ORIGINAL RESEARCH

Change in Depressive Symptoms During the First Month of Discharge and 1-Year Clinical Outcomes in Patients Hospitalized for Heart Failure

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BACKGROUND: The patterns of depressive symptom change during the first month after discharge, as well as their prognostic implications, and predictors of persistent or new-onset depressive symptoms are not well characterized.

METHODS AND RESULTS: We included patients hospitalized for heart failure undergoing Patient Health Questionnaire-2 before discharge and at 1 month after discharge in a multicenter prospective cohort. We characterized 4 patterns of change in depressive symptoms—persistent, new-onset, remitted depressive symptoms, and no depressive symptom—and examined the associations between the 4 patterns and 1-year clinical outcomes. We analyzed the factors associated with persistent or new-onset depressive symptoms. A total of 4130 patients were included. Among 1175 (28.5%) symptomatic patients and 2955 (71.5%) symptom-free patients before discharge, 817 (69.5%) had remission, and 366 (12.2%) had new-onset depressive symptoms, respectively. Compared with no depressive symptom, persistent depressive symptoms were associated with an increased risk of cardiovascular death (hazard ratio [HR], 2.10 [95% CI, 1.59–2.79]) and heart failure rehospitalization (HR, 1.56 [95% CI, 1.30–1.87]); new-onset depressive symptoms were associated with an increased risk of cardiovascular death (HR, 1.78 [95%CI, 1.32–2.40]) and heart failure rehospitalization (HR, 1.54 [95% CI, 1.29–1.83]). Remitted depressive symptoms were associated with a slightly increased risk of cardiovascular death but had no significant association with heart failure rehospitalization. Patients who were female or had poor socioeconomic status, stroke history, renal dysfunction, or poor health status had a higher risk of persistent or new-onset depressive symptoms.

CONCLUSIONS: Sex, socioeconomic status, clinical characteristics, and health status help identify patients with high risks of depressive symptoms at 1 month after discharge. Dynamic capture of depressive symptom change during this period informs long-term risk stratifications and targets patients who require psychological interventions and social support to improve clinical outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier (NCT02878811).

Key Words: death ■ depressive symptom ■ heart failure ■ postdischarge period ■ rehospitalization

Heart failure (HF) is a leading cause of hospitalization associated with substantial mortality, morbidity, and health care expenditures.[1,2] Depression is a frequent and debilitating comorbidity affecting 10% to 30% of patients with acute HF,[3,4] and the number of those with depressive symptoms is even larger. Comorbid depressive

CLINICAL PERSPECTIVE

What Is New?

- By leveraging a contemporary multicenter prospective cohort of patients hospitalized for heart failure, our study first examined the associations between change in depressive symptoms during the first month after discharge and 1-year risk of death or rehospitalization.
- Patients with persistent, new-onset, or remitted depressive symptoms at 1 month after discharge had 110%, 80%, and 30% higher risk of 1-year cardiovascular death compared with those without depressive symptom, respectively.
- Patients who were female or had poor socioeconomic status, stroke history, renal dysfunction, or poor health status had a higher risk of persistent or new-onset depressive symptoms at 1 month after discharge.

What Are the Clinical Implications?

- Persistent or new-onset depressive symptoms during the first month of discharge are associated with worse clinical outcomes among patients hospitalized for heart failure, highlighting the importance of repeated assessment of depression to target high-risk patients for psychological intervention and social support to improve their outcomes.

Nonstandard Abbreviations and Acronyms

China PEACE 5p-HF Study	China Patient-Centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study
KCCQ-12	Kansas City Cardiomyopathy Questionnaire-12
PHQ-2	Patient Health Questionnaire-2
RASI	renin-angiotensin system inhibitors

symptoms compromised patients' adherence to therapies[5] and healthy lifestyles[6] and were associated with impaired quality of life,[7] recurrent rehospitalization,[8] increased mortality,[4] and augmented costs.[9]

Depressive symptoms are characterized by relapsing and remitting courses,[10] and repeated measurements of symptoms after discharge may better reflect future risks of adverse events than a single measurement. Johansson et al reported that among patients with HF enrolled in a randomized controlled trial, 26.2% of patients had persistent or new-onset depressive symptoms at 18 months after hospital discharge that were associated with a higher risk of death or rehospitalization.[11] However, the long time interval may have concealed any remission or recurrence. Although the preliminary results from a small study suggested patients with acute HF experienced significant change in depressive symptoms during the first month of discharge,[12] the patterns of depressive symptom change in this vulnerable period,[13,14] as well as their prognostic significance and associated patient characteristics, remain unknown. Multiple stressors during this period, including changes in diet, lack of physical activity, or confrontation with family or social stresses,[15] can hypothetically arouse fluctuations of ongoing depressive symptoms or even provoke new depressive episodes.

Accordingly, we used data from a multicenter prospective cohort of real-world patients hospitalized for HF and aimed to characterize the changes in depression symptoms from before discharge to 1 month after discharge, to examine the associations between the patterns of depressive symptom change and 1-year clinical outcomes and to identify the predictors of persistent depressive symptoms or new-onset depressive symptoms. Addressing these issues could provide important insights for targeting psychological intervention and social support to improve clinical outcomes.

METHODS

Data Availability

The data underlying this article currently cannot be shared publicly.

Study Design and Population

China PEACE 5p-HF Study (China Patient-Centered Evaluative Assessment of Cardiac Events Prospective Heart Failure Study) is a nationwide prospective cohort of patients with acute HF from 52 hospitals located in 20 provinces between August 2016 and May 2018. The design has been detailed elsewhere.[16] Briefly, we invited consecutive patients who were aged 18 years or older and hospitalized for newly diagnosed or acute decompensated HF to participate in the study within 48 hours of their admission. Patients who signed informed consent were enrolled and followed up at 1, 6, and 12 months after discharge. The diagnosis criteria of HF were based on the Chinese guidelines of HF,[17] which are consistent with those of the American College of Cardiology/American Heart Association[18] and European Society of Cardiology.[19] Patients who did not complete the

Patient Health Questionnaire-2 (PHQ-2), a simple and user-friendly screening test for depressive symptoms, either before discharge or at 1 month after discharge were excluded from the current analysis. The study was approved by ethics committees of Fuwai Hospital and local sites. The study was registered on www.clinicaltrials.gov (NCT02878811).

We divided the patients into 4 groups according to their baseline and 1-month PHQ-2 score: no depressive symptom (no depressive symptom before discharge and 1 month), remitted depressive symptoms (depressive symptoms before discharge and remitted at 1 month), new-onset depressive symptoms (no depressive symptom before discharge and developed at 1 month), and persistent depressive symptoms (depressive symptoms before discharge and 1 month).

Data Collection and Definition

Demographics (age, sex), socioeconomic status (education level, marital status, employment status, medical debt), smoking, and self-reported health status were collected by standardized questionnaire through face-to-face interviews during index hospitalization. Education level was categorized as less than high school or high school or above. Employed was defined as undertaking nonmanual or manual work before the index hospitalization. Unemployed was defined as previously employed (including retirement, layoff, unable to work because of permanent illness or disability, unwilling to work, and the need to take care of family) or never employed.[20] Medical debt was defined as having borrowed money from others to pay for medical expenses during the past 12 months. Patients' health status at admission was measured by Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12). The total score ranged from 0 to 100, and a lower score was regarded as worse health status.[21] Cognitive function was assessed by Mini-Cog test before discharge, with scores ranging from 0 to 5 (scores ≤2 indicating cognitive impairment).[22] Cardiovascular risk factors, New York Heart Association class, comorbidities, systolic blood pressure, and heart rate were obtained through central medical record abstraction. Left ventricular ejection fraction (LVEF) was measured before discharge. LVEF phenotypes were categorized as HF with reduced EF (HFrEF, LVEF<40%), HF with mildly reduced EF (40% ≤LVEF<50%) and HF with preserved EF (LVEF≥50%). NT-proBNP N-terminal pro-brain-type natriuretic peptide and creatinine were analyzed at central laboratory with samples collected within 48 hours of admission. 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 patients with chronic kidney disease.[23] Self-reported use of medications was recorded at each follow-up. Major adverse cardiovascular events (MACE) were collected and adjudicated centrally based on medical records by trained clinicians, comprising hospitalization for angina, nonfatal myocardial infarction, cardiac arrest with successful resuscitation, HF rehospitalization, and stroke.

Assessment of Depressive Symptoms

Depressive symptoms were assessed before discharge by PHQ-2, a short version of PHQ-9. PHQ-2 has comparable reliability in identifying patients at an increased risk of adverse outcomes, and higher feasibility than PHQ-9.[24] PHQ-2 evaluates the symptoms of depressed mood and anhedonia via 2 items, including "little interest or pleasure in doing things" and "feeling down, depressed, or hopeless." For each symptom, a score of 0, 1, 2, or 3 is assigned to 4 response options ranging from "not at all" to "nearly every day" to estimate the frequency. The total score ranges from 0 to 6, and exceeding 3 is considered as having depression symptoms, with a sensitivity of 83% and a specificity of 92% for depression in patients from primary care settings.[25]

Outcomes

The outcomes of the study included cardiovascular death, all-cause death, HF rehospitalization, and all-cause rehospitalization during 1 year of discharge and were collected and adjudicated centrally based on medical records by trained clinicians. Survival status and cause of death were further confirmed according to the national database of death cause.

Statistical Analysis

Continuous variables were described by mean with SD or median with interquartile range, and categorical variables were described by frequency with percentage. Baseline characteristics were compared using Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables, grouped by patterns of depressive symptom change. We plotted outcomes of 4 patterns by Kaplan–Meier curves and compared them by the log-rank test.

Cox proportional hazards models with shared gamma frailty approach were used to assess the associations of depressive symptom change and the outcomes, counting hospitals as random effects, and adjusting for age (<65, ≥65 years), sex (male, female), smoking status (current smoker, nonsmoker), education level (less than high school, high school or above), New York Heart Association class at admission (II, III, IV), prior HF (new-onset HF, decompensated chronic

HF), hypertension, diabetes, prior myocardial infarction, stroke, anemia, systolic blood pressure at admission (<120, 120–140, ≥140 mm Hg), LVEF phenotype (HFrEF, HF with mildly reduced EF, HF with preserved EF), NT-proBNP (stratified into trichotomies), and eGFR (<45, ≥45 mL/min per 1.73 m^2), self-reported use of medications at 1 month, including renin-angiotensin system inhibitors, β-blocker, and spironolactone and MACE within 1 month after discharge. Proportional hazard assumptions were not violated according to Schoenfeld residual analyses. For cardiovascular death or rehospitalization, noncardiovascular death or all-cause death was censored, respectively. We also added interaction terms of age (<65, ≥65 years), sex (male, female), and LVEF phenotype (HFrEF, HF with mildly reduced EF, HF with preserved EF) to identify potential modification effects. We also examined the association of 4 patterns of change in depressed mood or anhedonia identified from 2 PHQ-2 items with 1-year clinical outcomes separately. For each item, we considered score exceeding 0 as having corresponding symptoms and generated 4 patterns of change in corresponding symptoms: persistent (having symptoms before discharge and 1 month), new-onset (no symptom before discharge and developed at 1 month), remitted (having symptoms before discharge and remitted at 1 month) symptoms, and no symptom (no symptom before discharge and 1 month). To confirm the robustness of the results from the Cox proportional hazards models, we also fitted generalized linear mixed models counting hospitals as random effects adjusting for the same variables as the Cox models.

