SHORT COMMUNICATION

Minimal subphenotyping model for acute heart failure with preserved ejection fraction

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Abstract

Aims   Application of the latent class analysis to acute heart failure with preserved ejection fraction (HFpEF) showed that the heterogeneous acute HFpEF patients can be classified into four distinct phenotypes with different clinical outcomes. This model-based clustering required a total of 32 variables to be included. However, this large number of variables will impair the clinical application of this classification algorithm. This study aimed to identify the minimal number of variables for the development of optimal subphenotyping model.

Methods and results   This study is a *post hoc* analysis of the PURSUIT-HFpEF study (*N* = 1095), a prospective, multi-referral centre, observational study of acute HFpEF [UMIN000021831]. We previously applied the latent class analysis to the PURSUIT-HFpEF dataset and established the full 32-variable model for subphenotyping. In this study, we used the Cohen's kappa statistic to investigate the minimal number of discriminatory variables needed to accurately classify the phenogroups in comparison with the full 32-variable model. Cohen's kappa statistic of the top-X number of discriminatory variables compared with the full 32-variable derivation model showed that the models with ≥16 discriminatory variables showed kappa value of >0.8, suggesting that the minimal number of discriminatory variables for the optimal phenotyping model was 16. The 16-variable model consists of C-reactive protein, creatinine, gamma-glutamyl transferase, brain natriuretic peptide, white blood cells, systolic blood pressure, fasting blood sugar, triglyceride, clinical scenario classification, infection-triggered acute decompensated HF, estimated glomerular filtration rate, platelets, neutrophils, GWTG-HF (Get With The Guidelines-Heart Failure) risk score, chronic kidney disease, and CONUT (Controlling Nutritional Status) score. Characteristics and clinical outcomes of the four phenotypes subclassified by the minimal 16-variable model were consistent with those by the full 32-variable model. The four phenotypes were labelled based on their characteristics as 'rhythm trouble', 'ventricular-arterial uncoupling', 'low output and systemic congestion', and 'systemic failure', respectively.

Conclusions   The phenotyping model with top 16 variables showed almost perfect agreement with the full 32-variable model. The minimal model may enhance the future clinical application of this clustering algorithm.

Background

Few evidence-based medical therapies for heart failure with preserved ejection fraction (HFpEF) have been established. One reason for this may be the multifactorial pathophysiology of the disease, which involves impairments in cardiac, vascular, and peripheral reserve caused by common risk factors such as aging, adiposity, hypertension, and metabolic stress.[1] This pathophysiological heterogeneity makes the conventional 'one-size-fits-all' approach difficult. In order to identify some distinct phenogroups, unsupervised machine learning technique was first applied to chronic HFpEF.[2,3] We recently applied the technique to acute HFpEF and found that the heterogeneous acute HFpEF patients can be classified into four distinct phenotypes with different clinical outcomes[4]: Phenotypes 1–4 were labelled based on group characteristics as 'rhythm trouble', 'ventricular-arterial uncoupling', 'low output and systemic congestion', and 'systemic failure', respectively. A total of 32 variables were selected by the latent class analysis for the best subphenotyping model. However, the large number of variables will impair the clinical application of this classification algorithm.

Aims

This study aimed to identify the minimal phenotyping model to accurately and comparably subclassify acute decompensated HFpEF patients to the full 32-variable model.

Methods

The present study is a post-hoc analysis of the database of the **P**rospective m**U**lticente**R** ob**S**ervational st**U**dy of pat**I**en**T**s with **H**eart **F**ailure with **p**reserved **E**jection **F**raction (PURSUIT-HFpEF) study (*N* = 1095), a prospective, multi-referral centre, observational study [UMIN-CTR ID: UMIN000021831].[4–6] Consecutive patients with acute decompensated heart failure and preserved ejection fraction (≥50%) were prospectively registered. Acute decompensated heart failure was diagnosed on the basis of the following criteria: (i) clinical symptoms and signs according to the Framingham Heart Study criteria[7]; and (ii) a serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of ≥400 pg/mL or brain natriuretic peptide (BNP) level of ≥100 pg/mL. Basic patient characteristics, echocardiography, laboratory tests, and lists of medications were obtained on admission, at discharge, and at each annual follow-up time point. The study conformed to the ethical guidelines outlined in the Declaration of Helsinki and the study protocol was approved by the ethics committee of each participating hospital. All patients provided written informed consent for participation in this study.

