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Distinct Associations Between Postdischarge Cognitive Change Patterns and 1-year Outcomes in Patients Hospitalized for Heart Failure

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ABSTRACT

Background: The patterns of patients' cognitive function after hospital discharge for heart failure (HF), their prognostic implication and the predictors for new-onset cognitive impairment remain unknown.

Methods and Results: We included 2307 patients (64 ± 14 years, 36.4% female sex) hospitalized for HF from a cohort who completed cognitive testing before discharge and after 1 month. Among 1658 patients with normal cognition before discharge, 229 (13.8%) and 1429 (86.2%) had new-onset cognitive impairment and normal cognition at 1 month, respectively. Of the 649 with cognitive impairment, 315 (48.5%) and 334 (51.5%) had transient and persistent cognitive impairment, respectively. Multivariable analyses showed that, compared with normal cognition, patients with new-onset cognitive impairment had an increased risk of cardiovascular death or HF rehospitalization (hazard ratio 1.35, 95% confidence interval 1.07−1.70); patients with persistent cognitive impairment showed an increased risk, but it was not statistically significant (hazard ratio 1.17, 95% confidence interval 0.95−1.44); patients with transient cognitive impairment had a similar risk (hazard ratio 0.91, 95% confidence interval 0.73−1.13). Older age, females, lower education level, prior atherosclerotic cardiovascular diseases, lower health status, and lower Mini-Cog score before discharge predicted new-onset cognitive impairment.

Conclusions: Acute HF substantially affects short-term cognition. Patients who have developed new-onset cognitive impairment have an increased risk of adverse outcomes. Monitoring cognition is necessary, particularly in high-risk patients. (*J Cardiac Fail 2023;00:1−10*)

Key Words: Heart failure, cognitive function, rehospitalization, death.

Heart failure (HF) is a major disease burden, particularly for countries with an aging population.[1−3] Hospitalization is a critical event in the clinical course of HF and may represent disease progression.[4,5] Cognitive impairment is common in patients hospitalized with HF with a prevalence of 30%−80%.[6−9] Hospitalization may cause significant change in cognitive function and may affect patient outcomes. Understanding the dynamic change in cognitive function could guide clinicians to target high-risk patients and make tailored treatment and follow-up plans to improve outcomes.

The cognitive change caused by HF hospitalization, its impact on patient outcomes, and its risk factors remain unclear. Previous studies demonstrated that the cognitive function of patients with HF improved from admission to discharge.[10] However, the effects of hospitalization on cognitive change

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over time is unknown. The first month after hospital discharge is considered a vulnerable phase for patients with HF and is associated with a greater risk of death or rehospitalization.[11] Multiple stressors during this period, including sleep deprivation, poor nutrition, or sensory changes, may adversely affect cognitive function.[12] Therefore, the first month after hospital discharge may be an appropriate time window to study the effects of HF hospitalization on cognitive function.

Accordingly, using data from a multicenter, prospective cohort of patients hospitalized for HF, we aimed to evaluate cognitive function during the first month after hospital discharge via the Mini-Cog test, a simple and user-friendly cognitive assessment tool. We also examined the impact of cognitive change patterns on 1-year clinical outcomes, as well as the patient characteristics associated with new-onset cognitive impairment at 1 month after hospital discharge.

Methods

Study Design and Population

We used data from a nationwide prospective cohort, China Patient-centered Evaluative Assessment of Cardiac Events prospective heart failure study (China PEACE 5p-HF Study).[13] The China PEACE 5p-HF Study enrolled patients aged 18 years or older and hospitalized primarily for new-onset HF or acute decompensated HF from 52 hospitals located in 20 provinces between August 2016 and May 2018 (participating hospitals listed in Supplementary Table 1). Patients provided written informed consent to participate in the study. The diagnosis of HF complied with the Chinese guidelines for the diagnosis and treatment of HF which are consistent with the American College of Cardiology/American Heart Association or European Society of Cardiology guidelines.[14–16] We interviewed the enrolled patients during the index hospitalization to collect comprehensive baseline information and followed up at 1, 6, and 12 months from discharge. We measured cognitive function before discharge and at 1 month after hospital discharge. We included all patients who had both cognitive function measurements before discharge and at 1 month. The ethics committee of Fuwai Hospital and the local ethics committees at all other sites approved the study. The study was registered on www.clinicaltrials.gov (NCT02878811).

