

Prognostic Importance of Hippocampal Atrophy in Patients With Chronic Heart Failure



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Mild cognitive impairment (MCI) impedes a patient's decision-making ability to support self-care and is associated with increased mortality in patients with chronic heart failure (CHF). Thus, screening for MCI is very important. The assessment of hippocampal atrophy using magnetic resonance imaging can effectively diagnose early MCI. The purpose of this study was to assess the prevalence and prognostic significance of hippocampal atrophy using magnetic resonance imaging in patient with CHF. Of the 491 patients with CHF included in the study, 170 demonstrated hippocampal atrophy. Patients with hippocampal atrophy were older, and showed a higher rate of renal dysfunction and cardiac events than patients without hippocampal atrophy. A total of 180 cardiac events occurred during the follow-up period. A Cox proportional hazards regression model and Kaplan-Meier analysis showed that hippocampal atrophy was significantly associated with cardiac events. In conclusion, hippocampal atrophy is a significant and independent predictor of poor prognosis in patients with CHF and can aid risk stratification of these patients. © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2019;123:1109–1113)

Chronic heart failure (CHF) is a major cause of death and hospitalization.^{1–3} Mild cognitive impairment (MCI) is often a latent co-morbidity in patients with CHF.⁴ Inadequate cerebral perfusion and acute or chronic hypoxic brain injury are the most likely etiological contributors to MCI in patients with CHF.⁵ Reportedly, self-care maintenance after discharge is inadequate in patients with CHF and concomitant MCI, which necessitates early rehospitalization.⁴ Self-care at home is essential because rehospitalization necessitated by heart failure and its treatment contributes to a significant economic burden. Thus, patients at a higher risk of failed self-care require screening for MCI. However, the diagnosis of early MCI remains challenging. Following advances in magnetic resonance imaging (MRI) technology, the evaluation of hippocampal atrophy using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) software is reported to be effective for the early diagnosis of MCI.⁶ However, to date, no study (using MRI-based analysis) has investigated the effect of hippocampal atrophy on the prognosis in patient with CHF. This study evaluated the prevalence and clinical significance of hippocampal atrophy (detected by MRI) in 491 consecutive patients with CHF.

Methods

Between November 2014 and May 2018, we prospectively analyzed 491 consecutive patients who were admitted for treatment of worsening CHF or to establish a diagnosis and for pathophysiological investigations. CHF

was diagnosed based on the universal Framingham criteria and clinical features, including signs of pulmonary congestion or peripheral edema or evidence of left ventricular enlargement or dysfunction documented by chest radiography or echocardiography.⁷ Idiopathic dilated cardiomyopathy was diagnosed based on the definition of the World Health Organization and/or International Society and Federation of Cardiology Task Force.⁸ Venous blood samples were analyzed in all patients at discharge. The estimated glomerular filtration rate (eGFR) was calculated based on the Japanese Society of Nephrology Chronic Kidney Disease Practice Guidelines using the following formula: $eGFR \text{ (ml/min/1.73 m}^2\text{)} = 194 \times [\text{serum creatinine level (mg/dl)}]^{-1.094} \times [\text{age (years)}]^{-0.287}$.⁹ The product of this equation was multiplied by a correction factor of 0.739 in women. Transthoracic echocardiography was performed within a week after admission. Optimal medical therapy was determined based on symptom improvement, physical examination findings, and the degree of pulmonary congestion observed on chest radiographs.¹⁰ Data regarding a diagnosis of hypertension, diabetes, and/or hyperlipidemia were obtained from patients' medical records or from the patient's history of present or previous medical therapy.

All patients were prospectively followed-up until the occurrence of cardiac events. The end points were cardiac death (defined as death from worsening CHF or sudden cardiac death) and worsening CHF requiring rehospitalization. Exclusion criteria for this study were acute coronary syndrome within 3 months before admission, renal insufficiency (manifested by a serum creatinine concentration >1.5 mg/dl), active hepatic and lung disease, and patients with a definitive diagnosis of dementia or those receiving treatment for dementia.