We applied the latent class analysis ('VarSelLCM' package in R 4.0.5) to the PURSUIT-HFpEF dataset.[4] A total of 160 variables on hospital admission were considered as primary candidates for latent class analysis, and finally the latent class analysis selected 32 variables for the best model. In the present study, we used the Cohen's kappa statistic to investigate the minimal number of discriminatory variables needed to accurately classify the phenogroups in comparison with the full 32-model with the 'irr' package. The Cohen's kappa statistic is an inter-rater reliability metric that takes into consideration the possibility of agreement by chance. Scores range from

Figure 1 Cohen's kappa statistic of the top-X number of discriminatory variables compared with the full 32-variable derivation model. Kappa value >0.8 indicates almost perfect agreement (horizontal dotted line). The minimal number of discriminatory variables for the optimal phenotyping model was 16.
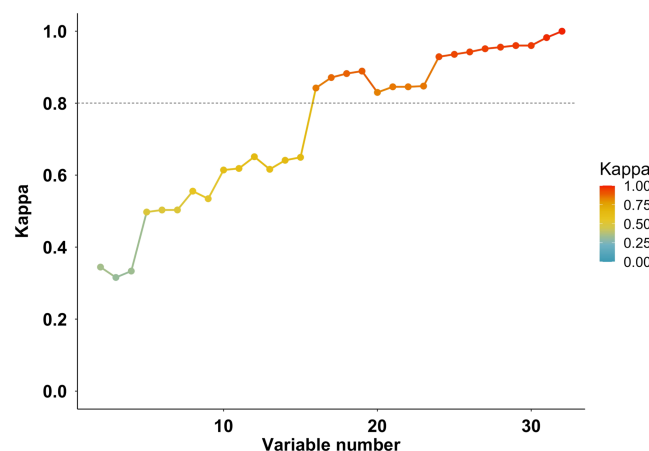
−1 to +1 and a score greater than 0.80 indicates almost perfect agreement.[8] The dataset of the PURSUIT-HFpEF study (2016–2020) was categorized based on enrollment period into a derivation cohort (*N* = 623) to construct a subphenotyping model and a validation cohort (*N* = 472) to assess the validity of the model. Risk of the clinical outcomes across the phenogroups was assessed in a time-to-first-event fashion with the Kaplan–Meier method and compared with the log-rank test and Cox proportional hazards model ('survival' package). The proportional hazards assumption of the phenogroups for the primary endpoint was confirmed by Schoenfeld residuals (*P* = 0.13).

Results

Cohen's kappa statistic of the top-X number of discriminatory variables compared with the full 32-variable derivation model is presented in *Figure 1*. The models with ≥16 discriminatory variables showed kappa value of >0.8 (almost perfect agreement), indicating that the minimal number of discriminatory variables for the optimal phenotyping model was 16. The 16-variable model consists of C-reactive protein, creatinine,

gamma-glutamyl transferase, brain natriuretic peptide, white blood cells, systolic blood pressure, fasting blood sugar, triglyceride, clinical scenario classification,[9] infection-triggered acute decompensated HF, estimated glomerular filtration rate, platelets, neutrophils, GWTG-HF (Get With The Guidelines-Heart Failure) risk score,[10] chronic kidney disease, and CONUT (Controlling Nutritional Status) score[11] (*Table 1*). The following variables in the full model were excluded from this minimal model: uric acid, low-density lipoprotein cholesterol, uncontrollable hypertension-triggered hospital admission, age, sodium, atrial fibrillation, HF hospitalization history, the ratio of mitral peak velocity of early filling E to the velocity of mitral annulus early diastolic motion e', total bilirubin, rhythm on admission, arrhythmia-triggered hospital admission, haemoglobin, hyperuricemia, diabetes mellitus, left ventricular mass index, and plasma volume status.[12]

Characteristics of phenotypes subclassified by the minimal model are summarized in *Table 2*. Clinical outcome data are illustrated in *Figure 2* and *Figure 3*. Like the original paper,[4] Groups 1–4 may be labelled based on group characteristics as 'rhythm trouble', 'ventricular-arterial uncoupling', 'low output and systemic congestion', and 'systemic failure', respectively. In Group 1 'rhythm trouble', arrhythmia triggering was the frequent reason for acute worsening of HF. Diabetes