Data Collection

Demographics, socioeconomic status, smoking, self-reported health status, and depressive symptoms were collected or assessed by standardized questionnaires through face-to-face interviews during the index hospitalization. Education level was categorized as less than a high school education or high school or above. Quality of life status was measured by the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) with scores ranging from 0 to 100 (lower scores indicating lower health status).[17] Depressive symptoms were evaluated by the Patient Health Questionnaire-2 with scores ranging from 0 to 6 (with scores of $\geq$3 indicating depressive symptoms).[18] Cardiovascular disease (CVD) risk factors, New York Heart Association functional class, comorbidities, systolic blood pressure, heart rate, length of hospital stay, laboratory examination, and medications were obtained through central medical record abstraction. The left ventricular ejection fraction (LVEF) was measured within 7−10 days of hospital admission. LVEF groups included HF with reduced ejection fraction (LVEF of $<$40%), HF with mildly reduced ejection fraction (40% $\leq$ LVEF $<$ 50%), and HF with preserved ejection fraction (LVEF of $\geq$50%). N-terminal pro-brain natriuretic peptide (NT-proBNP) and creatinine were collected. We calculated the estimated glomerular filtration rate with an equation developed by adaptation of the Modification of Diet in Renal Disease equation based on the data from Chinese patients with chronic kidney disease.[19] Self-reported medication use was recorded at each follow-up.

Cognitive Assessment

Before discharge and at the 1-month follow-up, a trained physician assessed cognitive function using the Mini-Cog test according to a standard protocol. The Mini-Cog test is an instrument consisting of 2 components that include a 3-item recall and a clock drawing. It gives a total score ranging from 0 to 5 (1 point for each word correctly recalled and 2 points for correct clock drawing).[20] A total score of 2 or below indicated cognitive impairment.[21] The test has been shown to have high accuracy and good feasibility in measuring cognitive impairment. Sensitivity and specificity were 90% and 71%, respectively, in patients in the neurology clinics.[22] The prognostic validity of the Mini-Cog test in patients hospitalized for HF has been established previously.[23] Compared with other cognitive measurement tools like the Mini-Mental State Examination, the Mini-Cog is not influenced by language or education level and can be administered quickly.[21]

Outcomes

The study included 2 outcomes: a composite outcome of 1-year cardiovascular death or HF rehospitalization and a composite outcome of 1-year all-cause death or rehospitalization. We observed the outcomes after the second cognitive testing at 1 month after discharge. Cardiovascular death was

defined as sudden cardiac death or death owing to HF, cerebrovascular events, coronary heart disease, or other cardiovascular causes. If there was no evidence of an alternative nonvascular cause of death, we counted it as a cardiovascular death. All outcomes were adjudicated centrally based on medical records by trained clinicians. Survival status and cause of death were further confirmed according to the national death database.

Statistical Analyses

Patient characteristics were presented as means ± standard deviation or medians with interquartile ranges for continuous variables and frequencies with percentages for categorical variables. Patient characteristics stratified by the patterns of cognitive change were compared using the Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables. To evaluate the potential differences between our analytical cohort and those excluded because they lacked cognitive function measurement at 1 month, we further compared their characteristics and outcomes.

We divided the patients into 4 groups according to their baseline (before discharge) and 1-month cognitive performance: normal cognition (normal at baseline and at 1 month), transient cognitive impairment (impaired at baseline and normal at 1 month), new-onset cognitive impairment (normal at baseline and impaired at 1 month), and persistent cognitive impairment (impaired at baseline and at 1 month). We used a histogram to show the distribution of the Mini-Cog score change from baseline to 1 month after discharge.

The outcomes of the 4 patterns were shown with Kaplan–Meier curves and compared using a log-rank test. We evaluated the associations between different patterns of cognitive change and 1-year clinical outcomes using Cox proportional hazards models with normal cognition as a reference. We adjusted for age, sex, education level, marital status, New York Heart Association functional class, new-onset HF or acute decompensated HF, hypertension, diabetes, prior myocardial infarction, atrial fibrillation, stroke, peripheral artery disease, chronic obstructive pulmonary disease, systolic blood pressure, LVEF group, estimated glomerular filtration rate, NT-proBNP tertiles, depressive symptoms, and self-reported medication use at 1 month (ie, renin–angiotensin system inhibitors, β-blockers, and aldosterone receptor antagonists). Proportional hazard assumptions were not violated according to Schoenfeld residual analyses. For the composite outcome of cardiovascular death or HF rehospitalization, we performed Fine–Gray analyses with noncardiovascular death as a competing risk. We performed subgroup analyses of sex (male, female) by adding interaction terms in the Cox models.

We conducted 2 sensitivity analyses. The first was carried out to account for the probability of missing values of the Mini-Cog score via propensity scores.[24] Propensity scores were generated using logistic regression to estimate the probability of a missing score before discharge or at 1 month after discharge and incorporating demographic and clinical characteristics as predictors. We used the inverse of the propensity score as a means of weighting the observed proportion of 4 patterns of cognitive change[24,25] and reperformed the Cox regression models. The second analysis adjusted for sex, education level, marital status, Get With the Guidelines–Heart Failure risk score,[26] LVEF group, new-onset HF or acute decompensated HF, NT-proBNP, and self-reported use of medications at 1 month, including renin–angiotensin system inhibitors, β-blockers, and aldosterone receptor antagonists.

