Relationship between the spread of COVID-19, social frailty, and depressive symptoms in patients with heart failure

Saki Shakuta1 · Masashi Yamashita1,2 · Kentaro Kamiya1,3 · Nobuaki Hamazaki4 · Kensuke Ueno1 · Kohei Nozaki4 · Shota Uchida1,5 · Takumi Noda1 · Emi Maekawa6 · Minako Yamaoka-Tojo1,3 · Atsuhiko Matsunaga1,3 · Junya Ako6

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Abstract
In community-dwelling older people, coronavirus disease 2019 (COVID-19) has been reported to be associated with the development of frailty and depressive symptoms. We aimed to investigate whether the spread of COVID-19 is associated with the development of frailty in patients with heart failure (HF). The presence of the multi-domain of frailty in 257 patients with HF was assessed at hospital discharge. The spread of COVID-19 was significantly associated with the development of social frailty and depressive symptoms. Evaluation of these symptoms during hospitalization would support disease management and understanding of their social and psychological conditions.

Keywords Heart failure · Coronavirus disease 2019 · Social frailty · Depressive symptoms

Introduction
Coronavirus disease 2019 (COVID-19) is still endemic, and policies to prevent its spread affect people. Although the situation has improved, people have still refrained from going out unnecessarily and have maintained social distancing due to the spread of COVID-19. These new lifestyle approaches have affected people physically, psychologically, and socially [1]. Previous studies on community-dwelling older people have reported that decreased social participation due to the spread of COVID-19 was associated with physical inactivity and depressive symptoms [2, 3]. Patients with heart failure (HF) are more likely to have social frailty, physical frailty, cognitive impairment, and depressive symptoms [4, 5], and an overlap of these conditions leads to adverse events [6]. Therefore, multi-domain assessment and understanding of...
the conditions of patients with HF are important for disease management. The spread of COVID-19 is a predicted risk factor for these events, but its impact on patients with HF has not been comprehensively investigated thus far. Examining the adverse events associated with social policy toward the spread of COVID-19 to date may help in the development of strategies for the management of patients with HF in the event of a future flare-up of infection. Therefore, we investigated whether the spread of COVID-19 is associated with the development of the multi-domain of frailty in patients with HF.

\section*{Methods}

\subsection*{Study population and procedures}

This study is a sub-analysis of a prospective study conducted at Kitasato University Hospital on patients hospitalized with cardiovascular diseases between September 2018 and December 2020. Except for the period from January 2020 to March 2020, which was determined to be a period of indeterminate exposure, we included patients who had independent activities of daily living before being hospitalized at Kitasato University Hospital with a diagnosis of HF between September 2018 and December 2020 and patients in whom data on multi-domain frailty were available. We identified patients with HF who presented with acute or worsening HF symptoms. HF diagnosis was performed by an experienced cardiologist based on the Framingham criteria. We excluded patients with a history of COVID-19, patients who were admitted to a nursing home, patients with severe HF (left ventricular ejection fraction [LVEF] of < 10%), and patients who received new treatments such as angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter 2 inhibitors, and MitraClips. An overview of the comprehensive study protocol was in accordance with the tenets of the Declaration of Helsinki, approved by the Ethics Committee of Kitasato University Hospital (B18-083), and published in a publicly available University Hospital Information Network (UMIN000038373).

\subsection*{Assessment of symptoms}

We assessed the presence of social frailty, physical frailty, cognitive impairment, and depressive symptoms in these patients at hospital discharge.

\subsection*{Definitions}

Social frailty was defined as ≥ 2 positive responses to Makizako’s five items: living alone, going out less frequently compared with last year, visiting friends sometimes, feeling helpful to friends or family, and talking with someone every day [7]. Physical frailty was defined as ≥ 3 in the Fried phenotype model, which consists of five items: slowness (walking speed), weakness (grip strength), weight loss, fatigue, and physical inactivity [8]. Cognitive impairment was defined as ≤ 2 on Mini-Cog, a combination of a 3-item recall test and a clock drawing test [9]. Depressive symptoms were defined as ≥ 3 on the Patient Health Questionnaire-2, which includes questions about the frequency of feelings of apathy and hopelessness in the past 2 weeks [10].

