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ORIGINAL RESEARCH

Prognostic Value of Objective Social Isolation and Loneliness in Older Patients With Heart Failure: Subanalysis of FRAGILE-HF and Kitasato Cohort

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BACKGROUND: Social factors encompass a broad spectrum of nonmedical factors, including objective (social isolation [SI]) and perceived (loneliness) conditions. Although social factors have attracted considerable research attention, information regarding their impact on patients with heart failure is scarce. We aimed to investigate the prognostic impact of objective SI and loneliness in older patients with heart failure.

METHODS AND RESULTS: This study was conducted using the FRAGILE-HF (Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure; derivation cohort) and Kitasato cohorts (validation cohort), which included hospitalized patients with heart failure aged ≥65 years. Objective SI and loneliness were defined using the Japanese version of Lubben Social Network Scale-6 and diagnosed when the total score for objective and perceived questions on the Lubben Social Network Scale-6 was below the median in the FRAGILE-HF. The primary outcome was 1-year death. Overall, 1232 and 405 patients in the FRAGILE-HF and Kitasato cohorts, respectively, were analyzed. Objective SI and loneliness were observed in 57.8% and 51.4% of patients in the FRAGILE-HF and 55.4% and 46.2% of those in the Kitasato cohort, respectively. During the 1-year follow-up, 149 and 31 patients died in the FRAGILE-HF and Kitasato cohorts, respectively. Cox proportional hazard analysis revealed that objective SI, but not loneliness, was significantly associated with 1-year death after adjustment for conventional risk factors in the FRAGILE-HF. These findings were consistent with the validation cohort.

CONCLUSIONS: Objective SI assessed using the Lubben Social Network Scale-6 may be a prognostic indicator in older patients with heart failure. Given the lack of established SI assessment methods in this population, further research is required to refine such methods.

Key Words: heart failure ■ objective and perceived social isolation ■ social frailty

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CLINICAL PERSPECTIVE

What Is New?

- The Lubben Social Network Scale-6 was used to evaluate objective social isolation (SI) and loneliness.
- Although objective SI was independently associated with 1-year death, loneliness was not significantly associated with 1-year death.

What Are the Clinical Implications?

- When evaluating SI, clinicians should not only focus on SI itself but also on its intricate components.
- Due to the absence of established assessment methods for SI, additional research is necessary to enhance and refine these evaluation techniques.

Nonstandard Abbreviations and Acronyms

FRAGILE-HF	Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure
LSNS-6	Lubben Social Network Scale-6
SI	social isolation

Heart failure (HF) is a clinical syndrome characterized by a high mortality rate and morbidity globally.[1] Recently, there has been a global escalation in the incidence of HF, attributable to the advancing age of the population. Notably, Japan has one of the world's fastest aging populations, with >85% of patients hospitalized for HF aged >65 years.[2,3]

Older patients with HF have a particularly high mortality rate; thus, specific treatments or management strategies are warranted. The proportion of HF-related or cardiovascular deaths is low in comparison with noncardiovascular deaths in this population.[4–6] Therefore, it is indispensable to tackle matters beyond medical factors, including social factors.

Social factors encompass multiple types of nonmedical factors, such as social isolation (SI) and loneliness. SI is characterized as an "objective" condition where limited or infrequent social contact is experienced by the individual, whereas loneliness denotes a "perceived" sense of isolation, which can cause distress for the individual.[7,8] SI and loneliness have recently attracted considerable attention in the field of cardiovascular disease because these 2 conditions are associated with an increased risk of cardiovascular disease,[9,10] including HF.[11] Furthermore, these concepts are considered essential, particularly in older patients with HF, because the population is at a substantially greater risk of conditions that affect their mobility and social life, such as physical frailty,[12] sarcopenia,[13] and depression.[14,15] A meta-analysis of those with HF demonstrated that 37.2% and 32.8% of cases were complicated by objective SI and loneliness,[16] respectively.

In numerous studies thus far, social factors, including SI, are reportedly associated with increased mortality rates in older patients with HF.[17–22] However, there are no established metrics to assess SI and loneliness, and the distinction between them is highly ambiguous. The Lubben Social Network Scale-6 (LSNS-6), a self-reported scale, is widely used to screen the status of an individual's social network in the older population.[23–25] In community-dwelling populations, 11% to 20% of people were socially isolated, according to LSNS-6.[26–28] In contrast, the corresponding frequency in Japanese patients with HF was numerically higher, ranging from 28% to 49%. This population also had a high risk of HF readmission or death.[29,30] However, these previous studies involved a restricted number of study patients.[29,30] Furthermore, although LSNS-6 encompasses both objective SI and loneliness, differences in the 2 factors' prognostic impact have not yet been clearly evaluated in older patients with HF. Therefore, we herein aimed to elucidate the association between objective SI and loneliness and 1-year death using LSNS-6 in Japanese older patients with HF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Population

