Association among mild cognitive impairment, social frailty, and clinical events in elderly patients with cardiovascular disease

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Word count: 2543

Declarations of Interest: none

Abstract

Background: Social support is considered a key factor for secondary prevention in patients with cardiovascular disease (CVD) and mild cognitive impairment (MCI). Recent studies have suggested the clinical importance of social frailty in CVD.

Objectives: This study aimed to examine the association among coexistent MCI, social frailty, and clinical events in patients with CVD.

Methods: This study included 184 hospitalized elderly patients with CVD who participated in inpatient cardiac rehabilitation (median age, 75 years; male, 66.3%). MCI was defined as a Montreal Cognitive Assessment score of ≤25 points at discharge. Social frailty was defined using the Makizako criteria. Lack of caregiver support was also assessed as an indicator of poor social support. The Kaplan-Meier survival curve analysis and Cox regression analysis were conducted to evaluate the combined impact of MCI and social frailty or the lack of caregiver support on the composite endpoint of all-cause mortality or unplanned rehospitalization.

Results: The prevalence of MCI, social frailty, and lack of caregiver support were 65.2%, 70.7%, and 19.0%, respectively. There was a significant difference among subgroups by MCI and a lack of caregiver support (log-rank test, $p = 0.018$), and the MCI/non-caregiver group showed the worst prognosis (adjusted hazard ratio 3.96; 95% confidence interval 1.57–9.98). Likewise, MCI/social frailty group showed a significantly high event risk (3.94; 1.20–12.9) among the subgroups by MCI and social frailty.

Conclusions: Our results highlight the clinical importance of assessing the presence of caregiver support along with conventional social frailty for patients with CVD and MCI.

Keywords: cognitive decline, social isolation, cardiovascular disease, cohort study

Highlights

- MCI was independently associated with clinical events in elderly patients with CVD
- Social frailty increased the event risk in elderly CVD patients with MCI
- A lack of caregiver support increased the event risk in patients with MCI
- The results highlight the importance of social support in patients with MCI

Introduction

Secondary cardiovascular prevention has been considered any strategy aimed to reduce the probability of a recurrent cardiovascular event in patients with known cardiovascular disease (CVD).[1] Additionally, due to the aging population, there is a growing importance of comprehensive disease management based on each patient's condition, including multimorbidity and geriatric conditions.[2] Thus, tailored and multidisciplinary practice and patient care plans should be considered for both reducing recurrent CVD and controlling comorbidities in elderly patients.

Previous studies have suggested that even mild cognitive impairment (MCI), which is a transient stage that is associated with a high risk of developing dementia, results in poor disease management in elderly patients with CVD.[3] Previous studies documented that the prevalence of MCI was 30–60%[4–6] and 50–75%[7–9] in patients with coronary heart disease and with heart failure, respectively, which seems higher than that among the general elderly population of up to 42%.[10] Therefore, to optimize comprehensive disease management in the elderly, an increase in social support, including the involvement of family and caregivers, was recommended in the CVD prevention guidelines in clinical practice.[11]

Social isolation is acknowledged as a risk factor for rehospitalization in patients with CVD.[12,13] Additionally, the clinical significance of social frailty among elderly patients with CVD has recently been studied. Social frailty, usually conceptualized as being at risk of losing or having lost sufficient social support, activities, or resources,[14] has been reported to be associated with poor prognosis in CVD.[15,16] Although the underlying mechanisms of this relationship remain unclear, social frailty may reflect a poor link in social support for disease management. The risk of adverse clinical events

is likely to increase due to social frailty in patients with MCI and an inherently high risk for poor self-care management; however, this association is yet to be examined.

A lack of support from caregivers, including family members, seems to be another key component of the social networks of patients with CVD. Generally, social frailty scales focus on reduced social activity, possibly increasing disability risk among community-dwelling elderly individuals.[17] On the other hand, in terms of chronic disease management, caregiver support may play a key role in secondary prevention, especially among elderly patients with cognitive impairment. However, it remains to be examined whether conventional social frailty indicators and lack of caregiver support are independently associated with adverse clinical events in patients with CVD.

Therefore, this study aimed to examine the association among MCI, poor social network assessed by social frailty, lack of caregiver support, and adverse clinical events in elderly patients with CVD.