\subsection*{Statistical analyses}

We divided the patients into two groups: before and after the spread of COVID-19. Patient characteristics were compared between the groups using the $\chi^2$ test or Mann-Whitney $U$ test. Multivariate logistic regression analyses were used to examine the impact of the spread of COVID-19 on the development of the multi-domain of frailty in patients with HF. In the multivariate analyses, we selected variables that were considered to be related to the development of frailty and severity of HF in patients with HF. The variables used in the multivariate analyses were as follows: before and after the spread of COVID-19; age; sex; body mass index; LVEF; New York Heart Association functional classification at the time of hospitalization; blood and biochemical test indices at the time of hospitalization (log B-type natriuretic peptide, estimated glomerular filtration rate, and hemoglobin); and history of hypertension, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, prior HF, or prior myocardial infarction. Statistical significance was considered at $p < 0.05$ and was analyzed using JMP (version 15.1; SAS Institute Inc., Cary, NC, USA).

\section*{Results}

During the patient recruitment period, 272 patients with HF were hospitalized. After exclusion, 257 patients were enrolled in this study. The median patient age was 73 years, and 66.9% (172/257) were male. The prevalence of physical frailty, social frailty, cognitive impairment, and depressive symptoms in all cases were 26.5% (68/257), 65.4% (168/257), 20.2% (52/257), and 22.6% (58/257), respectively. There were no significant differences between before and after the spread of COVID-19 except for the presence of social frailty and depressive symptoms (Table 1). In multivariate logistic regression analyses, the spread of COVID-19 was significantly associated with the development of social frailty (odds ratio [OR], 2.52; 95% confidence interval [CI], 1.17–5.41) and depressive symptoms (OR, 2.23; 95% CI, 1.01–4.92) but not with the development of physical frailty and cognitive impairment (Table 2).
Table 1  Patient characteristics

|                                | Before the spread of COVID-19 (n = 182) | After the spread of COVID-19 (n = 75) | P value |
|--------------------------------|----------------------------------------|--------------------------------------|---------|
| Age [years]                    | 73 [62–80]                             | 71 [58–79]                           | 0.276   |
| Male, n (%)                    | 119 (65.4)                             | 53 (70.7)                            | 0.467   |
| Body mass index [kg/m²]        | 23.5 [21.2–26.2]                       | 24.0 [21.4–27.0]                     | 0.550   |
| Left ventricular ejection fraction [%] | 41.0 [30.0–59.2]                   | 41.0 [27.0–60.0]                     | 0.655   |
| NYHA classification ≥ III, n (%) | 152 (94.4)                             | 64 (95.5)                            | 1.000   |
| Medications, n (%)             |                                        |                                      |         |
| ACE inhibitor                  | 78 (42.9)                              | 34 (45.3)                            | 0.782   |
| ARB                            | 80 (44.0)                              | 30 (40.0)                            | 0.582   |
| Beta-blocker                   | 155 (85.2)                             | 59 (78.7)                            | 0.204   |
| MRA                            | 103 (56.6)                             | 36.0 (48.0)                          | 0.218   |
| Comorbidities, n (%)           |                                        |                                      |         |
| Hypertension                   | 99 (54.4)                              | 46 (61.3)                            | 0.335   |
| Diabetes mellitus              | 64 (35.2)                              | 25 (33.3)                            | 0.886   |
| Dyslipidemia                   | 52 (28.6)                              | 24 (32.0)                            | 0.652   |
| Atrial fibrillation            | 80 (44.0)                              | 28 (37.3)                            | 0.404   |
| COPD                           | 14 (7.7)                               | 2 (2.7)                              | 0.163   |
| Dementia                       | 2 (1.1)                                | 0 (0.0)                              | 1.000   |
| Prior heart failure            | 78 (42.9)                              | 26 (34.7)                            | 0.264   |
| Prior myocardial infarction    | 18 (9.9)                               | 10 (13.3)                            | 0.509   |
| Laboratory data                |                                        |                                      |         |
| B-type natriuretic peptide [pg/mL] | 824.8 [444.3–1527.9]              | 747.2 [357.9–1323.4]                 | 0.239   |
| C-reactive protein [mg/dL]     | 0.5 [0.2–1.4]                          | 0.3 [0.1–1.1]                        | 0.063   |
| eGFR [mL/min/1.73 m²]          | 43.0 [29.0–54.3]                       | 43.0 [29.0–54.0]                     | 0.902   |
| Hemoglobin [g/dL]              | 12.4 [10.7–13.7]                       | 12.8 [10.6–14.8]                     | 0.243   |
| White blood cells [× 10³ μL]   | 6.9 [5.5–9.0]                          | 7.3 [5.8–9.5]                        | 0.450   |
| Physical frailty, n (%)        | 44 (24.2)                              | 24 (32.0)                            | 0.215   |
| Social frailty, n (%)          | 111 (61.0)                             | 57 (76.0)                            | 0.022   |
| Cognitive impairment, n (%)    | 36 (19.8)                              | 16 (21.3)                            | 0.865   |
| Depressive symptoms, n (%)     | 34 (18.7)                              | 24 (32.0)                            | 0.032   |