This study was conducted using data from 2 registries: the FRAGILE-HF (Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure) study (as a derivation cohort) and Kitasato cohort (as a validation cohort). The FRAGILE-HF study is a multicenter prospective observational study conducted in Japan to investigate the association between multidomain frailty and prognosis in older patients with HF.[12,31–33] A total of 1332 patients admitted to 15 hospitals in Japan were enrolled between September 2016 and March 2018. The study inclusion criteria were as follows: patients aged ≥65 years, diagnosed with HF, and capable of walking at the time of discharge. Follow-up information on prognosis was investigated for up to 1 year after enrollment, and the results were reported.[12] The exclusion criteria for the FRAGILE-HF study were patients

with a history of heart transplantation or left ventricular assist device implantation; those undergoing chronic peritoneal dialysis or hemodialysis; patients with acute myocarditis, BNP (brain-type natriuretic peptide) levels <100 pg/mL, or N-terminal pro-BNP levels <300 pg/mL at admission; and patients for whom these data were not available. Medications taken at the time of discharge were recorded, and physical examinations, echocardiography, and blood sampling were conducted in a stable condition before discharge.

The Kitasato cohort study, a retrospective study conducted at the Cardiovascular Center of Kitasato University Hospital, was designed to externally validate the FRAGILE-HF study. It comprises 3383 patients aged ≥65 years who were hospitalized for HF and underwent cardiac rehabilitation between January 2007 and January 2021.

In both studies, the Framingham criteria were specifically used to diagnose HF because the accuracy of HF diagnosis is notably low in the national health care database in Japan.[34,35]

In the FRAGILE-HF study, all participants were informed of the process before their participation and that they could withdraw from the study at any time during the research period without any consequences. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. As this was an observational study without any invasive procedures or interventions, written informed consent based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labour, and Welfare was not required. The ethics committee of each participating hospital approved the research protocol. Study information, including objectives, inclusion and exclusion criteria, primary outcomes, and names of the participating hospitals, was publicly disclosed on the University Hospital Medical Information Network before the enrollment of the first patient (unique identifier: UMIN000023929). The Kitasato cohort study received approval from the Research Ethics Committee of Kitasato University Hospital (B22-143) and adhered to the principles outlined in the Declaration of Helsinki. Participants were informed of their right to opt out of the study if they chose not to participate.

Definition of Total and Objective SI and Loneliness

Total SI was assessed using the Japanese version of the LSNS-6, which showed good reliability and validity in older Japanese community residents.[36] This scale consists of 3 questions regarding the patients' family (Q1–Q3) and friendships (Q4–Q6). Participants provided the number of people who fit each category, and the total score was calculated on the basis of their responses (0=none, 1=1, 2=2, 3=3 or 4, 4=5–8, 5=≥9). Therefore, the LSNS-6 total score ranged from 0 to 30. In the current study, total SI was diagnosed using the cutoff value (LSNS-6<12) from previous studies of the Japanese population with HF.[29,30,36]

A gold standard tool is yet to be established to evaluate objective and perceived social conditions; therefore, we developed a novel evaluation method using the LSNS-6 questionnaire items. Objective social condition was calculated by summing the scores of "Q1: How many relatives do you see or hear from at least once a month?" and "Q4: How many friends do you see or hear from at least once a month?" in the LSNS-6 questionnaire. Perceived social condition (ie, loneliness) was calculated by summing the scores of "Q2: How many relatives do you feel close to such that you could call on them for help?"; "Q3: How many relatives do you feel at ease with that you can talk about private matters?"; "Q5: How many friends do you feel close to such that you can call on them for help?"; and "Q6: How many friends do you feel at ease with that you can talk about private matters?" in the LSNS-6 questionnaire. The total scores for objective and perceived social conditions ranged from 0 to 10 and 0 to 20, respectively. The presence of objective SI and loneliness was identified if the aggregate score was below the median in the derivation cohort (FRAGILE-HF study).

Outcomes

The outcome of this study was all-cause death up to 1 year after discharge. Outcome data were collected from the electronic medical records of the clinics where the medical follow-ups were conducted. For patients who were followed up at other hospitals and for whom information was not available, data were obtained through telephone interviews with other hospitals or family members.

Statistical Analysis

Data are expressed as mean±SD for normally distributed variables and as median with interquartile range (IQR) for nonnormally distributed data. Categorical data were expressed as frequencies and percentages. When necessary, variables were log-transformed for further analysis. Group differences were evaluated using Student's *t* test or the Mann–Whitney *U* test for continuous variables and χ^2 or Fisher's exact test for categorical variables. The association between all-cause death and the presence or absence of SI was examined using Kaplan–Meier estimates and compared using the log-rank test. For survival analysis in the FRAGILE-HF study, we used the Meta-Analysis Global Group in Chronic Heart Failure risk score,[37]

and log-transformed BNP values as adjustment variables in multivariate Cox regression models. The Meta-Analysis Global Group in Chronic Heart Failure risk score consists of the patient's age, sex, left ventricular ejection fraction, body mass index, creatinine level, New York Heart Association class, smoking status, complications (diabetes and chronic obstructive pulmonary disease), history of HF, and medication use (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β blockers). This risk score has been validated to discriminate between the results for death and calibration in a Japanese population with HF, even after adding BNP levels.[38] As the Meta-Analysis Global Group in Chronic Heart Failure risk score was not obtained in the Kitasato cohort, the Seattle Heart Failure Model was used as an adjustment variable. The Seattle Heart Failure Model encompassed variables including age, sex, New York Heart Association functional classification, left ventricular ejection fraction, pathogenesis of ischemia, systolic blood pressure, dose of diuretic agents, use of allopurinol and statins, lymphocyte percentage, serum sodium levels, cholesterol levels, hemoglobin concentration, and uric acid levels.[39] Furthermore, body mass index, estimated glomerular filtration rate, and log-transformed BNP values were added to the multivariate model.

