantly greater risks of all-cause death. Nevertheless, the mortality was similar in the very high-marked decrease (HR: 0.94, 95%: CI 0.57–1.54) and persistently low trajectories (Figure 3).

Association of High-Sensitivity C-Reactive Protein Trajectories with Cardiovascular Mortality

In total, 293 (22.9%) patients died for cardiovascular causes. The unadjusted Kaplan–Meier curves of cardiovascular death are displayed in Figure 2B. Similarly, cardiovascular mortality was the highest in the persistently very high (44.7%) trajectory, followed by the persistently high (24.7%) and very high-marked decrease (19.2%) trajectories, and the lowest in the persistently low (15.0%) trajectory (Log-rank $P < 0.001$). After adjustment, the cardiovascular mortality

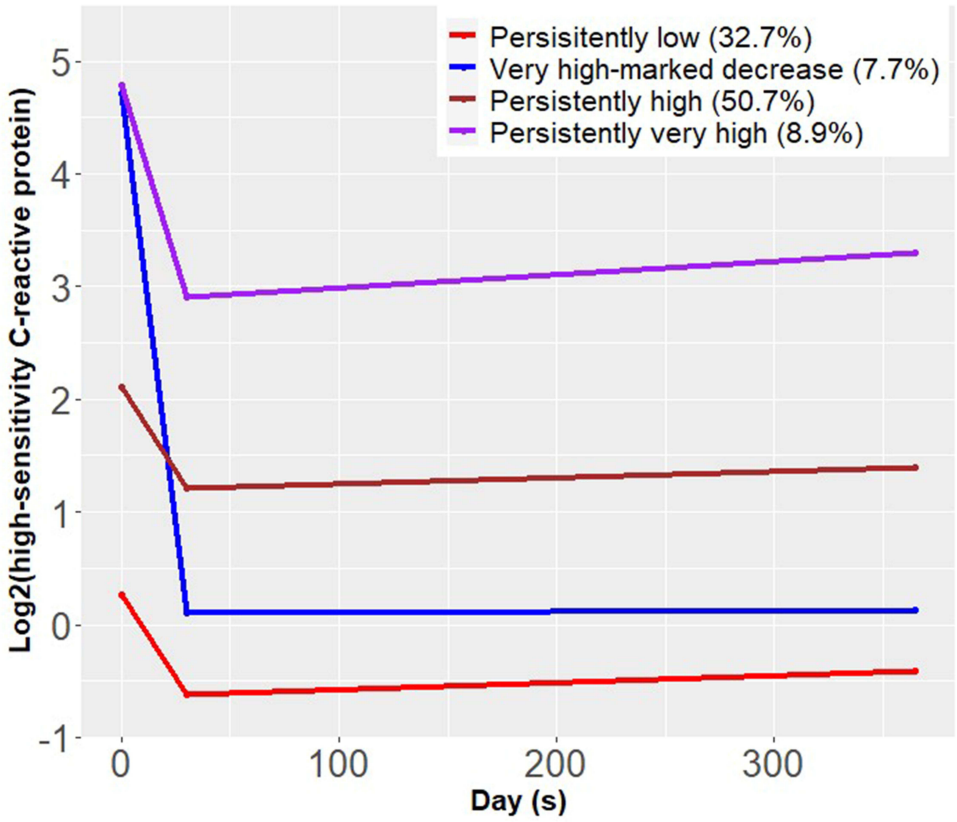

Figure 1 Trajectories of high-sensitivity C-reactive protein from admission to 12-month after discharge.

increased in a graded pattern in the persistently high (HR: 1.69, 95% CI: 1.24–2.28) and very high (HR: 2.97, 95% CI: 1.99–4.42) trajectories. However, the cardiovascular mortality was similar in the very high-marked decrease (HR: 1.14, 95% CI: 0.67–1.93) and persistently low trajectories (Figure 3).

Factors Associated with High-Sensitivity C-Reactive Protein Trajectories

The factors related to hsCRP trajectories were shown in Supplement Figure S8. Patients with reduced renal function (odds ratio [OR]: 1.53; 95% CI: 1.13–2.08), COPD (OR: 1.57; 95% CI: 1.14–2.16), and higher level of NT-proBNP levels (OR: 1.10; 95% CI: 1.04–1.17) at baseline were more likely to be in persistently high or very high trajectories whose prognosis was poor.