Table 1 Variables for the minimal optimal phenotyping model

Number	Features	Type of data	Unit[a]/Options[b]	Discriminative power[c]
1	C-reactive protein	Continuous	mg/dL	794.6
2	Creatinine	Continuous	mg/dL	480.8
3	Gamma-glutamyl transferase	Continuous	IU/L	277.6
4	Brain natriuretic peptide	Continuous	pg/mL	274.5
5	White blood cells	Continuous	$\times 10^3/\mu L$	142.4
6	Systolic blood pressure	Continuous	mmHg	114.2
7	Fasting blood sugar	Continuous	mg/dL	114.0
8	Triglyceride	Continuous	mg/dL	108.1
9	Clinical scenario classification[d]	Nominal	CS1/CS2/CS3/CS4/CS5	80.8
10	Trigger of acute decompensated HF: infection	Nominal	yes/no	77.0
11	Estimated glomerular filtration rate	Continuous	mL/min/1.73 m^2	73.5
12	Platelets	Continuous	$\times 10^4/\mu L$	56.9
13	Neutrophils	Continuous	%	46.8
14	GWTG-HF risk score[e]	Continuous	N/A	46.5
15	Chronic kidney disease[f]	Nominal	yes/no	43.4
16	CONUT score[g]	Ordinal	0–12	33.9

CONUT, Controlling Nutritional Status[11]; CS, clinical scenario[9]; GWTG-HF, Get With The Guidelines-Heart Failure[10]; HF, heart failure; N/A, not applicable.
Variables are listed in descending order of discriminative power.
[a]Unit for continuous value.
[b]Options for nominal or ordinal values.
[c]We computed the discriminative power of each variable as the logarithm of the ratio between the probability that the variable is relevant for clustering versus the probability that it is irrelevant for clustering.
[d]Clinical scenario is a classification system considering the systolic blood pressure and other symptoms: (CS1) dyspnoea and/or congestion with systolic blood pressure >140 mm Hg; (CS2) dyspnoea and/or congestion with systolic blood pressure 100–140 mm Hg; (CS3) dyspnoea and/or congestion with systolic blood pressure <100 mm Hg; (CS4) dyspnoea and/or congestion with signs of acute coronary syndrome; and (CS5) isolated right ventricular failure.
[e]GWTG-HF risk score is a scoring system that can predict in-hospital mortality in patients with preserved or impaired left ventricular systolic function using seven following clinical factors: age, systolic blood pressure, blood urea nitrogen, heart rate, sodium, chronic obstructive pulmonary disease, and nonblack race.[10]
[f]Chronic kidney disease is defined as kidney damage and/or glomerular filtration rate <60 mL/min/1.73 m^2 for 3 months or more. Kidney damage can be ascertained by the presence of albuminuria or proteinuria, defined as albuminuria >30 mg/gCr or proteinuria >0.15 g/gCr.
[g]CONUT score is a tool to identify undernourished patients. The score consists of serum albumin, total cholesterol, and lymphocyte counts.

