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Research paper

Overlap of frailty and malnutrition as prognosticators in older patients with heart failure

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ABSTRACT

Background: Physical frailty and malnutrition coexist in older patients with heart failure (HF) and form a vicious cycle exacerbating each other and can cause poor clinical outcomes. We aimed to clarify the association of prevalence of physical frailty and malnutrition and clinical outcomes in hospitalized patients with HF.
Methods: A total of 862 hospitalized patients aged ≥65 years with HF decompensation were included in this FRAGILE-HF post-hoc sub-analysis. Patients were categorized into Neither, Either, or Both groups based on the prevalence of physical frailty and malnutrition. The primary outcome was all-cause mortality within 1 year after discharge. Prognoses among the groups were compared in the entire cohort and in subgroups with preserved ejection fraction (pEF) and reduced/mildly reduced left ventricular ejection fractions (rEF/mrEF).
Results: The Neither, Either, and Both groups comprised 32 %, 40 %, and 28 % respectively. During a 1-year follow-up period, 101 (12 %) patients died. Kaplan–Meier analysis showed significant differences in the primary outcomes among the groups ($P < 0.001$). The Both group had a higher risk of mortality (HR: 2.47, 95 % CI: 1.38–4.42) than the Neither group, while the Either group showed insignificant risk increase (HR: 1.58, 95 % CI: 0.86–2.90). Similar trends were observed in the pEF and rEF/mrEF subgroups ($P = 0.60$).

Abbreviations: GLIM, Global Leadership Initiative on Malnutrition; HF, heart failure; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; pEF, preserved ejection fraction; rEF/mrEF, reduced/mildly reduced left ventricular ejection fractions.

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Conclusions: Physical frailty and malnutrition coexist in approximately one-quarter of hospitalized older patients with HF and are associated with an increased risk of mortality. Assessing both conditions is crucial for risk stratification and interventions to mitigate their interplay.

1. Introduction

Heart failure (HF) remains a significant global health challenge, with approximately 25 % readmission and 20 % mortality rates within a year of hospitalization [1]. The increasing proportion of elderly HF patients adds complexity to this issue [2]. Frailty, defined as a decline in physiological reserves and resistance to stressors, is strongly associated with systemic dysfunction in HF patients [3,4]. Physical frailty is highly prevalent in older patients with HF and is a strong predictor of mortality [5]. Similarly, malnutrition is a common comorbidity in patients with HF and is reportedly also a predictor of mortality [6–8]. HF can cause chronic inflammation, organ hypoperfusion, intestinal edema, and neurohormonal activation, which can induce cardiac cachexia and a catabolic state [9,10]. Particularly in older patients with HF, factors such as aging-related anorexia, deteriorating oral health, and taste disorders can significantly accelerate malnutrition. Aging anorexia, which involves a reduced appetite and decreased food intake, is often exacerbated by age-related physiological changes and medications that alter appetite. The oral environment in older adults can deteriorate due to dental issues, reduced salivation, and changes in swallowing function, further impairing their ability to eat and maintain proper nutrition. Taste disorders due to changes in taste buds and reduced sensory perception can diminish the appeal of food and further decrease nutritional intake. Together, these age-related factors compound the risk of malnutrition in older HF patients, making it a more pressing issue compared to younger individuals [11]. These two conditions interact and are significant in the vicious cycle of frailty [3]. Despite the recognized importance of both frailty and malnutrition in HF prognosis, there is a notable gap in studies evaluating their combined prevalence and impact. Therefore, the current study aims to investigate the prevalence of coexisting physical frailty and malnutrition in a large cohort of hospitalized older HF patients. Additionally, we seek to assess the prognostic implications of multiple frailty domains in relation to patient outcomes. We hypothesize that the coexistence of these conditions will be associated with worse clinical outcomes and higher mortality rates.

2. Methods

2.1. Study design and population

We performed a post-hoc analysis of a multicenter prospective observational cohort study conducted between September 2016 and March 2018 using the FRAGILE-HF database, including hospitalized patients aged ≥65 years with HF decompensation who could ambulate at discharge [12]. Patients who did not assessed The Framingham criteria were used to diagnose HF, as outlined in Supplemental Table 1. This study was conducted following the principles of the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects. As this was an observational study without invasive procedures or interventions, the requirement for written informed consent was waived under the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labor, and Welfare. The ethics committee of each participating hospital approved the study protocol.