Using the Signa HDxt (GE Healthcare, Tokyo, Japan), 1.5-Tesla MRI was performed, and sagittal 3-dimensional T1 images were obtained using the IR-prepared fast spoiled gradient recalled acquisition (fast SPGR), and the parahippocampal

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z-score was calculated using the VSRAD.⁶ The imaging sequence was performed under the conditions recommended by the VSRAD guidelines (repetition time 11.2 milliseconds, echo time 5.008 milliseconds, and flip angle 25°).^{6,11} Based on previous reports, a z-score ≥ 2 was considered indicative of hippocampal atrophy.¹¹ Cognitive function was evaluated before discharge (i.e., once patients were deemed clinically stable) using the Revised Hasegawa's Dementia Scale (HDS-R). HDS-R is commonly used in Japan to assess cognitive function.¹² It provides an overall rating of global functioning ranging between 0 and 30, with high scores indicating better performance.

The results are presented as mean \pm standard deviation values for continuous variables and as a percentage of the total patients for categorical variables. Skewed variables are presented as the median and interquartile range. The unpaired Student's *t* and chi-square tests were used for intergroup comparisons of continuous and categorical variables, respectively. Cox proportional hazards regression analysis was performed to evaluate the association between cardiac events and the measured variables. The cumulative probability of cardiac events was computed using the Kaplan-Meier method and compared using the log-rank test. All *p* values reported are 2-sided, and a *p* value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software version 19.0 (SPSS Inc., Chicago, Illinois).

Results

The z-score significantly increased with an advancing New York Heart Association (NYHA) functional class (Figure 1). A total of 180 cardiac events occurred, including 98 cardiac deaths and 82 rehospitalizations for worsening CHF during the follow-up period. The causes of cardiac death were worsening CHF in 81, fatal acute myocardial infarction in 4, and sudden cardiac death in 13 patients. Patients with cardiac events were older, showed a lower body mass index and HDS-R, demonstrated a more advancing NYHA functional class, and higher occurrence of atrial fibrillation than those without cardiac events. Furthermore,

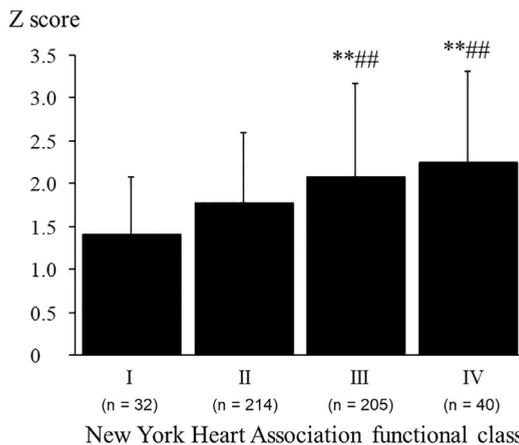


Figure 1. The z-score significantly increased with an advancing NYHA functional class. ***p* < 0.01 versus NYHA I and ###*p* < 0.01 versus NYHA II.

cardiac events were significantly associated with renal dysfunction, hyperuricemia, and greater levels of serum brain natriuretic peptide (BNP). The z-score in patients with cardiac events was significantly higher than that in patients without cardiac events. However, prevalence of hypertension, diabetes mellitus, and hyperlipidemia, etiology of CHF, and echocardiographic data did not significantly differ between patients with and without cardiac events. These results suggest that the prevalence of MCI in patients with cardiac events was higher than that in patients without cardiac events. Although there were 46 patients with lacunar stroke and 2 patients with old hemorrhagic findings in this study, cardiac events did not significantly differ between patients with and without lacunar stroke.

Based on the z-score, patients were categorized into 2 groups as follows: the high group (z-score ≥ 2 , *n* = 170) and the low group (z-score < 2 , *n* = 321). Comparisons of clinical characteristics between patients with and without hippocampal atrophy are presented in Table 1. Patients in the high group were older and demonstrated a more advanced NYHA functional class than that observed in the low group. Occurrence of renal dysfunction and the serum levels of BNP in the high group were higher than those in the low group. Additionally, the HDS-R score in the high group was lower than that observed in the low group. Furthermore, the rehospitalization and cardiac death rates in the high group were significantly higher than those in the low group (Figure 2). These findings suggested that higher z-scores (indicating patients with hippocampal atrophy) were significantly associated with the occurrence of cardiac events.