Table 2 Characteristics of phenotypes in the derivation and validation cohorts

	Derivation cohort (N = 623)				
	Group 1 'Rhythm trouble'	Group 2 'Ventricular-arterial uncoupling'	Group 3 'Low output and systemic congestion'	Group 4 'Systemic failure'	P value
Patient number	230	71	154	168	
Baseline characteristics					
Age, years	81.50 [76.00, 86.00]	77.00 [72.00, 83.00]	82.00 [78.00, 87.00]	84.00 [77.00, 89.00]	<0.001
Female sex	133 (57.8)	36 (50.7)	79 (51.3)	85 (50.6)	0.42
Clinical scenario classification					<0.001
CS 1	152 (66.1)	69 (97.2)	20 (13.0)	87 (51.8)	
CS 2	73 (31.7)	2 (2.8)	126 (81.8)	79 (47.0)	
CS 3	3 (1.3)	0 (0.0)	5 (3.2)	2 (1.2)	
CS 5	2 (0.9)	0 (0.0)	3 (1.9)	0 (0.0)	
Infection-triggered hospitalization	12 (5.2)	7 (9.9)	11 (7.1)	93 (55.4)	<0.001
Arrhythmia-triggered hospitalization	83 (36.1)	11 (15.5)	49 (31.8)	22 (13.1)	<0.001
Systolic blood pressure, mmHg	153.50 [133.50, 170.00]	191.00 [170.50, 209.00]	128.00 [117.25, 138.00]	141.00 [126.75, 157.25]	<0.001
Heart rate, b.p.m.	84.50 [69.25, 104.75]	90.00 [71.50, 109.00]	75.00 [61.25, 91.00]	80.00 [68.75, 97.25]	<0.001
Atrial fibrillation on admission	117 (50.9)	6 (8.5)	79 (51.3)	66 (39.3)	<0.001
Hypertension	193 (83.9)	65 (91.5)	126 (81.8)	146 (86.9)	0.229
Diabetes mellitus	56 (24.3)	40 (56.3)	48 (31.2)	66 (39.3)	<0.001
Dyslipidaemia	84 (36.5)	42 (59.2)	65 (42.2)	68 (40.5)	0.009
Chronic kidney disease	38 (16.5)	46 (64.8)	92 (59.7)	69 (41.1)	<0.001
White blood cell, $\times10^3$/μL	6.00 [5.00, 7.40]	8.80 [6.10, 11.55]	5.70 [4.60, 6.90]	8.90 [6.57, 11.03]	<0.001
Neutrophil, %	67.00 [61.00, 74.00]	69.00 [60.00, 76.00]	71.00 [63.00, 76.00]	78.00 [72.00, 84.00]	<0.001
Haemoglobin, g/dL	11.80 [10.53, 13.20]	11.00 [9.60, 12.10]	10.60 [9.50, 12.20]	10.90 [9.38, 12.10]	<0.001
Platelets, $\times10^4$/μL	19.10 [14.90, 23.82]	21.10 [16.40, 26.95]	16.25 [13.15, 20.58]	20.80 [16.17, 26.52]	<0.001
Creatinine, mg/dL	0.90 [0.70, 1.10]	1.80 [1.10, 3.80]	1.50 [1.20, 1.87]	1.10 [0.80, 1.60]	<0.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	54.10 [44.62, 68.60]	23.70 [11.90, 40.95]	30.50 [22.10, 42.15]	44.22 [28.40, 57.83]	<0.001
Albumin, g/dL	3.70 [3.40, 3.90]	3.50 [3.00, 3.80]	3.50 [3.20, 3.90]	3.30 [3.00, 3.50]	<0.001
γ-glutamyl transferase, IU/L	41.02 [23.00, 69.00]	30.00 [17.50, 50.08]	50.49 [25.00, 116.00]	38.00 [22.75, 68.00]	<0.001
Brain natriuretic peptide, pg/mL	451.95 [304.17, 605.18]	952.00 [447.80, 1842.10]	490.65 [319.53, 805.44]	462.16 [281.25, 653.02]	<0.001
C-reactive protein, mg/dL	0.32 [0.14, 0.69]	0.32 [0.14, 1.27]	0.50 [0.17, 1.19]	5.16 [2.39, 10.13]	<0.001
Triglyceride, mg/dL	72.00 [55.25, 93.00]	118.00 [81.00, 155.50]	76.50 [57.00, 110.00]	72.00 [56.00, 88.25]	<0.001
Fasting blood sugar, mg/dL	113.05 [99.25, 134.75]	162.00 [119.00, 223.50]	120.50 [104.00, 145.50]	137.50 [112.75, 187.50]	<0.001
GWTG HF risk score	37.00 [33.00, 42.00]	34.31 [31.00, 37.98]	43.00 [40.00, 47.00]	41.00 [37.00, 46.00]	<0.001
CONUT score	3.00 [2.00, 4.00]	3.00 [2.00, 5.00]	4.00 [3.00, 6.00]	5.00 [4.00, 6.00]	<0.001
Left ventricular mass index	96.00 [83.26, 116.19]	119.77 [96.21, 142.82]	98.13 [80.01, 118.82]	98.09 [82.40, 115.85]	<0.001
Clinical outcomes					
Follow up: 749 [531, 1091] days					
Death or heart failure readmission	89 (38.7)	32 (45.1)	96 (62.3)	81 (48.2)	<0.001
Cardiac death	15 (6.5)	5 (7.0)	27 (17.5)	21 (12.5)	0.005
Noncardiac death	30 (13.0)	8 (11.3)	27 (17.5)	31 (18.5)	0.302
Heart failure readmission	58 (25.4)	26 (37.1)	69 (46.3)	39 (25.2)	<0.001

CONUT, Controlling Nutritional Status[11]; CS, clinical scenario[9]; GWTG-HF, Get With The Guidelines-Heart Failure.[10]
Data are expressed as median [interquartile range] or number (percentage).