Sensitivity Analyses

In sensitivity analyses, the hsCRP trajectories and their associations with following outcomes remained consistent when excluding patients with pneumonia at baseline admission, excluding patients rehospitalized for HF, myocardial infarction, stroke, or infection within 12-month, or including patients with at least 2 hsCRP data at admission, 1-, and 12-month (Supplementary Figures S9 and S10), respectively.

Discussion

In this large multi-center prospective cohort study of patients hospitalized for HF, we reported four distinct hsCRP trajectories from admission to 12-month after discharge, and demonstrated distinctive associations of hsCRP trajectories with following mortality. There were 32.7% of patients with the persistently low hsCRP trajectory, 7.7% very high-marked decrease, 50.7% persistently high, and 8.9% persistently very high. Notably, we observed that in the very high-marked decrease trajectory, the hsCRP level was as high as the persistently very high trajectory at admission, but steeply

Table 1 Baseline Characteristics of High-Sensitivity C-Reactive Protein Trajectories

	Overall (n=1281)	Persistently Low (n=419)	Very High-Marked Decrease (n=99)	Persistently High (n=649)	Persistently Very High (n=114)	P value
Demographic						
Age, year, median (IQR)	64 (54–73)	64 (55–71)	65 (57–75)	64 (53–74)	69 (60–76)	0.025
Female, n (%)	453 (35.4)	152 (36.3)	30 (30.3)	236 (36.4)	35 (30.7)	0.452
Clinical characteristics						
SBP, mmHg, median (IQR)	130 (120–148)	130 (120–143)	131 (115–148)	131 (120–150)	140 (120–150)	0.042
DBP, mmHg, median (IQR)	80 (70–91)	80 (70–90)	80 (70–90)	80 (70–92)	83 (70–96)	0.200
Heart rate, b.p.m, median (IQR)	86 (72–104)	81 (69–99)	95 (82–118)	88 (74–104)	90 (78–109)	<0.001
NYHA class, n (%)						0.004
II	191 (14.9)	82 (19.6)	12 (12.1)	88 (13.6)	9 (7.9)	
III	576 (45.0)	194 (46.3)	46 (46.5)	289 (44.5)	47 (41.2)	
IV	514 (40.1)	143 (34.1)	41 (41.4)	272 (41.9)	58 (50.9)	
Medical history, n (%)						
Hypertension	768 (60.0)	232 (55.4)	64 (64.6)	393 (60.6)	79 (69.3)	0.032
Atrial fibrillation	481 (37.5)	151 (36.0)	44 (44.4)	245 (37.8)	41 (36.0)	0.467
Coronary heart disease	776 (60.6)	261 (62.3)	61 (61.6)	382 (58.9)	72 (63.2)	0.641
Myocardial infarction	287 (22.4)	102 (24.3)	29 (29.3)	133 (20.5)	23 (20.2)	0.151
Valvular heart disease	189 (14.8)	51 (12.2)	17 (17.2)	104 (16.0)	17 (14.9)	0.319
Stroke	250 (19.5)	80 (19.1)	21 (21.2)	124 (19.1)	25 (21.9)	0.868
COPD	236 (18.4)	64 (15.3)	14 (14.1)	131 (20.2)	27 (23.7)	0.060
Reduced renal function	307 (24.0)	72 (17.2)	21 (21.2)	162 (25.0)	52 (45.6)	<0.001
Anemia	146 (11.4)	39 (9.3)	15 (15.2)	71 (10.9)	21 (18.4)	0.031
Diabetes mellitus	412 (32.2)	122 (29.1)	26 (26.3)	218 (33.6)	46 (40.4)	0.058
Pneumonia at admission	206 (16.1)	42 (10.0)	32 (32.3)	105 (16.2)	27 (23.7)	<0.001
Hypoalbuminemia	169 (13.2)	39 (9.3)	19 (19.2)	82 (12.6)	29 (25.4)	<0.001
HF presentation, n (%)						0.494
New-onset HF	361 (28.2)	122 (29.1)	33 (33.3)	178 (27.4)	28 (24.6)	
Decompensated chronic HF	920 (71.8)	297 (70.9)	66 (66.7)	471 (72.6)	86 (75.4)	
LVEF, %, median (IQR)	44 (35–55)	43 (35–54)	44 (36–53)	43 (34–55)	46 (34–58)	0.676
LVEF subtypes, n (%)						0.748
HFrEF	472 (36.9)	159 (38.0)	36 (36.4)	243 (37.4)	34 (29.8)	
HFmrEF	355 (27.7)	118 (28.2)	27 (27.3)	173 (26.7)	37 (32.5)	
HFpEF	454 (35.4)	142 (33.9)	36 (36.4)	233 (35.9)	43 (37.7)	
Biomarkers at baseline, median (IQR)						
Hemoglobin, g/L	138 (125–151)	138 (127–150)	136 (125–148)	140 (125–152)	134 (122–148)	0.147
Albumin, g/L	39 (37–42)	40 (37–43)	38 (36–41)	39 (37–42)	37 (35–40)	<0.001