Among the patients with normal cognitive function at baseline, we fit fitted a logistic regression model to determine the factors associated with new-onset cognitive impairment at 1 month after discharge. Candidate variables in the multivariate analysis included age, sex, education level, marital status, new-onset HF or acute decompensated HF, smoking status, hypertension, diabetes, prior atherosclerotic CVDs (including coronary heart disease, stroke, or peripheral artery disease), atrial fibrillation, chronic obstructive pulmonary disease, LVEF group, disease severity at admission (estimated glomerular filtration rate, NT-proBNP), KCCQ-12 score, depressive symptoms, Mini-Cog score before discharge, length of hospital stay, and rehospitalization within 1 month of discharge.

The rates of missing values ranged from 0.04% (creatinine) to 3.90% (LVEF). The missing values of continuous variables were imputed with the median value and categorical variables were imputed with the mode value of the overall population. The tests for statistical significance were 2 sided with an alpha level of 0.05. All statistical analyses were performed by SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

A total of 4907 patients were enrolled in the China PEACE 5p-HF Study, among whom 148 died during hospitalization or within 1 month of discharge. Among the 4759 survivors at 1 month after discharge, we excluded 303 who did not complete the Mini-Cog before discharge and 2149 who did not complete the Mini-Cog at the 1-month follow-up. Finally, 2307 patients were included as the analytical cohort. Compared with the included cohort,

those excluded because of missing cognitive function measurements at 1 month were generally similar except for a small age differences, education level, NT-proBNP level, LVEF and baseline Mini-Cog score, and a much higher 1-year mortality (Supplemental Table 2, Supplemental Fig. 1).

Among the analytical cohort, the mean age was 64.0 ± 13.6 years and 36.4% were female. Most of the participants (95.8%) were Han Chinese. The Mini-Cog test was performed after 7 days (IQR 6−10 days) of admission. There were 1658 patients (71.9%) with normal cognitive function before discharge and 229 (13.8%) who developed new-onset cognitive impairment 1 month after discharge. Among the 649 patients (28.1%) with cognitive impairment before discharge, 315 (48.5%) had normal cognitive function 1 month after discharge (Fig. 1). After accounting for the missing Mini-Cog score with the inverse of propensity score weighting, the proportions of 4 patterns of cognitive change did not differ considerably compared with the main analyses (Fig. 1). Patients with persistent or new-onset cognitive impairment were more likely to be older and female, have a history of atrial fibrillation, stroke, peripheral artery disease, chronic obstructive pulmonary disease, higher NT-proBNP level, lower KCCQ-12 score, and lower Mini-Cog score at 1 month (Table 1). The median change of the Mini-Cog score from baseline to 1 month after discharge was 0 (IQR 0−1) (Supplemental Fig. 2).

Outcomes of Patients With 4 Patterns of Cognitive Change

After 1 year, a total of 788 composite events (34.2%) of cardiovascular death or HF rehospitalization occurred and 1083 composite events (46.9%) of all-cause death or rehospitalization occurred. Cumulative incidences of the 2 composite outcomes differed significantly among the 4 patterns of cognitive change (both $P < .001$). Specifically, normal cognition and transient cognitive impairment had relatively similar cumulative incidences; in contrast, new-onset cognitive impairment and persistent cognitive