A generalized linear mixed model counting hospitals as random effects was used to determine the factors associated with persistent or new-onset depressive symptoms at 1 month after discharge, with no depressive symptom or remitted depressive symptoms as reference. Candidate variables in the multivariate analysis included age (<65, ≥65 years), sex (male, female), marital status (in marriage, not in marriage), education level (under high school, high school or above), employment status (employed, unemployed), medical debt, prior HF (new-onset HF, decompensated chronic HF), hypertension, diabetes, prior myocardial infarction, stroke, anemia, LVEF phenotype (HFrEF, HF with mildly reduced EF/HF with preserved EF), eGFR (<45, ≥45 mL/min per 1.73 m^2), NT-proBNP (stratified into dichotomies), 5-unit decrease of KCCQ score at admission, and 1-unit decrease in Mini-Cog score before discharge and MACE within 1 month after discharge. For consistency analyses, we repeated the generalized linear mixed model using a multinomial distribution with patterns of depressive symptoms change as a 4-level dependent variable, with no depressive symptom as reference. We also incorporated persistent, new-onset, or remitted depressive symptoms as an event

of interest and determined the factors associated with this event.

To evaluate the effect of missing PHQ-2 score on the results, we conducted a sensitivity analysis using a propensity method.[26] Propensity scores were generated using logistic regression to estimate the probability of missing PHQ-2 score before discharge or at 1 month after discharge, incorporating demographic and clinical characteristics and health status as predictors. We used the inverse of the propensity score as a means of weighting the observed proportion of 4 patterns of depressive symptom change[27] and reperformed the similar Cox regression models and generalized linear mixed models as the main analyses. To minimize the effect of false negative results from PHQ-2 measurement, we altered the cutoff score of PHQ-2 from 3 to 2, which was reported to have a higher sensitivity,[28] and assessed the associations of depressive symptom change and the outcomes in a similar approach.

Rates of missing value ranged from 0.1% (creatinine) to 4.4% (LVEF). Missing values of continuous variables were imputed with the Markov chain Monte-Carlo method, taking the average of 10× imputation value as the final value. A 2-sided P value of <0.05 was considered statistically significant, and all statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

We enrolled 4907 patients in the China PEACE 5p-HF Study. We excluded 335 patients who did not complete the PHQ-2 before discharge and another 442 who did not complete the PHQ-2 at 1 month after discharge. Finally, 4130 patients were included in the current analysis. Compared with the study cohort, patients who did not complete the PHQ-2 were less likely to have low education level, be marrried, be unemployed, have medical debt, and be current smokers; they were more likely to have anemia, higher NT-proBNP level, lower eGFR level, lower systolic blood pressure level, higher heart rate level, HFrEF, lower KCCQ-12 score, lower Mini-Cog score; less likely to receive renin-angiotensin system inhibitors, β-blocker, or spironolactone at discharge; and more likely to have MACE within 1 month after discharge (Table S1).

The average age of the study cohort was 65.1±13.5 years, and 38.0% were female. PHQ-2 was performed after 7 (6–10) days of admission. There were 1175 (28.5%) patients with depressive symptoms before discharge, 817 (69.5%) of whom had remission at 1 month after discharge. Among 2955 (71.5%) symptom-free patients before discharge, 366 (12.4%) developed new-onset depressive symptoms at 1 month after discharge. The patterns of depressive
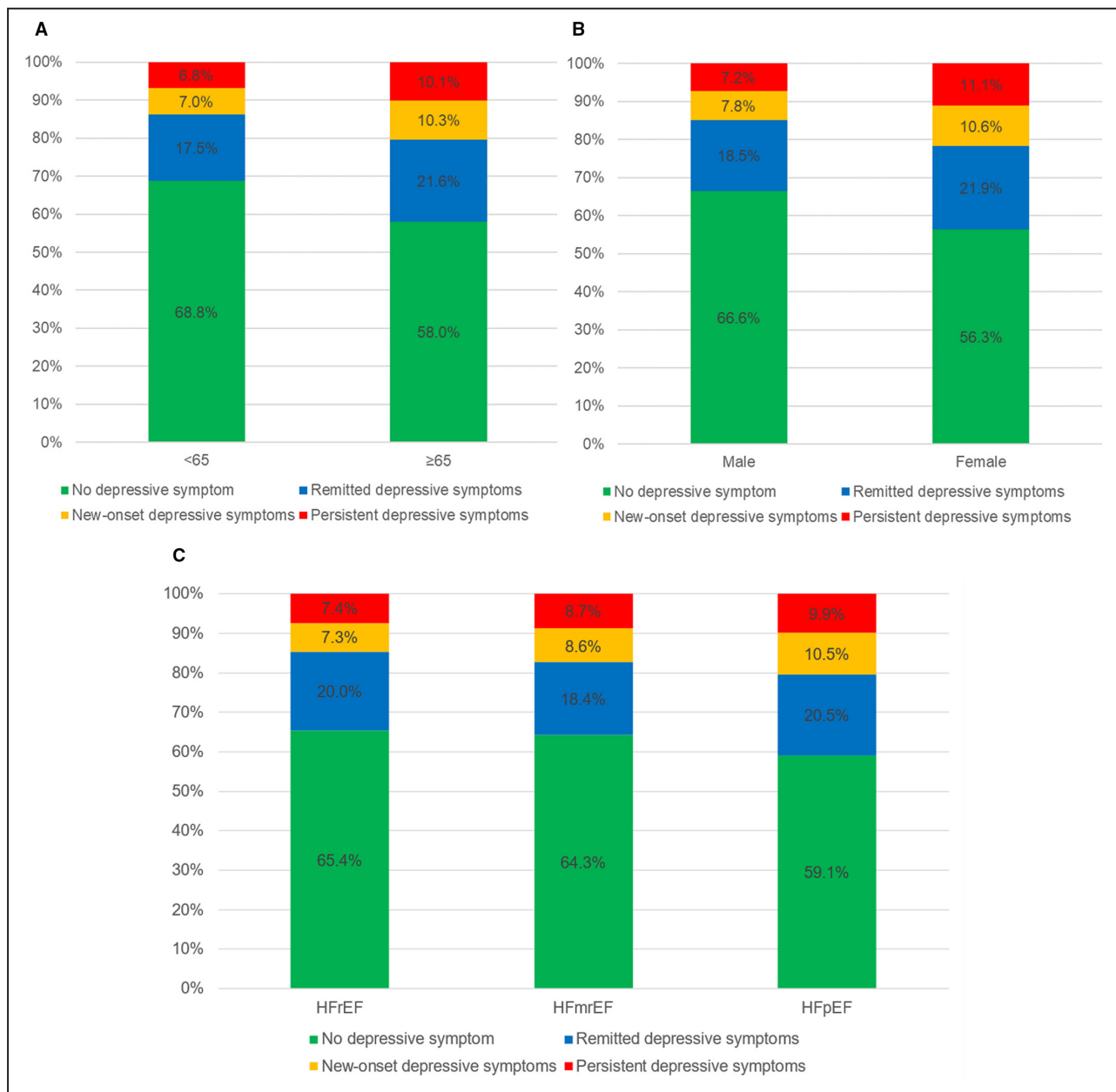
Figure 1.   Patterns of depressive symptom change stratified by age, sex, and LVEF phenotype.

(**A**) Age (<65, ≥65), (**B**) sex (male, female), (**C**) LVEF phenotype (HFrEF, HFmrEF, HFpEF). No depressive symptom: PHQ-2 <2 before discharge and <2 at 1 month; remitted depressive symptoms: PHQ-2 ≥3 before discharge and <2 at 1 month; new-onset depressive symptoms: PHQ-2 <2 before discharge and ≥3 at 1 month; persistent depressive symptoms: PHQ-2 ≥3 before discharge and ≥3 at 1 month. HFmrEF indicates heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

symptom change were generally similar across subgroups of age, sex, and LVEF phenotype (Figure 1). Compared with the patients without depressive symptom, those with persistent or new-onset depressive symptoms were more likely to be female and unemployed and have low education level, medical debt, poor New York Heart Association cardiac function, history of diabetes or stroke, higher NT-proBNP level, lower eGFR, and lower KCCQ-12 score; were less likely to have HFrEF and to receive evidence-based medications both at discharge and at 1 month postdischarge; and were more likely to have MACE within 1 month after discharge. The characteristics of patients with remitted depressive symptoms mostly resembled those of patients with persistent or new-onset depressive symptoms, except that the prevalence of HFrEF was similar to that in patients without depressive symptom (Table 1).

Table 1. Baseline Characteristics by Patterns of Depressive Symptom Change at 1 Month After Discharge

Variables	Total (N=4130)	No depressive symptom (N=2589)	Remitted depressive symptoms (N=817)	New-onset depressive symptoms (N=366)	Persistent depressive symptoms (N=358)	P value
Age, y, mean±SD	65.1±13.5	63.5±13.7	67.2±13.1	67.7±12.3	69.0±12.0	<0.001
Female sex, n (%)	1569 (38.0)	884 (34.1)	344 (42.1)	167 (45.6)	174 (48.6)	<0.001
Socioeconomics, n (%)						
Education level: under high school	2964 (71.8)	1803 (69.6)	608 (74.4)	283 (77.3)	270 (75.4)	0.001
In marriage	3328 (80.6)	2161 (83.5)	622 (76.1)	279 (76.2)	266 (74.3)	<0.001
Unemployed	3400 (82.3)	2010 (77.6)	718 (87.9)	336 (91.8)	336 (93.9)	<0.001
Medical debt	418 (10.1)	193 (7.5)	111 (13.6)	48 (13.1)	66 (18.4)	<0.001
Cardiovascular risk factors, n (%)						
Current smoker	1055 (25.5)	749 (28.9)	173 (21.2)	72 (19.7)	61 (17.0)	<0.001
Hypertension	2421 (58.6)	1499 (57.9)	472 (57.8)	219 (59.8)	231 (64.5)	0.104
Diabetes	1305 (31.6)	787 (30.4)	261 (31.9)	118 (32.2)	139 (38.8)	0.015
Decompensated chronic HF, n (%)	2914 (70.6)	1730 (66.8)	622 (76.1)	268 (73.2)	294 (82.1)	<0.001
New York Heart Association class, n (%)						<0.001
II	605 (14.7)	426 (16.5)	96 (11.7)	45 (12.3)	38 (10.6)	
III	1864 (45.1)	1199 (46.3)	346 (42.4)	185 (50.5)	134 (37.4)	
IV	1661 (40.2)	964 (37.2)	375 (45.9)	136 (37.2)	186 (52.0)	
Comorbidities, n (%)						
Myocardial infarction	867 (21.0)	529 (20.4)	179 (21.9)	64 (17.5)	95 (26.5)	0.017
Stroke	842 (20.4)	462 (17.8)	186 (22.8)	85 (23.2)	109 (30.4)	<0.001
Anemia	919 (22.3)	501 (19.4)	214 (26.2)	92 (25.1)	112 (31.3)	<0.001
Laboratory test						
N-terminal pro-B-type natriuretic peptide, pg/mL, median (interquartile range)	1370 (574, 2996)	1204 (517, 2624)	1659 (709, 3301)	1527 (649, 3559)	2184 (729, 4829)	<0.001
Estimated glomerular filtration rate, mean±SD	73.5±25.2	75.6±24.7	71.2±24.9	72.0±26.6	65.4±25.4	<0.001
Clinical characteristics						
Systolic blood pressure, mmHg, mean±SD	134±24	134±24	134±25	133±23	135±27	0.797
Heart rate, bpm, mean±SD	89±23	89±22	90±23	90±24	88±22	0.845
Left ventricular EF phenotype, n (%)						0.001