We extracted data from the FRAGILE-HF database for patients who underwent physical frailty assessment using the Fried frailty phenotype (Supplemental Table 2) and malnutrition diagnosis using the Global Leadership Initiative on Malnutrition (GLIM) criteria (Supplemental Table 3). Patients who could not be assessed for either physical frailty or malnutrition during hospitalization were excluded. Fried et al. developed a phenotype model globally recognized as the standard model for physical frailty [3]. The GLIM criteria are a consensus scheme used to diagnose malnutrition in adults in clinical settings worldwide [13]. We have previously validated the superiority of the GLIM criteria over the preexisting definition, the geriatric nutritional risk index, in the FRAGILE-HF cohort [14].

In the Fried frailty phenotype, scores of 0, 1–2, and ≥3 are classified as robust, prefrail, and frail, respectively [3]. In this study, patients with scores of ≥3 were defined as having physical frailty. The GLIM criteria define malnutrition as meeting at least one phenotypic and one etiologic criterion [13]. Since all patients included in this study were hospitalized owing to HF decompensation, they were suggested to have a chronic inflammatory disease, which is an etiological criterion for malnutrition. Patients were classified into three groups based on the presence of physical frailty and malnutrition during index hospitalization: Neither (no physical frailty or malnutrition), Either (physical frailty or malnutrition), and Both (physical frailty and malnutrition).

Prognoses were initially evaluated and compared across the three groups involving all patients. Subsequently, the comparison was further performed in subgroups stratified by left ventricular ejection fraction (LVEF), preserved LVEF (pEF), and reduced or mildly reduced LVEF (rEF/mrEF). The baseline clinical, physiological, and echocardiographic findings and prognosis after discharge were compared among the three groups.

2.2. Outcomes

The primary endpoint of this study was all-cause mortality within 1 year of discharge, and the secondary endpoints were cardiovascular death (CVD) and hospitalization for heart failure (HHF). To assess these endpoints, patients were followed up regularly by visiting clinics at least once every 3 months or more frequently, as required for their medical condition. In cases where patients did not attend follow-up clinics, prognostic data were obtained through telephone interviews with the patient's family or from the medical records of other medical facilities that had treated the patient.

2.3. Statistical analysis

Descriptive statistics, such as mean and standard deviation, median and interquartile range, and percentages, were used to summarize the data. Chi-squared or Fisher's exact tests were used for categorical variables, and Student's *t*-test or Mann–Whitney *U* test were used for continuous variables, as appropriate, to compare the differences between groups. Kaplan–Meier survival curves were used to compare event-free survival between the groups, and differences were assessed using the log-rank test. The primary outcome of all-cause mortality was adjusted using the Meta-analysis Global Group in Chronic (MAGGIC) risk score for HF and log-transformed brain natriuretic peptide (BNP) at discharge. The MAGGIC risk score has been validated in Japanese patients with HF and includes several variables, such as age, sex, comorbidities, New York Heart Association class, medication use including beta-blockers and angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB), body mass index (BMI), systolic blood pressure, serum creatinine level, and LVEF [15]. The addition of BNP levels at discharge to the MAGGIC risk score was shown to be associated with improved discrimination and calibration [16]. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using R, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; http://www.R-project.org).

3. Results

This study included 1332 hospitalized patients aged >65 years during the study period. Of these, 862 patients had data available for physical frailty and malnutrition assessments using the Fried frailty phenotype and GLIM criteria, respectively.

A total of 367 and 488 patients were diagnosed with pEF and rEF/mrEF. LVEF data were unavailable for seven patients. Of the patients with available data, 53.6 % ($n = 462$) were classified as physically frail, and 42.9 % ($n = 370$) were classified as malnourished in all cohorts. Patient distributions among the three groups were as follows: 275 (31.9 %), 342 (39.7 %), and 245 (28.4 %) patients in the Neither, Either, and Both groups, respectively (Fig. 1).

3.1. Baseline profiles

The median age of the study cohort was 78 years, and 58.5 % were male. Age, history of hypertension and dyslipidemia, BMI, systolic and diastolic blood pressures, and heart rate differed significantly among the groups. Patients in the Both group had the highest average age and lowest average BMI. However, there were insignificant differences in LVEF or the proportion of patients receiving HF medications, including beta-blockers, ACEi/ARBs, and mineralocorticoid receptor antagonists, among the groups. Similarly, laboratory data showed significant differences among the groups, with the Both group exhibiting the lowest average hemoglobin, albumin, and sodium levels. No significant differences in BNP levels were observed among the groups (Table 1). The baseline profiles of the three groups of patients with pEF and rEF/mrEF are shown in Supplemental Table 4.