Length of stay of the index hospitalization, median (IQR)	10 (7–13)	9 (7–12)	10 (8–13)	10 (7–13)	10 (8–13)	0.005
HsCRP, mg/L, median (IQR)						
HsCRP at admission	3.5 (1.5–9.7)	1.1 (0.6–2.0)	30.3 (19.4–62.7)	4.3 (2.5–7.8)	30.0 (18.4–61.7)	<0.001
HsCRP at 1-month	1.5 (0.7–3.2)	0.6 (0.4–0.9)	0.9 (0.6–1.6)	2.2 (1.4–4.2)	7.8 (3.8–17.3)	<0.001
HsCRP at 12-month	1.7 (0.7–3.8)	0.7 (0.4–1.2)	0.9 (0.6–1.6)	2.7 (1.5–4.7)	11.6 (5.0–22.9)	<0.001
NT-proBNP, ng/L, median (IQR)						
NT-proBNP at admission	1081 (450–2280)	755 (314–1550)	1589 (761–3218)	1163 (501–2409)	1773 (790–3797)	<0.001
NT-proBNP at 1-month	742 (315–1495)	535 (208–1190)	789 (460–1323)	846 (344–1744)	1267 (424–2033)	<0.001
NT-proBNP at 12-month	606 (204–1360)	471 (137–1011)	498 (263–1182)	653 (229–1511)	941 (328–2077)	<0.001
Creatinine, μmol//L, median (IQR)						
Creatinine at admission	91 (77–108)	88 (74–101)	91 (78–105)	92 (78–110)	105 (82–124)	<0.001
Creatinine at 1-month	85 (72–102)	82 (70–96)	86 (70–101)	86 (72–104)	94 (76–117)	<0.001
Creatinine at 12-month	88 (75–106)	85 (72–98)	87 (75–103)	90 (76–110)	95 (82–122)	<0.001
Medication at 12-month, n (%)						
ACEI/ARB/ANRIs	590 (46.1)	208 (49.6)	58 (58.6)	276 (42.5)	48 (42.1)	0.006
β-blockers	817 (63.8)	279 (66.6)	75 (75.8)	398 (61.3)	65 (57.0)	0.009
Aldosterone antagonists	570 (44.5)	183 (43.7)	40 (40.4)	295 (45.5)	52 (45.6)	0.781
Diuretics	752 (58.7)	235 (56.1)	53 (53.5)	392 (60.4)	72 (63.2)	0.264
Statins	474 (37.0)	171 (40.8)	45 (45.5)	226 (34.8)	32 (28.1)	0.012
Number of HF rehospitalization within 12-month, median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	0.001

Abbreviations: IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA class, New York Heart Association class; COPD, chronic obstructive pulmonary disease; Reduced renal function: estimated glomerular filtration rate <60 mL/min/1.73m^2; HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.

