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ORIGINAL RESEARCH

Phenotyping of Elderly Patients With Heart Failure Focused on Noncardiac Conditions: A Latent Class Analysis From a Multicenter Registry of Patients Hospitalized With Heart Failure

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BACKGROUND: The burden of noncardiovascular conditions is becoming increasingly prevalent in patients with heart failure (HF). We aimed to identify novel phenogroups incorporating noncardiovascular conditions to facilitate understanding and risk stratification in elderly patients with HF.

METHODS AND RESULTS: Data from a total of 1881 (61.2%) patients aged ≥65 years were extracted from a prospective multicenter registry of patients hospitalized for acute HF (N=3072). We constructed subgroups of patients with HF with preserved ejection fraction (HFpEF; N=826, 43.9%) and those with non-HFpEF (N=1055, 56.1%). Latent class analysis was performed in each subgroup using 17 variables focused on noncardiovascular conditions (including comorbidities, Clinical Frailty Scale, and Geriatric Nutritional Risk Index). The latent class analysis revealed 3 distinct clinical phenogroups in both HFpEF and non-HFpEF subgroups: (1) robust physical and nutritional status (Group 1: HFpEF, 41.2%; non-HFpEF, 46.0%); (2) multimorbid patients with renal impairment (Group 2: HFpEF, 40.8%; non-HFpEF, 41.9%); and (3) malnourished patients (Group 3: HFpEF, 18.0%; non-HFpEF, 12.1%). After multivariable adjustment, compared with Group 1, patients in Groups 2 and 3 had a higher risk for all-cause death over the 1-year postdischarge period (hazard ratio [HR], 2.79 [95% CI, 1.64–4.81] and HR, 2.73 [95% CI, 1.39–5.35] in HFpEF; HR, 1.96 [95% CI, 1.22–3.14] and HR, 2.97 [95% CI, 1.64–5.38] in non-HFpEF; respectively).

CONCLUSIONS: In elderly patients with HF, the phenomapping focused on incorporating noncardiovascular conditions identified 3 phenogroups, each representing distinct clinical outcomes, and the discrimination pattern was similar for both patients with HFpEF and non-HFpEF. This classification provides novel risk stratification and may aid in clinical decision making.

Key Words: elderly patients ■ heart failure ■ noncardiovascular conditions ■ phenotyping

Heart failure (HF) has become the leading cause of death in most developed countries.[1,2,3] In particular, elderly patients with HF have a high incidence of adverse clinical events, including both cardiovascular-related and noncardiovascular events.[4,5,6] The exponential rise in the prevalence of coexisting noncardiovascular conditions, such as comorbidity, frailty, and malnutrition with aging, is thought to contribute significantly to HF in elderly patients.[6,7,8,9,10,11,12]

The complex interplay of cardiovascular and noncardiovascular conditions complicates the underlying

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CLINICAL PERSPECTIVE

What Is New?

- The present phenomapping focused on incorporating noncardiovascular conditions such as comorbidity, physical function, and nutritional status. It identified 3 phenogroups with distinct clinical prognoses (ie, robust, systemic impairment, and cachexia groups) in elderly patients with heart failure.
- The discrimination pattern was similar for both patients with heart failure with preserved ejection fraction and non–heart failure with preserved ejection fraction.
- This suggests that noncardiovascular conditions play a significant role in pathophysiology and prognosis among elderly patients with heart failure.

What Are the Clinical Implications?

- The clinically recognizable classification reflecting elderly-inherent phenotypes provides not only risk stratifications but also crucial information for a better understanding of the complicated pathophysiology of elderly patients with heart failure.
- Because a similar discrimination pattern was observed in patients with both heart failure with preserved ejection fraction and non–heart failure with preserved ejection fraction, the present classification may apply to a broad range of elderly patients with heart failure.

Nonstandard Abbreviations and Acronyms

BIC	Bayesian information criterion
CFS	Clinical Frailty Scale
GNRI	Geriatric Nutritional Risk Index
HFpEF	heart failure with preserved ejection fraction
LCA	latent class analysis

pathophysiology[10] and results in challenging clinical decision making for these patients.[13] The current diagnosis of HF focuses primarily on cardiovascular conditions, and homogeneous phenotypic classification based on abnormalities in cardiac function may not fully encompass the diversity of pathophysiology.[14] In addition, previous phenomapping studies have included both young and elderly populations, which differ substantially in terms of long-term prognosis and treatment application.[8,15,16,17] Furthermore, the assessment of individualized noncardiovascular conditions, as performed in previous observational studies, may not have adequately captured the burden of noncardiovascular conditions.[9,12,18]

Latent class analysis (LCA) has received growing attention in recent epidemiological literature. LCA was originally developed to isolate specific groups of individuals with similar characteristics based on probability calculations and offers a strategy to identify subgroups of patients with HF who are more susceptible to adverse clinical events.[19] Furthermore, previous studies have demonstrated the feasibility of LCA for phenomapping in HF with preserved ejection fraction (HFpEF) with heterogeneous pathophysiologies.[16,17,20] We hypothesized that phenomapping focused on incorporating noncardiovascular conditions could identify the novel elderly-inherent phenotypic subgroups with distinct clinical prognoses. To facilitate use of the complexity of noncardiovascular clinical variables, we aimed to perform the LCA in a cohort of elderly patients hospitalized for acute HF, with a particular focus on conditions such as multimorbidity, physical frailty, and malnutrition.

METHODS

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

Data Sources

This study is a nonprespecified post hoc analysis of the WET-HF (West Tokyo Heart Failure Registry), which was a prospective multicenter cohort registry designed to collect data on clinical backgrounds and outcomes from consecutive patients with acute HF who were hospitalized for requiring urgent treatment.[21,22] The WET-HF registry has provided insights on the national current status of clinical outcomes[23] in patients with HF, as well as in international collaborative projects.[24,25,26] Individuals with acute HF were diagnosed by a cardiologists at each institution based on the Framingham criteria.[27] Between January 2006 and December 2017, patients with HF were registered at 6 tertiary hospitals in the Tokyo area. We added 2 further institutions in April 2018 (WET-HF2 Registry) with an update of the collected variables, including the Clinical Frailty Scale (CFS) at the time of discharge.[28]

Patient data were entered into an electronic data capture system with a robust data query engine and system validations for data quality. The principal investigators (Y.S. and S.K.) conducted periodic queries to verify the reporting quality at least once a year. Patients who refused to participate in the study or presented with concurrent HF and acute coronary syndrome were excluded from registration. As for the end points, all death-related events were reviewed by the investigators and classified into the following groups: those

requiring adjudication and those with a clearly defined mode of death. Subsequently, central committee members (Y.S., S.K., and T.Y.) reviewed the abstracted records and adjudicated the modes of death.

Before the launch of this registry, information on the present study's objectives and social significance, as well as an abstract, were provided for clinical trial registration to the University Hospital Medical Information Network of Japan (UMIN000001171). The institutional review boards at each site approved the study protocol, and the research was conducted according to the Declaration of Helsinki. Written or oral informed consent was obtained from each patient before the study.

Study Population

A total of 3072 consecutive patients with HF were registered in the WET-HF2. We excluded patients aged <65 years (n=566 [18.4%]), those who died during the index hospitalization (n=155 [5.0%]), those who were not followed up on (n=370), and those without left ventricular ejection fraction (LVEF) data (n=100 [3.3%]). The remaining 1881 (61.2%) patients aged ≥65 years were included in the present study. We then categorized the participants into 2 groups based on their LVEF status: non-HFpEF (n=1055 [56.1%]), LVEF <50%, HF with mildly reduced ejection fraction and HF with reduced ejection fraction; and HFpEF (n=826 [43.9%], LVEF≥50%) (Figure 1). During the index hospitalization after the HF signs and symptoms stabilized, board-certified physicians or physiology technicians assessed LVEF on echocardiography using the modified Simpson method.