3.2. Prognoses

During the follow-up period, 101 (12 %) patients died; patients with physical frailty and malnutrition had significantly worse all-cause mortality rates than those without the conditions. Specifically, patients with physical frailty had significantly worse all-cause mortality (log-rank test, $P < 0.001$) similar to those with malnutrition (log-rank test, $P = 0.001$).

The Neither group had the best prognosis, with 6 % mortality, whereas the Both group had the worst prognosis, with 18 % mortality. Kaplan–Meier analysis indicated that the risk of all-cause death was well stratified among the three groups (log-rank for trend, P < 0.001, Fig. 2).

In a univariate Cox regression model, the Both and Either groups were associated with higher all-cause mortality than the Neither group. In a multivariable Cox regression model adjusted for covariates including MAGGIC HF risks and log-transformed BNP at discharge, the Both group (HR: 2.47, 95 % CI: 1.38–4.42, $P = 0.002$, Table 2) was

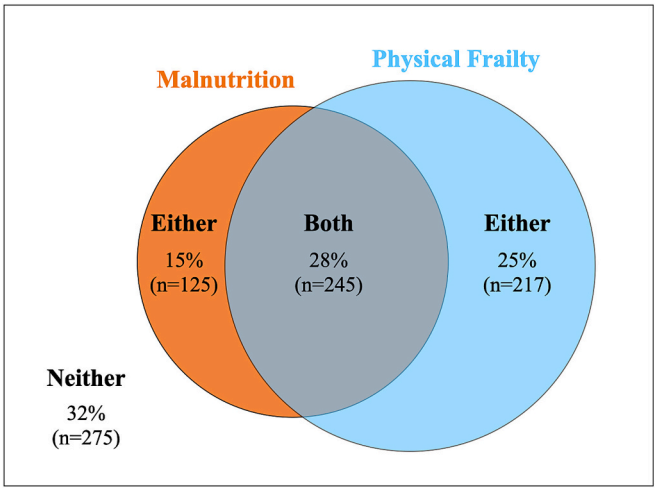

Fig. 1. Representation of the intersection between physical frailty and malnutrition in the study cohort. The percentages indicate the proportion relative to the entire cohort.

Table 1
Patient backgrounds.

Variables	Both $n = 245$	Either $n = 342$	Neither $n = 275$	*P* value
Age (years)	80.6 ± 7.6	79.7 ± 7.6	77.8 ± 7.3	<0.001
Male	134 (55 %)	204 (60 %)	166 (60 %)	0.36
Hypertension	163 (67 %)	254 (74 %)	208 (76 %)	0.047
Diabetes	84 (34 %)	129 (38 %)	96 (35 %)	0.65
Dyslipidemia	77 (31 %)	136 (40 %)	114 (41 %)	0.04
COPD	26 (11 %)	49 (14 %)	26 (9 %)	0.15
Malignant neoplasms	52 (21 %)	44 (13 %)	37 (13 %)	0.01
BMI (kg/m^2)	19.7 ± 3.4	22.0 ± 3.8	23.8 ± 2.9	<0.001
SBP (mmHg)	113.7 ± 16.9	113.3 ± 16.2	116.8 ± 17.1	0.02
DBP (mmHg)	60.9 ± 11.1	62.2 ± 10.4	63.7 ± 10.8	0.01
Heart rate (bpm)	70.6 ± 15.4	72.0 ± 13.2	69.0 ± 14.4	0.002
LVEF (%)	45.5 ± 16.8	46.5 ± 17	45.8 ± 15.7	0.74
ACEi/ARB	162 (66 %)	236 (69 %)	200 (73 %)	0.26
Beta-blocker	179 (73 %)	259 (76 %)	209 (76 %)	0.71
MRA	121 (49 %)	168 (49 %)	135 (49 %)	0.99
Oral anticoagulants	125 (51 %)	192 (56 %)	159 (58 %)	0.27
Hemoglobin (g/dL)	11.7 ± 2.0	11.9 ± 2.0	12.2 ± 2.0	0.02
Hematocrit (%)	36.1 ± 6.1	36.5 ± 5.7	37.2 ± 5.9	0.07
Albumin (g/dL)	3.3 ± 0.5	3.5 ± 0.4	3.6 ± 0.5	<0.001
Creatinine (mg/dL)	1.3 ± 0.8	1.4 ± 0.7	1.4 ± 0.8	0.14
eGFR (mL/min/1.73 m^2)	54.8 ± 21.8	53.4 ± 22.3	53.2 ± 21.8	0.66
BUN (mg/dL)	28.6 ± 12.4	28.9 ± 15.2	28.4 ± 13.2	0.89
Sodium (mEq/L)	138.5 ± 3.5	139.1 ± 3.8	139.8 ± 3.5	<0.001
BNP (pg/mL)	499.7 ± 663.1	397.2 ± 441	440.6 ± 746.5	0.08

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; SBP: systolic blood pressure.

