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Factors associated with poor prognosis in elderly patients with congestive heart failure with comorbid cognitive impairment: impact of life circumstances

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According to the Japanese Ministry of Health, Labour, and Welfare, 14.2% of people were aged > 75 years in Japan in 2018, and this number continues to rise. With population aging, the incidence of congestive heart failure (CHF) is also increasing.[1–3] Reports have shown that the presence of cognitive impairment (CI) in patients with CHF is associated with poor prognosis,[4–6] and the degree of CI is related to CHF severity.[7] In Japan, the number of older adults with CI was estimated to be 4.62 million in 2012 and is predicted to reach approximately 7 million by 2025, resulting in 20% of whole population aged > 65 years. An epidemiological report suggested that the mortality risk of patients with CI is approximately 1.7-times that of patients without cognitive symptoms.[8] Therefore, the presence of comorbid CI in elderly patients with CHF may result in higher mortality than in patients with CHF without CI. The CHF with CI tends to coexist with left ventricular dysfunction,[9,10] atrial fibrillation,[11] and cerebrovascular disease,[12] negatively influencing prognosis. However, the exact factors that influence the prognosis of patients with CHF with comorbid CI have not been elucidated. In this study, we aim to identify the prognostic factors in patients with CHF with CI, focusing on both patients' life circumstances and conventional prognostic factors.

This single-center prospective cohort study included consecutive elderly patients who were hospitalized for CHF at South Miyagi Medical Center, Shibata, Miyagi, Japan, from April 2019 to March 2020. This study was approved by the Institutional Review Board of South Miyagi Medical Center and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

Figure 1 shows the patient selection flowchart. Overall, 276 consecutive patients aged > 75 years with New York Heart Association class 3 or 4 CHF were enrolled. The Mini-Mental State Examination (MMSE) was performed after recovery from the acute phase. An MMSE score < 23 points during hospitalization was used to diagnose CI and divide the patients into the CI group and the non-CI group. Differential diagnoses for the cause of CI (e.g., Alzheimer's disease, cerebrovascular disease) were not considered. Of the 276 patients, two patients were unable to undergo the MMSE because of their character and/or delirium, and six patients refused participation when asked for informed consent. Furthermore, it was not possible to obtain follow-up information after discharge for 74 patients. Finally, 194 patients were included. Then we compared clinical outcomes between the CI group and the non-CI group and explored the prognostic factors on long-term mortality in the CI group.

All continuous data are expressed as mean ± SD or medians (interquartile range), while categorical variables are expressed as counts (percentages). Comparisons were performed using the independent Student's *t*-test for continuous variables and the Pearson's chi-squared test for categorical variables. Multivariate logistic regression analysis was performed by adjusting for the factors potentially related to adverse cardiac events ($P < 0.1$) identified in the univariate analysis. Established prognostic factors for adverse cardiac events were only included as confounding factors when they reached $P < 0.1$ in the univariate analysis. *P*-value < 0.05 was considered statistically significant in the multivariate analysis. All statistical analyses were performed using JMP® statistical software (version 17; SAS Institute Inc., Cary, NC, USA).

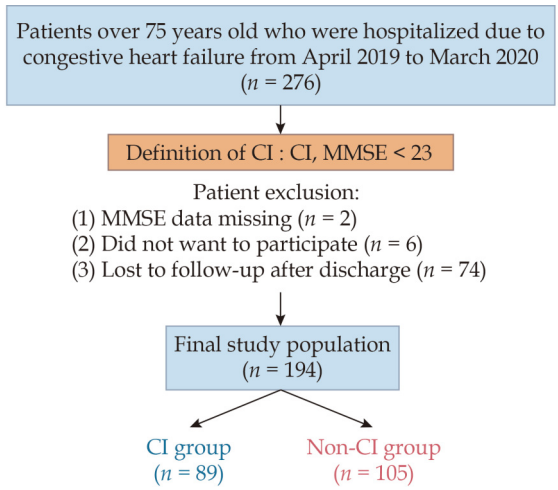


Figure 1 Schematic representation of the categorization of all participants. CI: cognitive impairment; MMSE: Mini-Mental State Examination.