Methods

Study design and participants

This was a retrospective cohort study. The inclusion criteria of this study were patients hospitalized for CVD, aged ≥65 years, who participated in inpatient cardiac rehabilitation. The exclusion criteria were death during hospitalization, transfer to a different hospital or institution, inability to walk, inability to answer the questionnaire appropriately, having a diagnosis of probable psychiatric or neurological conditions, having physician-diagnosed dementia or receiving anti-dementia drugs, or having missing data regarding Montreal Cognitive Assessment (MoCA) or social frailty assessment. We retrieved the data of patients with CVD who were admitted to Nagoya

Ekisaikai Hospital in Nagoya City, Japan, between January 2020 and October 2021.

In Japan, inpatient cardiac rehabilitation has become standard care for patients hospitalized for cardiovascular disease. In 2017, the implementation rates of inpatient cardiac rehabilitation were 76.5%, 65.6%, and 46.9% in patients hospitalized for cardiac surgery, acute coronary syndrome, and heart failure, respectively,[18] of which are the main population of this study. Health insurance is mandatory in Japan and has covered cardiac rehabilitation in the Japanese health care system. Hence, the study participants in the present study were not a population requiring special medical care. Inpatient cardiac rehabilitation included a gradual mobilization program at the bedside, exercises in the rehabilitation room, and patient education by medical professionals including nurses and physical therapists. Patients participated in the rehabilitation program for 20–60 min, 5 days per week, during the period of hospitalization. The inpatient cardiac rehabilitation was provided according to the guidelines of the Japanese Circulation Society.[19]

Cognitive function

In this analysis, MCI was defined using the Japanese version of the MoCA (MoCA-J), a standard screening test for MCI.[20,21] Trained physical therapists performed cognitive assessments within 3 days before discharge as part of routine clinical practice. The physical therapists performing the cognitive function assessment have been evaluated for inter-and intra-rater reliability beforehand, as routine practice. The MoCA assesses nine domains of cognition, such as attention, concentration, executive functions, memory, language, visuoconstruction skills, conceptual thinking, calculations, and orientation. The maximum score on the MoCA-J is 30 points, and we used a cut-off of

≤25 points for defining MCI as described in a previous study (sensitivity, 93%; specificity, 87%).[21]

Social frailty and caregiver support

Social frailty was evaluated using the definition proposed by Makizako et al[17]. The following five components were included: going out less frequently than last year (yes), visiting friends sometimes (no), feeling like helping friends or family (no), living alone (yes), and talking with someone every day (no). Social frailty was defined as the presence of ≥ 2 components. The questionnaire was originally derived from community-dwelling elderly adults and has been reported to predict future need for long-term care.[17] In addition to the social frailty assessment, each patient was asked if they had a caregiver who could help them in disease management after discharge. There is an increasing number of elderly individuals living with only a spouse in Japan. Since the elderly spouse is not necessarily able to support the patient, each patient was asked about the presence of caregiver support for their disease management or daily living.

Clinical data

Patient medical records were reviewed to collect data regarding age, sex, body mass index, principal etiology, length of hospital stay, comorbidities, left ventricular ejection fraction, biochemical parameters, prescribed medications at discharge, the ability to visit hospitals, the need for a walking device, or assistance for walking during the hospital stay. Anemia was defined as hemoglobin levels < 13 g/dL for men and <12 g/dL for women according to previous reports.[22]

Comorbidities were also evaluated using the Charlson Comorbidity Index.[23] The

Charlson Comorbidity Index was calculated as the sum of the scores assigned to several comorbidities (e.g., myocardial infarction, cerebrovascular disease, diabetes, chronic kidney disease, liver disease, cancer, leukemia, etc.) based on the original definition (range: 0–37 points). The presence of comorbidities included in the Charlson Comorbidity Index was confirmed by a retrospective review of the medical record. Thus, there is a possibility to underestimate the score in the present analysis.

The level of long-term care insurance was also noted. In Japan, every person aged ≥65 years is eligible and needs to be certified and classified according to their physical and cognitive dysfunction.[24] The long-term care insurance system certifies a person to belong to one of seven levels (support levels 1–2 and care levels 1–5) depending on their disease condition or functional ability. Those with support levels require partial support to prevent progression to long-term care levels or to perform daily activities that could still be improved by the use of facility services. Those who are at a certificated care level 1–2 had some difficulties in performing activities of daily living. Those who are at a certified care level 3 or higher require total assistance for daily activities, such as walking indoors or dressing.