Multiple imputation was conducted to address missing clinical data, with all variables listed in Table 1 undergoing the imputation process. Incomplete variables were imputed through fully conditional specifications, assuming random missingness. Employing the 'mice' package version 3.14.0 in R (R Foundation for Statistical Computing, Vienna, Austria), a chained-equation procedure was used to generate 20 imputed data sets, minimizing potential biases in the presence of missing data.

Sensitivity analyses were performed to verify the robustness of our findings. As objective SI and loneliness are considered to be related to each other, the 2 factors were included simultaneously in the original model (ie, the Meta-Analysis Global Group in Chronic Heart Failure risk score and log-transformed BNP). Furthermore, depressive status and low physical activity were entered into the original model. Depression was evaluated using the Patient Health Questionnaire-2, with a score range of 0 to 6. A score of ≥3 was regarded as depressive status.[40] Physical activity was assessed by the revised Japanese version of the Cardiovascular Health Study criteria.[41] Low physical activity was defined as answering "no" to both of the following questions: (1) "Do you engage in moderate levels of physical exercise or sports aimed at health?" and (2) "Do you engage in low levels of physical exercise aimed at health?" Furthermore, the cutoff values of LSNS-6 were modified to verify whether the original cutoff values (median cutoff) were valid. The cutoff values for defining objective SI and loneliness were reset to the 75th percentile instead of the median, and Kaplan–Meier curves were illustrated.

Statistical significance was defined as a 2-tailed *P*-value <0.05, and statistical analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing; ISBN 3-900051-07-0; URL: http://www.R-project.org).

RESULTS

Patient Characteristics

Of the 1332 participants registered in the FRAGILE-HF study, 1232 individuals (response rate, 93.5%) were eligible for the LSNS-6 evaluation. The median age was 81 years (IQR, 74–86 years), and 57.6% of the patients were men. Total SI was present in 38.4% of the patients. The median score for the objective social condition was 5 (IQR, 3–7), and 712 patients (57.8%) were diagnosed with objective SI. The median score for perceived social condition was 8 (IQR, 6–12), and 633 (51.4%) patients were regarded as experiencing loneliness (Figure 1). Overall, 545 (44.2%) patients had both objective SI and loneliness (Table S1).

Of the 3383 patients registered in the validation cohort (Kitasato cohort), 405 were eligible for the LSNS-6 evaluation. The median age was 78 years (IQR, 73–83 years), and 58.3% were men. Total SI was observed in 32.8% of these patients. From the cutoff values of 5 for objective SI and 8 for loneliness, 223 (55.1%) and 187 (46.2%) patients were regarded as experiencing objective SI and loneliness, respectively (Figure S1). In total, 162 patients (40.0%) experienced both objective SI and loneliness (Table S1).

Table 1 and Table S2 present the baseline patient profiles of both studies. Living status showed significant differences among all the social conditions in the FRAGILE-HF study. However, there were no significant differences in age, left ventricular ejection fraction, estimated glomerular filtration rate, or BNP levels in both studies.

Outcomes

In the FRAGILE-HF study, the survival analysis included data from 1209 patients, as prognostic information for 23 patients (1.8%) could not be obtained. During the 1-year follow-up period, 149 (12.3%) and 31 (7.7%) patients died in the FRAGILE-HF study and Kitasato cohort, respectively. According to the Kaplan–Meier analysis, total SI was not significantly associated with death in either study (FRAGILE-HF: log-rank *P*=0.205; Kitasato cohort: log-rank *P*=0.094; Figure 2). Objective SI was significantly associated with an increase in death (FRAGILE-HF: log-rank *P*=0.008; Kitasato cohort: *P*=0.017); however, loneliness was

Table 1. Baseline Characteristics Based on Social Isolation Status in the FRAGILE-HF Study