Table 2 (continued)

	Validation cohort (N = 472)				
	Group 1 'Rhythm trouble'	Group 2 'Ventricular-arterial uncoupling'	Group 3 'Low output and systemic congestion'	Group 4 'Systemic failure'	P value
Patient number	201	74	92	105	
Baseline characteristics					
Age, years	83.00 [78.00, 88.00]	82.00 [72.00, 86.00]	84.50 [81.00, 89.00]	83.00 [77.00, 88.00]	0.003
Female sex	125 (62.2)	39 (52.7)	44 (47.8)	60 (57.1)	0.116
Clinical scenario classification					<0.001
CS 1	144 (71.6)	69 (93.2)	23 (25.0)	53 (50.5)	
CS 2	53 (26.4)	5 (6.8)	66 (71.7)	47 (44.8)	
CS 3	4 (2.0)	0 (0.0)	3 (3.3)	5 (4.8)	
CS 5					
Infection-triggered hospitalization	7 (3.5)	11 (14.9)	5 (5.4)	49 (46.7)	<0.001
Arrhythmia-triggered hospitalization	66 (32.8)	17 (23.0)	31 (33.7)	22 (21.0)	0.070
Systolic blood pressure, mmHg	156.00 [138.00, 170.00]	181.00 [166.25, 207.75]	127.50 [113.00, 142.00]	141.00 [122.00, 163.00]	<0.001
Heart rate, b.p.m.	78.00 [63.00, 97.00]	86.00 [73.25, 104.75]	76.00 [58.75, 92.00]	95.00 [78.00, 107.00]	<0.001
Atrial fibrillation on admission	95 (47.3)	19 (25.7)	54 (58.7)	64 (61.0)	<0.001
Hypertension	160 (79.6)	73 (98.6)	75 (81.5)	91 (86.7)	0.001
Diabetes mellitus	46 (22.9)	36 (48.6)	31 (33.7)	39 (37.1)	<0.001
Dyslipidaemia	77 (38.3)	38 (51.4)	39 (42.4)	43 (41.0)	0.281
Chronic kidney disease	40 (19.9)	55 (74.3)	57 (62.0)	38 (36.2)	<0.001
White blood cell, $\times 10^3/\mu L$	6.00 [4.70, 6.90]	8.55 [6.67, 10.97]	5.65 [4.60, 6.60]	9.00 [6.90, 11.30]	<0.001
Neutrophil, %	68.00 [61.00, 74.00]	71.33 [57.00, 76.00]	69.00 [64.00, 75.00]	79.00 [73.00, 85.00]	<0.001
Haemoglobin, g/dL	11.80 [10.20, 12.80]	10.70 [9.70, 13.15]	10.65 [9.17, 12.00]	11.30 [9.90, 12.50]	0.005
Platelets, $\times 10^4/\mu L$	18.60 [14.90, 23.50]	20.65 [17.60, 26.28]	16.70 [14.00, 20.80]	20.00 [15.30, 27.10]	<0.001
Creatinine, mg/dL	0.90 [0.70, 1.00]	1.70 [1.02, 2.90]	1.40 [1.10, 1.83]	1.10 [0.80, 1.40]	<0.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	53.80 [44.80, 62.30]	25.35 [13.62, 41.15]	31.25 [24.48, 38.95]	42.00 [32.40, 60.40]	<0.001
Albumin, g/dL	3.70 [3.40, 3.90]	3.50 [3.32, 3.72]	3.50 [3.20, 3.80]	3.20 [2.90, 3.60]	<0.001
γ-glutamyl transferase, IU/L	39.00 [24.00, 63.00]	30.00 [21.25, 45.94]	43.00 [20.00, 111.25]	35.00 [23.00, 82.00]	0.069
Brain natriuretic peptide, pg/mL	465.00 [308.40, 600.70]	677.14 [456.28, 1029.05]	500.00 [273.45, 745.16]	484.10 [341.00, 702.00]	<0.001
C-reactive protein, mg/dL	0.25 [0.10, 0.58]	0.62 [0.23, 1.77]	0.34 [0.14, 1.13]	4.13 [2.46, 8.25]	<0.001
Triglyceride, mg/dL	75.00 [56.00, 95.42]	101.00 [83.00, 147.50]	74.35 [54.00, 98.75]	71.00 [55.00, 92.36]	<0.001
Fasting blood sugar, mg/dL	117.00 [103.00, 137.00]	166.50 [112.25, 229.25]	117.00 [103.00, 157.00]	148.00 [112.00, 191.00]	<0.001
GWTG HF risk score	37.00 [33.00, 41.00]	35.00 [32.00, 39.00]	45.00 [41.00, 48.25]	43.00 [37.00, 48.00]	<0.001
CONUT score	3.00 [2.00, 4.02]	3.00 [1.00, 4.00]	4.00 [3.00, 6.00]	5.00 [3.00, 7.00]	<0.001
Left ventricular mass index	96.64 [82.84, 115.48]	112.47 [99.96, 137.40]	96.54 [77.36, 113.93]	94.26 [77.35, 111.59]	<0.001
Follow up: 327.5 [18.75, 390.25] days					
Clinical outcomes					
Death or heart failure readmission	30 (14.9)	17 (23.0)	25 (27.2)	22 (21.0)	0.083
Cardiac death	4 (2.0)	3 (4.1)	9 (9.8)	5 (4.8)	0.028
Noncardiac death	7 (3.5)	8 (10.8)	3 (3.3)	9 (8.6)	0.045
Heart failure readmission	25 (20.2)	10 (22.7)	18 (30.0)	12 (17.6)	0.355