(Continued)

Table 1. (Continued)

Variables	Total (N=4130)	No depressive symptom (N=2589)	Remitted depressive symptoms (N=817)	New-onset depressive symptoms (N=366)	Persistent depressive symptoms (N=358)	P value
HF with reduced EF	1537 (37.2)	1005 (38.8)	307 (37.6)	112 (30.6)	113 (31.6)	
HF with mildly reduced EF	1007 (24.4)	647 (25.0)	185 (22.6)	87 (23.8)	88 (24.6)	
HF with preserved EF	1586 (38.4)	937 (36.2)	325 (39.8)	167 (45.6)	157 (43.9)	
Mini-Cog score, mean±SD	3.4±1.7	3.5±1.6	3.1±1.7	3.1±1.7	2.9±1.8	<0.001
Kansas City Cardiomyopathy Questionnaire-12 score, mean±SD	44.5±22.7	49.7±22.1	36.3±21.2	40.3±21.1	29.6±19.4	<0.001
Medications at discharge, n (%)						
RASI	2187 (53.0)	1449 (56.0)	398 (48.7)	169 (46.2)	171 (47.8)	<0.001
ACEI	1319 (31.9)	880 (34.0)	247 (30.2)	91 (24.9)	101 (28.2)	0.001
ARB	880 (21.3)	576 (22.2)	153 (18.7)	79 (21.6)	72 (20.1)	0.177
β-receptor blocker	2478 (60.0)	1652 (63.8)	455 (55.7)	190 (51.9)	181 (50.6)	<0.001
Aldosterone antagonists	2642 (64.0)	1698 (65.6)	516 (63.2)	216 (59.0)	212 (59.2)	0.014
Medications at 1 mo, n (%)						
RASI	1550 (37.5)	1035 (40.0)	258 (31.6)	132 (36.1)	125 (34.9)	<0.001
ACEI	916 (22.2)	620 (23.9)	158 (19.3)	66 (18.0)	72 (20.1)	0.005
ARB	641 (15.5)	419 (16.2)	102 (12.5)	67 (18.3)	53 (14.8)	0.030
β-receptor blocker	2305 (55.8)	1509 (58.3)	432 (52.9)	185 (50.5)	179 (50.0)	<0.001
Aldosterone antagonists	2063 (50.0)	1238 (47.8)	457 (55.9)	178 (48.6)	190 (53.1)	<0.001
Major adverse cardiovascular events within 1 mo after discharge, n (%)	321 (7.8)	176 (6.8)	70 (8.6)	37 (10.1)	38 (10.6)	0.012

No depressive symptom: PHQ-2 <2 before discharge and <2 at 1 month; remitted depressive symptoms: PHQ-2 ≥3 before discharge and <2 at 1 month; persistent depressive symptoms: PHQ-2 ≥3 before discharge and ≥3 at 1 month; new-onset depressive symptoms: PHQ-2 <2 before discharge and ≥3 at 1 month. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; EF, ejection fraction; HF, heart failure; PHQ-2, Patient Health Questionnaire-2; and RASI, renin-angiotensin system inhibitor.

Association Between Clinical Outcomes and 4 Patterns of Depressive Symptom Change

During 1-year follow-up, 522 (12.6%) patients died, and 456 (11.0%) died of cardiovascular causes; 2024 (49.0%) patients experienced rehospitalization, and 1364 (33.0%) had HF rehospitalization. Cumulative incidences of the outcomes differed significantly among the 4 patterns of depressive symptom change (all $P<0.001$). Cumulative incidences of death demonstrated a downward gradient from patients with persistent, new-onset, or remitted depressive symptoms compared with those with no depressive symptom; patients with persistent or new-onset depressive symptoms had similar incidences of HF rehospitalization or all-cause rehospitalization and substantially higher incidences than those with remitted depressive symptoms or no depressive symptom (Figure 2).

After adjusting potential confounders, compared with no depressive symptom, persistent depressive symptoms had an increased risk of cardiovascular death (hazard ratio [HR], 2.10 [95% CI, 1.59–2.79], $P<0.001$), all-cause death (HR, 1.91 [95% CI, 1.46–2.48], $P<0.001$), HF rehospitalization (HR, 1.56 [95% CI, 1.30–1.87], $P<0.001$), and all-cause rehospitalization (HR, 1.36 [95% CI, 1.17–1.58], $P<0.001$). Similarly, new-onset depressive symptoms had an increased risk of cardiovascular death (HR, 1.78 [95% CI, 1.32–2.40], $P<0.001$), all-cause death (HR, 1.60 [95% CI, 1.20–2.12], $P=0.001$), HF rehospitalization (HR, 1.54 [95% CI, 1.29–1.83], $P<0.001$), and all-cause rehospitalization (HR, 1.46 [95% CI, 1.26–1.69], $P<0.001$). Although remitted depressive symptoms had a slightly
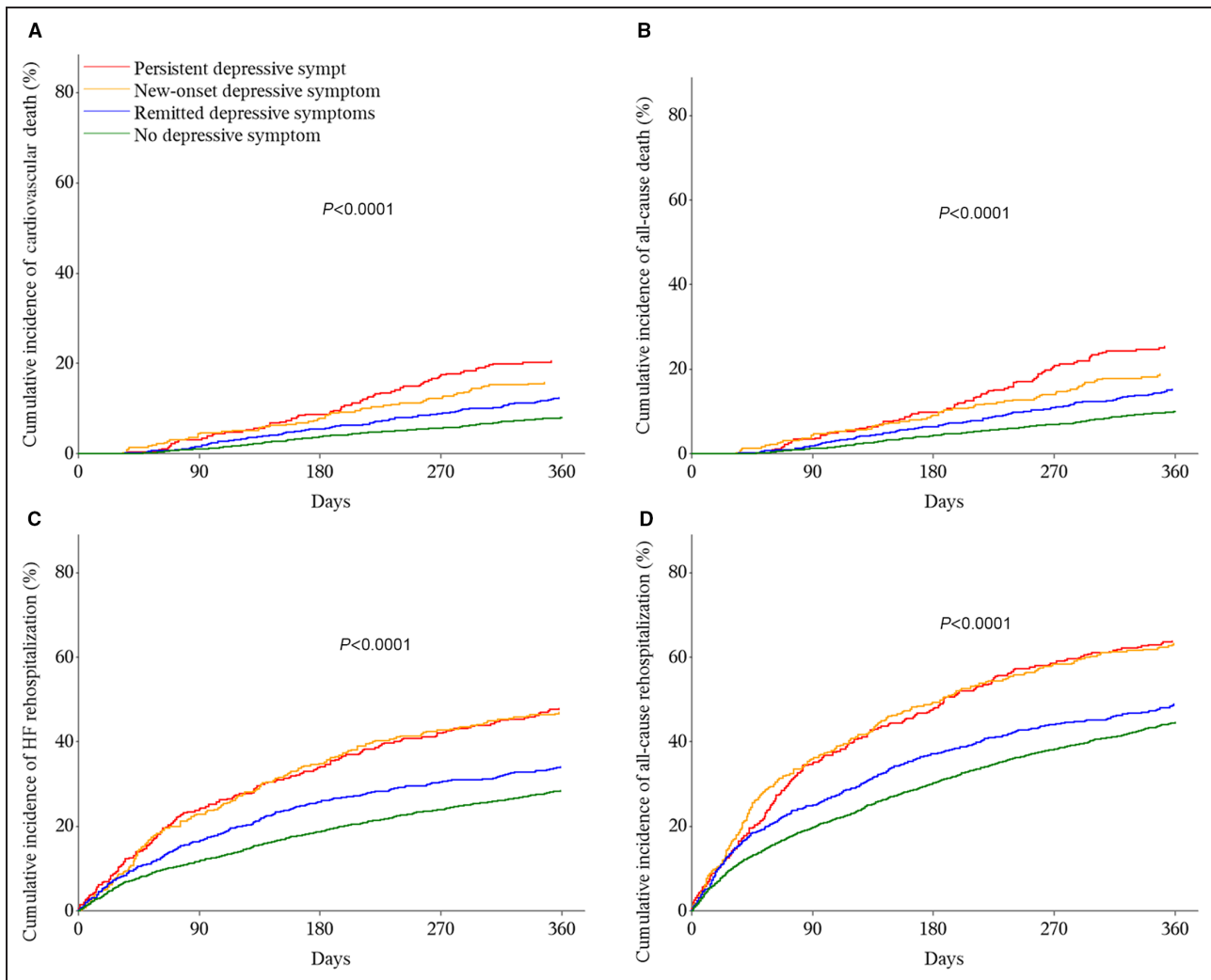
Figure 2.   Outcomes of patients stratified by patterns of depressive symptom change.
(**A**) Cardiovascular death, (**B**) all-cause death, (**C**) heart failure rehospitalization, (**D**) all-cause rehospitalization. No depressive symptom: PHQ-2 <2 before discharge and <2 at 1 month; remitted depressive symptoms: PHQ-2 ≥3 before discharge and <2 at 1 month; new-onset depressive symptoms: PHQ-2 <2 before discharge and ≥3 at 1 month; persistent depressive symptoms: PHQ-2 ≥3 before discharge and ≥3 at 1 month. HF indicates heart failure; and PHQ-2, Patient Health Questionnaire-2.