Study outcome

The study outcome was composed of multiple all-cause clinical events, including all-cause mortality and all-cause unplanned rehospitalization.[25] Planned rehospitalizations, defined as elective readmissions, were excluded. Events were confirmed by reviewing the hospital medical records. The number of days from discharge to the date of the event was also noted.

Statistical analysis

Continuous variables are expressed as the mean and standard deviation for normally distributed variables and as median with interquartile range for non-normally distributed data. Categorical data are expressed as numbers and percentages. Differences in patient characteristics between those with and without the events were compared using the t-test, Mann−Whitney U test, or chi-square test, as appropriate.

The prevalence of MCI, social frailty, and a lack of caregiver support is presented using Euler diagrams (area-proportional diagrams) to visualize the overlap of the three factors. The Euler diagrams were drawn using R with the "eulerr" package version R package version 6.1.1.

The event-free survival rate was evaluated using the Kaplan–Meier survival method and compared using the log-rank test. Then, multivariable Cox regression analysis was performed to examine the association among MCI, social frailty, a lack of caregiver support, and their combinations with the study outcome. Due to the limited sample size, the main analysis was adjusted for age, the reason for hospitalization (heart failure or not), Charlson Comorbidity Index, and walking ability. Additionally, the secondary analysis was performed adjusted for the characteristics that were significantly different between those with and without the events. The proportional hazards assumption was checked using the Schoenfeld residuals test.

All statistical analyses were performed using Stata/SE software (version 15.1; StataCorp LP, College Station, TX, USA). Results were considered statistically significant at $p < 0.05$.

Ethics

The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Nagoya Ekisaikai Hospital, Japan (No. 2019-043). Informed consent was obtained using the website in the form of an opt-out system. No patient opted out of the study at the time of the analysis.

Results

A total of 184 elderly patients with CVD were included in this study (Figure 1). The median age was 75 years (interquartile range [IQR], 73–82 years), and 66.3% were men. The prevalence of patients hospitalized for the treatment of congestive heart failure was 53.3%. The prevalence of MCI, social frailty and lack of caregiver support were 65.2%, 70.7%, and 19.0%, respectively.

The Euler diagrams (area-proportional diagrams) showing the overlap of MCI, social frailty, and a lack of caregiver support are presented in Figure 2. Of the patients with MCI, 75% suffered from comorbid social frailty, and this population accounted for 50% of the overall study participants. The prevalence of social frailty was 80% in patients without caregiver support, and many patients had caregiver support but still suffered from social frailty.

A total of 60 composite outcomes occurred over a median follow-up period of 358 days (IQR, 187–624). A comparison of patient characteristics between patients with and without the study outcomes is presented in Table 1. Patients with the study outcome showed a statistically higher Charlson Comorbidity Index, lower estimated glomerular filtration rate, lower prescription rates of beta-blockers and anticoagulants, higher prescription rate of diuretics, higher prevalence of living alone, need for assistance for visiting hospitals, and a need for a walking device or assistance, compared to those

without the outcome ($p < 0.05$). The prevalence of MCI and lack of caregiver support were higher in those with the study outcome than in those without ($p < 0.05$), whereas social frailty was not ($p = 0.053$).

Figure 3 shows the Kaplan–Meier survival curves according to MCI, social frailty, and lack of caregiver support. MCI and lack of caregiver support were significantly associated with increased study outcomes ($p = 0.018$ and $p = 0.015$, respectively). Social frailty tended to be associated with the study outcome but was not statistically significant ($p = 0.077$). The Kaplan–Meier survival curves of groups based on MCI and social frailty or a lack of caregiver support are presented in Figure 4. There was a significant difference among subgroups by MCI and a lack of caregiver support ($p = 0.008$), and those with MCI without caregiver showed the worst prognosis. When stratified by MCI and social frailty, patients with both MCI and social frailty showed the worst prognosis, although the difference among subgroups was not statistically significant ($p = 0.052$).