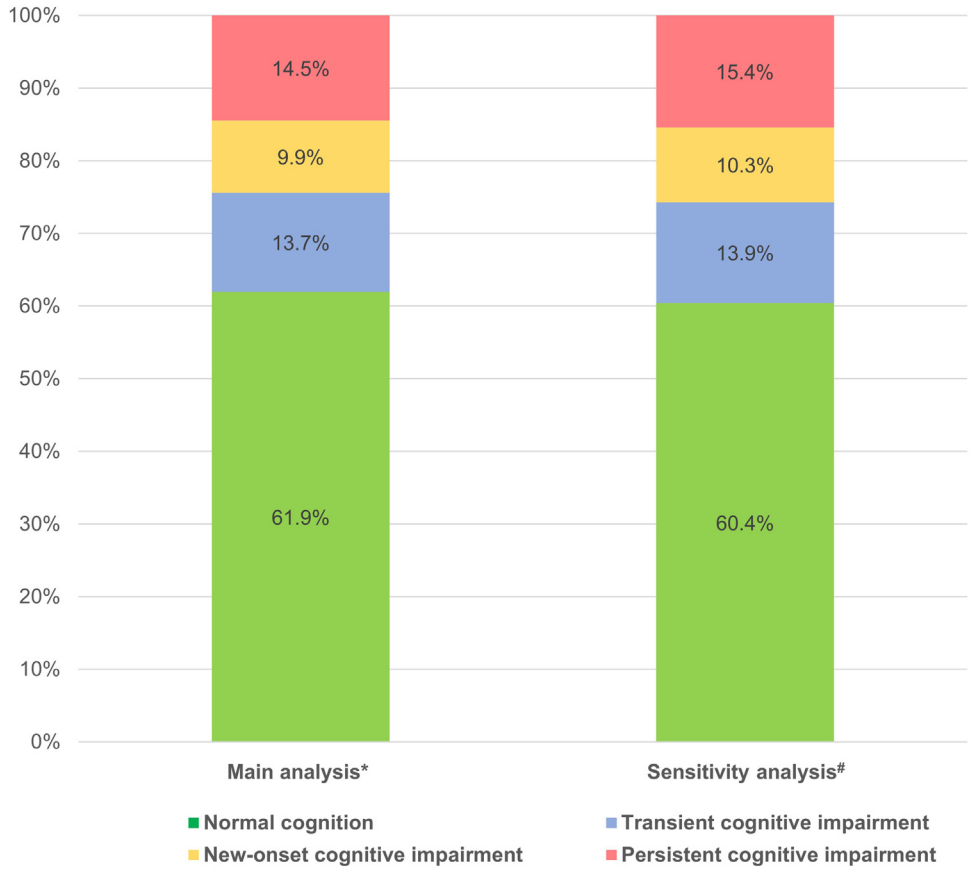

Fig. 1. Proportion of cognitive change patterns in the main analysis and sensitivity analysis. *Complete-case analysis with cognitive impairment defined by Mini-Cog≤2; #Analysis accounting for a missing Mini-Cog score with cognitive impairment defined by Mini-Cog≤2. Normal cognition, no cognitive impairment before discharge and at 1 month; transient cognitive impairment, cognitive impairment before discharge and no cognitive impairment at 1 month; new-onset cognitive impairment, no cognitive impairment before discharge and cognitive impairment at 1 month; persistent cognitive impairment, cognitive impairment before discharge and at 1 month.

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

Variables	Total ($N = 2307$)	Normal Cognition ($n = 1429$)	Transient Cognitive Impairment ($n = 315$)	New-onset Cognitive Impairment ($n = 229$)	Persistent Cognitive Impairment ($n = 334$)	*P* Value
Age years, mean ± SD	64 ± 14	61 ± 14	67 ± 11	69 ± 11	72 ± 11	<0.001
Age≥65 years, n (%)	1225 (53.1)	606 (42.4)	196 (62.2)	155 (67.7)	268 (80.2)	<0.001
Female, n (%)	839 (36.4)	418 (29.3)	140 (44.4)	106 (46.3)	175 (52.4)	<0.001
Han Chinese, n (%)	2211 (95.8)	1367 (95.7)	309 (98.1)	206 (90.0)	329 (98.5)	<0.001
Socioeconomics, n (%)						
Less than high school education	1616 (70.0)	896 (62.7)	247 (78.4)	178 (77.7)	295 (88.3)	<0.001
Married	1875 (81.3)	1207 (84.5)	249 (79.0)	179 (78.2)	240 (71.9)	<0.001
CVD risk factors, n (%)						
Currently smokes tobacco	631 (27.4)	439 (30.7)	75 (23.8)	45 (19.7)	72 (21.6)	<0.001
Hypertension	1350 (58.5)	835 (58.4)	187 (59.4)	134 (58.5)	194 (58.1)	0.989
Diabetes	733 (31.8)	462 (32.3)	89 (28.3)	68 (29.7)	114 (34.1)	0.345
Comorbidities, n (%)						
MI	542 (23.5)	343 (24.0)	70 (22.2)	51 (22.3)	78 (23.4)	0.877
Stroke	464 (20.1)	245 (17.1)	68 (21.6)	55 (24.0)	96 (28.7)	<0.001
PAD	279 (12.1)	173 (12.1)	30 (9.5)	46 (20.1)	30 (9.0)	<0.001
Atrial fibrillation	833 (36.1)	471 (33.0)	120 (38.1)	90 (39.3)	152 (45.5)	<0.001
COPD	436 (18.9)	233 (16.3)	63 (20.0)	57 (24.9)	83 (24.9)	<0.001
Laboratory values						
NT-proBNP pg/mL, median (IQR)	1323 (556−2802)	1246 (541−2603)	1394 (577−2748)	1347 (479−2967)	1838 (704−3621)	0.001
eGFR mL/min/1.73 m^2, mean ± SD	74.0 ± 24.7	76.3 ± 24.8	72.7 ± 25.2	68.6 ± 22.6	68.9 ± 23.9	<0.001
Clinical features						
SBP mm Hg, mean ± SD	134 ± 24	133 ± 24	133 ± 25	135 ± 24	137 ± 25	0.030
HR bpm, mean ± SD	90 ± 23	90 ± 23	92 ± 25	88 ± 22	92 ± 25	0.237
LVEF group, n (%)						<0.001
HFrEF	858 (37.2)	597 (41.8)	110 (34.9)	66 (28.8)	85 (25.4)	
HFmrEF	639 (27.7)	379 (26.5)	97 (30.8)	55 (24.0)	108 (32.3)	
HFpEF	810 (35.1)	453 (31.7)	108 (34.3)	108 (47.2)	141 (42.2)	
NYHA functional class, n (%)						<0.001
II	314 (13.6)	231 (16.2)	35 (11.1)	25 (10.9)	23 (6.9)	
III	1009 (43.7)	621 (43.5)	144 (45.7)	109 (47.6)	135 (40.4)	
IV	984 (42.7)	577 (40.4)	136 (43.2)	95 (41.5)	176 (52.7)	
HF type, n (%)						0.002
New-onset HF	641 (27.8)	437 (30.6)	74 (23.5)	52 (22.7)	78 (23.4)	
Acute decompensated HF	1666 (72.2)	992 (69.4)	241 (76.5)	177 (77.3)	256 (76.6)	
Depressive symptoms, n (%)	622 (27.0)	342 (23.9)	95 (30.2)	70 (30.6)	115 (34.4)	<0.001
KCCQ-12 score, mean ± SD	45.2 ± 23.0	47.6 ± 23.0	43.7 ± 22.4	41.3 ± 22.3	38.7 ± 21.8	<0.001
Mini-Cog score at baseline, median (IQR)	4 (2, 5)	5 (4, 5)	2 (1, 2)	4 (3, 5)	1 (0, 2)	<0.001
Mini-Cog score at 1 month, median (IQR)	4 (3, 5)	5 (4, 5)	4 (3, 5)	2 (1, 2)	1 (0, 2)	<0.001
Medications at discharge, n (%)						
RASI	1239 (53.7)	768 (53.7)	162 (51.4)	131 (57.2)	178 (53.3)	<0.001
β-Receptor blocker	1428 (61.9)	885 (61.9)	205 (65.1)	141 (61.6)	197 (59.0)	0.613
Aldosterone antagonist	1506 (65.3)	917 (64.2)	208 (66.0)	151 (65.9)	230 (68.9)	0.463
Medications at 1 month, n (%)						
RASI	1040 (45.1)	652 (45.6)	137 (43.5)	106 (46.3)	145 (43.4)	0.425
β-Receptor blocker	1282 (55.6)	824 (57.7)	180 (57.1)	118 (51.5)	160 (47.9)	0.801
Aldosterone receptor antagonist	1280 (55.5)	783 (54.8)	175 (55.6)	124 (54.1)	198 (59.3)	0.006
All-cause rehospitalization within 1 month after discharge	228 (9.9)	125 (8.8)	33 (10.5)	31 (13.5)	39 (11.7)	0.077