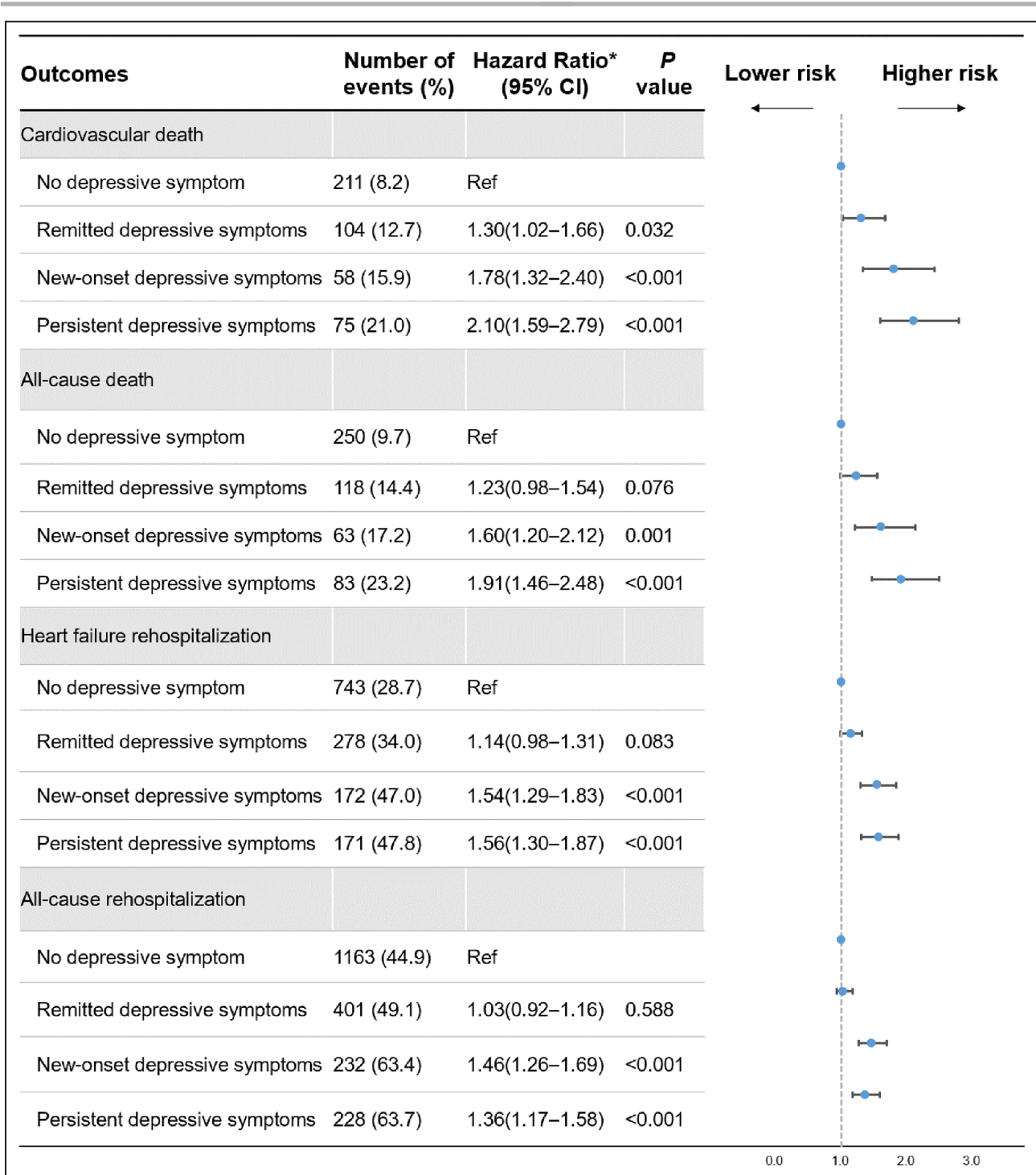| Outcomes	Number of events (%)	Hazard Ratio* (95% CI)	P value	Lower risk ⟵ Higher risk ⟶
Cardiovascular death				
No depressive symptom	211 (8.2)	Ref		
Remitted depressive symptoms	104 (12.7)	1.30(1.02–1.66)	0.032	
New-onset depressive symptoms	58 (15.9)	1.78(1.32–2.40)	<0.001	
Persistent depressive symptoms	75 (21.0)	2.10(1.59–2.79)	<0.001	
All-cause death				
No depressive symptom	250 (9.7)	Ref		
Remitted depressive symptoms	118 (14.4)	1.23(0.98–1.54)	0.076	
New-onset depressive symptoms	63 (17.2)	1.60(1.20–2.12)	0.001	
Persistent depressive symptoms	83 (23.2)	1.91(1.46–2.48)	<0.001	
Heart failure rehospitalization				
No depressive symptom	743 (28.7)	Ref		
Remitted depressive symptoms	278 (34.0)	1.14(0.98–1.31)	0.083	
New-onset depressive symptoms	172 (47.0)	1.54(1.29–1.83)	<0.001	
Persistent depressive symptoms	171 (47.8)	1.56(1.30–1.87)	<0.001	
All-cause rehospitalization				
No depressive symptom	1163 (44.9)	Ref		
Remitted depressive symptoms	401 (49.1)	1.03(0.92–1.16)	0.588	
New-onset depressive symptoms	232 (63.4)	1.46(1.26–1.69)	<0.001	
Persistent depressive symptoms	228 (63.7)	1.36(1.17–1.58)	<0.001	

(x-axis: 0.0   1.0   2.0   3.0)

Figure 3.   Associations between 4 patterns of depressive symptom change at 1 month after discharge and clinical outcomes.
No depressive symptom: PHQ-2 <2 before discharge and <2 at 1 month; remitted depressive symptoms: PHQ-2 ≥3 before discharge and <2 at 1 month; new-onset depressive symptoms: PHQ-2 <2 before discharge and ≥3 at 1 month; persistent depressive symptoms: PHQ-2 ≥3 before discharge and ≥3 at 1 month. *Counting hospitals as random effects and adjusting for age (<65, ≥65 years), sex (male, female), smoking status (current smoker, nonsmoker), education level (less than high school, high school or above), prior HF, New York Heart Association class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, systolic blood pressure (<120, 120–140, ≥140 mm Hg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), N-terminal pro-B-type natriuretic peptide (stratified into trichotomies), eGFR (<45, ≥45 mL/min per 1.73 m²), self-report use of medications at 1 month after discharge (including renin-angiotensin system inhibitors, β-blocker, and spironolactone), and MACE within 1 month after discharge. eGFR indicates estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ-12; LVEF, left ventricular ejection fraction; OR, odds ratio; MACE, major adverse cardiovascular events; and PHQ-2, Patient Health Questionnaire-2.

increased risk of cardiovascular death (HR, 1.30 [95% CI, 1.02–1.66], *P*=0.032), no significant association was observed with all-cause death (HR, 1.23 [95% CI, 0.98–1.54], *P*=0.076), HF rehospitalization (HR, 1.14 [95% CI, 0.98–1.31], *P*=0.083), or all-cause rehospitalization (HR, 1.03 [95% CI, 0.92–1.16], *P*=0.588) (Figure 3). After fitting generalized linear mixed models, the results were similar with the main analyses (Figure S1). There was no significant heterogeneity across subgroups of age, sex, and LVEF phenotype (Tables S2 through S4). After separating 2 symptoms identified from PHQ-2 to assess the association with outcomes, new-onset or persistent depressed mood was associated with higher risks of death or hospitalization. Similar findings were observed for new-onset or persistent anhedonia, although the effect size seemed larger (Table S5).

Factors Associated With Change in Depressive Symptoms

Unemployed status (odds ratio [OR], 1.68 [95% CI, 1.21–2.34]), medical debt (OR, 1.78 [95% CI, 1.38–2.31]), eGFR<45 mL/min per 1.73 m^2 (OR, 1.30 [95% CI, 1.01–1.68]), a 5-unit decrease of KCCQ-12 score at admission (OR, 1.10 [95% CI, 1.08–1.12]), and a 1-unit decrease in Mini-Cog score before discharge (OR, 1.08 [95% CI, 1.02–1.14]) were associated with a higher risk of persistent or new-onset depressive symptoms (Table 2). Female sex (OR, 1.20 [95% CI, 1.00–1.45]) and stroke history (OR, 1.22 [95% CI, 0.99–1.50]) were marginally associated with a higher risk. When treating persistent, new-onset, or remitted depressive symptoms as a 4-level dependent variable, most factors associated with persistent or new-onset depressive symptoms remained consistent with those identified in the main analyses (Table S6). When treating persistent, new-onset, or remitted depressive symptoms as an entity, all the aforementioned factors were consistently relevant, except that eGFR<45 mL/min per 1.73 m^2 was not significant, and there were additional significant factors of prior HF and high NT-proBNP level (Table S7).

Sensitivity Analyses

After accounting for missing PHQ-2 scores by adjusting them with the inverse of propensity score weighting, the proportion of 4 patterns of depressive symptom change did not differ considerably with the main analyses (Figure S2). Association of change in depressive symptoms with the outcomes, as well as predictors of persistent or new-onset depressive symptoms, were also similar (Table S8, Figure S3). Applying a lower PHQ-2 cutoff score of 2 did not affect the association of change in depressive symptoms with the outcomes, except that remitted depressive symptoms were associated with all-cause death (HR, 1.29 [95% CI, 1.02–1.64], *P*=0.035) (Figure S4).

Table 2. Patient Characteristics Associated With Persistent or New-Onset Depressive Symptoms

Factors (reference or unit of change)	Multivariate analysis	
	Odds ratio (95% CI)	*P* value
Age ≥65 y (<65 y)	1.03 (0.84–1.26)	0.793
Female sex (male sex)	1.20 (1.00–1.45)	0.056
In marriage (not in marriage)	0.97 (0.79–1.20)	0.793
Less than high school (high school or above)	1.02 (0.83–1.27)	0.825
Unemployed (employed)	1.68 (1.21–2.34)	0.002
Medical debt (no medical debt)	1.78 (1.38–2.31)	<0.001
Decompensated chronic HF (new-onset HF)	1.18 (0.96–1.45)	0.118
Hypertension (no hypertension)	0.99 (0.82–1.19)	0.875
Diabetes (no diabetes)	1.11 (0.92–1.34)	0.284
Prior MI (no MI)	0.94 (0.76–1.17)	0.591
Stroke (no stroke)	1.22 (0.99–1.50)	0.064
Anemia (no anemia)	1.12 (0.90–1.38)	0.308
HF with mildly reduced EF/ HF with preserved EF (HF with reduced EF)	1.15 (0.94–1.41)	0.183
Estimated glomerular filtration rate <45 (≥45 mL/ min per 1.73 m^2)	1.30 (1.01–1.68)	0.041
High N-terminal pro-B-type natriuretic peptide level (low level)	1.11 (0.92–1.34)	0.280
Kansas City Cardiomyopathy Questionnaire-12 score (per 5-unit decrease)	1.10 (1.08–1.12)	<0.001
Mini-Cog score (per 1-unit decrease)	1.08 (1.02–1.14)	0.008
MACE within 1 mo after discharge (no MACE)	1.32 (0.98–1.77)	0.063

New-onset depressive symptoms: PHQ-2 <2 before discharge and ≥3 at 1 month; persistent depressive symptoms: PHQ-2 ≥3 before discharge and ≥3 at 1 month. EF indicates ejection fraction; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; and PHQ-2, Patient Health Questionnaire-2.

DISCUSSION

By leveraging a contemporary multicenter prospective cohort of patients hospitalized for HF, our study first demonstrated significant change in depressive symptoms during the first month of discharge, which was associated with 1-year risk of death or rehospitalization. One-third of patients with depressive symptoms remained depressed, and 1 in 10 symptom-free patients developed new-onset depressive symptoms. We revealed a stepwise gradient in the overall risks of adverse prognosis from persistent, new-onset, and remitted symptoms to no depressive symptom. Compared with patients without depressive symptom, those with persistent, new-onset, and remitted depressive symptoms had 110%, 80%, and 30% higher

risks of cardiovascular death, respectively, regardless of demographics, socioeconomics, clinical profiles, health status, and therapies. Persistent or new-onset depressive symptoms also had a higher risk of rehospitalization. Women and patients with poor socioeconomics, stroke history, lower eGFR, or poor health status had a higher risk of persistent or new-onset depressive symptoms. Our study highlighted the importance of repeated PHQ-2 measurements, particularly in patients with acute HF with an increased risk of depressive symptoms, and targeted psychological intervention and social support.