The results of the Cox proportional hazards model adjusted for age, heart failure, Charlson Comorbidity Index and walking ability are summarized in Table 2. MCI was associated with the study outcome independent of social frailty and caregiver support (hazard ratio, 1.82; 95% confidence interval 1.00–3.41; $p = 0.048$, Model 1). The lack of caregiver support also tended to be associated with the study outcome (1.78; 0.99–3.20; $p = 0.054$), whereas social frailty was not. Patients with both MCI and social frailty showed higher event risk than those without both the factors (3.87; 1.17–12.87; $p = 0.027$, Model 2); however, those with either MCI or frailty did not show statistically higher event rates. In Model 3, patients with either MCI or a lack of caregiver support had higher event risk than those without both (MCI: 2.38; 1.07–5.27; $p = 0.033$, lack of

caregiver: 3.06; 1.06–8.85; $p = 0.038$), and those with the coexistence of the two factors showed the worst prognosis (MCI + lack of caregiver: 3.71; 1.46–9.40; $p = 0.006$). As presented in the supplementary Table A1, similar results were observed even after adjusting for the statistically significant variables ($p < 0.05$) in the comparison between those with and without the events. The proportional hazards assumptions for a composite outcome in all the above Cox regression analyses were confirmed (Schoenfeld residuals test, $p > 0.05$)

Discussion

In elderly patients hospitalized for CVD, MCI was associated with an increased risk of all-cause mortality and unplanned rehospitalization after discharge, and its impact was increased by coexisting social frailty or lack of caregiver support. The findings of this study emphasize the clinical importance of social support for reducing adverse clinical events in elderly patients with CVD and comorbid MCI.

Clinical guidelines for CVD prevention recommend family or caregiver support for secondary prevention among elderly patients with CVD.[11] However, there is still room for examining effective social support to reduce post-discharge clinical outcomes. In this study, MCI was independently associated with a composite outcome of unplanned rehospitalization and mortality, which is consistent with the results of another recent study in patients with coronary heart disease.[26] These observations suggest that adjustments to the living environment, including social support, should be considered in the early stages of cognitive decline in CVD. The present study evaluated social frailty and a lack of caregiver support as social isolation indicators, both of which were associated with an increased risk of adverse clinical outcomes in patients with

MCI. The generalizability should be carefully discussed due to the retrospective design with the limited sample size. The higher prevalence of MCI in this study compared to previous studies may be related to selection bias, as we retrospectively evaluated patients who underwent cognitive assessments as part of routine clinical practice. Nevertheless, our findings suggest the possibility of enhancing social networks as a measure for secondary CVD prevention in patients with MCI.

Social frailty has emerged as a new prognostic factor in patients with CVD. Although social frailty assessment tools are not well established yet, Makizako's criteria have been widely used in Japan[17] and reported to be associated with disability risk among elderly adults. A recent cohort study in Japan reported that social frailty, defined by Makizako's criteria, is independently associated with heart failure prognosis.[16] The present study adds further evidence that social frailty could have a negative effect, especially in patients with cognitive impairment who are at risk of poor disease management. The prevalence of social frailty in this study was approximately 70%, and it coexisted with MCI at a high rate. These results suggest the need for routine clinical assessments of social frailty and cognitive decline. In contrast, social frailty alone did not predict the study outcomes in the multivariate analysis. Since social frailty scales were originally developed among the general elderly population, further studies may be needed to explore components associated with disease-specific outcomes.

Another finding of this study was the relationship between caregiver support and post-discharge clinical events in elderly patients with CVD. Social frailty scales generally include common items, such as living alone and having infrequent contact with family or friends[17,27,28] but not the presence of caregiver support for chronic disease management. This is probably due to the focus on preventing long-term care

caused by a physical and cognitive decline in old age. Self-care management, including medication adherence and lifestyle modification, is a key component of secondary CVD prevention. Caregiver support tends to function as social support for such disease management behaviors; however, its association with CVD prognosis has not been well documented. In this study, the lack of caregiver support alone was independently associated with the study outcome and led to a further increase in event risk in patients with MCI. This result supports the recommendation of the guidelines of secondary cardiovascular prevention to involve family and caregivers for secondary prevention.[29] The small sample size of this study did not allow for sub-analysis to examine the association between social frailty and specific clinical outcomes, such as cardiac rehospitalization or mortality. This issue should be addressed by future large-scale studies.

Although the coexistence of MCI and a poor social network was an independent predictor of post-discharge adverse events, other prognostic factors should also be assessed for appropriate risk stratification. For instance, patients with adverse events had a high prevalence of reduced walking ability and need of assistance for visiting hospitals, suggesting the presence of physical frailty that is a known prognostic factor of CVD.[30,31] A high Charlson Comorbidity Index, decreased eGFR, and low prescription rates of cardioprotective medications including beta-blockers are observed among those with adverse events in this study. This may also lead to fragile conditions and an increased risk of adverse outcomes. These results indicate that in clinical practice, multidomain frailty should be assessed along with medical conditions and comorbidities, which is associated with a poor prognosis.