We performed Cox proportional hazards regression analysis to determine the predictive risk factors for cardiac events (Table 2). Univariate Cox proportional hazards regression analysis showed that high-z scores were significantly associated with the occurrence of cardiac events. Furthermore, age, atrial fibrillation, serum levels of creatinine, uric acid, and BNP, as well as the eGFR were significantly associated with the occurrence of cardiac events. These variables were subsequently subjected to multivariate Cox proportional hazards regression analysis. Because creatinine and eGFR are similar parameters reflecting renal function, only the eGFR was subjected to multivariate Cox proportional hazards regression analysis, and we observed that high z-scores, age, atrial fibrillation, and serum BNP levels were independent predictors of cardiac events.

Kaplan-Meier analysis clearly demonstrated that the rate of occurrence of cardiac events in the high group was significantly higher than that in the low group (Figure 3). Our results are clinically important because this powerful risk prediction tool may potentially help to improve the management and consequent prognosis of patients with CHF. Therefore, we infer that MRI is a useful diagnostic modality in patients with CHF to detect hippocampal atrophy and can aid risk stratification and decision-making for optimal individualized treatment, which includes intense monitoring, self-care supports after discharge, and specialist care.

Discussion

Our study highlights the following findings: (1) The prevalence of hippocampal atrophy in patients with cardiac

Table 1
Comparisons of clinical characteristics between patients with and without hippocampal atrophy

Variable	Hippocampal atrophy High (n = 170)	Hippocampal atrophy Low (n = 321)	p value
Age (years)	84 ± 8	76 ± 12	<0.0001
Male/female	78/92	184/137	0.0157
Body mass index (kg/m ²)	21.4 ± 4.1	23.1 ± 5.0	0.0001
NYHA functional class (I/II/III/IV)	4/64/89/13	28/150/116/27	0.0011
Hypertension (%)	151 (89%)	286 (89%)	0.9268
Diabetes mellitus (%)	43 (25%)	105 (33%)	0.0858
Hyperlipidemia (%)	74 (44%)	149 (46%)	0.2166
Atrial fibrillation (%)	94 (55%)	160 (50%)	0.2499
Etiology of chronic heart failure			
Idiopathic dilated cardiomyopathy (%)	22 (13%)	67 (21%)	
Ischemic cardiomyopathy (%)	66 (39%)	115 (36%)	
Hypertensive heart disease (%)	82 (48%)	139 (43%)	0.0846
Laboratory markers			
Creatinine (mg/dl)	1.03 ± 0.39	0.93 ± 0.35	0.0045
Sodium (mmol/L)	140 ± 4	139 ± 4	0.2358
Uric acid (mg/dl)	6.6 ± 2.3	6.3 ± 2.0	0.0903
BNP (pg/ml)	421 (189 – 761)	265 (110 – 501)	0.0004
HbA1c (%)	6.1 ± 0.8	6.2 ± 1.2	0.2147
eGFR (ml/min/1.73 m ²)	52 ± 22	59 ± 22	0.0007
z-score	3.05 ± 0.92	1.28 ± 0.38	<0.0001
HDS-R	15 ± 8	22 ± 7	<0.0001
Echocardiography			
LAD (mm)	43 ± 9	44 ± 9	0.1560
LVEDD (mm)	49 ± 9	50 ± 9	0.2004
LVEF (%)	52 ± 15	51 ± 16	0.1849
Medications at discharge			
ACE inhibitors and/or ARBs (%)	115 (68%)	243 (76%)	0.0580
β-blockers (%)	121 (71%)	251 (78%)	0.0870
Calcium channel blockers (%)	60 (35%)	117 (36%)	0.7997
Spironolactone (%)	46 (27%)	98 (31%)	0.4198
Loop diuretics (%)	101 (59%)	180 (56%)	0.4765
Tolvaptan (%)	42 (25%)	56 (17%)	0.0583
Digoxin (%)	7 (4%)	23 (7%)	0.1667
Statins (%)	67 (39%)	128 (40%)	0.5037
Amiodaron (%)	10 (6%)	29 (9%)	0.2088
Warfarin (%)	18 (11%)	41 (13%)	0.4749
DOAC (%)	73 (43%)	121 (38%)	0.2589