	Total SI (–) (n=759)	Total SI (+) (n=473)	*P* value	Objective SI (–) (n=520)	Objective SI (+) (n=712)	*P* value	Loneliness (–) (n=599)	Loneliness (+) (n=633)	*P* value
Age, y	81 (74–86)	81 (75–86)	0.446	80 (74–85)	81 (74–86)	0.202	81 (74–86)	81 (75–86)	0.452
Male sex, %	406 (53.5)	304 (64.3)	<0.001	261 (50.2)	449 (63.1)	<0.001	307 (51.3)	305 (48.2)	0.305
Living status, %			<0.001			<0.001			0.004
Living with someone	604 (79.6)	332 (70.2)		425 (81.7)	511 (71.8)		476 (79.5)	460 (72.7)	
Living alone	135 (17.8)	119 (25.2)		88 (16.9)	166 (23.3)		111 (18.5)	143 (22.6)	
Living in nursing home	20 (2.6)	22 (4.7)		7 (1.3)	35 (4.9)		12 (2.0)	30 (4.7)	
NYHA class III/IV, %	100 (13.2)	75 (15.9)	0.208	65 (12.5)	110 (15.4)	0.160	70 (11.7)	105 (16.6)	0.014
Body mass index, kg/m^2	21.1 (18.9–23.7)	20.7 (18.7–23.2)	0.022	21.1 (19.0–23.9)	20.8 (18.8–23.2)	0.063	21.1 (19.0–23.9)	20.7 (18.7–23.2)	0.014
Systolic blood pressure, mm Hg	112 (102–125)	112 (100–124)	0.296	112 (103–126)	112 (101–124)	0.235	111 (102–124)	112 (102–124)	0.727
Diastolic blood pressure, mm Hg	61 (56–61)	61 (54–68)	0.467	62 (56–68)	60 (54–68)	0.064	61 (55–68)	61 (56–68)	0.841
Heart rate, bpm	70 (60–80)	70 (60–80)	0.621	70 (60–78)	70 (60–80)	0.190	70 (60–79)	70 (60–80)	0.851
LVEF, %	44 (32–60)	46 (32–61)	0.710	45 (32–61)	45 (31–60)	0.397	45 (32–60)	45 (32–61)	0.659
Comorbidities, %									
Atrial fibrillation	352 (46.6)	195 (41.2)	0.077	248 (47.7)	299 (42.0)	0.049	284 (47.4)	263 (41.5)	0.039
Coronary artery disease	265 (34.9)	172 (36.4)	0.624	179 (34.4)	258 (36.2)	0.547	208 (34.7)	229 (36.2)	0.634
COPD	79 (10.4)	56 (11.8)	0.454	55 (10.6)	80 (11.2)	0.782	63 (10.5)	72 (11.4)	0.649
Diabetes	267 (35.2)	174 (36.8)	0.583	187 (36.9)	254 (35.7)	0.952	209 (34.9)	232 (36.7)	0.552
Hypertension	533 (70.2)	342 (72.3)	0.439	381 (73.3)	494 (69.4)	0.144	424 (70.8)	451 (71.2)	0.900
History of heart failure			0.115			0.745			0.653
None	357 (47.0)	193 (40.8)		238 (45.9)	312 (43.8)		271 (45.3)	279 (44.1)	
<18 mo	109 (14.4)	78 (16.5)		79 (15.2)	108 (15.2)		85 (14.2)	102 (16.1)	
>18 mo	292 (38.5)	202 (42.7)		202 (38.9)	292 (41.0)		242 (40.5)	252 (39.8)	
Prescription of medications, %									
ACE-I/ARB	517 (68.1)	317 (67.0)	0.707	348 (66.9)	486 (68.3)	0.622	408 (68.1)	426 (67.3)	0.761
β Blocker	558 (73.5)	344 (72.7)	0.791	380 (73.1)	522 (73.3)	0.984	451 (75.3)	451 (71.2)	0.122
MRA	381 (50.2)	231 (48.8)	0.682	269 (51.7)	343 (48.2)	0.226	307 (51.3)	305 (48.2)	0.305
Laboratory data at discharge									
Hemoglobin, g/dL	11.7 (10.2–13.1)	11.7 (10.3–13.1)	0.605	11.7 (10.4–13.1)	11.7 (10.2–13.1)	0.777	11.7 (10.2–13.0)	11.7 (10.3–13.1)	0.546
Hematocrit, %	35.6 (31.9–40.0)	36.2 (32.2–40.3)	0.280	35.8 (32.3–40.1)	36.0 (31.8–40.1)	0.922	35.6 (32.0–39.9)	36.1 (32.1–40.2)	0.387
Albumin, g/dL	3.5 (3.2–3.8)	3.4 (3.1–3.7)	0.107	3.5 (3.2–3.8)	3.4 (3.1–3.7)	0.039	3.5 (3.2–3.8)	3.4 (3.1–3.7)	0.123
Creatinine, mg/dL	1.15 (0.90–1.58)	1.19 (0.95–1.57)	0.266	1.15 (0.89–1.58)	1.19 (0.94–1.58)	0.132	1.16 (0.90–1.58)	1.17 (0.95–1.57)	0.338
eGFR, mL/min per 1.73 m^2	54 (35–70)	51 (36–68)	0.850	54 (34–72)	52 (36–69)	0.755	53 (35–71)	52 (36–68)	0.935
BUN, mg/dL	25 (19–35)	27 (20–37)	0.084	25 (19–35)	27 (20–36)	0.043	25 (19–35)	27 (20–36)	0.201
Sodium, mEq/L	139 (137–142)	139 (137–141)	0.054	140 (137–141)	139 (137–141)	0.071	140 (137–142)	139 (137–141)	0.042
BNP, pg/mL	258 (131–466)	298 (139–549)	0.174	274 (141–477)	276 (131–521)	0.970	254 (130–458)	287 (139–548)	0.168

Values are expressed as median (interquartile range) or n (%). ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FRAGILE-HF, Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; and SI, social isolation.