Cardiac rehabilitation, an established comprehensive disease management

program for secondary CVD prevention, can play a supportive role in elderly patients after discharge. However, nationwide studies have reported that the participation rate in cardiac rehabilitation remains low in Japan.[32,33] Barriers to cardiac rehabilitation are multifactorial[34]; a lack of transportation has been reported to be a major cause, even in relatively young patients in Japan.[35] Therefore, home-based disease management has become more important than hospital-based cardiac rehabilitation, especially for elderly patients. A previous study demonstrated the association between the use of home- or community-based care services and a reduced risk of rehospitalization in patients with heart failure.[36] Such long-term care services have the potential to be substituted for family support. Remote monitoring by medical staff may become another solution if there are limitations in adjusting the home environment,[37,38] although there still exists limited clinical evidence. The effects of social services and digital health as measures of poor social support on secondary prevention in elderly patients with CVD may be studied in the future.

This study has several limitations. First, there was a potential for selection bias in the present analysis because of the nature of this single-centered retrospective study. Hence, the generalizability of our results should be carefully discussed. In particular, the impact of social factors may vary by country or region, and our results need to be confirmed by further studies. Second, confounding factors were not fully considered in the multivariate analysis due to the limited sample size. Third, survival analysis in this study was performed based on the follow-up data based on the medical records. Primary care physicians provide information when a patient dies at home. Additionally, most patients are usually rehospitalized to our hospital since it is a major acute hospital in the region. Yet, this study had a limitation that accurate data was not available on patients

who may have been admitted to other hospitals or moved to another city. Fourth, our findings may be affected by the COVID-19 pandemic. A recent study in Japan demonstrated that physical activity among community-dwelling older individuals decreased due to the COVID-19 pandemic.[39] Therefore, a part of social frailty observed in this study can be derived from the COVID-19 pandemic. Fifth, there may be unknown confounding factors, such as educational level and socioeconomic status, that were not assessed in this study. Although health insurance is mandatory in Japan, the economic status may have confounded the study findings. This limited the discussion on the independent or causal relationship among the coexistence of cognitive impairment, social frailty, and clinical events. Finally, the small sample size limited the subgroup analysis to conduct a sensitivity analysis. Consistency of the results across different ages and patient characteristics, including etiologies, should be examined.

Conclusions

MCI was significantly associated with post-discharge adverse clinical events among elderly patients with CVD, and the risk was further increased in patients with a poor social network (social frailty or lack of caregiver support). Our results suggest that the presence of caregiver support after discharge should be assessed along with conventional social frailty for planning home-based secondary prevention in elderly patients.

Acknowledgments

The authors sincerely appreciate Mr. Akihito Matsuoka, Ms. Takako Kameyama, Mr. Koya Kobayashi, and Ms. Rina Terasawa for their contributions to data collection.

Funding

This work was partly supported by JSPS KAKENHI (Grant Number 19K24311).

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Figure legends

Figure 1. Flowchart of patient selection

CVD, cardiovascular disease; MoCA, Montreal Cognitive Assessment

Figure 2. Euler diagrams for the proportion of overlap and non-overlap among MCI, social frailty, and lack of caregiver support

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

Social frailty: ≥ 2 of Makizako's social frailty score

Figure 3. Kaplan-Meier survival curves according to MCI, social frailty, and lack of social support

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

Social frailty: ≥ 2 of Makizako's social frailty score

Figure 4. Kaplan-Meier survival curves according to coexistence of MCI and social frailty or lack of social support