Definition of Comorbidity, Malnutrition, and Physical Frailty

The following comorbidities were defined as having a history of the following diagnoses. Particularly, atrial fibrillation was defined as having a history on an electrocardiogram; anemia was defined according to the World Health Organization criteria (hemoglobin at discharge <13 g/dL for men and <12 g/dL for women[29]); chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) at discharge <60 mL/min per 1.73 m^2 (the eGFR was calculated using the Modification of Diet in Renal Disease Equation for Japanese Patients, proposed by the Japanese Society of Nephrology[30]); and hyperuricemia was defined as serum uric acid at discharge ≥8.0 mg/dL. Given the extremely high risk for adverse clinical events in patients with HF with ≥3 comorbidities in our previous research,[21] we defined them as having multimorbidity in the present study. Physical frailty was defined as a CFS score ≥5; the CFS is a simple screening tool for the identification of frailty.[31] Furthermore, based on previous findings,[31,32,33] malnutrition and physical frailty were defined as a geriatric Nutritional Risk Index (GNRI) <82 at the time of discharge; the GNRI is a simple formula that has been demonstrated to be clinically useful among patients with various medical conditions.[32]

Candidate Variables for LCA

We selected the following 19 available variables a priori as candidates for the LCA in terms of comorbidities, physical function, cognitive status, nutritional

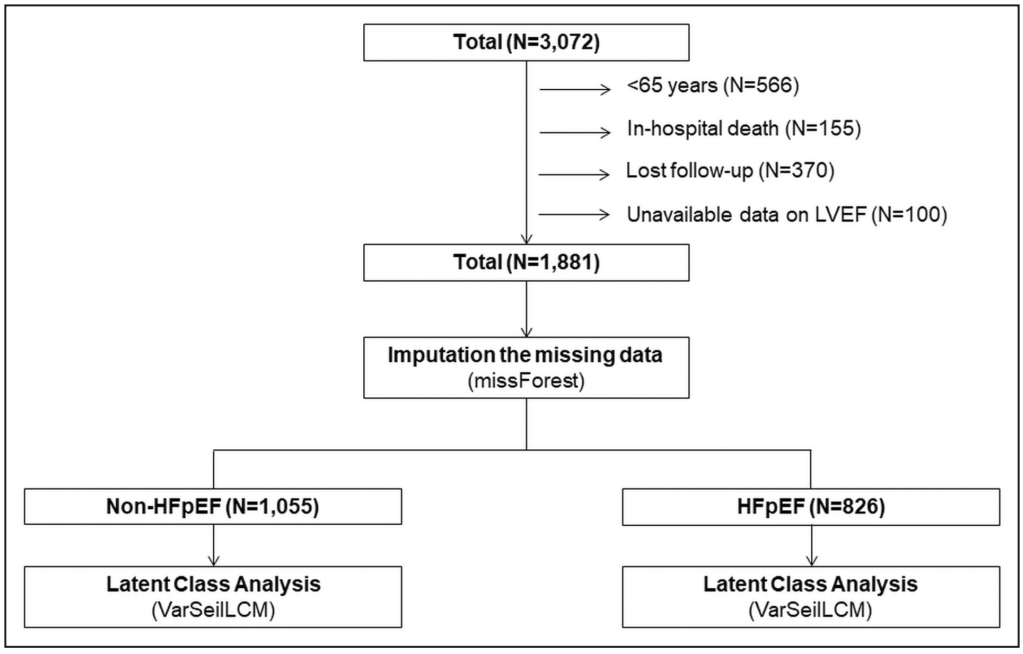

Figure 1. Study flowchart.
HFpEF indicates heart failure with preserved ejection fraction; and LVEF, left ventricular ejection fraction.

status, and social environment, which were essential domains when considering multidimensional assessments for elderly patients with HF, based on previous literature[10,34]: (1) demographic data: age, sex, body mass index, and smoking status; (2) comorbidities: hypertension, diabetes, atrial fibrillation, dyslipidemia, hyperuricemia, previous stroke, chronic obstructive pulmonary disease/asthma, malignancy, renal function assessed via eGFR, anemia assessed via hemoglobin level; (3) physical function: CFS and Barthel Index at the time of discharge (assessed by the attending physician); (4) cognitive status: dementia or lack thereof; (5) nutrition status: GNRI; and (6) social environment: living alone or not. All of these variables had <10% missing data (Table S1). Variables with a correlation coefficient >0.6 were excluded, thus keeping only the clinically meaningful variables; the Barthel Index and body mass index were highly associated with the CFS and GNRI, respectively. Therefore, they were excluded from the LCA. Consequently, a total of 17 continuous and categorical variables were used in the final analysis (Table S2).

Latent Class Analysis

LCA is a statistical approach of unsupervised clustering to identify phenogroups defined by specific combinations of variables and assumes that observed patterns result from a finite mixture of underlying clusters.[35,36] Clusters are assigned through iterative generation of an estimated probability of membership in each of a prespecified number of clusters via mixture modeling. Particularly, LCA is thought to have the 2 following advantages: the classifications are not predefined or limited by current conceptual frameworks, given that grouping originated from the data,[19] and that it allows for loss of information minimization by directly modeling the inherent nature of continuous and categorical data.[16,17,37]

The VarSelLCM package in R software implements a modified expectation–maximization algorithm, which performs feature selection using Bayesian information criterion (BIC) and maximum likelihood inference simultaneously for a fixed number of clusters.[38] Furthermore, it also implements a penalized complete-data log-likelihood function to identify relevant variables for better discrimination.[39]

We conducted the LCA using the VarSelLCM package (2–8 clusters) for variable selection in each subset of the non-HFpEF and HFpEF categories (Figure 1). Each model was estimated with the maximum 1000 iterations for the expectation–maximization algorithm to accomplish the stable model. To identify the optimal number of phenogroups, we used the first minimum of the BIC.[40] The BIC is suggested to provide for even the most parsimonious model selection and is recommended in LCA.[16,17] Particularly, a prior study demonstrated that the BIC worked best at identifying the correct number of classes in data with both categorical and continuous variables.[41] Following confirmation of the optimal number of phenogroups, the probability of each patient belonging to each subgroup was calculated, and each patient was assigned to a subgroup with the highest likelihood.[19] Finally, we assessed the reproducibility between grouping in the full 17-variable model, as well as that with variable selection (the top numbers of discriminatory variables) using the Cohen κ statistic.

Before clustering, we performed imputation of the missing data using the missForest package, considering the benefits of random forest imputation compared with those of multiple imputation by chained equations.[42]

Clinical Outcomes

The primary outcome of this study was a composite of all-cause death and HF readmission over the 1-year postdischarge period. Treating physicians at each participating hospital identified HF rehospitalizations according to standard definitions.[22] HF death, sudden cardiac death, and other cardiovascular deaths, including acute coronary syndrome, acute aortic syndrome, intracranial hemorrhage, and stroke, were considered cardiovascular deaths. Noncardiovascular deaths were all other causes of death.

Statistical Analysis

We first divided the patients into non-HFpEF and HFpEF groups and compared the patient characteristics among the 3 phenogroups within each of these groups. Parametric and nonparametric variables, as well as their respective differences, were assessed using a 1-way ANOVA or the Kruskal-Wallis test. Significant differences between the independent categorical variables were assessed using the χ^2 test. The incidence of composite events or all-cause death was estimated using the Kaplan-Meier survival function and compared among the 3 phenogroups using the log-rank test. We also compared the incidence of composite events in patients who received both β-blockers and renin-angiotensin system inhibitors at the time of discharge and those who did not, in each of the non-HFpEF phenogroup, using the log-rank test. The incidence of each mode of death was estimated, accounting for competing risks. For this, cardiovascular deaths and noncardiovascular deaths were considered competing events.

Cox-proportional hazard analyses were used to evaluate the risk for all-cause death among phenogroups. The covariates included in the multivariable model were LVEF, Get With The Guidelines-Heart Failure risk score at discharge, and New York Heart Association functional

class ≥III at discharge. Furthermore, when analyzing patients with non-HFpEF, we added the prescription of β-blockers or angiotensin coenzyme inhibitor/angiotensin II receptor blockers as covariates. In addition, we conducted a weighted Cox proportional hazard model using odds ratio based on the probability for membership in each of the 3 phenogroups as a sensitivity analysis. Statistical significance was set at $P<0.05$. All statistical analyses were performed using R software (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

The baseline characteristics of the overall study population (n=1881) are described in Tables S1–S5. Overall, the mean age (SD) was 80.7 (7.8) years, and 817 (43.4%) were women. Multimorbidity (≥3 comorbidities), physical frailty (CFS score ≥5), and malnutrition (GNRI <82) were identified in 79.7%, 37.2%, and 23.7% of the analyzed patients, respectively (Figure 2).