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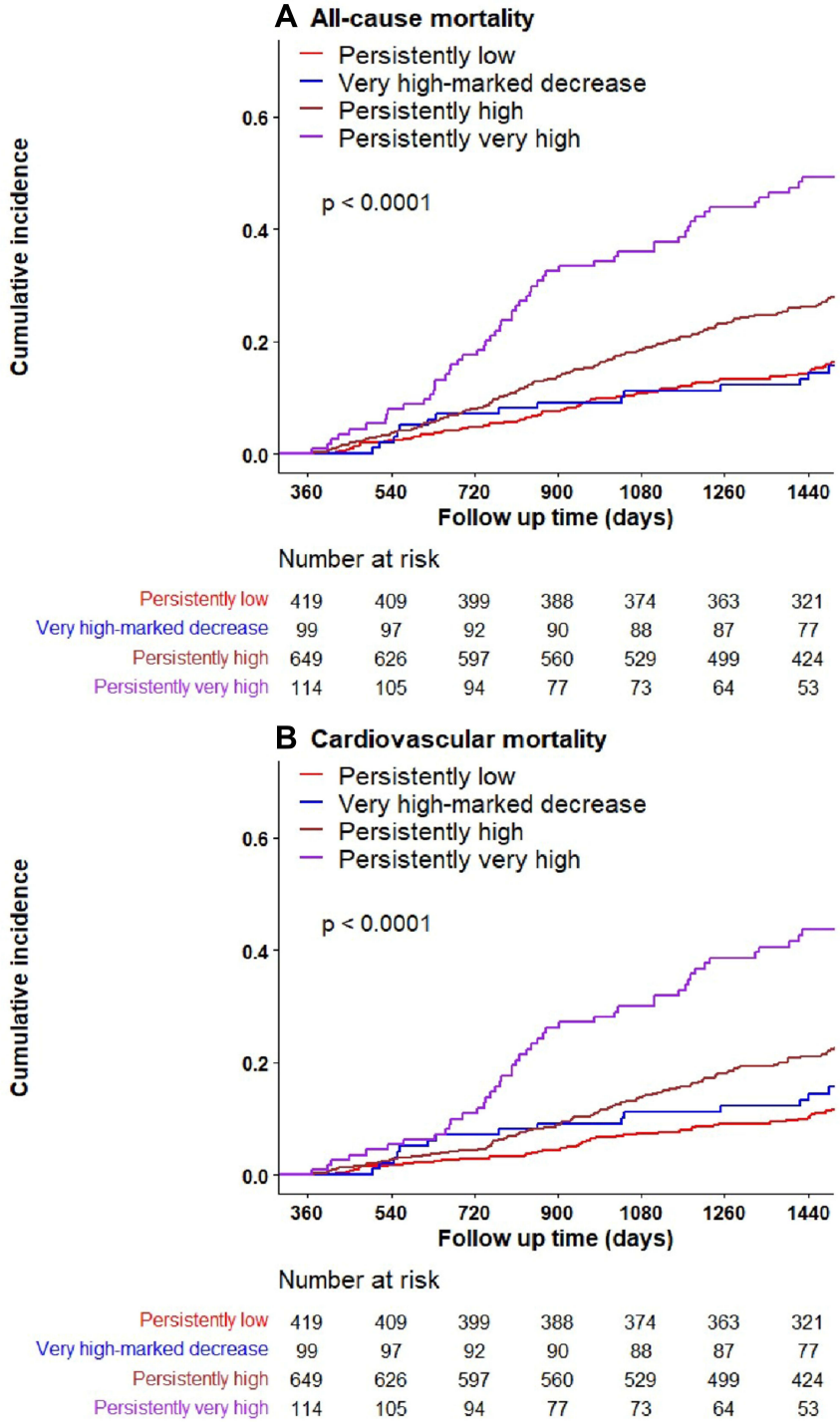

Figure 2 Unadjusted Kaplan–Meier curves.
Notes: (**A**) All-cause mortality by high-sensitivity C-reactive protein trajectories. (**B**) Cardiovascular mortality by high-sensitivity C-reactive protein trajectories.

decreased to a low level close to the persistently low trajectory after discharge. Compared with the persistently low trajectory, the risks of all-cause death increased in a graded pattern in the persistently high (1.6-fold) and very high (2.6-fold) trajectories. However, the mortality was similar in the persistently low and very high-marked decrease trajectories. Our findings indicated that inflammatory trajectories are heterogeneous among patients with acute HF, and various inflammatory trajectories imply different outcome risks.