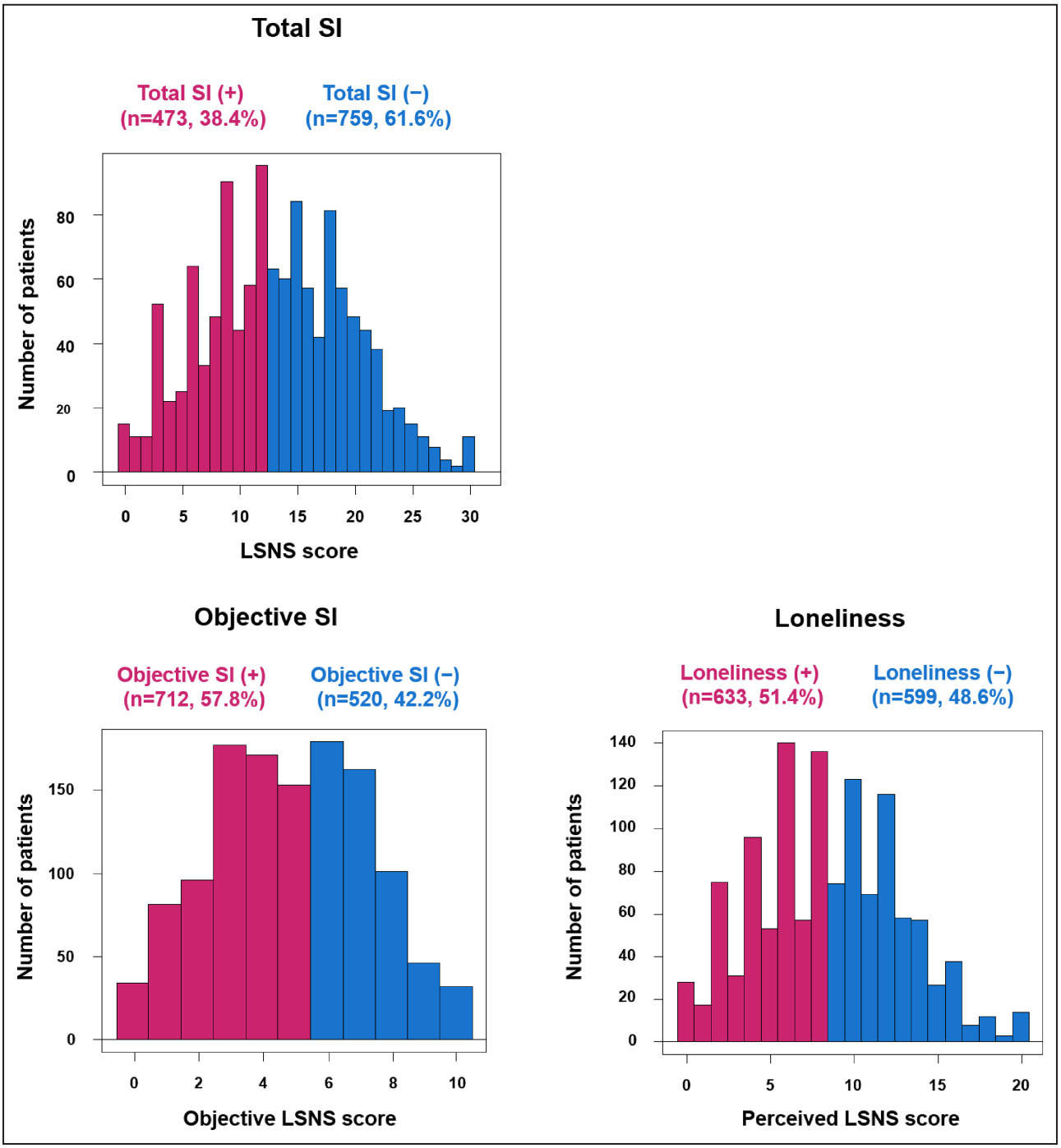

Figure 1. Histogram of social isolation in the FRAGILE-HF study.
Total SI was defined as the cutoff value (LSNS-6<12). Objective SI was defined as a total score for objective social conditions below a median of 5. Loneliness was defined as a total score for the perceived social condition below a median of 8. FRAGILE-HF indicates Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure; LSNS-6, Lubben Social Network Scale-6; and SI, social isolation.

not significantly associated with death in either study (FRAGILE-HF: log-rank *P*=0.055; Kitasato cohort: *P*=0.246; Figures 3 and 4). In the Cox regression analysis, objective SI remained significantly associated with increased death (FRAGILE-HF: hazard ratio [HR], 1.56 [95% CI, 1.08–2.26]; *P*=0.017; Kitasato cohort: HR, 2.42 [95% CI, 1.07–5.48]; *P*=0.033; Table 2). However, total SI (FRAGILE-HF: HR, 1.25 [95% CI, 0.88–1.76]; *P*=0.207; Kitasato cohort: HR, 1.81 [95% CI, 0.88–3.71]; *P*=0.106) and loneliness (FRAGILE-HF:

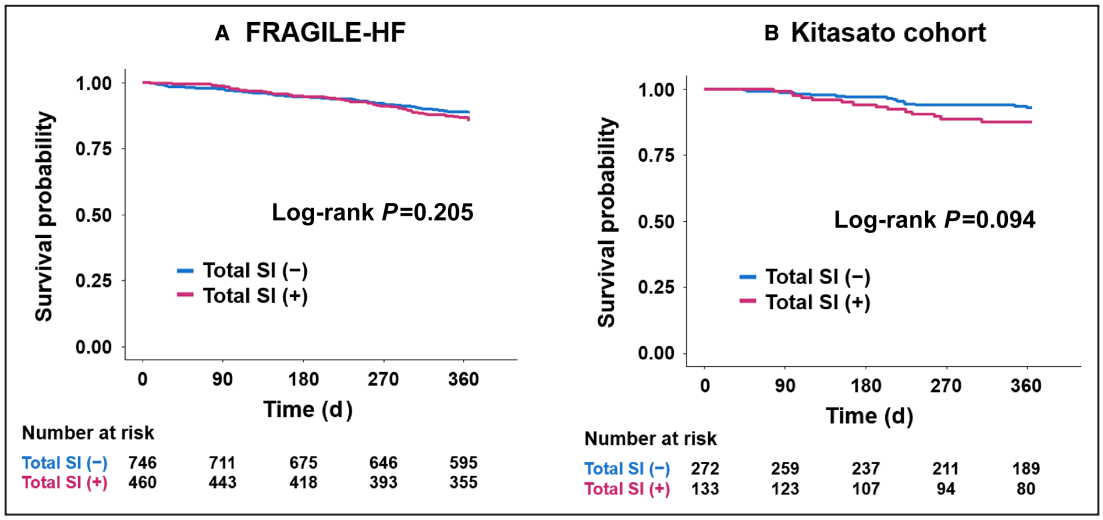

Figure 2. Kaplan–Meier curves for all-cause death according to the presence or absence of total social isolation in the FRAGILE-HF study (A) and Kitasato cohort (B).
There is no significant difference in mortality in both studies. FRAGILE-HF indicates Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure; and SI, social isolation.

HR, 1.30 [95% CI, 0.91–1.85]; *P*=0.146; Kitasato cohort: HR, 1.51 [95% CI, 0.74–3.07]; *P*=0.259) were not significantly associated with death (Table 2).

Sensitivity Analysis

The sensitivity analyses from the FRAGILE-HF study demonstrated that the main findings were consistent. First, both objective SI and loneliness were entered simultaneously into the adjusted Cox regression model (objective SI: HR, 1.55 [95% CI, 1.03–2.33]; *P*=0.038; loneliness: HR, 1.05 [95% CI, 0.72–1.55]; *P*=0.808; Table S3). Furthermore, depressive status and low physical activity were included in the adjusted Cox model (objective SI: HR, 1.53 [95% CI, 1.09–2.16]; *P*=0.015; loneliness: HR, 1.32 [95% CI, 0.95–1.82]; *P*=0.096; Table S4).

The 75th percentile scores of the LSNS-6 for the objective and perceived conditions were 7 and 12, respectively. Using these cutoff values, the Kaplan–Meier curves showed a consistent result: objective SI was significantly associated with 1-year death (log-rank *P*=0.026), whereas loneliness was not (log-rank *P*=0.081; Figure S2).