Classification of Elderly Patients With HF

The optimal number of classified phenogroups (based on the BIC values) was 3 in both the non-HFpEF and HFpEF subsets (Table S3). In addition, the optimal numbers of discriminatory variables to predict the phenogroups in each subset of non-HFpEF and HFpEF were 10 and 5, respectively (Table S4). The κ coefficients for the full 17-variable model were 0.94 in non-HFpEF and 0.82 in HFpEF, with high reproducibility. Hemoglobin level at discharge was the most discriminatory variable for the phenogroups, regardless of LVEF categories.

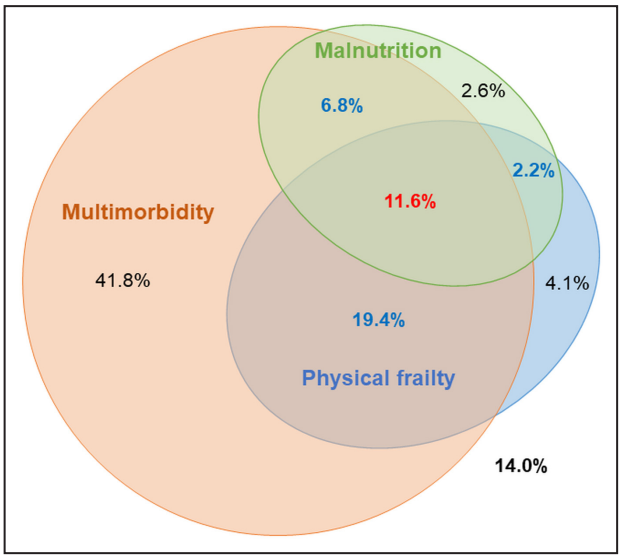

Figure 2. Proportion of multimorbidity, physical frailty, and malnutrition.
The percentage is in reference to the total cohort (N=1881).

The comparisons of patient characteristics among the 3 phenogroups in each subset of non-HFpEF and HFpEF are summarized in Tables 1 and 2, respectively. In both LVEF categories, patients within each phenogroup were characterized as follows: Group 1 (46.0% in non-HFpEF and 41.2% in HFpEF) consisted of more men, the youngest age, lowest burden of physical frailty, and highest GNRI level (well nourished). In contrast, patients in Group 2 (40.8% in non-HFpEF and 41.9% in HFpEF) had the oldest age, highest burden of multimorbidity, and lowest eGFR and hemoglobin levels. Lastly, patients in Group 3 (18.0% in non-HFpEF and 12.1% in HFpEF) had the lowest GNRI level, lowest burden of multimorbidity, and highest eGFR level.

Based on the above clinical characteristics, these phenogroups were labeled as robust (Group 1), systemic impairment (Group 2), and cachexia (Group 3). The phenotypic characteristics based on each variable's transformed Z scores are shown in a heatmap in Figure 3A (non-HFpEF) and Figure 3B (HFpEF). In addition, in the non-HFpEF subset, patients within Group 1 were more likely to receive β-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and mineralocorticoid receptor antagonists (Table 1).

Clinical Outcomes After Discharge

In the non-HFpEF subset, the robust group had a lower incidence of composite events and all-cause deaths over the 1-year postdischarge period than the systemic impairment or cachexia groups (composite events: 22.1%, 30.8%, and 31.3% [Figure 4A]; all-cause death: 5.6%, 13.3%, and 17.2% [Figure 4B], respectively; both log-rank $P<0.001$). In the HFpEF subset, the cumulative incidence of the composite events was highest in the systemic impairment group, followed by that in the robust and cachexia groups (systemic impairment, 30.9%; robust, 21.5%; cachexia, 16.8%; log-rank $P<0.001$) (Figure 4C). However, in this subset, the incidence of all-cause death was lowest in the robust group (robust, 4.3%; systemic impairment, 15.1%; cachexia, 12.1%; log-rank $P<0.001$) (Figure 4D). In addition, we found no significant difference in the crude incidence of composite events between patients who received both β-blockers and renin-angiotensin system inhibitors and those without across the phenogroups (Figures S1–S3).

After adjustment for cardiovascular conditions using multivariable Cox models, the systemic impairment and cachexia groups remained at a higher risk for both composite events and all-cause deaths than the robust group in the non-HFpEF subset (Figure 5A). In the HFpEF subset, the systemic impairment group also had a higher risk for both clinical outcomes than the robust group. However, the cachexia group had a higher risk of all-cause death than the robust group, and there was no significant difference in composite

Table 1. Patient Characteristics at Discharge in Patients With Non-HFpEF

Characteristic	Phenogroup 1, N=485, robust	Phenogroup 2, N=442, systemic impairment	Phenogroup 3, N=128, cachexia	*P* value
Age, y	76.0 (6.8)	82.5 (7.3)	80.4 (8.2)	<0.001
Men	73.4%	57.2%	50.8%	<0.001
Body mass index, kg/m^2	22.1 (3.6)	19.9 (2.8)	18.0 (2.8)	<0.001
Living alone	26.2%	17.6%	11.7%	<0.001
Smoking	16.1%	4.8%	8.6%	<0.001
Clinical frailty scale	3 (3–4)	4 (4–6)	5 (4–7)	<0.001
Physical frailty (Clinical Frailty Scale ≥5)	15.1%	48.6%	58.6%	<0.001
Barthel Index	100 (90–100)	85 (55–100)	65 (45–100)	<0.001
GNRI	96.0 (8.4)	86.0 (7.9)	78.6 (8.4)	<0.001
Malnutrition, GNRI <82	2.9%	30.3%	63.3%	<0.001
Systolic blood pressure, mm Hg	112.2 (16.7)	113.6 (18.5)	110.3 (15.8)	0.133
Diastolic blood pressure, mm Hg	65.2 (12.6)	61.0 (12.0)	62.2 (13.0)	<0.001
NYHA functional class ≥III	6.0%	13.4%	11.8%	<0.001
GWTG-Heart Failure risk score	40.9 (7.2)	44.0 (7.1)	43.7 (6.7)	<0.001
Comorbidities				
No. of morbidities	3 (2–4)	4 (3–5)	2 (2–4)	<0.001
Multimorbidity	71.3%	93.2%	50.0%	<0.001
Atrial fibrillation	45.6%	34.4%	33.0%	<0.001
Hypertension	65.6%	69.7%	50.0%	<0.001
Diabetes	32.6%	34.6%	21.1%	0.015
Dyslipidemia	43.1%	40.7%	25.8%	0.002
Hyperuricemia	26.6%	35.7%	0.8%	<0.001
Previous stroke	11.3%	14.0%	12.5%	0.468
Anemia	26.8%	91.9%	75.0%	<0.001
Chronic kidney disease	75.9%	99.3%	22.7%	<0.001
COPD/asthma	4.7%	3.6%	3.9%	0.686
Malignant tumor	1.4%	2.3%	0.8%	0.434
Dementia	5.4%	12.0%	21.1%	<0.001
Echocardiography				
LVDD, mm	56.0 (9.0)	53.8 (8.1)	50.2 (8.3)	<0.001
LVESD, mm	46.5 (10.0)	44.3 (8.9)	40.9 (9.5)	<0.001
Left ventricular ejection fraction, %	34.4 (9.3)	35.0 (8.8)	35.6 (8.2)	0.339
Left atrium diameter, mm	45.2 (8.0)	42.6 (8.2)	40.3 (9.2)	<0.001
Cause				
Ischemic cardiomyopathy	33.4%	43.0%	34.4%	<0.001
Dilated cardiomyopathy	21.9%	12.4%	9.4%	
Hypertrophic cardiomyopathy	2.1%	0.9%	0	
Valvular heart disease	14.4%	21.3%	23.4%	
Others	28.2%	22.4%	32.8%	
Examinations at discharge				
Hemoglobin, g/dL	13.6 (1.7)	10.6 (1.2)	11.5 (1.4)	<0.001
eGFR, mL/min per 1.73 m^2	50.7 (15.4)	34.2 (13.5)	75.7 (19.5)	<0.001
Serum sodium, mEq/L	138.9 (3.2)	138.6 (3.9)	137.9 (4.0)	0.012
Serum potassium, mEq/L	4.4 (0.4)	4.4 (0.5)	4.2 (0.5)	0.003
BNP, pg/mL	240 (125–413)	429 (208–802)	302 (184–560)	<0.001
NT-proBNP, pg/mL	1716 (823.5–3071)	4158 (1564–8239)	4451 (1553–11 373)	<0.001