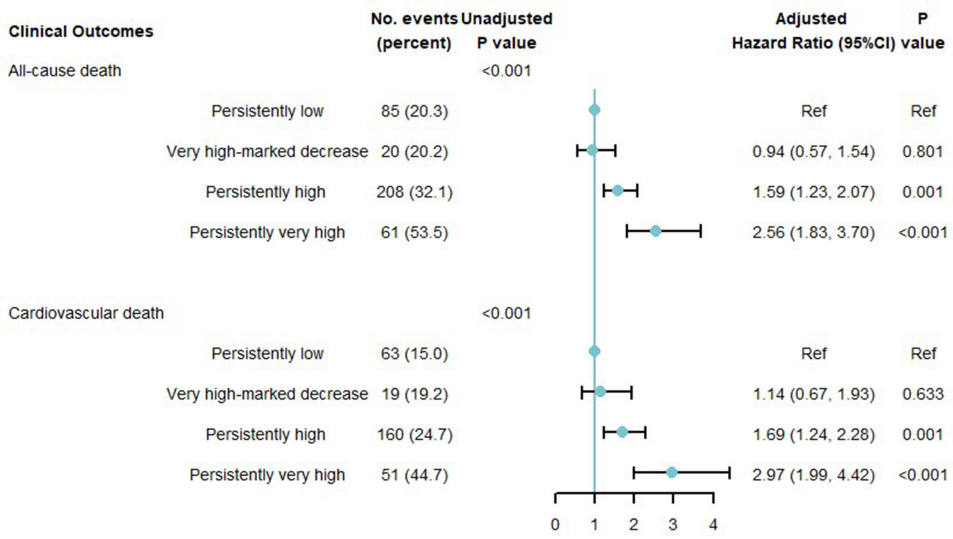

Figure 3 Adjusted association between high-sensitivity C-reactive protein trajectories and following clinical outcomes.
Notes: Adjusted for age, sex, New York Heart Association class, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, anemia, hypoalbuminemia, diabetes, reduced renal function, COPD, stroke, pneumonia at admission, heart failure presentation (new-onset heart failure, decompensated chronic heart failure), left ventricular ejection fraction subtypes (heart failure with reduced ejection fraction, heart failure with mildly reduced ejection fraction, heart failure with preserved ejection fraction), 12-month N-terminal pro-B type natriuretic peptide levels, self-reported 12-month medication of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors, β-blockers, and aldosterone antagonists.
Abbreviation: CI, confidence interval.

Based on a large cohort of patients hospitalized for HF to capture the inflammation trajectories across 3 repeated assays, we provided real-world evidence on the long-term fluctuant nature of hsCRP levels using a group-based trajectory modeling. The group-based trajectory modeling takes into account the variations over time to distinguish hsCRP changes and heterogeneity within multiple hsCRP measurements. It assigns individuals sharing similar hsCRP trajectories to the same subgroup based on multiple measurements over a long-time period.[30,32] In our analyses, hsCRP levels in all trajectories significantly decreased from admission to 1-month after discharge, then slightly increased from 1- to 12-month. Similar to our results, Kalogeropoulos et al also reported a decrease within 1-month after discharge.[11] The decrease of hsCRP from admission to 1-month after discharge might attribute to the in-hospital treatment and recovery from the acute-phase response during the decompensated HF episode.[33–37] Interestingly, the very high-marked decrease trajectory had a very high hsCRP level at admission and then experienced the largest hsCRP decrease. Considering the very high-marked decrease trajectory had the highest prevalence of pneumonia (32.3%) at admission, the steep decrease of hsCRP might reflect the recovery from infection. Moreover, we also found that reduced renal function, COPD, and higher NT-proBNP level were associated with persistently high or very high hsCRP trajectories. Our results suggested that the long-term hsCRP trajectory patterns varied considerably among patients with acute HF.

Our study was distinguished by revealing the different mortality along with the various hsCRP trajectories in patients hospitalized for HF. Some previous studies had shown that the increased hsCRP levels were independently associated with a worse prognosis.[11,38,39] However, our results indicated that a single hsCRP measurement at baseline might overestimate the mortality in the very high-marked decrease hsCRP trajectory. We found that the patients in the very high-marked decrease trajectory had similar mortality to those with the persistently low trajectory. The possible mechanism might be that HF progression depends on a prolonged inflammatory condition rather than a transiently elevated inflammation at one time.[38,40] Moreover, as expected, compared with the persistently low trajectory, individuals with persistently high and very high trajectories had 1.6- and 2.6-fold risks of death, respectively. The mechanism of inflammation contributing to HF progression and excess mortality was not quite clear yet, and the possible mechanism included left ventricular dysfunction, altering cardiac metabolism, and cardiac remodeling.[41] Our study indicated that hsCRP trajectories might facilitate identifying high-risk patients and delivering appropriate therapies.

Although current guidelines have not recommended routinely measurements of hsCRP,[20,21] our findings added to the evidence base supporting a potential role for hsCRP testing in patients with acute HF. HsCRP assay is simple and convenient, without requiring any high-tech equipment or highly educated physicians, which makes it feasible in the medical resource-limited setting. With our findings, physicians could routinely assay hsCRP levels and identify the patients with the persistently high and very high trajectories, who were prone to deteriorated survival. Furthermore, hsCRP trajectories might help design future studies. Although several medications could improve the survival of patients with HF via various mechanisms,[20] the efforts of anti-inflammatory therapies were mostly unsuccessful, such as the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial of infliximab, Randomized Etanercept Worldwide Evaluation (RENEWAL) trial of etanercept, Epidemiology of Acute Heart Failure in the Emergency Departments (EAHFE) registry study of corticosteroid, and a clinical trial of colchicine.[42–45] They enrolled patients without distinguishing their dynamic inflammatory trajectory patterns. However, according to our results, the trajectories of inflammatory levels were heterogeneous among patients with HF, and only persistently high and very high trajectories were associated with increased risks of death. Therefore, future anti-inflammatory studies might be warranted to specifically focus on these precise subpopulations of patients with HF.