Normal cognition, Mini-Cog of >2 before discharge and at 1 month; transient cognitive impairment, Mini-Cog of ≤2 before discharge and at 1 month; new-onset cognitive impairment, Mini-Cog of >2 before discharge and ≤2 at 1 month; persistent cognitive impairment, Mini-Cog of ≤2 before discharge and ≤2 at 1 month.

bpm, beat per minute; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; eGFR, 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; HR, heart rate; IQR, interquartile range; KCCQ-12, Kansas City Cardiomyopathy Questionnaire-12; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral vascular disease; RASI, renin−angiotensin antagonist system inhibitor; SBP, systolic blood pressure; SD, standard deviation.

impairment had notably higher cumulative incidences than the former 2 patterns (Fig. 2).

After accounting for potential confounders, new-onset cognitive impairment was significantly associated with an increased risk of cardiovascular death or HF rehospitalization (hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.07−1.70, $P = .010$), whereas persistent cognitive impairment showed an increased risk but was not statistically significant (HR 1.17, 95% CI 0.95−1.44, $P = .133$). Patients with transient cognitive impairment had a similar risk (HR 0.91, 95% CI, 0.73−1.13, $P = .395$) compared with

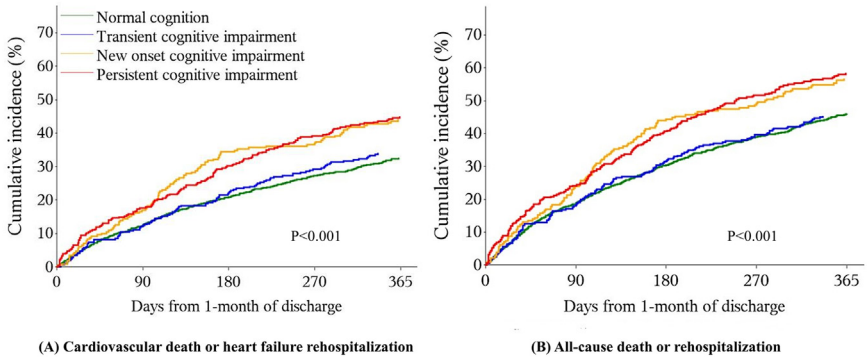

Fig. 2. One-year outcomes of patients stratified by cognitive change patterns. (**A**) A composite outcome of cardiovascular death or heart failure rehospitalization. (**B**) A composite outcome of all-cause death or rehospitalization. Normal cognition, no cognitive impairment before discharge and at 1 month; transient cognitive impairment, cognitive impairment before discharge and no cognitive impairment at 1 month; new-onset cognitive impairment, no cognitive impairment before discharge and cognitive impairment at 1 month; persistent cognitive impairment, cognitive impairment before discharge and at 1 month.

those with normal cognition. New-onset cognitive impairment and persistent cognitive impairment showed an increased risk of all-cause death or rehospitalization, but were not statistically significant (new-onset cognitive impairment: HR 1.22, 95% CI, 1.00−1.49, $P = .051$; persistent cognitive impairment: HR 1.17, 95% CI, 0.99−1.40, $P = .074$), whereas transient cognitive impairment had a similar risk (HR 0.90, 95% CI, 0.74−1.08, $P = .243$) compared with normal cognition (Fig. 3). We observed no significant heterogeneity between male and female sex (Supplemental Table 3). Two sensitivity analyses showed similar associations compared with the main analysis (Fig. 3).