(*Continued*)

Table 1. Continued

Characteristic	Phenogroup 1, N=485, robust	Phenogroup 2, N=442, systemic impairment	Phenogroup 3, N=128, cachexia	*P* value
Examinations, 1 y after discharge				
BNP, pg/mL	160 (67–357)	280 (116–603)	141 (85–315)	<0.001
NT-proBNP, pg/mL	1532 (761–2915)	3864 (1510–7744)	2218 (1151–7951)	<0.001
Medications, discharge, %				
β-Blocker	86.6%	78.3%	78.9%	0.002
ACE-I/ARB	72.0%	54.3%	57.0%	<0.001
Mineralocorticoid receptor antagonist	49.2%	36.7%	43.0%	0.001
SGLT-2 inhibitor	12.8%	5.2%	2.3%	<0.001
Loop diuretic	87.6%	89.1%	83.6%	0.239
Thiazide diuretic	2.9%	4.5%	0.8%	0.088
Digoxin	5.8%	3.2%	5.5%	0.152
Oral anticoagulant	65.8%	46.2%	56.2%	<0.001
Antiplatelet agent	41.0%	51.4%	41.4%	0.004
Statin	50.5%	50.7%	34.4%	0.003
Antihyperuricemic	31.8%	33.9%	8.6%	<0.001
Medications, 1 y after discharge, %				
β-Blocker	87.2%	77.6%	77.5%	0.004
ACE-I/ARB	69.5%	52.0%	58.6%	<0.001
Mineralocorticoid receptor antagonist	48.6%	34.4%	48.5%	0.001
SGLT-2 inhibitor	16.7%	11.0%	1.4%	0.001
Loop diuretic	80.6%	80.9%	74.3%	0.441
Thiazide diuretic	1.6%	5.3%	0	0.009

Values are expressed as mean (SD) or median (interquartile range). ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; GWTG, Get With The Guidelines; HFpEF, heart failure with preserved ejection fraction; LVDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SGLT-2, sodium-glucose transport protein 2.

events between them (Figure 5B). Furthermore, these trends were robust in weighted Cox models based on the probability for membership in each of the 3 phenogroups (Table S5).

The crude cardiovascular deaths and noncardiovascular deaths in each subset of patients with non-HFpEF and HFpEF are presented in Figures 6A and 6B, respectively. The proportion of cardiovascular deaths was consistently higher in patients with non-HFpEF than in those with HFpEF. Patients in the systemic impairment group had the highest proportion of cardiovascular death, followed by those in the cachexia and robust groups, regardless of the LVEF category (robust versus systemic impairment versus cachexia: non-HFpEF, 46.4% versus 62.7% versus 59.1%; HFpEF, 31.6% versus 51.0% versus 38.9%).

DISCUSSION

This study performed clustering analyses focused on noncardiovascular conditions in elderly patients with HF to facilitate the understanding of phenotypic diversity. These patients were successfully classified into 3 phenogroups: robust, systemic impairment, and cachexia, regardless of the systolic function status. We found that the prescription patterns of HF-specific medications varied among the 3 phenogroups in patients with non-HFpEF. Both the systemic impairment and cachexia groups had similarly poorer prognoses than the robust group. Furthermore, patients in the cachexia group died more often from noncardiovascular causes.

Although the importance of a multidimensional and integrated clinical assessment is advocated for the optimal management of elderly patients with HF,[10,43] it is often difficult for clinicians to comprehend the individual pathophysiology in routine care. This is because of the complex interactions of multiple coexisting noncardiovascular disorders. Therefore, it is crucial to comprehend the overlapping of noncardiovascular conditions and its influences on clinical prognosis, particularly in elderly patients. In this context, the present phenomapping focused on incorporating noncardiovascular conditions following clinical implications. First, we

Table 2. Patient Characteristics at Discharge in Patients With HFpEF

Characteristic	Phenogroup 1, N=340, robust	Phenogroup 2, N=337, systemic impairment	Phenogroup 3, N=149, cachexia	*P* value
Age, y	80.5 (7.0)	84.8 (6.6)	82.1 (7.9)	<0.001
Men	53.5%	42.7%	43.0%	<0.001
Body mass index, kg/m^2	22.5 (4.0)	20.4 (3.3)	18.6 (2.9)	<0.001
Living alone	23.5%	17.8%	16.1%	<0.001
Smoking	7.9%	4.7%	6.0%	<0.001
Clinical Frailty Scale	4 (3–5)	5 (4–6)	5 (4–6)	<0.001
Physical frailty (Clinical Frailty Scale ≥5)	25.3%	52.5%	51.7%	<0.001
Barthel Index	100 (80–100)	80 (60–100)	85 (50–100)	<0.001
GNRI	96.8 (9.9)	86.4 (8.7)	81.5 (8.6)	<0.001
Malnutrition, GNRI <82	5.9%	32.9%	51.7%	<0.001
Systolic blood pressure, mm Hg	115.6 (17.1)	119.9 (18.4)	115.6 (17.8)	0.003
Diastolic blood pressure, mm Hg	64.7 (12.7)	60.7 (11.4)	62.2 (11.8)	<0.001
NYHA functional class ≥III	7.1%	13.7%	8.8%	0.015
GWTG-Heart Failure risk score	40.5 (7.7)	42.0 (6.9)	41.5 (7.9)	0.03
Comorbidities				
No. of morbidities	4 (3–5)	4 (4–5)	3 (2–4)	<0.001
Multimorbidity	77.1%	95.0%	63.1%	<0.001
Atrial fibrillation	55.9%	47.8%	43.6%	0.021
Hypertension	55.9%	47.8%	43.6%	0.101
Diabetes	26.8%	27.3%	21.5%	0.371
Dyslipidemia	33.5%	32.9%	27.5%	0.395
Hyperuricemia	28.8%	31.8%	3.4%	<0.001
Previous stroke	12.6%	17.2%	12.1%	0.161
Anemia	43.8%	99.4%	91.3%	<0.001
Chronic kidney disease	77.6%	98.5%	16.1%	<0.001
COPD/asthma	5.9%	5.0%	7.4%	0.595
Malignant tumor	0.9%	1.8%	2.0%	0.509
Dementia	7.6%	12.2%	15.4%	0.024
Echocardiography				
LVDD, mm	45.0 (6.9)	45.6 (7.1)	43.4 (6.5)	0.005
LVESD, mm	30.4 (6.1)	30.2 (6.5)	28.4 (5.8)	0.004
Left ventricular ejection fraction, %	59.9 (6.9)	61.3 (7.2)	61.5 (8.1)	0.02
Left atrium diameter, mm	45.4 (9.1)	44.9 (10.0)	41.0 (8.9)	<0.001
Cause				
Ischemic cardiomyopathy	11.5%	15.4%	10.7%	<0.001
Dilated cardiomyopathy	1.5%	0.6%	1.3%	
Hypertrophic cardiomyopathy	5.0%	1.5%	2.0%	
Valvular heart disease	34.1%	40.4%	45.6%	
Others	47.9%	42.1%	40.3%	
Examinations at discharge				
Hemoglobin, g/dL	12.8 (1.5)	9.9 (1.0)	10.6 (1.3)	<0.001
eGFR, mL/min per 1.73 m^2	48.7 (14.5)	33.4 (13.7)	76.3 (21.2)	<0.001
Serum sodium, mEq/L	139.4 (3.0)	138.7 (3.6)	137.8 (4.4)	<0.001
Serum potassium, mEq/L	4.3 (0.5)	4.4 (0.5)	4.2 (0.5)	0.017
BNP, pg/mL	205 (95–362)	297 (140–548)	224 (147–362)	0.014
NT-proBNP, pg/mL	1060 (668–1694)	2957 (1273–4912)	2240 (941–3902)	<0.001
Examinations, 1 y after discharge				
BNP, pg/mL	214 (112–479)	167 (92–321)	145 (85–309)	0.032
NT-proBNP, pg/mL	1707 (851–2917)	3005 (1372–6293)	906 (479–1977)	<0.001
Medications, discharge, %				
β-Blocker	67.9%	51.0%	56.4%	<0.001
ACE-I/ARB	51.5%	43.3%	46.3%	0.102

(*Continued*)