One strength of our study is that it is a national prospective cohort study with detailed information collected at baseline and well-maintained longitudinal follow-up data. This allowed us to identify distinguished hsCRP trajectories and comprehensively analyze the association of hsCRP with mortality with rigorous adjustment. Nevertheless, our study is also subject to several limitations. The first limitation is the observational nature of the study, the residual unmeasured confounding during evaluating the associations between hsCRP trajectories and mortality may persist despite adjustment for a variety of known clinical and laboratory variables. Secondly, we only included patients who survived within 12-month and had hsCRP data at 1- and 12-month after discharge, a considerable number of participants were excluded from the analyses. Our conclusions could be subject to selection bias. However, to test the robustness of our findings, we performed subgroup analyses and sensitivity analyses, and the results were similar. Thirdly, our analyses could not explain the pathophysiological mechanism of inflammatory trajectories, which still requires further research. Finally, our results were based on a Chinese population and the generalizability to other populations should be treated with caution.

Conclusion

The inflammatory trajectories varied considerably among patients who were hospitalized for HF and survived within 12-month after discharge, and four distinct trajectories were identified. Patients with the persistently high and very high hsCRP trajectories had significantly increased risks of all-cause and cardiovascular death. Serial measurements of hsCRP could help understand the longitudinal inflammatory fluctuation and identify high-risk patients.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to the government policy stipulates, it is not permissible for the researchers to make the raw data publicly available at this time. And currently, it is not yet possible for other researchers to apply for the access.

Ethics Approval and Consent to Participate

All traceable personal identifiers were removed from the analytic dataset to protect patients' privacy. The study protocol was approved by the ethics committees of all collaborate hospitals, including: The Center Hospital of Maanshan; Beijing Liangxiang Hospital; Beijing Chaoyang Hospital; Fuwai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College; The First Affiliated Hospital of Chongqing Medical University; Xiamen Cardiovascular Hospital Xiamen University; Guangdong Provincial People's Hospital; Pan Yu Branch of the Second Affiliated Hospital Of Guangzhou Medical University; The People's Hospital of Guangxi Zhuang Autonomous Region; The First Affiliated Hospital of Hebei North University; Luoyang Dongfang Hospital; Puyang Oilfield General Hospital; Qinyang People's Hospital; Xinxiang Central Hospital; The Affiliated Hospital of Xuzhou Medical University; The first Affiliated Hospital of Zhengzhou University; Brain Hospital of Hunan Province; The First Affiliated Hospital of University of South China; Inner Mongolia International Mongolian Hospital; Hulunbeir People's Hospital; Baogang Hospital; The Second Affiliated Hospital of Baotou Medical college; The Affiliated Hospital of Inner Mongolia Medical University; Inner

Mongolia People's Hospital; Inner Mongolia Hospital of Traditional Chinese Medicine; The Second Affiliated Hospital of Xuzhou Medical University; The First Hospital of Jilin University; China-Japan Union Hospital of Jilin University; Anshan Changda Hospital; Benxi Jinshan Hospital; Affiliated Zhongshan Hospital of Dalian University; Shenyang the Fourth Hospital of People; Shenyang First People's Hospital; Central Hospital of Shenyang Sujiatun District; Xinmin People's Hospital; Qinghai Cardiovascular and Cerebrovascular Hospital; Affiliated Hospital of Jining Medical University; Qingdao Fuwai Cardiovascular Hospital; Shanxi Fenyang Hospital; Quwo County People's Hospital; Second Hospital of Shanxi Medical University; Taiyuan City Central Hospital; The First Affiliated Hospital of Xi'an Jiaotong University; XIAN NO.1 Hospital; Nanchong Central Hospital; No.363 Hospital; Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region; First Affiliated Hospital of Kunming Medical University; The Affiliated Yueqing Hospital of Wenzhou Medical University; Ningbo First Hospital; Taizhou Hospital of Zhejiang Province; Zhejiang Hospital. The study was performed according to the declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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