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BNP = brain natriuretic peptide; DOAC = direct oral anticoagulants; eGFR = estimated glomerular filtration rate; HbA1c = Hemoglobin A1c; HDS-R = Revised Hasegawa's Dementia Scale; LAD = left atrial dimension; LVEDD = left ventricular dimension at end-diastole; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Data are expressed as mean ± standard deviation (SD), n (%), or median (interquartile range). Hypertension was defined as blood pressure of ≥140/90 mm Hg or hypertension treatment. Hyperlipidemia was defined as total cholesterol of ≥220 mg/dl, triglycerides of ≥150 mg/dl, or hyperlipidemia treatment.

events was higher than that in patients without cardiac events. (2) Multivariate Cox proportional hazards regression analysis and Kaplan-Meier analysis showed that hippocampal atrophy was significantly associated with the occurrence of cardiac events. CHF is widespread in aging populations globally,¹³ and constitutes an important public health issue.^{1–3} However, no national screening programs and classification systems are established for the early detection of CHF, in contrast to those available for patients with cancer and osteoporosis. Early identification of patients at a greater risk of CHF is critical to formulate and implement optimal prevention strategies. Thus, future studies are warranted to determine optimal screening and treatment of MCI to improve clinical outcomes.

MCI has been overlooked as an important factor that needs consideration in the clinical management of CHF. The HDS-R is a reliable screening tool used in Japan to assess cognitive function. However, most patients admitted with heart failure are elderly patients with disabilities and/or difficulty in communication or are medically unstable. Thus, MRI may be more reliable than HDS-R as a screening tool for MCI.

Clinicians must be aware that MCI may progress to dementia or Alzheimer's disease. Disease-modifying drugs may become available in the future in addition to symptom-improving drugs such as anticholinesterase inhibitors. Thus, preventive treatment before the onset of dementia would greatly benefit such patients. If early detection of MCI and early intervention in patients with CHF can lead

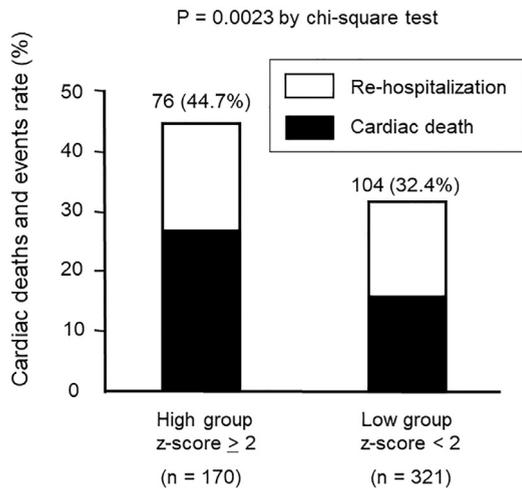


Figure 2. Based on the z-score, patients were categorized into 2 groups as follows: the high group (z-score ≥ 2 , n = 170) and the low group (z-score < 2 , n = 321). The rehospitalization and cardiac death rates in the high group were significantly higher than those in the low group.

to a reduced number of patients with CHF and concomitant dementia and a lower risk of rehospitalization, the clinical significance of early diagnosis of MCI using MRI appears to be very large.

Although the underlying mechanism causing cognitive impairment in patients with CHF remains unclear, inadequate cerebral perfusion and acute or chronic hypoxic brain injury are considered the most likely contributors.⁵ However, in our study, echocardiographic data were not significantly different between patients with and without hippocampal atrophy. Thus, we will examine the association with cognitive impairment and cardiac output in a future. Age, co-morbidities, hypertension, atrial fibrillation, depression, and the intake of specific medications may also lead to cognitive impairment. Furthermore, MCI represents cognitive frailty observed in patients with CHF. In this study, MCI was more common in elderly patients and in those with a lower body mass index. Recently, research has focused on frailty, and reports have shown that frailty is associated with the prognosis of heart failure.¹⁴ We intend to perform future studies to determine the relation between

Table 2
Univariate and multivariate Cox proportional hazard analyses of predicting total cardiac events