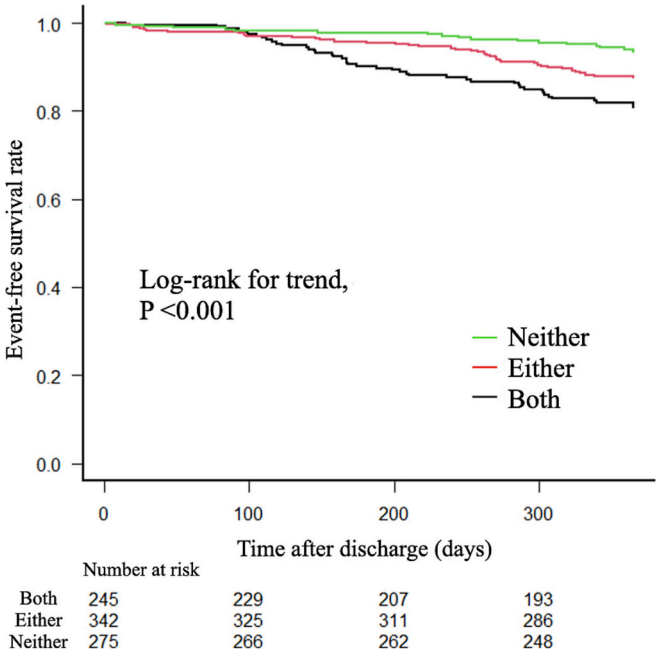

Fig. 2. Kaplan–Meier curves for all-cause mortality among three groups classified by comorbidities of frailty and malnutrition.

Table 2
Hazard ratio of the primary endpoint of patients in subgroups.

	Unadjusted Cox model			Adjusted Cox model		
	HR	95 % CI	P value	HR	95 % CI	P value
Neither	1 (reference)			1 (reference)		
Either	2.00	1.13–3.52	0.02	1.58	0.86–2.90	0.14
Both	3.21	1.84–5.63	<0.001	2.47	1.38–4.42	0.02

CI = confidence interval; HR = hazard ratio.

associated with higher all-cause mortality than the Neither group, and all-cause mortality was comparable between the Either and Neither groups (HR: 1.58, 95 % CI: 0.86–2.90, $P = 0.14$, Table 2).

When patients were further categorized into four groups, i.e., with physical frailty and malnutrition, with physical frailty alone, with malnutrition alone, and with neither, all-cause death differed significantly among the groups (log-rank test for trend, $P < 0.001$; Supplemental Fig. 1). The group with both conditions fared worst, whereas the group with neither condition had the best prognosis. The prognoses of patients with physical frailty or malnutrition alone were comparable (log-rank test, $P = 0.84$).

Examining the classification by baseline LVEF, the trends in prognosis among the three groups were consistent for patients with pEF and those with rEF/mrEF (Fig. 3). We further evaluated whether the LVEF classification (pEF or rEF/mrEF) altered the association among the three groups and mortality and found no statistically significant interaction ($P = 0.60$).

Regarding the secondary endpoints, a notable difference in CVD was observed among the three groups (log-rank test for trend, $P = 0.02$, Supplemental Fig. 2). However, there were no significant differences among the three groups concerning HHF (log-rank for trend, $P = 0.77$, Supplemental Fig. 3).