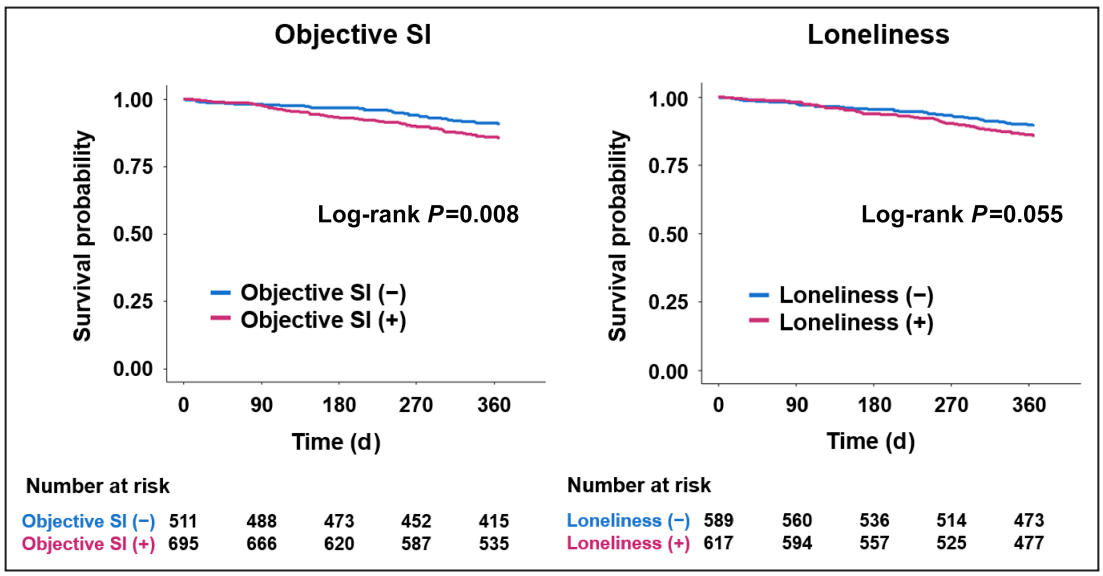

Figure 3. Kaplan–Meier curves for all-cause death between SI groups in the FRAGILE-HF study.
Objective SI is significantly associated with mortality, whereas loneliness is not found to be associated with mortality. FRAGILE-HF indicates Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure; and SI, social isolation.

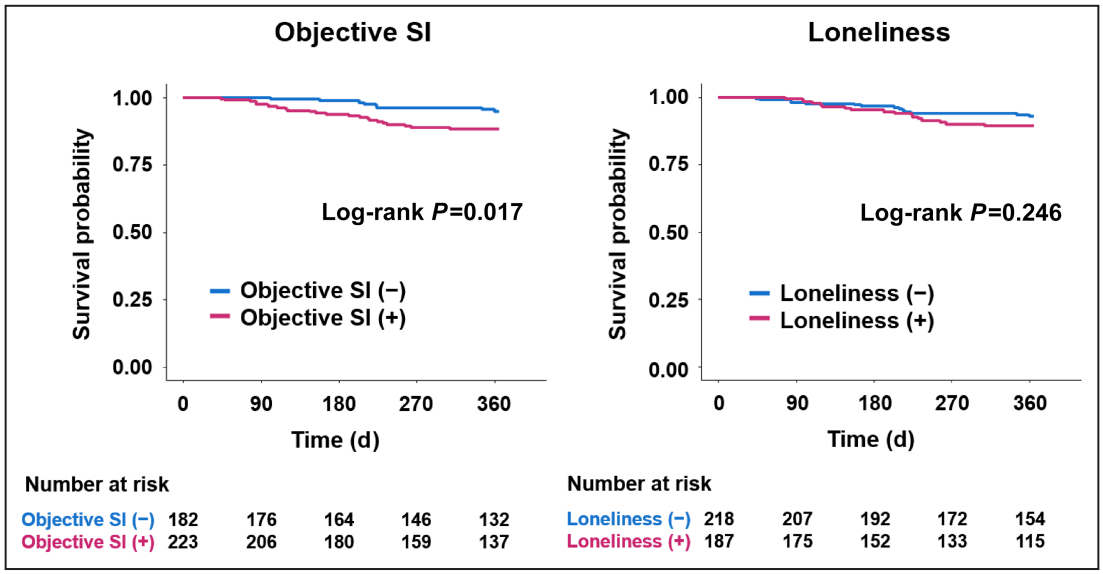

Figure 4. Kaplan–Meier curves for all-cause death between social isolation groups in the Kitasato cohort.
Objective SI shows a significant association with death, whereas loneliness does not exhibit such an association with death. FRAGILE-HF indicates Prevalence and Prognostic Value of Physical and Social Frailty in Geriatric Patients Hospitalized for Heart Failure; and SI, social isolation.

DISCUSSION

The key findings of the study were as follows: (1) total SI, defined by the cutoff previously suggested for the LSNS-6 (<12), was not associated with death; (2) objective SI, but not loneliness, was associated with death; (3) the association between objective SI and death was independent of known prognostic factors; and (4) these findings were consistent across the derivation (FRAGILE-HF study) and validation cohorts (Kitasato cohort). Therefore, objective SI, as assessed using the LSNS-6, may serve as a prognostic indicator in older patients with HF. Given the lack of established assessment methods for the SI in this population, further research is required to refine these evaluation methods.

Prevalence of SI

A systematic review demonstrated that the prevalence of SI was 25.0% among community-dwelling older adults.[42] Furthermore, a comparison of SI between Japan and the United Kingdom was conducted in the general population, wherein SI was assessed using an isolation risk score consisting of marital status; regular contact with children, relatives, and friends; and social participation. The study showed that the Japanese population had a higher proportion of SI than the UK

Table 2. Cox Proportional Hazard Analyses for 1-Year Death

	Unadjusted model			Adjusted model*		
FRAGILE-HF	HR	95% CI	*P* value	HR	95% CI	*P* value
Total SI	1.24	0.89–1.71	0.206	1.25	0.88–1.76	0.207
Objective SI	1.59	1.13–2.25	0.008	1.56	1.08–2.26	0.017
Loneliness	1.38	0.99–1.92	0.057	1.30	0.91–1.85	0.146
	Unadjusted model			Adjusted model†		
Kitasato cohort	HR	95% CI	*P* value	HR	95% CI	*P* value
Total SI	1.81	0.89–3.68	0.099	1.81	0.88–3.71	0.106
Objective SI	2.57	1.15–5.74	0.022	2.42	1.07–5.48	0.033
Loneliness	1.52	0.75–3.07	0.250	1.51	0.74–3.07	0.259