CONUT, Controlling Nutritional Status[11]; CS, clinical scenario[9]; GWTG-HF, Get With The Guidelines-Heart Failure.[10]
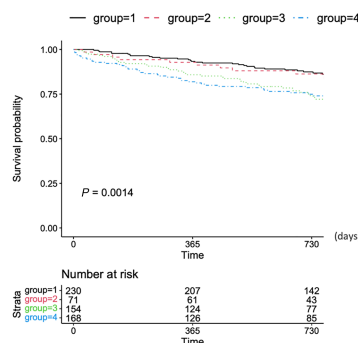Data are expressed as median [interquartile range] or number (percentage).

Figure 2 Kaplan–Meier analysis. Survival analysis using the Kaplan Meier method for (A, D) a composite of all-cause death and HF readmission, (B, E) all-cause death, and (C, F) HF readmission in the derivation cohort (upper panel) and the validation cohort (lower panel). *Analysis was carried out with patients who survived to discharge and had follow-up data after discharge. HF, heart failure.
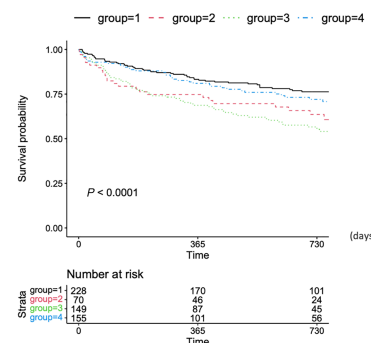
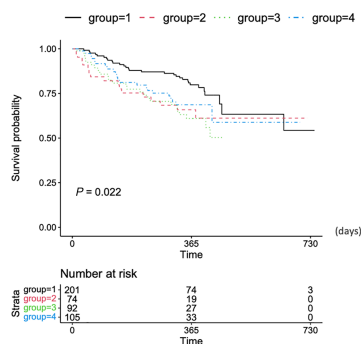## Derivation cohort
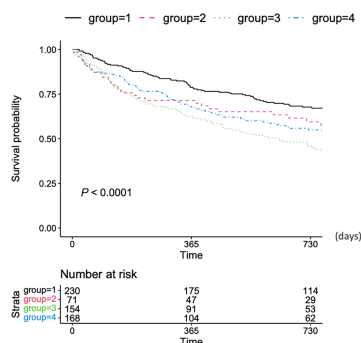
(A) **All-cause death or HF readmission** (B) **All-cause death** (C) **HF readmission***