The baseline clinical characteristics are shown in Table 1. Among 194 patients, the CI group and the non-CI group included 89 patients (45%) and 105 patients (55%), respectively. The CI group was with older patients (86 ± 6 years *vs.* 83.5 ± 5 years, $P < 0.001$). We used the Short Physical Performance Battery to diagnose frailty[13], defined as its score < 8, and found that the CI group had a higher proportion of frailty (83% *vs.* 49%, $P < 0.001$). Cerebrovascular disease history had higher proportion in the CI group (36% *vs.* 13%, $P < 0.001$). The nutritional status was indicated using the Geriatric Nutritional Risk Index (GNRI), which was a simple and established nutritional assessment tool for elderly patients.[14] We estimated the cutoff GNRI for mortality in each group using the receiver operating characteristic curve, producing a value of 95.3 in the CI group and 85.8 in the non-CI group, and found that the difference was not statistically significant. Other comorbidities, such as cardiovascular, respiratory, and malignant diseases, were comparable. Laboratory data, cardiac function assessed by echocardiography, and medication use during hospitalization were not significantly different. We also evaluated the family structure in the CI group and the non-CI group to understand the patients' lives and social circumstances. Information was obtained through interviews with the patients or their families during hospitalization. The family structure was divided into two categories: small (living alone or with a small number of family members such as a partner or a child) or large (living with a large number of family members, such as children or a partner and children). Approximately 60% of patients in both groups had a small family structure, indicating less support.

Table 2 presents the patients' clinical outcomes. The follow-up period was shorter in the CI group (372 ± 313 days *vs.* 599 ± 270 days, $P < 0.001$). The hospitalization duration and period until rehospitalization did not differ between the groups. The frequency of rehospitalization due to CHF was comparable between the groups at both 360 days and 730 days; however, the New York Heart Association class at rehospitalization was significantly higher in the CI group. The rate of all-cause mortality at 730-day was significantly higher in the CI group (69% *vs.* 24%, $P < 0.01$; risk ratio = 2.83, 95% CI: 1.94–4.02). The rate of cardiac mortality was significantly higher in the CI group. In the Kaplan-Meier analysis, the CI group had a significantly worse prognosis ($P < 0.001$) (Figure 2).

We explored the factors responsible for mortality in the CI group and the non-CI group. Focusing on life circumstances, the 730-day survival rate was compared between the small and large family subgroups (Figure 3). Mortality was significantly higher in the subgroup with a small family structure among patients with CI (78% *vs.* 22%, $P < 0.05$), but it was comparable between the subgroups among those without CI (24% *vs.* 20%). Multivariate regression analysis with adjustment for confounding factors, including family structure, age, GNRI, presence of frailty, and history of respiratory disease, was performed in the CI group. Small family structure and GNRI were independent prognostic factors for 730-day mortality (Figure 4A). On the other hand, GNRI was an independent prognostic factor, but family structure was not related to mortality in the non-CI group (Figure 4B). Frailty, which is a poor prognostic factor for CHF,[15] was not associated with mortality in both groups.

Studies have shown that CHF prognosis in patients with CI is poorer than in patients without CI.[5,6,16] However, the exact prognostic factors remain unknown. In recent times, there have been dramatic developments in medical therapies for CHF.[17–19] However, despite optimal medical therapy, the prognosis of elderly patients with CHF is still poor, especially in those with comorbid CI. Thus, it is necessary to consider factors other than medical treatment, such as social circumstances. A previous review comprehensively reported the prognosis of CHF in elderly patients,[20] but it did not consider the presence or absence of CI. In this study, we revealed that family structure is a prognostic factor in patients with CHF with comorbid CI. We also confirmed that nutritional status is a prognostic factor in these patients.

In our previous study involving patients with CI and

Table 1 Comparison of patient characteristics between the CI group and the non-CI group.