HR indicates hazard ratio; and SI, social isolation.
*Adjusted for the Meta-Analysis Global Group in Chronic Heart Failure risk score and log-transformed brain natriuretic peptide.
†Adjusted for the Seattle Heart Failure Model, body mass index, log-transformed brain-type natriuretic peptide, and estimated glomerular filtration rate.

population (5.5% versus 2.7%).[43] These frequencies were numerically low compared with those in our study (FRAGILE-HF, 38.4%; Kitasato cohort, 32.8%), partially owing to the difference in population. Previous studies revealed that the prevalence of SI (defined as LSNS-6 <12 points) ranges from 28.3% to 49.3%,[29,30] which is consistent with our results.

There is little information on the agreement between objective SI and loneliness. A study of 3613 individuals aged ≥50 years in the United States showed that objective SI (18%) and loneliness (19%) were common; however, only a small percentage of individuals (5%) experienced both.[44] Whereas in our study, 44.2% and 40.0% of patients in the FRAGILE-HF and Kitasato cohorts, respectively, had concomitant objective SI and loneliness. This implies that separately assessing objective SI and loneliness is important.

SI and Death

Few studies have investigated the association between SI and death in patients with HF. A study of 120 patients with HF showed that SI, defined as LSNS-6 <12, the same cutoff used for the presence of total SI in our study, was associated with an increased risk of 180-day death.[29] This differs from our results. Data on the association between objective SI or loneliness and prognosis, particularly death, are extremely limited. A clinical study including 1681 patients with HF identified by the *International Classification of Diseases* (*ICD*) code assessed loneliness by sending a letter to eligible patients who were asked to fill out a Patient-Reported Outcomes Measurement Information System Social Isolation Short Form. Although this study showed a significant association between loneliness and death during a mean follow-up period of 8 months,[45] it did not take into account clinical information associated with HF. A meta-analysis including 6468 patients with HF showed that both objective SI and loneliness were significantly associated with rehospitalization and that the odds thereof did not differ between objective SI and loneliness.[16] However, this meta-analysis did not evaluate the impact of objective SI or loneliness on death, and the LSNS-6 was considered a tool to assess only objective SI, not loneliness. Our study examined the LSNS-6 in more detail and dichotomized it into objective SI and loneliness. Thereafter, we clearly showed that objective SI, but not loneliness, was related to 1-year death. Therefore, it may be necessary to establish standard methods for objectively assessing SI (eg, contact frequency). Furthermore, studies are warranted to determine whether interventions with objective SI can improve the prognosis of patients with HF. For instance, interventions such as online cardiac rehabilitation programs may increase opportunities for regular face-to-face interactions through web-based platforms, potentially improving exercise tolerance and SI.[46]

Although our study was not designed to investigate the mechanisms behind the association between objective SI and death, there are several possible mechanisms. First, objective SI might lead to poorer health-promoting behaviors, such as smoking or alcohol consumption.[35,36] Additionally, objective SI may adversely affect some biological aspects. For instance, objective SI has been associated with delayed blood pressure recovery, leading to psychological stress and higher postwake and total cortisol levels.[47] Notably, this association was independent of loneliness and other possible covariates.[47] Furthermore, social factors have been reported to be related to immune function or immune-mediated inflammation processes.[48,49] All these factors can adversely affect the prognosis of patients with HF. The influence of such factors may be even stronger in Japan due to the greater prevalence of older people in objective SI compared with other countries.[43] However, further research is necessary to clarify the mechanisms underlying the association between SI and prognosis.

Clinical Implications

Although its mechanisms are beyond the scope of our study, we found that objective SI was associated with 1-year death, whereas loneliness was not. Our study results imply that we should pay attention not only to the SI itself but also to its detailed components, particularly when assessing SI in older patients with HF. This finding could impact health care practitioners' or policymakers' decisions when considering how to address the problem of SI. Moreover, the intervention could be promising in terms of improving the prognosis of patients with HF.

Limitations

This study had several limitations. First, we categorized objective SI and loneliness below the median on the basis of the LSNS-6 scores. As this is a novel approach developed by our research team, it has not yet been tested and validated. Therefore, to ensure that the SI classification system is robust, further examination of its validity is warranted. In particular, a self-reported assessment method was used to determine objective SI, similar to the methods used in previous literature[11,47,50]; however, whether the questionnaire format is necessarily objective is debatable. Our arbitrarily established definitions of objective SI and loneliness and their association with death need to be externally validated in future studies. Second, this study evaluated SI before hospitalization; however, SI may change

after discharge, and such changes were not assessed. Finally, as this study focused on Asian individuals, there is a possibility that similar results may not be obtained in other racial or ethnic groups.

CONCLUSIONS

In older patients with HF, an objective SI, defined using the LSNS-6, may be a potential prognostic indicator. This finding suggests that a greater focus should be given to the detailed components of SI to gain greater insight into the mechanisms behind conditions such as HF. As there is no established method to evaluate SI in older patients with HF, further improvements in assessment methods are warranted.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S2

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