Based on the largest cohort with HF to capture the depressive symptom changes across 2 successive assessments, we provided real-world evidence on the fluctuant nature of depressive symptoms during the early postdischarge period. Although over two- thirds of patients with depressive symptoms had remission along with HF stabilization over the postdischarge period, a significant proportion experienced persistent or even new-onset depressive symptoms, regardless of age, sex, and LVEF phenotype. Previous small studies also reported that 12% of patients negative for depression at discharge screened by the Geriatric Depression Scale had a positive screen at 4 weeks,[12] and about 60% of patients with mild depression measured by Hamilton Depression Rating Scale went into remission at 6 weeks.[29] Similar patterns were also observed in the studies that had longer assessment intervals with more sophisticated assessment tools.[7,11,30]

Our study was distinguished by revealing the distinctive clinical outcomes along with the different depressive symptom changes at 1 month after discharge. Although studies reported that positive depression screening before discharge was associated with worse outcomes,[31,32] our study indicated that a single measurement was insufficient to orientate the fluctuant depressive symptoms and may ignore some patients with substantially elevated risks of death and rehospitalization. Compared with remitted symptoms, persistent or new-onset depressive symptoms markedly deviated from the prognostic trajectory and had a more deleterious impact on death and rehospitalization. The ongoing depressive symptoms compromised patients' subjective physical function,[33,34] health-related quality of life,[35] and medication adherence[36] and therefore induced adverse events.[37] Data from a randomized trial showed that compared with patients without depressive symptom, those with new-onset depressive symptoms at 18 months after discharge had an increased risk of 3-year mortality,[11] whereas persistent depressive symptoms had a slightly higher risk. Undetected fluctuations of depressive symptoms during the long-term interval and highly selective patients in this study may account for the difference in the conclusions.[11] Previous studies in patients with chronic HF also found

that worsening depressive symptoms over the 1-year period was associated with an increased risk of all-cause death.[38,39] Our study highlighted that clinicians could easily perform PHQ-2 screening before discharge as well as at 1 month after discharge to identify the patients with high risks of depressive symptoms. Those patients may benefit from cognitive behavior therapies[40] or collaborative care interventions including nurse-led assessment and monitoring, as well as structured psychosocial care from social workers.[41]

Our study informed clinical care by identifying sex, socioeconomics, clinical profiles, and health status that predispose patients to persistent or new-onset depressive symptoms. Sex disparity prevails in depression,[42] and a previous study also demonstrated that women were more vulnerable to depressive symptoms than men among patients with HF.[43] As important social determinants of health in patients with HF,[44] unemployed status and medical debt have been identified to predict incident depressive symptoms, echoing the findings from previous studies in patients with HF[45,46] or general populations.[47,48] Impaired renal function has been found to correlate with the development of depression,[49] and depression could also in turn accelerate the progression of chronic kidney disease and lead to poor outcomes in patients with chronic kidney disease.[50] Stroke history was associated with distress and impaired functional status from poststroke disabilities,[51] which may disturb the emotion regulation process after discharge. Lower KCCQ-12 score indicated a worse functioning status and quality of life,[52] which were strongly associated with lower positive emotions in patients.[53,54] Havranek et al found a graded relationship between lower KCCQ-12 score and an increased risk of depression in patients with acute HF.[45] The correlation between cognitive impairment and depression has been reported,[55,56] and a meta-analysis demonstrated that about 32% of patients with mild cognitive impairment had depression.[57] Deteriorating memory function in the early stage of cognitive decline may induce depressive symptoms.[58]

Our findings should be interpreted in the light of the following limitations. First, we did not collect the information of other psychiatric diseases or prescriptions of antidepressants or assess the social support or stressful events that could possibly influence the courses of the depressive symptoms.[59] Second, we could not preclude false-negative results from PHQ-2. However, we performed sensitivity analyses by applying a lower threshold and obtained consistent results. Third, patients who did not complete PHQ-2 at 1 month after discharge had lower KCCQ-12 scores and Mini-Cog scores than those who completed it, suggesting their vulnerability to depressive symptoms. The proportion of persistent or new-onset depressive symptoms, therefore, may be underestimated. We also performed

several sensitivity analyses by accounting for the missing value of PHQ-2, which obtained similar results. Fourth, our observational design could not rule out unmeasured confounding factors, although we collected and adjusted extensive clinical and nonclinical factors.

CONCLUSIONS

In conclusion, the significant change in depressive symptoms during the first month of HF hospitalization discharge and its association with clinical outcomes highlight the importance of repeated PHQ-2 screens before discharge and 1 month later. Particular attention should be paid to women and patients with poor socioeconomic status, stroke history, renal dysfunction, or poor health status. Timely identification of patients with persistent or new-onset symptoms at 1 month after discharge can target psychological interventions and social support, which may improve patient outcomes.

ARTICLE INFORMATION

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Supplemental Material

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of patients who completed PHQ-2 and who did not

Variables	Total (N=4907)	Non-completed (N=777)	Completed (N=4130)	*P* value
Age, years, mean ± SD	65.2 ± 13.5	66.0 ± 13.4	65.1 ± 13.5	0.090
Female, n (%)	1846 (37.6)	277 (35.6)	1569 (38.0)	0.217
Socioeconomics, n (%)				
Education level: Under high school	3421 (69.7)	457 (58.8)	2964 (71.8)	<0.001
In marriage	3836 (78.2)	508 (65.4)	3328 (80.6)	<0.001
Unemployed	3918 (79.8)	518 (66.7)	3400 (82.3)	<0.001
Medical debt	470 (9.6)	52 (6.7)	418 (10.1)	0.003
CV risk factors, n (%)				
Current smoker	1226 (25.0)	171 (22.0)	1055 (25.5)	0.037
Hypertension	2860 (58.3)	439 (56.5)	2421 (58.6)	0.271
Diabetes	1542 (31.4)	237 (30.5)	1305 (31.6)	0.546
Decompensated chronic HF, n (%)	3443 (70.2)	529 (68.1)	2914 (70.6)	0.167
NYHA class, n (%)				<0.001
II	693 (14.1)	88 (11.3)	605 (14.7)	
III	2181 (44.5)	317 (40.8)	1864 (45.1)	
IV	2033 (41.4)	372 (47.9)	1661 (40.2)	
Comorbidities, n (%)				

MI	1015 (20.7)	148 (19.0)	867 (21.0)	0.219
Stroke	1004 (20.5)	162 (20.8)	842 (20.4)	0.770
Anemia	1152 (23.5)	233 (30.0)	919 (22.3)	<0.001
Laboratory test				
NT-proBNP, pg/ml, median (IQR)	1482 (611, 3282)	2269 (933, 5627)	1370 (574, 2996)	<0.001
eGFR, mean ± SD	72.7 ± 25.6	68.6 ± 27.5	73.5 ± 25.2	<0.001
Clinical characteristics				
SBP, mmHg, mean ± SD	133 ± 25	130 ± 26	134 ± 24	<0.001
Heart rate, bpm, mean ± SD	89 ± 22	91 ± 22	89 ± 23	0.004
LVEF phenotype, n (%)				<0.001
HFrEF	1906 (38.8)	369 (47.5)	1537 (37.2)	
HFmrEF	1161 (23.7)	154 (19.8)	1007 (24.4)	
HFpEF	1840 (37.5)	254 (32.7)	1586 (38.4)	
Mini-Cog score, mean ± SD	3.3 ± 1.7	2.8 ± 1.5	3.4 ± 1.7	<0.001
KCCQ-12 score, mean ± SD	44.0 ± 22.7	41.4 ± 22.2	44.5 ± 22.7	0.005
Medications at discharge, n (%)				
RASI	2541 (51.8)	354 (45.6)	2187 (53.0)	<0.001
ACEI	1520 (31.0)	201 (25.9)	1319 (31.9)	0.001
ARB	1034 (21.1)	154 (19.8)	880 (21.3)	0.351
β-receptor blocker	2879 (58.7)	401 (51.6)	2478 (60.0)	<0.001

Aldosterone antagonists	3100 (63.2)	458 (58.9)	2642 (64.0)	0.008
MACE within 1 month after discharge, n (%)	424 (8.6)	103 (13.3)	321 (7.8)	<0.001

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; bpm, beats per minute; CV: cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR: interquartile range; KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PHQ-2, Patient Health Questionnaire-2; RASI, renin-angiotensin system inhibitor; SD, standard deviation; SBP, systolic blood pressure.

Table S2. Outcomes of patients with four patterns of depressive symptom change stratified by age

Age	Clinical outcomes	Patterns of depressive symptom change			
		No depressive symptom	Remitted depressive symptoms	New-onset depressive symptoms	Persistent depressive symptoms
<65 [Adjusted Hazard Ratio* (95%CI)]					
	cardiovascular death	1.00	1.44 (0.98-2.13)	1.64 (0.96-2.81)	2.46 (1.57-3.86)
	all-cause death	1.00	1.47 (1.02-2.13)	1.70 (1.02-2.83)	2.36 (1.52-3.66)
	heart failure rehospitalization	1.00	1.34 (1.06-1.69)	2.07 (1.54-2.78)	1.54 (1.12-2.12)
	all-cause rehospitalization	1.00	1.23 (1.01-1.49)	1.82 (1.41-2.34)	1.52 (1.18-1.97)

≥65 [Adjusted Hazard Ratio* (95%CI)]

cardiovascular death	1.00	1.23 (0.90-1.66)	1.82 (1.27-2.61)	1.93 (1.36-2.73)
all-cause death	1.00	1.11 (0.84-1.46)	1.53 (1.09-2.14)	1.71 (1.25-2.36)
heart failure rehospitalization	1.00	1.03 (0.86-1.24)	1.34 (1.08-1.65)	1.54 (1.24-1.90)
all-cause rehospitalization	1.00	0.94 (0.81-1.09)	1.31 (1.10-1.57)	1.27 (1.06-1.52)

P for interaction

cardiovascular death	-	0.514	0.749	0.388
all-cause death	-	0.221	0.731	0.238
heart failure rehospitalization	-	0.077	0.018	0.984

| | all-cause rehospitalization | - | 0.030 | 0.036 | 0.249 |

No depressive symptom: PHQ-2<2 before discharge and <2 at 1 month; Remitted depressive symptoms: PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: CI, confidence interval.

*Counting hospitals as random effects and adjusting for sex (male, female), smoking status (current smoker, nonsmoker), education level (under high school, high school or above), prior HF, NYHA class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, SBP (<120, 120-140, ≥140mmHg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), NT-proBNP (stratified into trichotomies) and eGFR (<45, ≥45 mL/min/1.73 m^2), self-report use of medications at 1 month after discharge, including renin-angiotensin system inhibitors (RASI), β-blocker and spironolactone, and MACE within 1 month after discharge.