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

Social frailty: ≥ 2 of Makizako's social frailty score

Tables

Table 1. Characteristics of the study participants

	Without event (n=124)	With event (n=60)	p
Age, years	75 (72– 81)	76 (74–83)	0.21
Male, n (%)	82 (66.1)	40 (66.7)	0.94
Body mass index, kg/m^2	22.3±5.7	20.8±6.2	0.11
Reason for hospitalization			
Heart failure, n (%)	61 (49.2)	37 (61.7)	0.11
Acute coronary syndrome, n (%)	42 (33.9)	19 (31.7)	0.60
Aortic disease, n (%)	12 (9.7)	3 (5.0)	0.23
Chronic coronary syndrome, n (%)	9 (7.1)	1 (1.7)	0.38
Cardiac surgery during hospitalization, n (%)	42 (33.9)	12 (20.0)	0.053
Length of hospital stay, days	17 (13–25)	17 (12–24)	0.57
Comorbidities			
Hypertension, n (%)	86 (69.4)	41 (68.3)	0.89
Dyslipidemia, n (%)	52 (41.9)	23 (38.3)	0.64
Diabetes mellitus, n (%)	35 (28.2)	21 (35.0)	0.35
Prior heart failure, n (%)	25 (20.2)	17 (28.3)	0.22
Stroke, n (%)	22 (17.7)	8 (13.3)	0.45
Charlson Comorbidity Index, points	1 (1–2)	2 (1–3)	0.047
Left ventricular ejection fraction, %	50 (44–59)	50 (42–53)	0.50
Biochemical data			
Albumin, g/dL	3.5 (3.3–3.7)	3.5 (3.2–3.7)	0.38
Anemia, n (%)	75 (60.5)	45 (75.0)	0.053
eGFR, mL/min/1.73m^2	54.5 (42.6–66.3)	41.6 (30.0–59.8)	<0.001
Medications			
Beta blocker, n (%)	98 (79.0)	35 (58.3)	0.003
ACEi/ARB, n (%)	77 (62.1)	29 (48.3)	0.077
MRA, n (%)	43 (34.7)	29 (48.3)	0.075
Diuretic, n (%)	50 (40.3)	39 (65.0)	0.002
Statin, n (%)	76 (61.3)	39 (65.0)	0.63
Anticoagulant, n (%)	67 (54.0)	20 (33.3)	0.008
Living alone, n (%)	21 (16.9)	18 (30.0)	0.042

Able to visit hospitals without help, n (%)	92 (74.2)	28 (46.7)	0.001
Long-term care insurance level			0.736
None, n (%)	101 (81.5)	46 (76.7)	
Support level 1–2, n (%)	13 (10.5)	6 (10.0)	
Care level 1–2, n (%)	5 (4.0)	4 (6.65)	
Care level 3–5, n (%)	5 (4.0)	4 (6.65)	
Walking device or assistance			<0.001
None, n (%)	113 (91.1)	45 (75.0)	
Walking device, n (%)	6 (4.8)	15 (23.3)	
Assistance, n (%)	5 (4.0)	1 (1.7)	
MCI, n (%)	74 (59.7)	46 (76.7)	0.023
Social frailty, n (%)	82 (66.1)	48 (80.0)	0.053
Lack of caregiver support, n (%)	17 (13.7)	18 (30.0)	0.008

Continuous variables were presented as mean±standard deviation or median (interquartile range).

Categorical variables were expressed as number (percentage).

MCI: ≤ 25 of Montreal Cognitive Assessment

Social frailty: ≥ 2 of Makizako's social frailty score

Abbreviations: eGFR, estimated glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; angiotensin II receptor blocker; MRA, mineralocorticoid receptor blocker; MCI, mild cognitive impairment

Table 2. Results of Cox proportional hazards model

	Hazard ratio	[95% confidence interval]	p
Model 1			
MCI	1.82	[1.00–3.41]	0.048
SF	1.41	[0.73–2.72]	0.30
LC	1.78	[0.99–3.20]	0.054
Model 2			
MCI (-) SF (-)	1 (reference)		
MCI (-) SF (+)	2.62	[0.73–9.44]	0.14
MCI (+) SF (-)	3.09	[0.83–11.52]	0.093
MCI (+) SF (+)	3.87	[1.17–12.83]	0.027
Model 3			
MCI (-) LC (-)	1 (reference)		
MCI (-) LC (+)	3.06	[1.06–8.85]	0.038
MCI (+) LC (-)	2.38	[1.07–5.27]	0.033
MCI (+) LC (+)	3.71	[1.46–9.40]	0.006

Adjusted for age, heart failure (heart failure hospitalisation or prior heart failure), Charlson Comorbidity Index, and walking ability (use of walking device or assistance)