Table 2. Continued

Characteristic	Phenogroup 1, N=340, robust	Phenogroup 2, N=337, systemic impairment	Phenogroup 3, N=149, cachexia	*P* value
Mineralocorticoid receptor antagonist	33.5%	29.1%	36.2%	0.235
SGLT-2 inhibitor	6.8%	1.5%	3.4%	0.002
Loop diuretic	80.9%	82.5%	74.5%	0.118
Thiazide diuretic	2.6%	3.6%	1.3%	0.383
Digoxin	5.8%	3.2%	5.5%	0.152
Oral anticoagulant	71.5%	52.8%	55.0%	<0.001
Antiplatelet agent	26.8%	35.9%	39.6%	0.006
Statin	36.5%	40.1%	33.6%	0.353
Antihyperuricemic	27.9%	32.9%	7.4%	<0.001
Medications, 1 y after discharge, %				
β-Blocker	68.0%	45.8%	61.5%	<0.001
ACE-I/ARB	50.5%	39.2%	50.0%	0.074
Mineralocorticoid receptor antagonist	34.3%	27.1%	32.1%	0.345
SGLT-2 inhibitor	7.9%	3.6%	3.8%	0.168
Loop diuretic	75.6%	77.6%	69.2%	0.366
Thiazide diuretic	3.6%	4.8%	3.8%	0.833

Values are expressed as mean (SD) or median (interquartile range). ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; GWTG, Get With The Guidelines; HFpEF, heart failure with preserved ejection fraction; LVDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SGLT-2, sodium-glucose transport protein 2.

successfully identified novel and clinically recognizable phenogroups, which differed from previous clustering analyses.[8,15,16,17] Notably, although patients in the systemic impairment group were expected to have the poorest prognosis simply based on biomarker assessments (eg, natriuretic peptide), patients assigned to the cachexia group had equally poor prognosis compared with those in the systemic impairment group. These findings suggest that our phenomapping offers novel risk stratification, which cannot be yielded by existing clustering analyses, for elderly patients with HF. Second, despite the distinct pathophysiology between

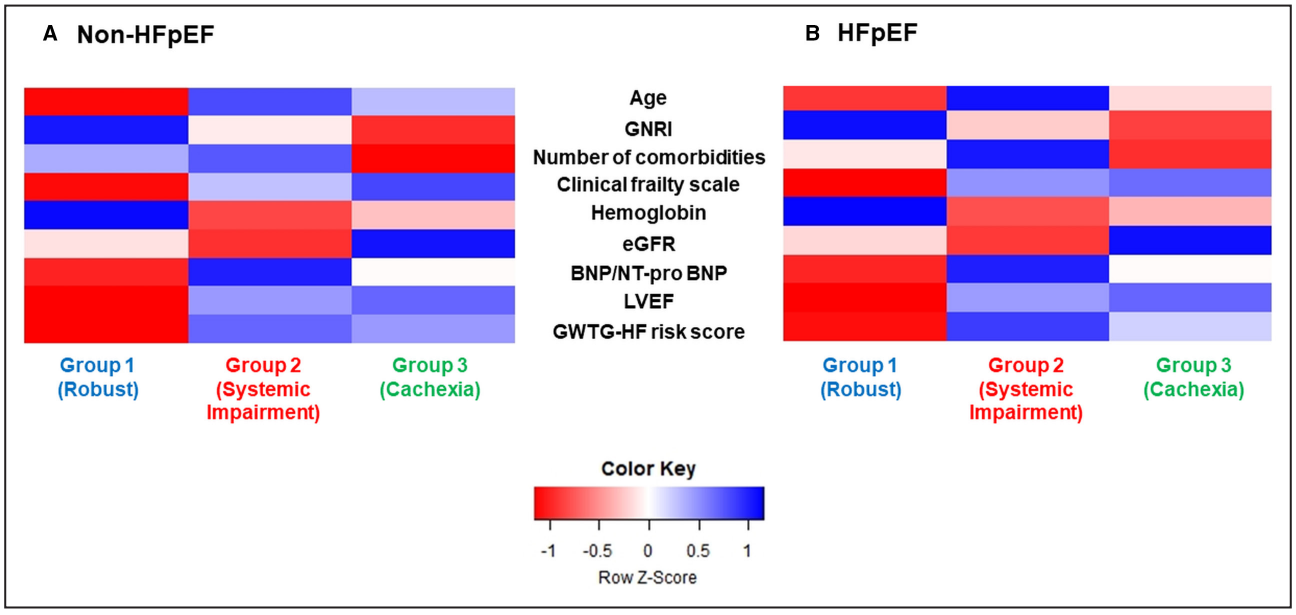

Figure 3. Heat map of the phenotypic characteristics across the 3 phenogroups.
A, Non-HFpEF. **B**, HFpEF. BNP indicates brain natriuretic peptide; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; GWTG, Get With The Guidelines; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

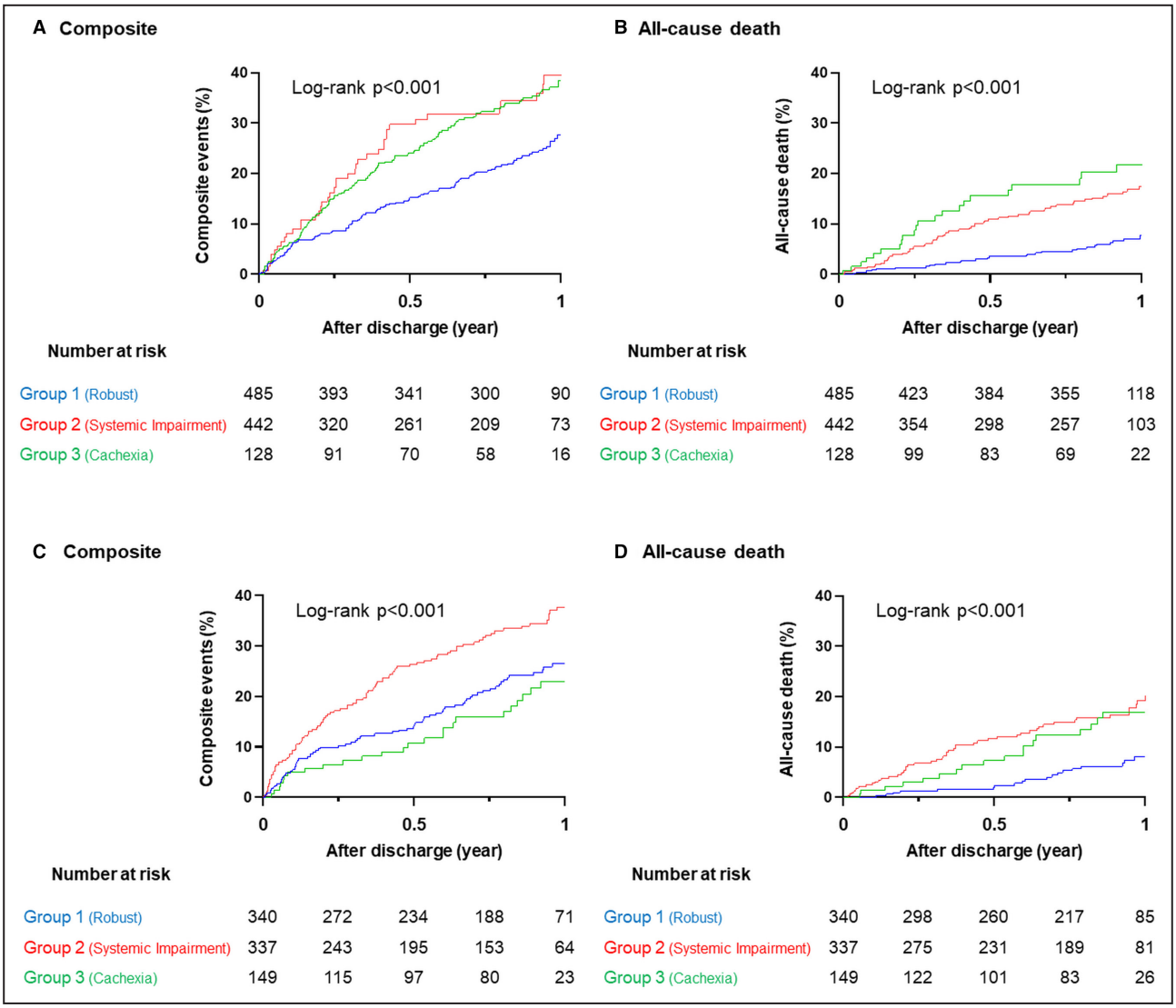

Figure 4. Cumulative incidence of clinical outcomes among the 3 phenogroups.
A, Composite events. **B**, All-cause death in non-HFpEF. **C**, Composite events. **D**, All-cause death in HFpEF. The composite event was defined as all-cause death and heart failure readmission. HFpEF indicates heart failure with preserved ejection fraction.

non-HFpEF and HFpEF, similar phenogroups were identified in both LVEF categories. These findings indicate that noncardiovascular conditions play a significant role in the pathophysiology and prognosis of elderly patients with HF, regardless of systolic function status. Thus, the novel classifications may apply to a wide range of elderly patients and assist in more tailored clinical decision making, as well as the design of more targeted future trials. Furthermore, we suggest that future clinical trials for elderly patients should consider noncardiovascular conditions. Hereafter, the detailed characteristics of each phenogroup are described.