Outcomes/groups	Number of events (%)	Main analysis*		Sensitivity analysis 1#		Sensitivity analysis 2†	
		Hazard ratios (95%CI)	P value	Hazard ratios (95%CI)	P value	Hazard ratios (95%CI)	P value
Cardiovascular death or heart failure rehospitalization							
Normal cognition	440 (30.8)	Ref		Ref		Ref	
Transient cognitive impairment	105 (33.3)	0.91 (0.73-1.13)	0.395	0.90 (0.73-1.12)	0.346	0.94 (0.75-1.17)	0.559
New-onset cognitive impairment	98 (42.8)	1.35 (1.07-1.70)	0.010	1.35 (1.08-1.69)	0.009	1.37 (1.10-1.72)	0.005
Persistent cognitive impairment	145 (43.4)	1.17 (0.95-1.44)	0.133	1.17 (0.96-1.43)	0.118	1.26 (1.03-1.54)	0.025
All-cause death or rehospitalization							
Normal cognition	627 (43.9)	Ref		Ref		Ref	
Transient cognitive impairment	141 (44.8)	0.90 (0.74-1.08)	0.243	0.89 (0.74-1.07)	0.215	0.92 (0.76-1.11)	0.370
New-onset cognitive impairment	126 (55.0)	1.22 (1.00-1.49)	0.051	1.25 (1.03-1.51)	0.027	1.24 (1.02-1.50)	0.034
Persistent cognitive impairment	189 (56.6)	1.17 (0.99-1.40)	0.074	1.18 (0.99-1.40)	0.058	1.23 (1.04-1.46)	0.016

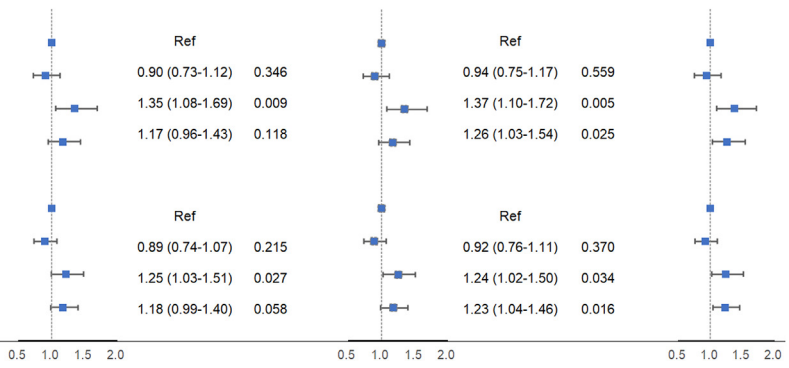

Fig. 3. Associations between cognitive change patterns and 1-year outcomes in the multivariable analyses. *Complete case multivariable analysis, adjusting for age, sex, education level, marital status, New York Heart Association functional class, new-onset heart failure (HF) or acute decompensated HF, hypertension, diabetes, prior myocardial infarction, atrial fibrillation, stroke, peripheral artery disease, chronic obstructive pulmonary disease, systolic blood pressure, left ventricular ejection fraction (LVEF) group, estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide tertiles, depressive symptoms, and self-report use of medications at 1 month, including renin−angiotensin system inhibitors, β-blockers, and aldosterone receptor antagonists. #Multivariable analysis accounting for propensity score method, adjusting for the same covariates. Multivariable analysis, adjusted for sex, education level, marital status, Get With the Guidelines−Heart Failure risk score, LVEF group, new-onset HF, or acute decompensated HF, N-terminal pro-B-type natriuretic peptide, and self-report use of medications at 1 month, including renin−angiotensin system inhibitors, β-blockers, and aldosterone receptor antagonists. CI, confidence interval. Normal cognition: no cognitive impairment before discharge and at 1 month; transient cognitive impairment: cognitive impairment before discharge and no cognitive impairment at 1 month; new-onset cognitive impairment: no cognitive impairment before discharge and cognitive impairment at 1 month; persistent cognitive impairment: cognitive impairment before discharge and at 1 month.