Validation cohort

(D) **All-cause death or HF readmission** (E) **All-cause death** (F) **HF readmission***
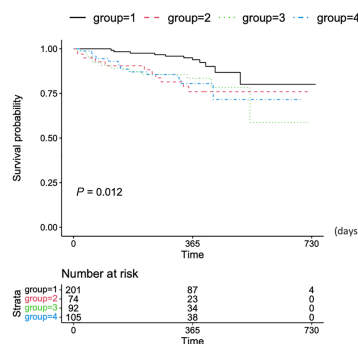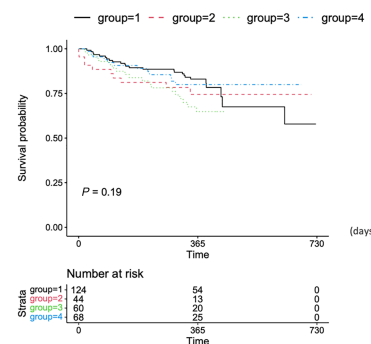
Figure 3 Association between phenogroups and clinical outcomes. Forest plots show risks in each phenogroup with reference to group 1 for the primary and secondary end points. The derivation cohort (A) and the validation cohort (B) showed similar results. HF, heart failure; ref, reference.
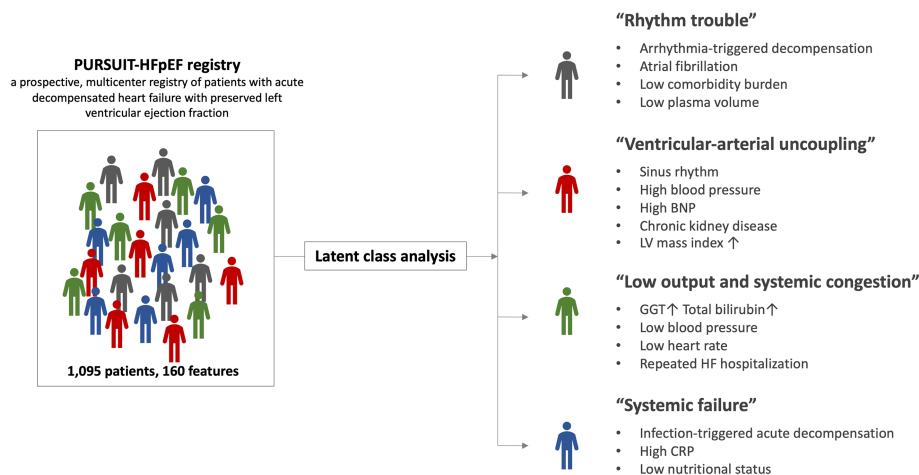

(A) Derivation cohort (2016-2018; n = 623)

All-cause death or HF readmission		
Group 1		Ref.
Group 2	1.37 (0.91,2.05)	0.130
Group 3	1.99 (1.49,2.65)	<0.001
Group 4	1.43 (1.06,1.93)	0.021
All-cause death		
Group 1		Ref.
Group 2	0.96 (0.52,1.78)	0.897
Group 3	1.96 (1.32,2.92)	0.001
Group 4	1.74 (1.17,2.60)	0.007
HF readmission		
Group 1		Ref.
Group 2	1.71 (1.07,2.71)	0.024
Group 3	2.19 (1.54,3.10)	<0.001
Group 4	1.07 (0.71,1.61)	0.734
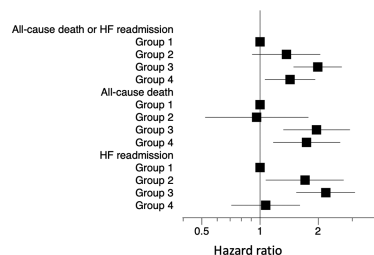
(B) Validation cohort (2019-2020; n = 472)