4. Discussion

The study's principal findings highlight that a quarter of the patients showed an overlap of physical frailty and malnutrition. This is the first study that evaluated the prevalence and prognostic impact of the coexistence of these two conditions in a large cohort of older patients with HF. Physical frailty and malnutrition are well-established factors contributing to poor prognosis and are significant in perpetuating the frailty cycle. Chronic malnutrition can cause sarcopenia, a condition characterized by the loss of muscle mass, resulting in reduced strength, power, walking speed, and activity levels. Coupled with age-related anorexia, chronic malnutrition can be further exacerbated [3]. The prevalence of physical frailty and malnutrition in our study was 54 % and 43 %, respectively. Regarding physical frailty, there have been some reports about the prevalence of it among HF patients. Although there are various methods for assessing frailty, such as Altimir scale, Short Physical Performance Battery and Gait speed definition, the prevalence ranges from 15 % to 51 % [17]. Bonilla-Palomas JL et al. previously conducted the analysis about the prevalence of malnutrition among hospitalized patients with HF in Spain. They used the Mini Nutritional Assessment to evaluate nutritional condition. They reported 13 % were classified as malnourished and 59.5 % at risk of malnutrition [18]. However, these previous studies did not involve assessing physical frailty and malnutrition simultaneously by grouping patients with physical frailty alone and those with physical frailty and malnutrition. In contrast, this study distinguished patients with both conditions from those with either alone. The coexistence of physical frailty and malnutrition was associated with a poor prognosis, whereas the existence of either condition alone was not associated with poor all-cause mortality after adjusting for covariates. Given the high prevalence of these conditions and prognostic impact, it is important to incorporate regular screening for both physical frailty and malnutrition simultaneously in hospitalized elderly HF patients to identify high-risk individuals early. Moreover, our findings underscore the significance of preventing the progression of physical frailty or malnutrition to a complicated state of

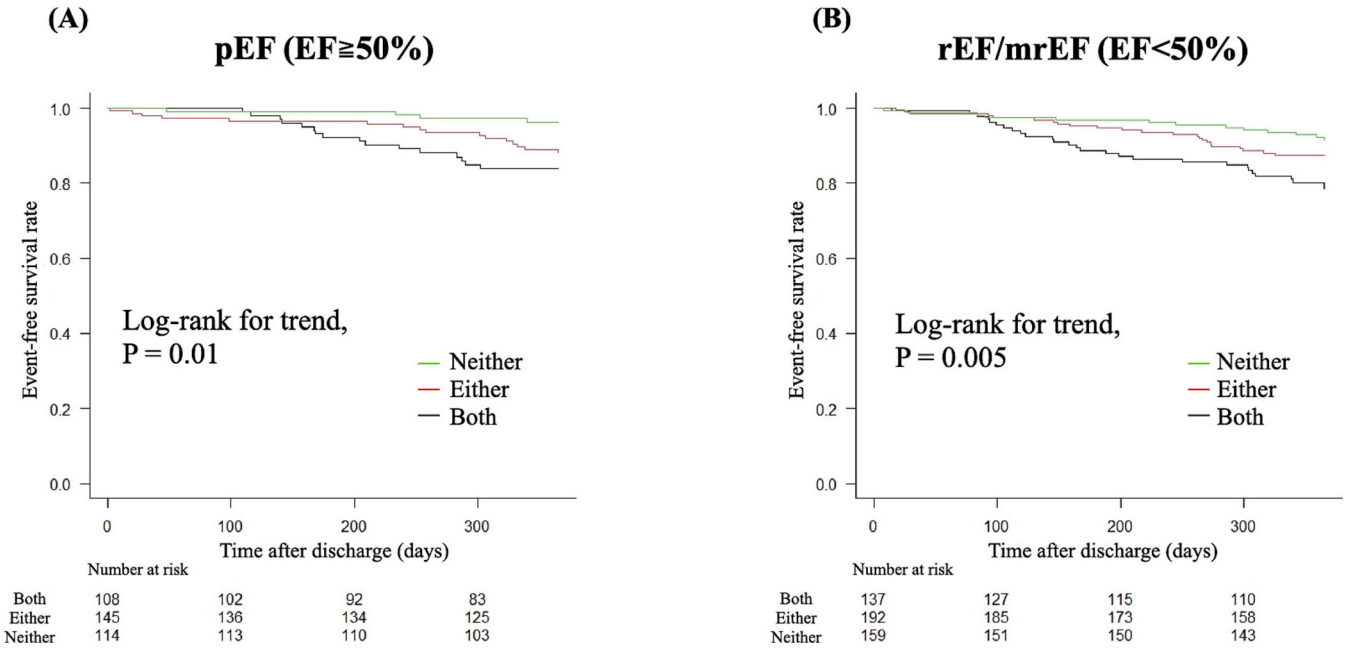

Fig. 3. Kaplan–Meier curves for all-cause mortality among three groups classified by comorbidities of frailty and malnutrition in patients with heart failure with preserved left ventricular ejection fraction (A) and with reduced/mildly reduced left ventricular ejection fraction (B).

coexisting conditions.