Patients in the systemic impairment group had a higher risk of cardiovascular events than the other groups, in the setting of considerable renal dysfunction, high prevalence of multimorbidity, and elevated natriuretic peptide levels. Therefore, developing optimal treatment strategies for these would remain challenging in both LVEF categories. The efficacy of HF-specific pharmacotherapies in patients with coexisting renal impairment is uncertain[44]; as such, patients have traditionally been recruited less in randomized controlled trials. This would lower the likelihood of initiating pharmacotherapy and promote poorer prognoses in this group. Additionally, the high prevalence of multimorbidity in conjunction with renal impairment induces chronic systemic inflammation and endothelial dysfunction, resulting in HFpEF worsening.[45] Therefore, integrated management focused on comorbid conditions is crucial for patients with this phenogroup. For instance, the management of anemia would be a modifiable factor toward improving clinical outcomes.[43,44]

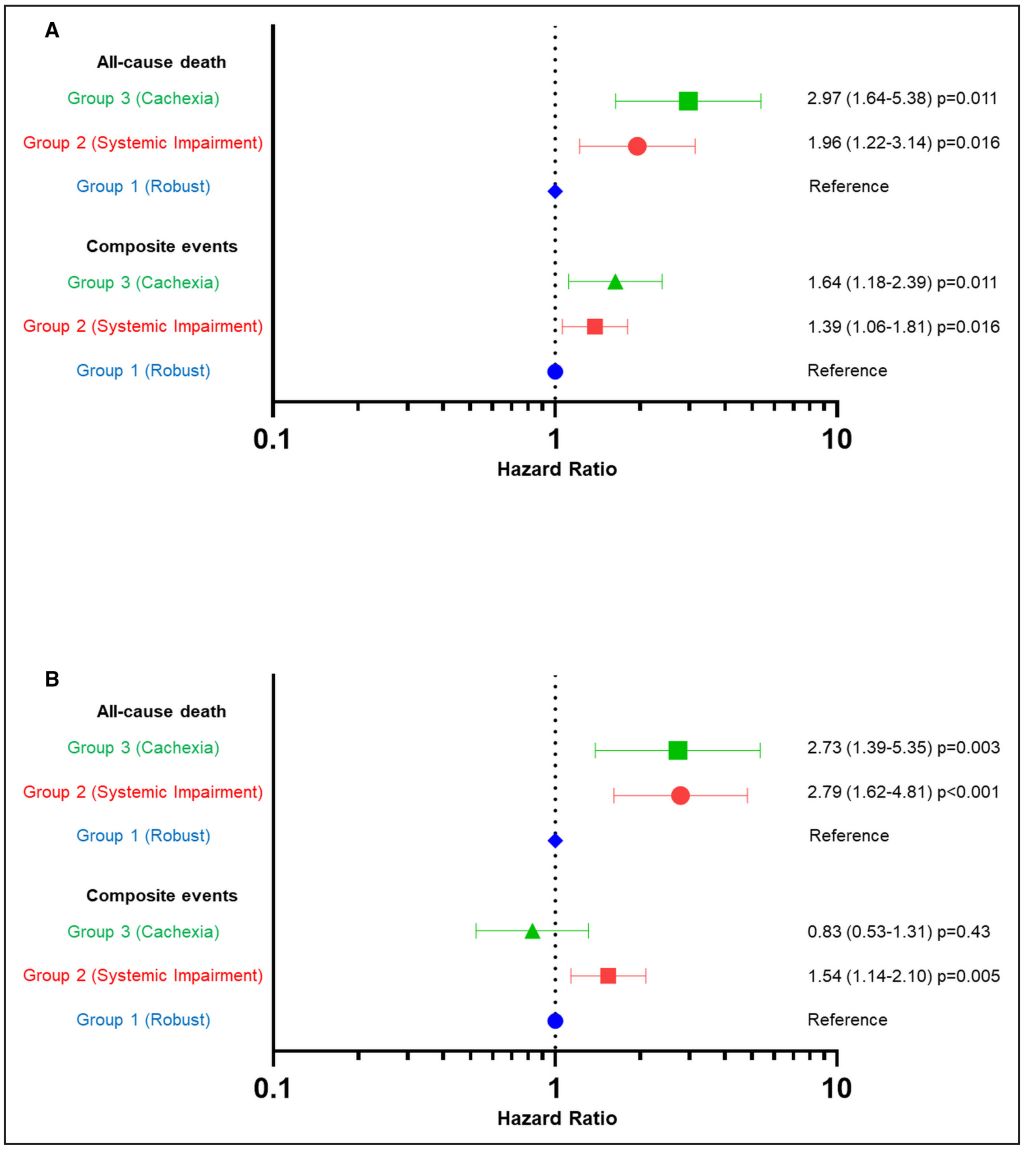

Figure 5. Associations between phenogroups and clinical outcomes.
A, Non-HFpEF. **B**, HFpEF. Forest plots show hazard ratios for clinical outcomes in Group 2 (systemic impairment) and Group 3 (cachexia), compared with Group 1 (robust).

Particularly, the administration of intravenous ferric carboxymaltose for patients with systolic dysfunction and iron deficiency has resulted in decreased hospitalization for HF, as well as improved quality of life.[46] These findings indicated the importance of anemia screening as a routine baseline assessment.

Patients in the cachexia group had a high incidence of all-cause death in the setting of low prevalence of diabetes (21.5%) and renal dysfunction, but a high prevalence of malnutrition and physical frailty, regardless of LVEF categories. Considering that previous clustering analyses have not identified such a phenotype,[8,15,16,17] this cachexia phenotype group reflects elderly-inherent characteristics via phenomapping focused on incorporating noncardiovascular conditions. Notably, the causes of poor prognosis in this group would be explained by not only poor use of HF-specific medical therapies but also the increased burden of noncardiovascular rather than cardiovascular events. Furthermore, the burden of noncardiovascular rather than cardiovascular events could explain the reasons for paradoxical results, in which patients with HFpEF in the cachexia group had a lower incidence of HF readmissions. These results emphasize that simply applying interventions targeting cardiovascular conditions is insufficient; instead, it is important to design integrated management protocols that intensively target noncardiovascular conditions. A recent clinical trial has demonstrated that, compared with a control group, individual nutrition support to reach energy, protein,