All-cause death or HF readmission		
Group 1		Ref.
Group 2	2.06 (1.13,3.75)	0.018
Group 3	2.10 (1.23,3.59)	0.006
Group 4	1.57 (0.91,2.73)	0.108
All-cause death		
Group 1		Ref.
Group 2	3.53 (1.52,8.19)	0.003
Group 3	2.51 (1.11,5.70)	0.027
Group 4	2.76 (1.25,6.08)	0.012
HF readmission		
Group 1		Ref.
Group 2	1.46 (0.70,3.05)	0.313
Group 3	1.88 (1.02,3.47)	0.043
Group 4	1.08 (0.54,2.17)	0.821
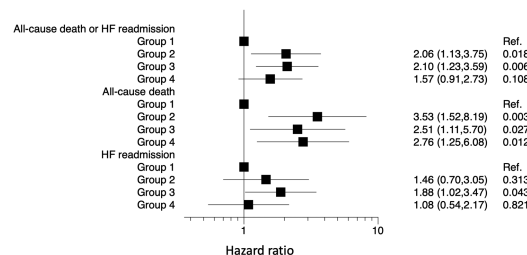
mellitus, chronic kidney disease and dyslipidaemia were less frequently observed, showing a lower comorbidity burden in this group. Group 2 'ventricular-arterial uncoupling' was characterized by sinus rhythm on admission but the highest BNP level among the groups. Clinical scenario 1 was the most frequent presentation on hospital admission.[9] Diabetes and chronic kidney disease were more frequently observed in this group, and they had the highest left ventricular mass index.

Group 3 'low output and systemic congestion' showed the highest level of γ-glutamyl transferase at initial presentation. Blood pressure and heart rate on hospital admission were lowest among the groups. Most of the patients in this group showed clinical scenario 2 on hospital admission. Group 4 'systemic failure' was characterized by high C-reactive protein, infection-triggered hospitalization, and the impaired nutritional status. During the follow-up period, a composite of death or heart failure hospitalization occurred most frequently in Group 3. These group features were almost consistent across the derivation and validation cohorts. The overall results were similar between the subclassification by the original full-model and the present minimal model.[4]

Conclusions

We recently reported four distinct phenotypes of acute decompensated HFpEF subclassified by the latent class analysis.[4] We have established the subclassification machine-learning-based algorithm consisting of the 32 variables. In this study, minimal model with 16 variables showed the comparable subclassification performance to the full 32-variable model.

Cohen's kappa statistically confirmed the comparable performance of the minimal model, which was further confirmed by the descriptive statistics of each phenotype. Characteristics and clinical outcomes were consistent across the full model and the current minimal model. The latent class analysis offers a stochastic modelling and can provide probability of each cluster membership, which allows prospective clinical application of the clustering model. Variables in the minimal model (*Table 1*) are all basic laboratory parameters and vital signs. Although we included various echocardiographic parameters as candidates for the clustering variables, no echocardiographic parameters remained after the selection process of the latent class analysis. Furthermore, although one of the phenotypes is characterized by rhythm disorder, no electrocardiogram data remained in the final model. We speculate that the basic laboratory data and vital signs may represent such detailed hemodynamic parameters. This minimal model does not require electrocardiogram and echocardiographic assessment. Subphenotyping can be done only with medical interview and blood sampling test, which will further enhance the clinical application also in the area with limited medical resources.

Our final goal is the establishment of a phenotype-specific treatment strategy for acute HFpEF. *Figure 4* illustrates specific characteristics of the four phenotypes. Different phenotypes may have different underlying pathophysiology (previously described in detail[4]), suggesting that specific effective treatment may exist in each phenotype. To achieve the goal, we need to conduct a prospective randomized study to evaluate a possible phenotype-specific treatment for a certain phenogroup. The minimal model established in this study will be the basis of future studies. Authors are planning to create an online tool based on the clustering model so that physicians can easily assess which phenotype a patient belongs to with the 16 variables. The website will be available soon.

The most important limitation of the present model is its generalizability. The differing healthcare system and the dietary and social differences in Japan compared with other countries would limit the generalizability of the findings to

other regions and ethnicities.[13,14] Furthermore, the derivation cohort of the phenotyping model consisted of very elderly patients (median age; 82 years), which may impair the applicability of the model to younger HFpEF patients.

In conclusion, the phenotyping model with top-16 variables showed almost perfect agreement with the full 32-variable model. The minimal model may enhance the future clinical application of this clustering algorithm. Our next scientific topic is to prospectively evaluate specific candidate treatments for each phenotype categorized by this minimal phenotyping model.

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Conflict of interest

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