Variables	CI group (n = 89)	Non-CI group (n = 105)	P-value
Age, yrs	86 ± 6	83.5 ± 5	< 0.001
Male sex	33 (38%)	52 (51%)	0.045
Body mass index, kg/m^2	21.9 ± 5.8	22.0 ± 4.7	0.925
Prevalence of frailty	73 (83%)	52 (49%)	< 0.001
Geriatric Nutritional Risk Index	91.9 ± 13.6	92.9 ± 13.9	0.505
Systolic blood pressure at admission, mmHg	141 ± 28	144 ± 28	0.503
Diastolic blood pressure at admission, mmHg	83 ± 20	81 ± 21	0.393
Comorbidity			
Cardiovascular disease	65 (73%)	66 (63%)	0.154
Cerebrovascular disease	32 (36%)	14 (13%)	< 0.001
Pulmonary disease	20 (22%)	16 (16%)	0.22
Malignant disease	21 (24%)	22 (24%)	0.711
Hypertension	68 (76%)	79 (76%)	0.943
Diabetes mellitus	37 (42%)	43 (42%)	0.981
Dyslipidemia	21 (24%)	37 (35%)	0.063
Laboratory data on admission			
White blood cell, × μL	7897 ± 5640	7446 ± 2790	0.846
Lymphocyte	17 (19.1%)	19 (18.1%)	0.147
Hemoglobin, g/dL	11.1 ± 2.3	11.3 ± 2.1	0.719
Albumin, g/mL	3.2 ± 0.5	3.5 ± 0.5	0.016
Cholinesterase, U/L	198 ± 68	247 ± 85	0.067
Estimated glomerular filtration rate, mL/min per 1.73 m^2	40 ± 21	45 ± 21	0.139
Low-density lipoprotein cholesterol, mg/dL	88 ± 34	89 ± 31	0.589
Brain natriuretic peptide, pg/mL	894 ± 1271	677 ± 761	0.076
Serum Na^+, mEq/L	136 ± 14	137 ± 13	0.935
Echocardiography on admission			
Left ventricular ejection fraction, %	51.3 ± 15.3	54.1 ± 17.1	0.181
Left atrial dimension, mm	49.5 ± 9.6	48.2 ± 9.6	0.385
E/A	1.0 ± 0.1	0.9 ± 0.1	0.541
Medications on admission			
Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers	56 (53%)	44 (54%)	0.9
Loop diureticus	37 (38%)	37 (44%)	0.4
Antiplatelet	29 (29%)	28 (35%)	0.4
Anticoagulant	42 (44%)	25 (30%)	0.07
Mineral corticoid inhibitor	19 (20%)	18 (22%)	0.69
Statins	35 (36%)	19 (21%)	0.05
Social circumstances			
Living with a small number of family members	54 (61%)	70 (67%)	0.34
Living with a large number of family members	35 (39%)	35 (33%)	0.45

Data are presented as means ± SD or n (%). CI: cognitive impairment; E/A: mitral ratio of peak early to late diastolic filling velocity.

ischemic heart disease, we showed that social circumstances, including family structure, were independent prognostic factors.[21] In the present study, focusing on CHF, we considered family structure as representative of life

Table 2 Comparison of clinical outcomes between the CI group and the non-CI group.

Variables	CI group (n = 89)	Non-CI group (n = 105)	P-value
Period of hospital stay, days	21 ± 15	17 ± 15	0.016
Follow-up periods, days	372 ± 313	599 ± 270	< 0.001
Rehospitalization due to congestive heart failure			
Within 360 days	18 (20%)	24 (23%)	0.215
Within 730 days	24 (27%)	37 (35%)	0.657
NYHA class 4 at rehospitalization	12 (60%)	9 (29%)	0.03
Period until rehospitalization, days	166 ± 205	233 ± 245	0.575
All-cause mortality within 730 days	61 (69%)	24 (24%)	< 0.001
Cardiac mortality within 730 days	31 (35%)	10 (10%)	< 0.001

Data are presented as means ± SD or n (%). CI: cognitive impairment; NYHA: New York Heart Association.

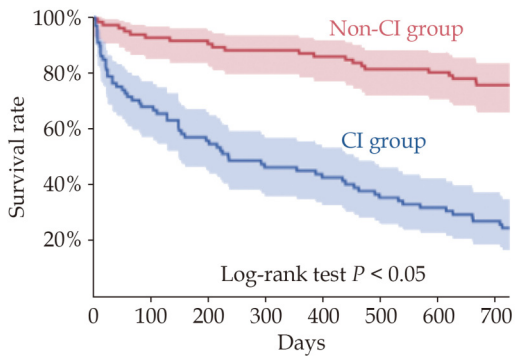


Figure 2 Kaplan-Meier curve comparing all-cause mortality between the CI group and the non-CI group during the 730-day follow-up period. CI: cognitive impairment.

circumstances and evaluated its influence on mortality with and without CI. A comparison of mortality between patients living with small and large families revealed that patients with CHF with CI living with small families had a poor prognosis; however, the mortality of non-CI patients was not influenced by family structure. The multivariate analysis supported that family size was an independent prognostic factor for CHF with CI, but not for CHF without CI. Generally, a fragile physical status, insufficient control of comorbid chronic illnesses, poor drug adherence, and social isolation are seen in elderly patients with CI.[21] A small family could be less supportive, resulting in poor recovery from above mentioned problems and thereby poor prognosis. Although patients' life circumstances are heterogeneous and difficult to quantify, our results suggest that family structure is a predictive indicator of patient care and/or assistance. Moreover, we speculate that optimal medical therapy for CHF is not sufficient to improve the prognosis of patients with CI; rather, family support also plays an important role.