This study revealed notable differences in all-cause mortality and CVD among three groups: Neither, Either, and Both. However, these differences were not evident in HHF. Although HF can cause physical frailty and malnutrition, these symptoms signify systemic concerns in patients with HF. The patients in the Both and Either group tended to be older than those in the Neither group, suggesting a more progressive stage of HF in the former. These age-related differences could be a factor in the marked disparities in critical outcomes, including all-cause mortality and CVD, as opposed to softer metrics such as HHF. There have been several reports highlighting the negative impact of frailty on subsequent HHF events. However, the methods used to assess physical frailty varied across these studies. Additionally, none of these studies specifically focused on "elderly" patients hospitalized with "acute" HF, which may explain the differences in findings. On the other hand, there have been few reports assessing the impact of malnutrition on subsequent HHF events. Liu J et al. reported that malnutrition significantly increases the risk of re-hospitalization for HF [19]. The median age in their study was 62 years, whereas the median age in our study was 78 years, indicating a significant difference in the target patient populations.

In a previous study by Sze et al., simple frailty and malnutrition screening tools were found to have a prognostic value in patients with acute HF owing to left ventricular systolic dysfunction [20]. According to this report, patients with frailty and malnutrition had an almost 30 times greater risk of mortality than those without frailty or malnutrition. One-year mortality was 1 % in those without frailty or malnutrition, 15 % in those with frailty or malnutrition, and 65 % in those with frailty and malnutrition. The finding that patients with coexisting frailty and malnutrition was a high-risk population was similar to that of our study. Our study had several strengths, including having a thrice larger number of patients, being a multicenter prospective study design, and involving precise assessment of physical frailty and malnutrition using the Fried phenotype model and GLIM criteria, which are the world standard evaluation methods. Furthermore, we examined the prognostic impact of the coexistence of physical frailty and malnutrition within subgroups categorized according to LVEF and observed similar results across these LVEF subgroups.

Although patients with physical frailty may benefit from exercise-based cardiac rehabilitation, previous meta-analyses have not shown significant effects on prognosis [21]. Similarly, nutritional interventions in patients with malnutrition have not shown significant effects on prognosis [22]. Therefore, defining effective populations for interventions targeting physical frailty and malnutrition is essential. Future clinical trial is warranted to evaluate the effectiveness of specific interventions for managing physical frailty and malnutrition in elderly HF patients. Based on our findings, patients with physical frailty or malnutrition alone may be suitable candidates for future trials on cardiac rehabilitation and nutritional interventions.

4.1. Limitations

This study had some limitations. First, this was a prospective observational study, implying that the treatment for HF and interventions for physical frailty and malnutrition after discharge were not evaluated. Second, the observational period was limited to 1 year after discharge, and long-term follow-up is ongoing. Third, the assessment of frailty and malnutrition was performed only once during hospitalization for HF. It can be the potential bias. Patients in this trial involved assessment of frailty and nutritional status and may have led to subsequent intervention and it may affect subsequent conditions and prognoses. Fourth, it is possible that there can be unmeasured confounding factors, which could influence the observed associations. Finally, the generalizability of the findings may also be limited. Japan is the leading aging society in the world and the proportion of elderly population among hospitalized HF patients are high [23]. In addition, the universal healthcare system ensures that all elderly individuals have access to uniform and equitable medical care in Japan. Moreover, the duration of hospitalization for HF are longer than the other countries [24]. The results from this specific cohort may not be applicable to other populations or settings with different healthcare practices. Despite these limitations, this study provides valuable insights that can inform clinical practice regarding the management of hospitalized older patients with HF.

5. Conclusions

Physical frailty and malnutrition coexist in approximately one-quarter of hospitalized older patients with HF and are associated with an increased risk of mortality. Assessing both conditions is crucial for risk stratification and interventions to mitigate their interplay.

CRediT authorship contribution statement

Takuro Abe: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Yudai Fujimoto:** Formal analysis, Data curation. **Daichi Maeda:** Data curation. **Yuki Ogasahara:** Data curation. **Kazuya Saito:** Data curation. **Kentaro Iwata:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation. **Masaaki Konishi:** Data curation. **Takatoshi Kasai:** Data curation. **Hiroshi Wada:** Data curation. **Shin-ichi Momomura:** Data curation. **Nobuyuki Kagiyama:** Data curation. **Kentaro Kamiya:** Data curation. **Emi Maekawa:** Data curation. **Yuya Matsue:** Validation, Supervision, Funding acquisition, Data curation.

Declaration of competing interest

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Appendix A. Supplementary data

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