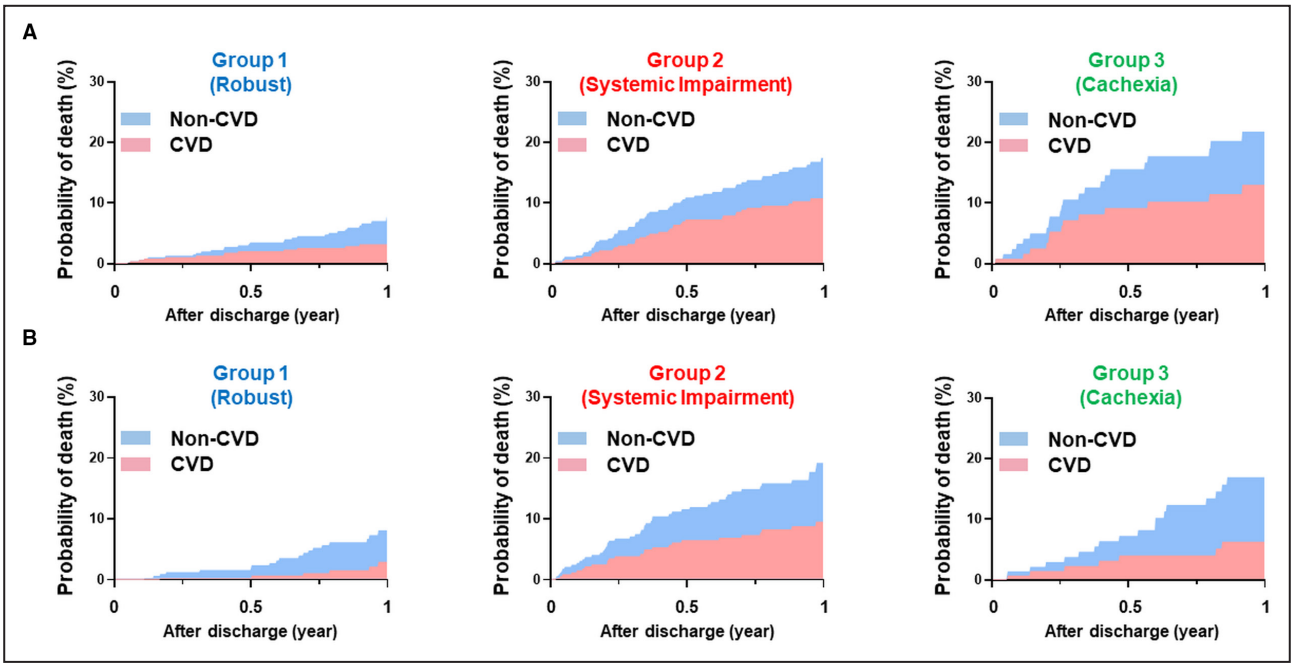

Figure 6. Incidence of CVD and non-CVD.
A, Non-HFpEF. **B**, HFpEF. The cumulative incidence was estimated by the Fine-Gray model. CVD indicates cardiovascular death.

and micronutrient goals reduced mortality, especially in patients with high nutritional risk.[18] Furthermore, the Rehabilitation Therapy in Older Acute Heart Failure Patients trial revealed that a tailored rehabilitation intervention resulted in physical function improvement in elderly patients with HF, especially those with coexisting physical frailty.[7] These interventions would be rather suitable options for patients in the cachexia group.

Finally, among the 3 groups, patients in the robust group were prevalently men and the youngest. These patients may suitably represent the profile of those who had been included in previous clinical trials for HF and account for less than half of the overall elderly patient population in real-world clinical settings. We found that angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonist therapies were underused in patients with non-HFpEF in the robust group. With recently rising concerns on doubts about the benefit of HF-specific medical therapies in patients with frailty, stratified analyses using frailty status were often conducted as subanalyses of clinical trials. Most of these analyses demonstrated no interactions of efficacy in pharmacotherapy (eg, angiotensin receptor-neprilysin inhibitors or sodium-glucose cotransporter 2 inhibitors) across the frailty status.[47,48] These findings suggest that attending physicians should persistently ensure that HF-specific medication doses are increased to target as tolerated.

Our research has several limitations. First, validation analyses for the classification system could not be performed. Particularly, given the inherent characteristics of the LCA, the number of phenogroups may vary according to each analytic cohort.[19] Therefore, we could not exclude the possibility of representing different patterns of phenogroups when analyzing different cohorts. However, as previously mentioned, similar patterns of phenogroups were identified across LVEF categories; this would partially relieve this major concern. Second, the participants in this study were mostly Japanese patients. The identified phenogroups, especially the cachexia group with extremely low body mass index levels, may not apply to patients in Western countries. Therefore, further validation analyses are required. Third, as we performed the LCA using 17 variables focused on noncardiovascular conditions, the variables were fewer than those in previous investigations.[15,16,17,49,50] However, considering that using numerous variables may inhibit the application for clinical settings, this simple phenomapping, focused on noncardiovascular conditions, would provide important clinical benefits in terms of addressing the diversity of elderly patients. Fourth, we did not account for several essential factors of elderly patients with HF (eg, mental health or financial status).[10] Thus, we could not exclude that phenomapping would differ if more complete data were available to us on noncardiovascular conditions. Fifth, this was a multicenter observational study. Because the treatment strategy for HF was not predetermined, it varied according to the physicians' and medical centers' discretion and protocols. Finally, similar to previous reports, this study only included patients who could be followed up on, potentially leading to selection bias.

CONCLUSIONS

In elderly patients who were hospitalized for acute HF, LCA identified 3 phenogroups, each representing distinct clinical outcomes, with the incorporation of noncardiovascular conditions. These findings highlight the heterogeneity of the elderly population with HF and show that such classification may be useful for a better understanding of tailored treatment in these patients.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5
Figures S1–S3

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Supplemental Material

Table S1. Patient characteristics

	All patients (N=1,881)	Missing
Age, years	80.7±7.75	0
Female	817 (43.4%)	0
Body mass index, kg/m^2	20.8±3.67	56 (3.0%)
HFpEF	826 (43.9%)	0
Living alone	383 (21.6%)	104 (5.5%)
Smoking	162 (8.6%)	
Clinical frailty scale	4 (3-6)	12 (0.6%)
Physical frailty (clinical frailty scale≥5)	694 (37.1%)	
Barthel Index	80 (65-100)	21 (1.1%)
GNRI	89.6 (82.5-96.7)	119 (6.3%)
Malnutrition (GNRI<82)	421 (23.9%)	
Systolic BP, mmHg	115±12.7	1 (0.05%)
Diastolic BP, mmHg	62.9±12.4	2 (0.1%)
NYHA class≥3	186 (10.0%)	12 (0.6%)
GWTG-Heart failure risk score	42 (37-47)	4 (0.2%)
Comorbidities		
Atrial fibrillation	827 (44.0%)	0
Hypertension	1223 (66.6%)	0
Diabetes	553 (29.4%)	0
Dyslipidemia	688 (36.6%)	0
Hyperuricemia	496 (27.0%)	47 (2.5%)
Previous stroke	252 (13.4%)	0
Anemia	1246 (66.5%)	8 (0.4%)
Chronic kidney disease	1460 (77.6%)	0
COPD/asthma	92 (4.9%)	0
Malignant tumor	30 (1.6%)	0
Dementia	196 (10.4%)	0
Number of morbidities	4 (3-5)	-
Multimorbidity	1089 (57.9%)	-

Echocardiography		
LVDd, mm	50.3±9.28	0
LVDs, mm	38.3±11.1	0
LVEF, %	46.2±15.3	0
LA diameter, mm	43.9±8.93	0
Etiology		
Ischemic cardiomyopathy	503 (26.7%)	0
Dilated cardiomyopathy	182 (9.7%)	0
Hypertrophic cardiomyopathy	39 (2.1%)	0
Valvular heart disease	514 (27.3%)	0
Others	643 (34.2%)	0
Examinations (at discharge)		
Hemoglobin, g/dL	11.7±2.01	8 (0.4%)
eGFR, mL/min/1.73m^2	45.5 (33.2-58.6)	0
Na, mEq/L	139 (137-141)	8 (0.4%)
K, mEq/L	4.3 (4.0-4.7)	7 (0.4%)
BNP, pg/mL	277 (144-520)	749 (39.8%)
NT-pro BNP, pg/mL	1898 (997-4646)	
Medications (discharge), %		
beta-blocker	1354 (72.0%)	0
ACE-I/ARB	1052 (55.9%)	0
MRA	721 (38.4%)	0
Loop-diuretics	1590 (84.5%)	0
Thiazide-diuretic	58 (3.1%)	0
Digitalis	79 (4.2%)	0
SGLT-2 inhibitor	121 (6.4%)	0
Oral anticoagulant	1098 (58.4%)	0
Antiplatelet agent	750 (39.9%)	0
Statin	822 (43.7%)	0

Values are mean (SD), median (interquartile range), or n (%). ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-cholesterol,

low density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction.

Table S2. Variables for the latent class analysis

Category	Variables	Type of variables
Demographic	Age	Continuous
	Male/Female	Categorical
	Smoking status	Categorical
	Living alone	Categorical
Comorbidity	Hypertension	Categorical
	Diabetes	Categorical
	Atrial fibrillation	Categorical
	Dyslipidemia	Categorical
	Hyperuricemia	Categorical
	Previous stroke	Categorical
	COPD/asthma	Categorical
	Malignant tumor	Categorical
	eGFR (renal function)	Continuous
	Hemoglobin (anemia)	Continuous
Physical function	Clinical frailty scale	Ordinal
Cognitive status	Dementia	Categorical
Nutrition status	GNRI	Continuous

COPD, chronic obstructive pulmonary disease; GNRI, geriatric nutritional risk index.