Table S3. Outcomes of patients with four patterns of depressive symptom change stratified by sex

Sex	Clinical outcomes	Patterns of depressive symptom change			
		No depressive symptom	Remitted depressive symptoms	New-onset depressive symptoms	Persistent depressive symptoms
Male [Adjusted Hazard Ratio* (95%CI)]					
	cardiovascular death	1.00	1.29 (0.95-1.74)	1.87 (1.29-2.72)	1.74 (1.20-2.53)
	all-cause death	1.00	1.26 (0.95-1.67)	1.80 (1.26-2.55)	1.72 (1.22-2.43)
	heart failure rehospitalization	1.00	1.10 (0.91-1.33)	1.71 (1.37-2.13)	1.37 (1.08-1.74)
	all-cause rehospitalization	1.00	0.99 (0.85-1.15)	1.74 (1.45-2.10)	1.23 (1.01-1.51)

Female [Adjusted Hazard Ratio* (95%CI)]					
	cardiovascular death	1.00	1.35 (0.90-2.02)	1.70 (1.04-2.77)	2.72 (1.79-4.15)
	all-cause death	1.00	1.17 (0.81-1.69)	1.34 (0.84-2.13)	2.18 (1.47-3.24)
	heart failure rehospitalization	1.00	1.19 (0.95-1.49)	1.35 (1.02-1.78)	1.85 (1.42-2.41)
	all-cause rehospitalization	1.00	1.11 (0.92-1.33)	1.17 (0.93-1.48)	1.52 (1.22-1.89)
P for interaction					
	cardiovascular death	-	0.855	0.751	0.113
	all-cause death	-	0.731	0.318	0.368
	heart failure rehospitalization	-	0.587	0.184	0.085

| all-cause rehospitalization | - | 0.331 | 0.008 | 0.165 |

No depressive symptom: PHQ-2<2 before discharge and <2 at 1 month; Remitted depressive symptoms: PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: CI, confidence interval.

*Counting hospitals as random effects and adjusting for sex (male, female), smoking status (current smoker, nonsmoker), education level (under high school, high school or above), prior HF, NYHA class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, SBP (<120, 120-140, ≥140mmHg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), NT-proBNP (stratified into trichotomies) and eGFR (<45, ≥45 mL/min/1.73 m^2), self-report use of medications at 1 month after discharge, including renin-angiotensin system inhibitors (RASI), β-blocker and spironolactone, and MACE within 1 month after discharge.

Table S4. Outcomes of patients with four patterns of depressive symptom change stratified by LVEF phenotype

LVEF phenotypes	Clinical outcomes	Patterns of depressive symptom change			
		No depressive symptom	Remitted depressive symptoms	New-onset depressive symptoms	Persistent depressive symptoms
HFrEF [Adjusted Hazard Ratio* (95%CI)]					
	cardiovascular death	1.00	1.46 (1.03-2.06)	1.81 (1.11-2.96)	2.06 (1.34-3.17)
	all-cause death	1.00	1.41 (1.01-1.96)	1.77 (1.11-2.83)	1.88 (1.24-2.86)
	heart failure rehospitalization	1.00	1.24 (1.00-1.54)	1.78 (1.34-2.37)	1.33 (0.98-1.80)
	all-cause rehospitalization	1.00	1.14 (0.95-1.38)	1.70 (1.32-2.19)	1.21 (0.92-1.58)

HFmrEF [Adjusted Hazard Ratio* (95%CI)]				
cardiovascular death	1.00	1.12 (0.67-1.86)	1.85 (1.07-3.22)	2.30 (1.38-3.86)
all-cause death	1.00	1.13 (0.71-1.79)	1.55 (0.90-2.66)	2.17 (1.35-3.51)
heart failure rehospitalization	1.00	1.13 (0.85-1.52)	1.24 (0.88-1.74)	1.72 (1.22-2.41)
all-cause rehospitalization	1.00	0.89 (0.70-1.14)	1.42 (1.07-1.88)	1.23 (0.92-1.64)
HFpEF [Adjusted Hazard Ratio* (95%CI)]				
cardiovascular death	1.00	1.22 (0.78-1.89)	1.66 (1.00-2.76)	1.98 (1.23-3.21)
all-cause death	1.00	1.07 (0.71-1.59)	1.44 (0.91-2.30)	1.73 (1.12-2.68)

heart failure rehospitalization	1.00	1.03 (0.81-1.31)	1.55 (1.17-2.05)	1.65 (1.26-2.17)
all-cause rehospitalization	1.00	1.02 (0.85-1.23)	1.32 (1.05-1.66)	1.55 (1.25-1.94)

P for interaction

cardiovascular death				
HFmrEF*patterns	-	0.393	0.951	0.741
HFpEF*patterns	-	0.525	0.813	0.906
all-cause death				
HFmrEF*patterns	-	0.451	0.708	0.653
HFpEF*patterns	-	0.292	0.541	0.777
heart failure rehospitalization				
HFmrEF*patterns	-	0.637	0.105	0.264

HFpEF*patterns	-	0.262	0.490	0.282
all-cause rehospitalization				
HFmrEF*patterns	-	0.113	0.347	0.943
HFpEF*patterns	-	0.416	0.140	0.148

No depressive symptom: PHQ-2<2 before discharge and <2 at 1 month; Remitted depressive symptoms: PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: CI, confidence interval.

*Counting hospitals as random effects and adjusting for sex (male, female), smoking status (current smoker, nonsmoker), education level (under high school, high school or above), prior HF, NYHA class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, SBP (<120, 120-140, ≥140mmHg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), NT-proBNP (stratified into trichotomies) and eGFR (<45, ≥45 mL/min/1.73 m^2), self-report use of medications at 1 month after discharge, including renin-angiotensin system inhibitors (RASI), β-blocker and spironolactone, and MACE within 1 month after discharge.

Table S5. Associations between four patterns of depressive symptom change in each item at 1 month after discharge and clinical outcomes

Outcomes	Item 1 (depressed mood): Hazard Ratio* (95% CI)	Item 2 (anhedonia): Hazard Ratio* (95% CI)
Cardiovascular death		
No symptom	Ref	Ref
Remitted symptoms	1.30 (1.01-1.68)	1.43 (1.08-1.89)
New-onset symptoms	1.33 (0.95-1.87)	2.10 (1.50-2.94)
Persistent symptoms	1.62 (1.24-2.12)	1.82 (1.38-2.41)
All-cause death		
No symptom	Ref	Ref
Remitted symptoms	1.30 (1.03-1.65)	1.37 (1.06-1.78)
New-onset symptoms	1.38 (1.01-1.88)	1.97 (1.44-2.71)
Persistent symptoms	1.58 (1.23-2.03)	1.74 (1.34-2.25)
Heart failure rehospitalization		
No symptom	Ref	Ref
Remitted symptoms	1.11 (0.96-1.29)	1.13 (0.97-1.32)
New-onset symptoms	1.33 (1.10-1.60)	1.31 (1.08-1.61)
Persistent symptoms	1.64 (1.40-1.92)	1.49 (1.27-1.75)
All-cause rehospitalization		
No symptom	Ref	Ref
Remitted symptoms	1.04 (0.92-1.17)	1.06 (0.94-1.20)
New-onset symptoms	1.29 (1.11-1.50)	1.35 (1.15-1.59)

Persistent symptoms	1.44 (1.27-1.63)	1.41 (1.24-1.60)

No symptom: score=0 before discharge and =0 at 1 month; Remitted symptoms: score>0 before

discharge and =0 at 1 month; New-onset symptoms: score=0 before discharge and >0 at 1 month;

Persistent symptoms: score>0 before discharge and >0 at 1 month.

Abbreviations: CI, confidence interval.

*Counting hospitals as random effects and adjusting for age (<65, ≥65 years), sex (male, female),

smoking status (current smoker, nonsmoker), education level (under high school, high school or above),

prior HF, NYHA class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, SBP

(<120, 120-140, ≥140mmHg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), NT-proBNP (stratified into

trichotomies) and eGFR (<45, ≥45 ml/min/1.73 m^2), self-report use of medications at 1 month after

discharge, including renin-angiotensin system inhibitors (RASI), β-blocker and spironolactone, and MACE

within 1 month after discharge.

Table S6. Patient characteristics associated with patterns of depressive symptom change at 1 month after discharge as a 4-level dependent

variable

Factors (reference or unit of change)	Patterns of depressive symptom change					
	Remitted versus no depressive symptoms	*P* value	New-onset versus no depressive symptoms	*P* value	Persistent versus no depressive symptoms	*P* value
Age≥65 (<65 years)	0.99 (0.81-1.22)	0.947	0.96 (0.72-1.29)	0.798	1.11 (0.85-1.45)	0.461
Female (male)	1.14 (0.94-1.37)	0.205	1.35 (1.04-1.76)	0.045	1.16 (0.91-1.49)	0.247
In marriage (not in marriage)	0.81 (0.65-1.00)	0.050	0.95 (0.70-1.28)	0.724	0.85 (0.64-1.13)	0.268
Under high school (high school or above)	0.94 (0.76-1.15)	0.533	0.88 (0.65-1.18)	0.405	1.11 (0.84-1.47)	0.487
Unemployed (employed)	1.21 (0.92-1.59)	0.196	1.63 (0.99-2.69)	0.076	1.85 (1.21-2.82)	0.014
Medical debt (no medical debt)	1.63 (1.24-2.14)	<0.001	2.48 (1.74-3.52)	<0.001	1.82 (1.27-2.60)	0.001
Decompensated chronic HF (new-onset HF)	1.32 (1.08-1.60)	0.018	1.57 (1.15-2.14)	0.015	1.10 (0.85-1.43)	0.494
Hypertension (no hypertension)	0.89 (0.74-1.07)	0.237	1.02 (0.78-1.33)	0.909	0.91 (0.71-1.16)	0.447
Diabetes (no diabetes)	1.01 (0.84-1.22)	0.936	1.17 (0.90-1.52)	0.237	1.05 (0.82-1.35)	0.691
Prior MI (no MI)	1.02 (0.83-1.27)	0.841	1.20 (0.89-1.60)	0.246	0.76 (0.56-1.03)	0.103

Stroke (no stroke)	1.17 (0.94-1.45)	0.177	1.53 (1.15-2.04)	0.012	1.10 (0.82-1.46)	0.539
Anemia (no anemia)	1.18 (0.96-1.46)	0.123	1.37 (1.02-1.83)	0.034	1.03 (0.77-1.37)	0.846
HFmrEF/HFpEF (HFrEF)	1.01 (0.83-1.23)	0.932	1.10 (0.82-1.47)	0.530	1.22 (0.93-1.61)	0.150
eGFR<45 (≥45 ml/min/1.73 m^2)	0.96 (0.73-1.26)	0.779	1.25 (0.89-1.77)	0.224	1.31 (0.93-1.85)	0.148
High NT-proBNP level (low level)	1.20 (1.00-1.44)	0.070	1.21 (0.93-1.58)	0.175	1.14 (0.89-1.45)	0.328
KCCQ-12 score (per 5-unit decrease)	1.13 (1.11-1.16)	<0.001	1.21 (1.17-1.25)	<0.001	1.08 (1.05-1.11)	<0.001
Mini-cog score (per 1-unit decrease)	1.18 (1.12-1.25)	<0.001	1.17 (1.09-1.27)	0.001	1.11 (1.03-1.19)	0.017
MACE within 1 month after discharge (no MACE)	1.05 (0.77-1.42)	0.780	1.24 (0.82-1.87)	0.305	1.38 (0.94-2.04)	0.103

Remitted depressive symptoms: PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12; MACE, major adverse cardiovascular events.