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

Social frailty: ≥ 2 of Makizako's social frailty score

Figures

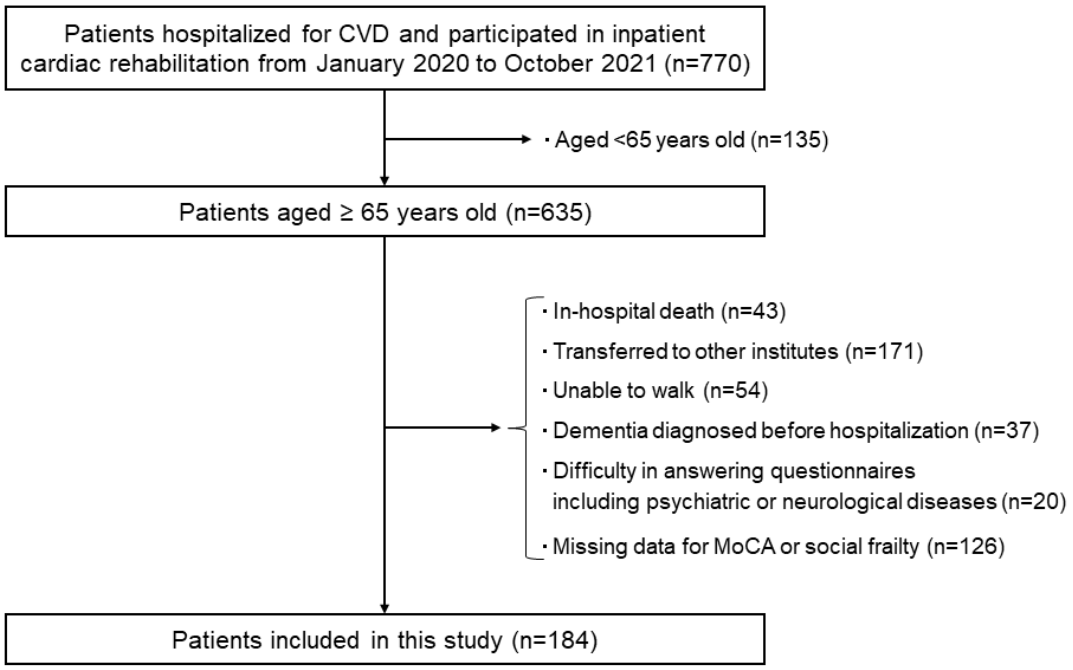

Figure 1. Flowchart of patient selection

CVD, cardiovascular disease; MoCA, Montreal Cognitive Assessment

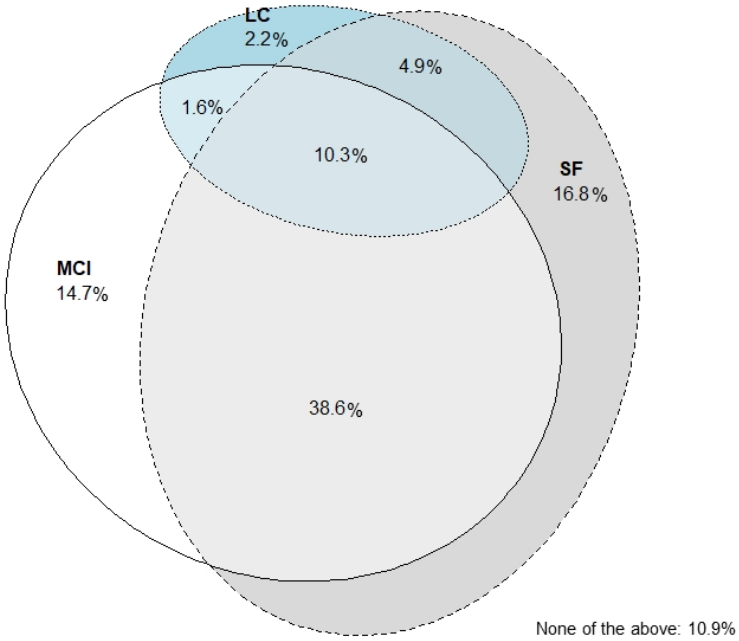

Figure 2. Euler diagrams for the proportion of overlap and non-overlap among MCI, social frailty, and lack of caregiver support

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

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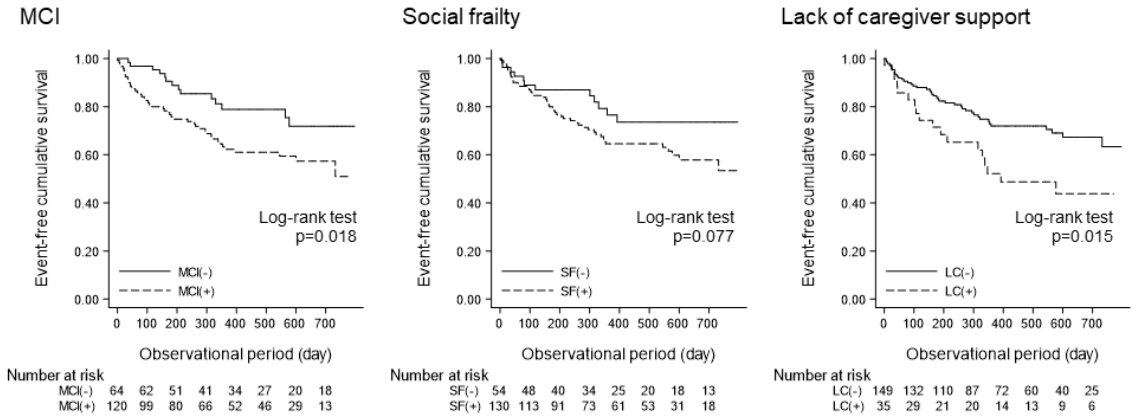