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)*	1.504	1.268-1.775	<0.0001	1.349	1.113-1.619	0.0030
Hypertension	1.361	0.802-2.309	0.2538	-	-	-
Diabetes mellitus	1.033	0.756-1.412	0.8383	-	-	-
Hyperlipidemia	0.859	0.639-1.153	0.3199	-	-	-
Atrial fibrillation	1.430	1.062-1.931	0.0186	1.563	1.136-2.151	0.0060
Creatinine (mg/dl)*	1.176	1.027-1.346	0.0187	-	-	-
Sodium (mmol/L)*	1.077	0.924-1.259	0.3476	-	-	-
Uric acid (mg/dl)*	1.178	1.021-1.361	0.0247	1.076	0.919-1.256	0.3596
BNP (pg/ml)*	2.105	1.000-2.104	<0.0001	2.105	1.000-2.104	<0.0001
HbA1c (%)*	0.973	0.841-1.128	0.7246	-	-	-
eGFR (ml/min/1.73 m ²)*	0.797	0.677-0.913	0.0028	0.977	0.814-1.145	0.7524
z-score ≥ 2 (vs z-score < 2)	1.887	1.319-2.699	0.0005	1.303	1.198-2.290	0.0229

CI = confidence interval; HR = hazard ratio.

Abbreviations as in Table 1.

* Per 1-SD increase.

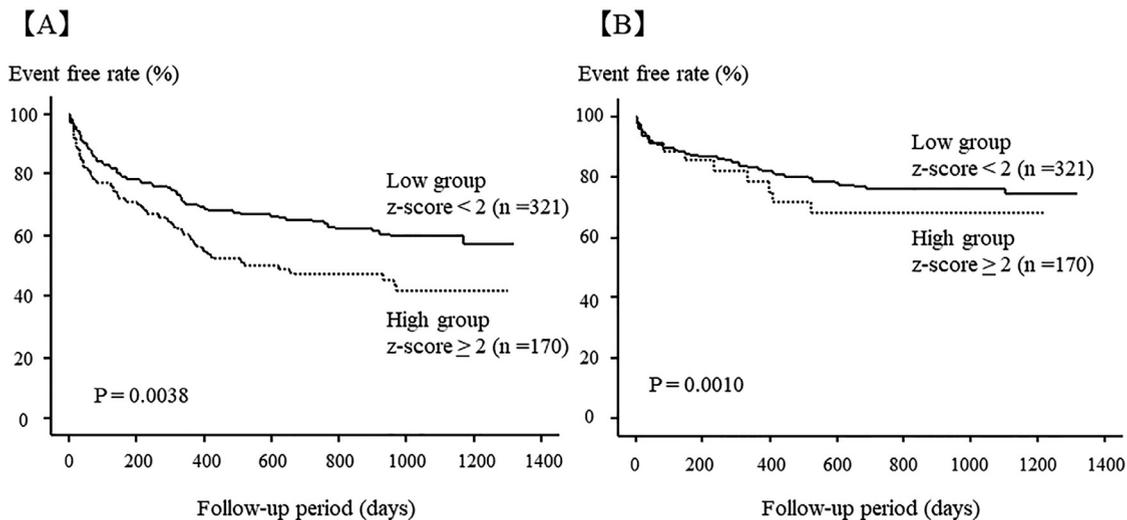


Figure 3. A Kaplan-Meier analysis in patients with chronic heart failure stratified into 2 groups based on z-score. The rates of occurrence of total cardiac events (A) and cardiac deaths (B) in the high group were significantly higher than that in the low group.

MCI and frailty, and the effect of improved frailty (through cardiac rehabilitation) on MCI.

Reportedly, self-care after discharge is insufficient in patients with CHF and concomitant MCI, and the incidence of cardiovascular events is high in this patient population.⁴ In patients with CHF, self-care includes adherence to medications and a low-sodium diet, as well as behaviors that maintain clinical stability.¹³ Interventions including the administration of oral medications, care support services for life management, and/or training for cognitive function preservation are necessary in patients with CHF and concomitant MCI. Recent reports have shown that higher education levels are associated with a lower prevalence of dementia and improved management of cardiovascular risk factors.¹⁵ Highly educated subjects are better able to understand and use health-related information, and therefore avoid risk factors that predispose to diabetes and dementia. Emphasizing the importance of education and creating a society where elderly subjects can lead meaningful and healthy lives by maintaining their physical and mental health could be useful strategies to prevent and/or control the heart failure pandemic. A multidisciplinary approach is necessary to manage the complexities of this clinical syndrome. We conclude that assessment of cognitive abilities in patients with CHF requires greater attention.

Disclosures

The authors have no conflicts of interest to disclose.

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