Table S3. Bayesian information criterion values per number of clusters

(A) non-HFpEF

Number of clusters	Bayesian information criterion
2	23374
3	23344
4	23348
5	23362
6	23381
7	23400
8	23420

(B) HFpEF

Number of clusters	Bayesian information criterion
2	18204
3	18187
4	18193
5	18207
6	18223
7	18243
8	18257

Table S4. The discriminative power ranking

(A) non-HFpEF

Variables	Discriminative power
Hemoglobin	369.9
Estimated glomerular filtration rate	293.3
The geriatric nutritional risk index	225.3
Clinical frailty scale	41.9
Hyperuricemia	29.2
Smoking	9.2
Dementia	7.4
Living alone	1.8
Gender	1.7
Atrial fibrillation	0.04

(B) HFpEF

Variables	Discriminative power
Hemoglobin	324.8
Estimated glomerular filtration rate	282.5
The geriatric nutritional risk index	136.4
Hyperuricemia	20.2
Clinical frailty scale	11.4

Table S5. A weighted Cox proportional-hazard model based on for clinical outcomes the probability for membership in each of the three phenogroups

(A) non-HFpEF

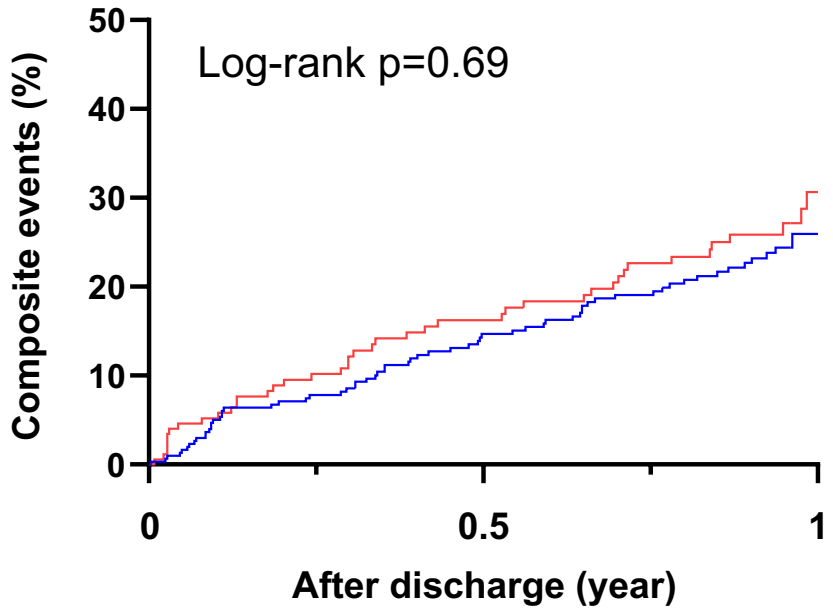
	Hazard Ratio	95% CI	P-value
All-cause death			
Group 3 (Cachexia)	2.91	1.63–5.20	<0.001
Group 2 (Systemic Impairment)	2.06	1.30–3.29	0.002
Group 1 (Robust)		Reference	
Composite events			
Group 3 (Cachexia)	1.64	1.13–2.39	0.010
Group 2 (Systemic Impairment)	1.45	1.12–1.89	0.005
Group 1 (Robust)		Reference	

(B) HFpEF

	Hazard Ratio	95% CI	P-value
All-cause death			
Group 3 (Cachexia)	2.38	1.19–4.74	0.013
Group 2 (Systemic Impairment)	2.43	1.38–4.27	0.002
Group 1 (Robust)		Reference	
Composite events			
Group 3 (Cachexia)	1.20	0.76–1.90	0.43
Group 2 (Systemic Impairment)	1.55	1.14–2.10	0.005
Group 1 (Robust)		Reference	

CI, confidence interval.

Figure S1.

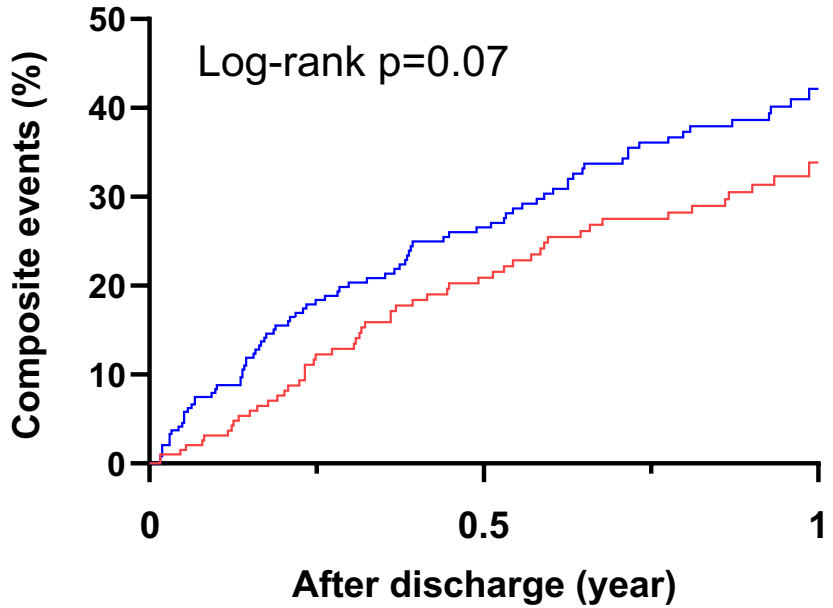


Number at risk

GDMT (+)	310	252	219	195	60
GDMT (-)	175	142	122	105	30

Figure S1. Incidence of composite events of all-cause death and HF rehospitalization according to the use of GDMT in non-HFpEF patients with the Robust group
GDMT, guideline-directed medical therapy; HF heart failure; HFpEF, heart failure with preserved ejection fraction.

Figure S2.

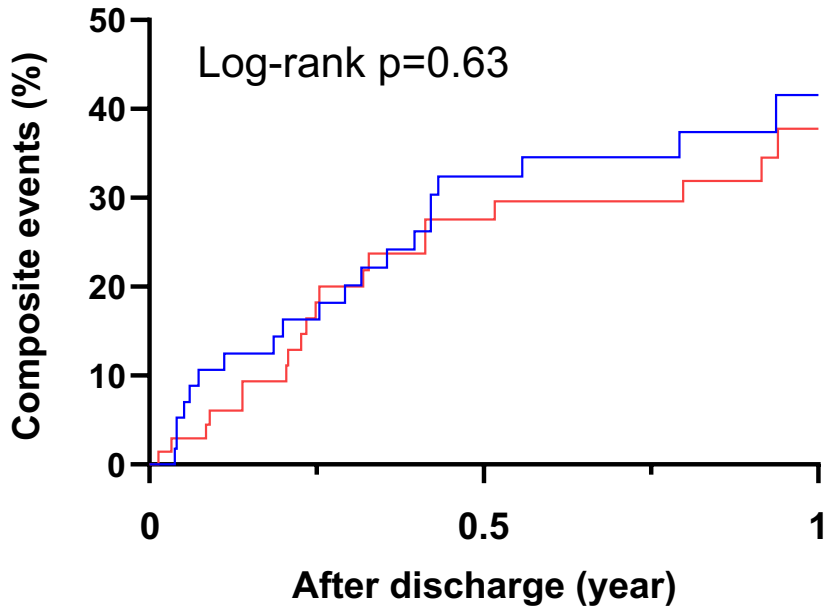


Number at risk

GDMT (+)	199	152	123	102	30
GDMT (-)	243	171	139	107	43

Figure S2. Incidence of composite events of all-cause death and HF rehospitalization according to the use of GDMT in non-HFpEF patients with the Systemic Impairment group
GDMT, guideline-directed medical therapy; HF heart failure; HFpEF, heart failure with preserved ejection fraction.

Figure S3.



Number at risk					
GDMT (+)	59	45	33	26	5
GDMT (-)	69	47	38	32	11

Figure S3. Incidence of composite events of all-cause death and HF rehospitalization according to the use of GDMT in non-HFpEF patients with the Cachexia group
GDMT, guideline-directed medical therapy; HF heart failure; HFpEF, heart failure with preserved ejection fraction.