Factors Associated With New-onset Cognitive Impairment 1 Month After Discharge

A total of 1658 patients were included to analyze the factors associated with new-onset cognitive impairment with normal cognition as a reference. Per 5-year age increase (odds ratio [OR] 1.21, 95% CI 1.12-1.31), female sex (OR 1.67, 95% CI 1.19−2.34), less than high school education (OR 1.45, 95% CI 1.02−2.07), prior atherosclerotic CVDs (OR 1.56, 95% CI 1.07−2.27), a 10−point KCCQ-12 score decrease (OR 1.08, 95% CI 1.01-1.16), and a 1-point Mini-Cog score decrease before discharge (OR 1.46, 95% CI 1.22−1.74) were associated with new onset of cognitive impairment at 1 month (Table 2).

Discussion

Based on a multicenter prospective cohort of patients hospitalized for HF, we first reported a substantial change in cognitive function 1 month after hospital discharge and demonstrated associations between cognitive change patterns and 1-year clinical outcomes. In nearly 30% of patients who experienced cognitive impairment before discharge, one-half had normal cognitive function at 1 month and did not have an increased risk of death or rehospitalization. In contrast, 1 in 7 patients with normal cognitive function at discharge developed cognitive impairment at 1 month and had a greater risk of adverse outcomes than those with persistent cognitive impairment. These findings demonstrate that patients with new-onset cognitive impairment require further study. Simple tests of cognitive function can help to identify patients who are more likely to develop new-onset cognitive impairment, such as the older adults, females, patients with a lower education level, and those with prior atherosclerotic CVDs, lower KCCQ-12 score, or lower Mini-Cog score before discharge.

Table 2. Factors Associated With New-onset Cognitive Impairment

Factors (Reference or Unit of Change)	Multivariate Analysis	
	Odds Ratio (95% CI)	*P* Value
Age (per 5-year increase)	1.21 (1.12−1.31)	<0.001
Female sex (male)	1.67 (1.19−2.34)	0.003
Less than high school education (high school education or above)	1.45 (1.02−2.07)	0.038
Married (not married)	1.12 (0.76−1.64)	0.583
Currently smokes tobacco (currently do not smoke tobacco)	0.97 (0.65−1.44)	0.881
Acute decompensated HF (new-onset HF)	1.32 (0.92−1.89)	0.130
Hypertension (no hypertension)	0.75 (0.54−1.02)	0.070
Diabetes (no diabetes)	0.79 (0.57−1.10)	0.169
ASCVD (no ASCVD)	1.56 (1.07−2.27)	0.022
Atrial fibrillation (no Atrial fibrillation)	1.02 (0.75−1.40)	0.889
COPD (no COPD)	1.35 (0.94−1.93)	0.106
NT-proBNP (log-transformed, <7)		
7−8	0.91 (0.63−1.29)	0.585
>8	0.95 (0.63−1.44)	0.816
eGFR <45 mL/min/1.73 m^2	1.13 (0.70−1.82)	0.614
LVEF group (HFrEF)		
HFmrEF	0.94 (0.62−1.43)	0.780
HFpEF	1.32 (0.88−1.96)	0.178
Depressive symptoms (no depressive symptoms)	1.01 (0.72−1.42)	0.958
KCCQ-12 score (per 10-point decrease)	1.08 (1.01−1.16)	0.027
Mini-Cog score at baseline (per 1-point decrease)	1.46 (1.22−1.74)	<0.001
Length of hospital stay (per 2-day increase)	1.00 (0.98−1.03)	0.889
Rehospitalization within 1 month of discharge	1.51 (0.95−2.37)	0.079

ASCVD, atherosclerotic cardiovascular diseases. Other abbreviations as in Table 1.

Our study found that significant proportions of patients had transient cognitive impairment or new-onset cognitive impairment, which suggests that HF exacerbation could affect patients' cognitive function, and some patients may display delayed effects. Previous studies reported that the cognition of patients hospitalized for HF improved during hospitalization.[10] However, data are limited regarding the short-term trajectory of cognitive changes during the vulnerable phase after discharge. We found the process of cognitive recovery continued for at least until 1 month after discharge and the recovered patients had a similar risk compared with those who had no cognitive impairment after discharge.

The underlying mechanisms for delayed cognitive impairment shortly after discharge remain speculative. Factors may be medically related or patient related.[12,27,28] Moreover, we found the predictors for new-onset cognitive impairment were generally similar to those for cognitive impairment in the general population (ie, age, sex and comorbidities),[29] suggesting that patients with new-onset cognitive impairment might have preexisting subclinical cognitive dysfunction. However, the incidence of cognitive impairment within such a short period (monthly incidence, 13.8%) was much higher than found in older adults (monthly incidence, 0.3%).[30] This indicates that the effects of acute HF also play important role in triggering the process of cognitive impairment. Notably, although NT-proBNP was slightly higher in patients with new-onset cognitive impairment compared with those with normal cognition, it was not significantly associated with new-onset cognitive impairment in a multivariable analysis. This finding suggests that the development of new-onset cognitive impairment was likely precipitated by HF exacerbation, but not much related to the severity of HF.