Figure 3. Kaplan-Meier survival curves according to MCI, social frailty, and lack of social support

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

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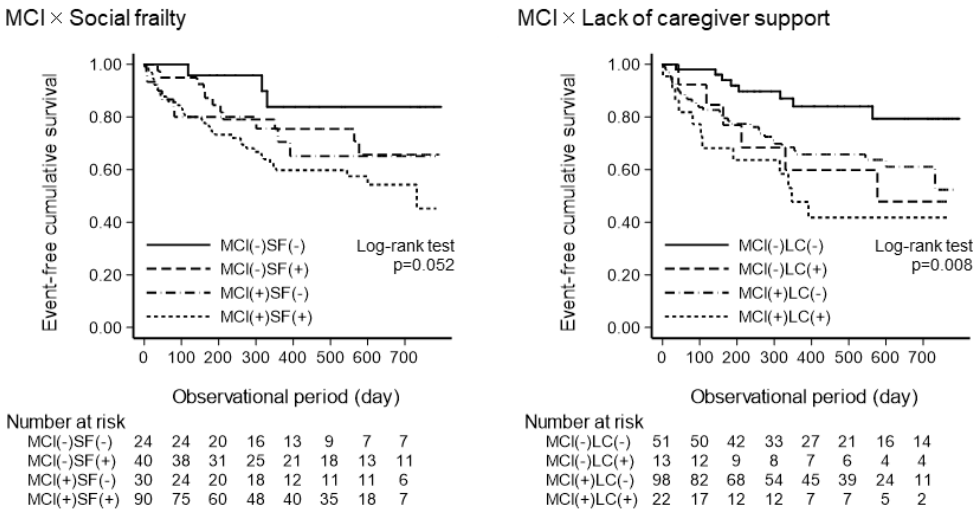

Figure 4. Kaplan-Meier survival curves according to coexistence of MCI and social frailty or lack of social support

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

Appendix

Supplementary Table A1. Results of Cox proportional hazards model adjusted for the variables with a p <0.05 for the comparisons between those with and without events

	Hazard ratio	[95% confidence interval]	p
Model 1			
MCI	1.80	[0.99–3.37]	0.061
SF	1.32	[0.68–2.56]	0.42
LC	1.83	[1.01–3.28]	0.044
Model 2			
MCI (-) SF (-)	1 (reference)		
MCI (-) SF (+)	1.68	[0.46–6.18]	0.43
MCI (+) SF (-)	2.99	[0.81–11.17]	0.10
MCI (+) SF (+)	3.05	[1.00–10.04]	0.049
Model 3			
MCI (-) LC (-)	1 (reference)		
MCI (-) LC (+)	2.79	[0.96–8.12]	0.059
MCI (+) LC (-)	2.25	[1.02–4.93]	0.042
MCI (+) LC (+)	3.25	[1.24–8.49]	0.016

Model 1: adjusted for Charlson Comorbidity Index, estimated glomerular filtration rate, beta blocker, diuretic, anticoagulant, ability to visit hospitals without help, and walking ability (use of walking device or assistance)

Model 2: adjusted for Charlson Comorbidity Index, estimated glomerular filtration rate, beta blocker, diuretic, anticoagulant, living alone, ability to visit hospitals without help, and walking ability (use of walking device or assistance)

Model 3: adjusted for Charlson Comorbidity Index, estimated glomerular filtration rate, beta blocker, diuretic, anticoagulant, ability to visit hospitals without help, and walking ability (use of walking device or assistance)

Living alone was excluded in the model 1 and model 3 because of the collinearity with lack of caregiver support.

Abbreviations: MCI, mild cognitive impairment; SF, social frailty; LC, lack of caregiver support

MCI: ≤ 25 of Montreal Cognitive Assessment

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