Values are presented as median [interquartile range] or number (%)

ACE inhibitor angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker; COPD chronic obstructive pulmonary disease; COVID-19 coronavirus disease 2019; eGFR estimated glomerular filtration rate; MRA mineralocorticoid receptor antagonist; NYHA classification New York Heart Association classification

Table 2  Multivariate logistic regression analyses of the association between the spread of coronavirus disease 2019 (COVID-19) and the multidomain of frailty in patients with heart failure

| Outcome: physical frailty | Odds ratio | 95% confidence interval | P value |
|---------------------------|------------|-------------------------|---------|
| After the spread of COVID-19 (vs before) | 1.72       | 0.79–3.76               | 0.175   |
| Outcome: social frailty   |            |                         |         |
| After the spread of COVID-19 (vs before) | 2.52       | 1.17–5.41               | 0.018   |
| Outcome: cognitive impairment |          |                         |         |
| After the spread of COVID-19 (vs before) | 1.51       | 0.61–3.73               | 0.374   |
| Outcome: depressive symptoms |           |                         |         |
| After the spread of COVID-19 (vs before) | 2.23       | 1.01–4.92               | 0.047   |
Discussion

The results of this study indicate that a series of policies, including refraining from going out, accompanied by the spread of COVID-19, were significantly associated with the development of social frailty and depressive symptoms in patients with HF. These findings provide important information for the support of patients with HF if disasters such as the spread of COVID-19 occur again in the future. Because social frailty and depressive symptoms in patients with HF are related to all-cause death, readmission for HF, and reduced quality of life, [5, 11] multi-domain assessment and understanding of the conditions of patients with HF are important for disease management [6]. To the best of our knowledge, only a few studies have examined the impact of the spread of COVID-19 in patients with HF. However, some previous studies conducted on community-dwelling older people have shown that the decline in social participation due to the spread of COVID-19 affects depressive symptoms and reduces the patient’s physical activity and social isolation [1–3]. The results of the previous studies support our study’s findings, which suggest that the spread of COVID-19 is a risk factor for the development of social frailty and depressive symptoms in patients with HF. Policies to prevent the spread of COVID-19 have limited the social participation of older people such as closing community organizations and restricting family visits [12]. Social isolation has been reported to be associated with the development of depressive symptoms among community-dwelling older people [13, 14]. It is possible that decreased social participation due to the spread of COVID-19 [12] is associated with the development of depressive symptoms in this study. Based on our results and the results of previous studies, it is important to evaluate the social frailty and depressive symptoms of patients with HF during the spread of COVID-19 from an early stage. To reduce loneliness, depressive symptoms, lack of social support, and physical inactivity in patients with HF, multifaceted interventions according to multidisciplinary guidelines and cooperation with relatives are necessary. Older patients with HF whose outpatient cardiac rehabilitation was interrupted due to the spread of COVID-19 have been reported to have worse frailty after the spread of COVID-19 compared to before [15]. Therefore, it remains essential to consider effective and safe intervention methods using online medical care and tele rehabilitation to maintain social distance as a preventive approach against the impact of the spread of infection. Further research focusing on interventions for social and psychological conditions would support the current study findings.

This study had several limitations. First, due to the small number of patients in this study, we were unable to sufficiently verify whether there were any differences in patients with HF between preserved, mildly reduced, or reduced ejection fraction due to the impact of the spread of COVID-19. Therefore, further investigation is needed to determine whether there is an interaction between the association of COVID-19 and frailty incident in different types of HF. Secondly, since this was a cross-sectional study, we were unable to examine long-term cardiovascular outcomes. Therefore, long-term follow-ups of patients with HF are needed to investigate whether the spread of COVID-19 affects long-term cardiovascular outcomes.

Conclusions

The spread of COVID-19 is associated with the development of social frailty and depressive symptoms in patients with HF. Evaluation of social frailty and depressive symptoms during hospitalization would support disease management and understanding of the patient’s social and psychological conditions that are specific to the spread of COVID-19.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SS, MY, KU, SU, and TN. The first draft of the manuscript was written by SS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request with the corresponding author.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Kitasato University Hospital (B18-083) and published in a publicly available University Hospital Information Network (UMIN000038373).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish The participant has consented to the submission of the paper to the journal.
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