Given that the Kaplan–Meier curve of new-onset cognitive impairment did not increase remarkably and surpassed other groups after 1 month, it is likely that the subsequent adverse events of new-onset cognitive impairment were not mediated through an increase baseline CVD risk. Interestingly, new-onset cognitive impairment was associated with a higher risk of death or hospitalization when compared with persistent cognitive impairment. New cognitive impairment may prevent self-care or family support to maintain HF management, consequently resulting in a higher risk of adverse outcomes. In contrast, long-term compensatory changes may have occurred in patients with persistent cognitive impairment, thereby limiting the extent of adverse outcomes. In addition, patients with persistent cognitive impairment were mostly older and had lower physical function and quality of life, which could contribute to the occurrence of high adverse events. Therefore, the net effect on the risk of adverse clinical outcomes by cognitive impairment might be relatively weak.

Our findings highlight the importance of regular monitoring of cognitive function of patients with acute HF during and after hospitalization. The Mini-Cog is a very simple, user-friendly tool and has little potential for bias in terms of education level or language.[21] Thus, clinicians can assess cognition routinely to identify the patients with persistent or new-onset cognitive impairment. Longitudinal surveillance of cognitive function could provide clues to the change in a patient's self-care ability and inform clinical decisions to determine the cause of cognitive decline.

Our study has several limitations. First, the proportion of patients with new-onset cognitive impairment may be underestimated. Compared with the analytical cohort, the excluded patients had a slightly higher likelihood of developing new-onset cognitive impairment because of the age differences, education level, and the baseline Mini-Cog score. Their worse clinical outcomes could be explained by their age and health status, as well as their potentially higher risk of new-onset cognitive impairment. Excluding these patients should not influence the strength of effect estimate of the association between cognitive function and clinical outcomes, but might decrease the statistical power. Second, almost all participants in our study were Han Chinese; therefore, the results of our study may not be generalizable to other populations. Third, 72% of our participants were diagnosed with acute decompensated HF and the time since their HF diagnosis was not known. The severity of illness may have an impact on cognitive function. Fourth, potential unmeasured confounders cannot be ruled out. Finally, our study did not collect neuroimaging data on structural brain changes and was unable to explore the influence of possible ischemic damage on cognitive changes.

Conclusions

Acute HF exacerbation substantially affects short-term cognitive function. Patients who developed new-onset cognitive impairment 1 month after discharge had an increased risk of death or rehospitalization. These high-risk patients could be easily identified by repeated simple cognitive screening measures, which are easily applied.

Brief Lay summary

Little is known about the short-term cognitive change after discharge from HF hospitalization and its impact on outcomes. In a multicenter prospective cohort of patients hospitalized for HF, 2307 patients who completed cognitive testing before discharge and 1 month after discharge were included. Among the patients with normal cognition before discharge, 13.8% developed new-onset cognitive impairment at 1 month. New-onset cognitive impairment was associated with an increased risk of worse outcomes. Older age, females, lower education level, prior atherosclerotic CVDs, lower health status, and lower Mini-Cog scores before discharge predicted new-onset cognitive impairment.

Bullet points

- Among the patients hospitalized for HF who experienced cognitive impairment before discharge, 48.5% had transient cognitive impairment at 1 month after discharge. Among patients with normal cognition before discharge, 13.8% developed new-onset cognitive impairment at 1 month after discharge.
- New-onset cognitive impairment was associated with an increased risk of death or rehospitalization.
- The predictors associated with new-onset cognitive impairment included older age, females, lower education level, prior atherosclerotic CVDs, lower health status, or lower Mini-Cog score before discharge.

Visual Take Home graphics. Post-discharge cognitive change patterns and 1-year outcomes in patients hospitalized for heart failure

A significant proportion of patients hospitalized for heart failure developed new-onset cognitive impairment 1 month after hospital discharge and have an increased risk of death or rehospitalization. Predictors may help identify patients at high risk of

developing new-onset cognitive impairment. ASCVD, atherosclerotic cardiovascular diseases; KCCQ-12, Kansas City Cardiomyopathy Questionnaire-12.

Author headshot photograph

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Conflict of interest statement

Dr. Li reports receiving research grants, through Fuwai Hospital, from the Chinese government and the Chinese Academy of Medical Sciences for work to improve the management of hypertension and blood lipids and to improve patient outcomes of cardiovascular disease and COVID-19; receiving research agreements, through the National Center for Cardiovascular Diseases and Fuwai Hospital; from Amgen for a multicenter clinical trial assessing the efficacy and safety of omecamtiv mecarbil and for dyslipidemic patient registration; receiving a research agreement, through Fuwai Hospital, from Sanofi for a multicenter clinical trial on the effects of sotagliflozin; receiving a research agreement, through Fuwai Hospital, with the University of Oxford for a multicenter clinical trial of empagliflozin; receiving a research agreement, through the National Center for Cardiovascular Diseases, from AstraZeneca for clinical research methods training outside the submitted work; and receiving a research agreement, through the National Center for Cardiovascular Diseases, from Lilly for physician training outside the submitted work. No other disclosures were reported.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cardfail.2023.01.006.

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