Table S7. Patient characteristics associated with persistent, new-onset or remitted depressive symptoms

Factors (reference or unit of change)	Multivariate analysis	
	Odds Ratio (95%CI)	*P* value
Age≥65 (<65 years)	1.00 (0.85-1.18)	0.996
Female (male)	1.19 (1.02-1.40)	0.025
In marriage (not in marriage)	0.85 (0.71-1.02)	0.086
Under high school (high school or above)	0.97 (0.82-1.16)	0.762
Unemployed (employed)	1.37 (1.09-1.73)	0.007
Medical debt (no medical debt)	1.83 (1.45-2.30)	<0.001
Decompensated chronic HF (new-onset HF)	1.30 (1.10-1.53)	0.002
Hypertension (no hypertension)	0.91 (0.78-1.06)	0.231
Diabetes (no diabetes)	1.05 (0.90-1.23)	0.527
Prior MI (no MI)	0.98 (0.82-1.18)	0.864
Stroke (no stroke)	1.21 (1.01-1.44)	0.042
Anemia (no anemia)	1.18 (0.99-1.41)	0.068
HFmrEF/HFpEF (HFrEF)	1.05 (0.89-1.25)	0.534
eGFR<45 (≥45 mL/min/1.73 m^2)	1.11 (0.89-1.39)	0.361
High NT-proBNP level (low level)	1.19 (1.02-1.38)	0.028
KCCQ-12 score (per 5-unit decrease)	1.14 (1.12-1.16)	<0.001
Mini-cog score (per 1-unit decrease)	1.17 (1.11-1.22)	<0.001

MACE within 1 month after discharge	1.19 (0.92-1.54)	0.181

Remitted depressive symptoms: PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12; MACE, major adverse cardiovascular events.

Table S8. Patient characteristics associated with persistent or new-onset depressive symptoms

adjusting for missing PHQ-2 score by the inverse of propensity score weighting

Factors (reference or unit of change)	Multivariate analysis	
	Odds Ratio (95%CI)	*P* value
Age≥65 (<65 years)	1.03 (0.84-1.27)	0.751
Female (male)	1.21 (1.00-1.46)	0.047
In marriage (not in marriage)	0.99 (0.81-1.22)	0.958
Under high school (high school or above)	1.01 (0.82-1.24)	0.949
Unemployed (employed)	1.61 (1.17-2.21)	0.003
Medical debt (no medical debt)	1.77 (1.36-2.30)	<0.001
Decompensated chronic HF (new-onset HF)	1.19 (0.97-1.47)	0.093
Hypertension (no hypertension)	0.96 (0.80-1.16)	0.699
Diabetes (no diabetes)	1.13 (0.94-1.36)	0.198
Prior MI (no MI)	0.97 (0.78-1.20)	0.787
Stroke (no stroke)	1.23 (1.00-1.51)	0.053
Anemia (no anemia)	1.13 (0.92-1.39)	0.251
HFmrEF/HFpEF (HFrEF)	1.17 (0.95-1.43)	0.141
eGFR<45 (≥45 mL/min/1.73 m^2)	1.33 (1.04-1.70)	0.025
High NT-proBNP level (low level)	1.10 (0.91-1.33)	0.313
KCCQ-12 score (per 5-unit decrease)	1.10 (1.07-1.12)	<0.001
Mini-cog score (per 1-unit decrease)	1.08 (1.02-1.14)	0.006

MACE within 1 month after discharge	1.31 (0.99-1.74)	0.058

New-onset depressive symptoms: PHQ-2<2 before discharge and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-12: Kansas City Cardiomyopathy Questionnaire-12; MACE, major adverse cardiovascular events.

Figure S1. Associations between four patterns of depressive symptom change at 1 month after discharge and clinical outcome measured by generalized linear mixed models

Outcomes	Number of events (%)	Odds Ratio* (95% CI)	P value	Lower risk	Higher risk
Cardiovascular death					
No depressive symptom	214 (8.3)	Ref			
Remitted depressive symptoms	106 (13.0)	1.33(1.02-1.73)	0.035		
New-onset depressive symptoms	58 (15.9)	1.80(1.29-2.51)	0.001		
Persistent depressive symptoms	78 (21.8)	2.34(1.71-3.21)	<0.001		
All-cause death					
No depressive symptom	253 (9.8)	Ref			
Remitted depressive symptoms	120 (14.7)	1.25(0.98-1.60)	0.080		
New-onset depressive symptoms	63 (17.2)	1.61(1.17-2.21)	0.004		
Persistent depressive symptoms	86 (24.0)	2.16(1.59-2.91)	<0.001		
Heart failure rehospitalization					
No depressive symptom	743 (28.7)	Ref			
Remitted depressive symptoms	278 (34.0)	1.05(0.87-1.26)	0.604		
New-onset depressive symptoms	172 (47.0)	2.02(1.59-2.56)	<0.001		
Persistent depressive symptoms	171 (47.8)	1.71(1.34-2.19)	<0.001		
All-cause rehospitalization					
No depressive symptom	1163 (44.9)	Ref			
Remitted depressive symptoms	401 (49.1)	1.02(0.86-1.21)	0.786		
New-onset depressive symptoms	232 (63.4)	1.95(1.53-2.47)	<0.001		
Persistent depressive symptoms	228 (63.7)	1.65(1.28-2.11)	<0.001		

No depressive symptom: PHQ-2<2 before discharge and <2 at 1 month; Remitted depressive symptoms:

PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge

and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: CI, confidence interval.

*Counting hospitals as random effects and adjusting for age (<65, ≥65 years), sex (male, female), smoking

status (current smoker, nonsmoker), education level (under high school, high school or above), prior HF,

NYHA class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, SBP (<120, 120-

140, ≥140mmHg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), NT-proBNP (stratified into trichotomies) and

eGFR (<45, ≥45 mL/min/1.73 m2), self-report use of medications at 1 month after discharge, including renin-

angiotensin system inhibitors (RASI), β-blocker and spironolactone, and MACE within 1 month after

discharge.

Figure S2. Proportion distribution of patterns of depressive symptom change in the main analyses

and sensitivity analyses by accounting for missing PHQ-2 score

No depressive symptom: PHQ-2<2 before discharge and <2 at 1 month; Remitted depressive symptoms:
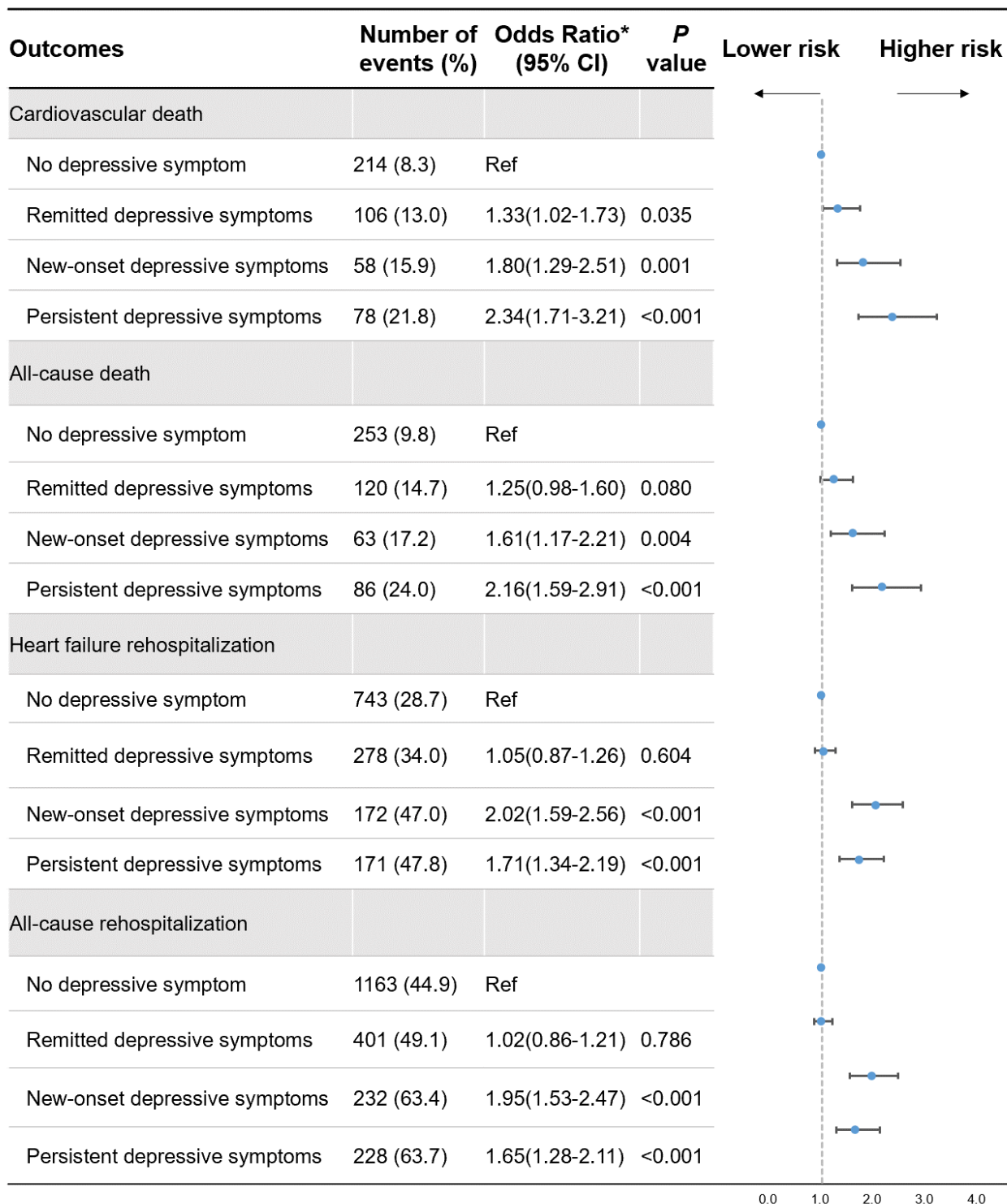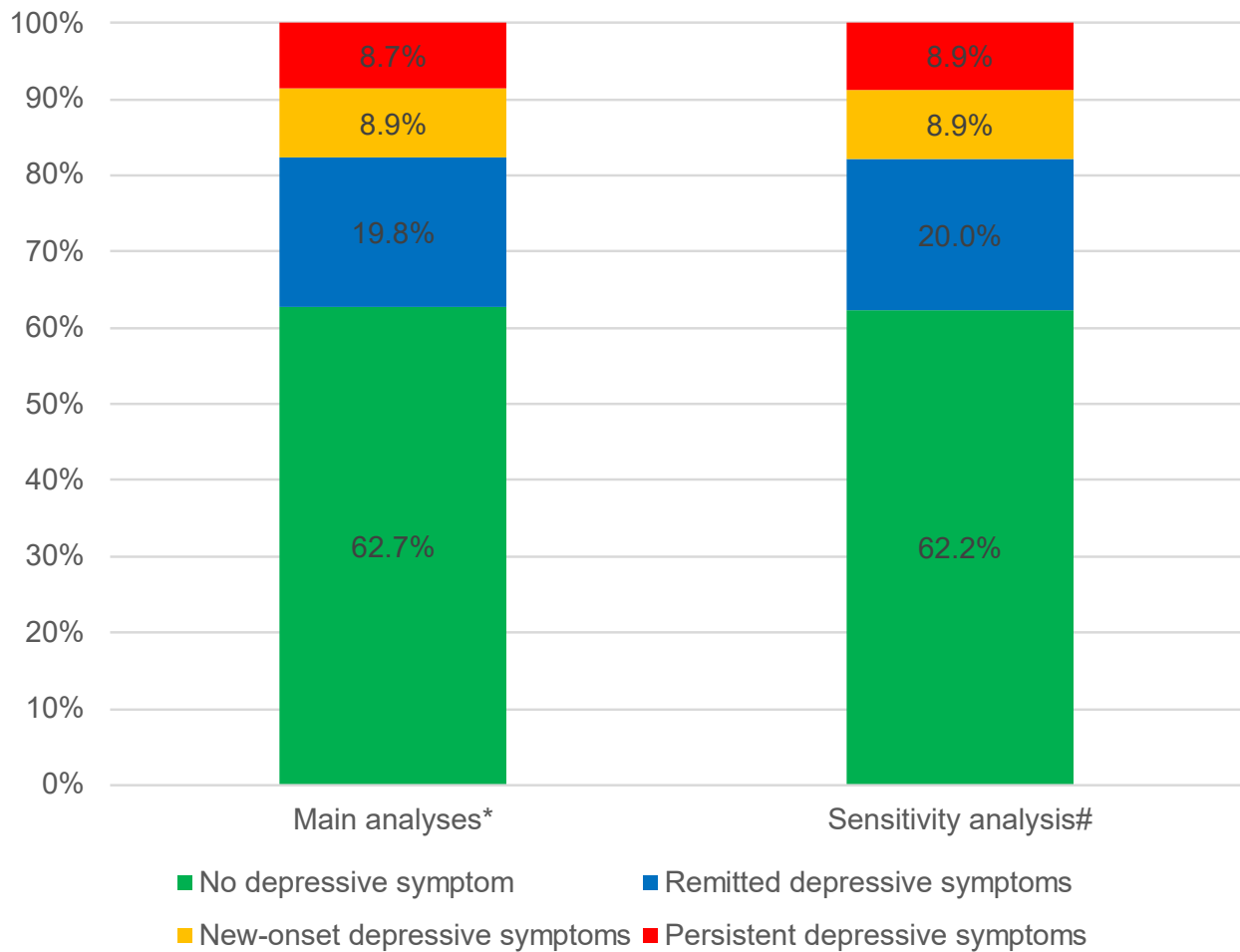
PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge

and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

* Complete-case analysis; # Analysis accounting for missing PHQ-2 score with propensity score method.

Figure S3. Outcomes of patients with four patterns of depressive symptom change adjusting for

missing PHQ-2 score by the inverse of propensity score weighting

Outcomes	Number of events (%)	Hazard Ratio* (95% CI)	*P* value		
				Lower risk	Higher risk
Cardiovascular death					
No depressive symptom	215 (8.4)	Ref			
Remitted depressive symptoms	108 (13.2)	1.32(1.04-1.67)	0.024		
New-onset depressive symptoms	60 (16.6)	1.81(1.35-2.42)	<0.001		
Persistent depressive symptoms	78 (21.5)	2.10(1.59-2.77)	<0.001		
All-cause death					
No depressive symptom	254 (10.0)	Ref			
Remitted depressive symptoms	125 (15.2)	1.25(1.00-1.57)	0.046		
New-onset depressive symptoms	66 (18.1)	1.62(1.22-2.14)	<0.001		
Persistent depressive symptoms	87 (23.9)	1.90(1.46-2.46)	<0.001		
Heart failure rehospitalization					
No depressive symptom	750 (29.4)	Ref			
Remitted depressive symptoms	288 (35.1)	1.14(0.99-1.32)	0.072		
New-onset depressive symptoms	178 (48.8)	1.52(1.28-1.81)	<0.001		
Persistent depressive symptoms	174 (47.8)	1.56(1.30-1.86)	<0.001		
All-cause rehospitalization					
No depressive symptom	1157 (45.3)	Ref			
Remitted depressive symptoms	411 (50.0)	1.05(0.93-1.18)	0.447		
New-onset depressive symptoms	233 (64.2)	1.47(1.26-1.69)	<0.001		
Persistent depressive symptoms	234 (64.2)	1.37(1.18-1.59)	<0.001		

0.0   1.0   2.0   3.0

No depressive symptom: PHQ-2<2 before discharge and <2 at 1 month; Remitted depressive symptoms:

PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before discharge

and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: CI, confidence interval.

*Counting hospitals as random effects and adjusting for age (<65, ≥65 years), sex (male, female), smoking status (current smoker, nonsmoker), education level (under high school, high school or above), prior HF, NYHA class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, SBP (<120, 120-140, ≥140mmHg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), NT-proBNP (stratified into trichotomies) and eGFR (<45, ≥45 mL/min/1.73 m^2), self-report use of medications at 1 month after discharge, including renin-angiotensin system inhibitors (RASI), β-blocker and spironolactone, and MACE within 1 month after discharge.

Figure S4. Outcomes of patients with four patterns of depressive symptom change screened by

PHQ-2 ≥ 2 at 1 month after discharge

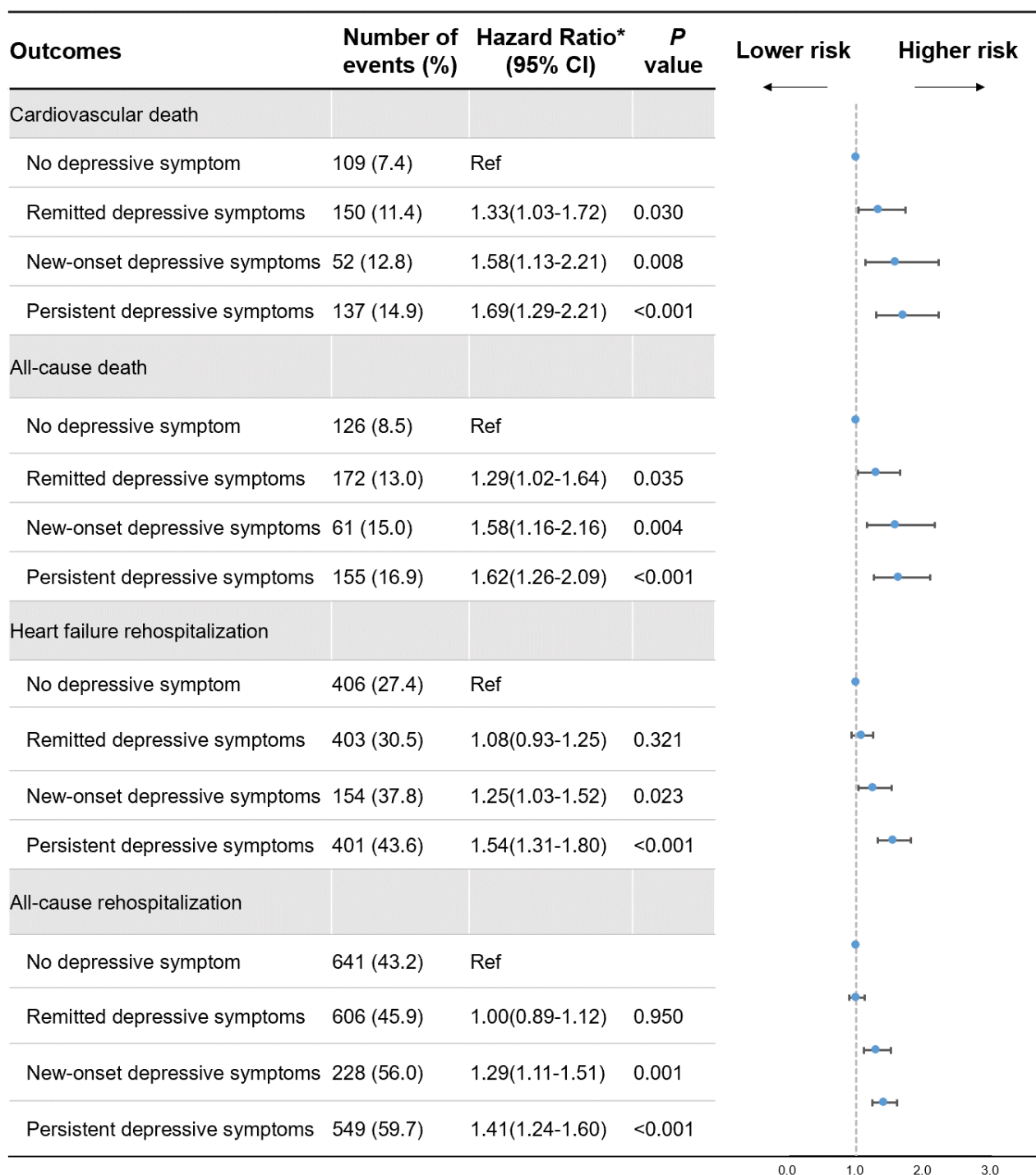| Outcomes	Number of events (%)	Hazard Ratio* (95% CI)	*P* value	Lower risk ←	Higher risk →
Cardiovascular death					
No depressive symptom	109 (7.4)	Ref			
Remitted depressive symptoms	150 (11.4)	1.33(1.03-1.72)	0.030		
New-onset depressive symptoms	52 (12.8)	1.58(1.13-2.21)	0.008		
Persistent depressive symptoms	137 (14.9)	1.69(1.29-2.21)	<0.001		
All-cause death					
No depressive symptom	126 (8.5)	Ref			
Remitted depressive symptoms	172 (13.0)	1.29(1.02-1.64)	0.035		
New-onset depressive symptoms	61 (15.0)	1.58(1.16-2.16)	0.004		
Persistent depressive symptoms	155 (16.9)	1.62(1.26-2.09)	<0.001		
Heart failure rehospitalization					
No depressive symptom	406 (27.4)	Ref			
Remitted depressive symptoms	403 (30.5)	1.08(0.93-1.25)	0.321		
New-onset depressive symptoms	154 (37.8)	1.25(1.03-1.52)	0.023		
Persistent depressive symptoms	401 (43.6)	1.54(1.31-1.80)	<0.001		
All-cause rehospitalization					
No depressive symptom	641 (43.2)	Ref			
Remitted depressive symptoms	606 (45.9)	1.00(0.89-1.12)	0.950		
New-onset depressive symptoms	228 (56.0)	1.29(1.11-1.51)	0.001		
Persistent depressive symptoms	549 (59.7)	1.41(1.24-1.60)	<0.001		

0.0   1.0   2.0   3.0

No depressive symptom: PHQ-2<2 before discharge and <2 at 1 month; Remitted depressive symptoms:

PHQ-2≥3 before discharge and <2 at 1 month; New-onset depressive symptoms: PHQ-2<2 before

discharge and ≥3 at 1 month; Persistent depressive symptoms: PHQ-2≥3 before discharge and ≥3 at 1 month.

Abbreviations: CI, confidence interval.

*Counting hospitals as random effects and adjusting for age (<65, ≥65 years), sex (male, female), smoking status (current smoker, nonsmoker), education level (under high school, high school or above), prior HF, NYHA class (II, III, IV), hypertension, diabetes, prior myocardial infarction, stroke, anemia, SBP (<120, 120-140, ≥140mmHg), LVEF phenotype (HFrEF, HFmrEF, HFpEF), NT-proBNP (stratified into trichotomies) and eGFR (<45, ≥45 mL/min/1.73 m^2), self-report use of medications at 1 month after discharge, including renin-angiotensin system inhibitors (RASI), β-blocker and spironolactone, and MACE within 1 month after discharge.