Another way in which family structure may influence prognosis is through patient nutrition. In this study, nutritional status was a prognostic factor for CHF, regardless of the presence of CI. Previous studies have also shown that malnutrition is an independent risk factor for a poor CHF prognosis.[22–24] Moreover, there is a relationship between malnutrition and systemic inflammation,[25] and CHF is strongly correlated with systemic inflammation.[26–28] Thus, patients with CHF with comorbid malnutrition may synergistically develop systemic inflammation, leading to cytokine release, cardiac cachexia progression, and physical disability. Moreover, an inflammatory state is associated with cognitive decline, resulting in deterioration of physical capacity.[29]

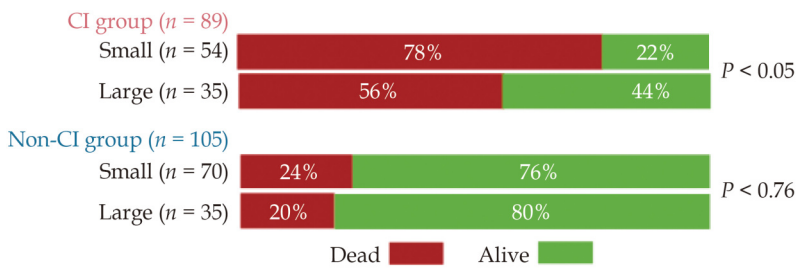
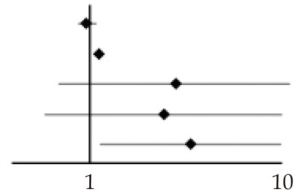


Figure 3 Differences in mortality based on the family structure in the CI group and the non-CI group. CI: cognitive impairment; Large: living with a large number of family members; Small: living with a small number of family members.

(A)

Variables	*P*-value	OR	95% CI
Age	0.09	0.91	0.83–1.03
GNRI < 95.3	< 0.01	1.07	1.02–1.12
Prevalence of frailty	0.17	2.82	0.64–12.38
Respiratory disease	0.22	2.47	0.54–11.12
Living with small number of families	0.03	3.45	1.09–10.96



(B)

Variables	*P*-value	OR	95% CI
Age	0.05	0.88	0.78–1.12
GNRI < 85.8	< 0.01	1.06	1.02–1.11
Prevalence of frailty	0.08	2.83	0.83–9.68
Respiratory disease	0.04	4.39	1.07–18.01
Malignant disease	0.06	3.71	0.64–12.02

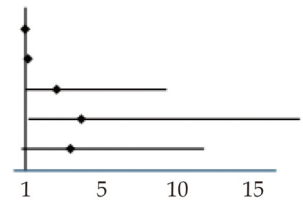


Figure 4 Factors associated with mortality in the CI group and the non-CI group. (A): Results of the multivariate logistic regression analysis (left) and odds ratio (right) of mortality in the CI group; and (B): results of the multivariate logistic regression analysis (left) and odds ratio (right) of mortality in the non-CI group. CI: cognitive impairment; GNRI: Geriatric Nutritional Risk Index.

We speculated that less family support would lead to poor nutrition in patients with CI, perhaps owing to poor nutritional management in daily life. To confirm the relationship between nutrition and family structure, we compared the GNRI between patients living with small and large number of family members in both the CI group and the non-CI group. In the CI group, the GNRI tended to be lower in patients living with small families; however, the difference was not significant (90 ± 14 *vs.* 95 ± 12, $P = 0.1$). In the non-CI group, the GNRI was comparable regardless of family structure (small *vs.* large: 92 ± 14 *vs.* 94 ± 15, $P = 0.4$). Family structure and nutritional status were independent prognostic factors for mortality, which means that family structure and nutritional status should not be correlated. This result is contrary to our speculation. There are two possible reasons for the discrepancy between the statistical results and our speculation. The first is the existence of a path other than nutrition; that is, less support may adversely affect therapy such as poor drug adherence, resulting in a direct correlation between family structure and mortality, weakening the correlation with nutrition. The second possibility is that a statistical correlation would exist between the GNRI and family structure if a large-scale population was analyzed to determine whether inadequate nutritional management due to less family support is one of the factors responsible for poor nutrition in CI patients.

This was a single-center prospective study with a small population. Therefore, larger studies are warranted to identify independent prognostic factors and elucidate the relationship between social circumstances and nutritional status. Moreover, we need to further investigate the relationship among frailty which is widely known as the poor prognostic factor of CHF, family structure and nutritional status.

We conclude that both nutritional status and family structure influence prognosis among patients with CHF with CI, whereas family structure is not a prognostic factor among patients without CI.

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