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Phenomapping in patients experiencing worsening renal function during hospitalization for acute heart failure

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Abstract

Aims   The impact of worsening renal function (WRF) on the prognosis of patients with acute heart failure (AHF) remains controversial. We aimed to identify phenotypically distinct subgroups among individuals with both AHF and WRF using cluster analysis.
Methods and results   Overall, the data of 483 patients with both AHF and WRF enrolled in the West Tokyo Heart Failure Registry were analysed. Using cluster analysis, we identified three phenotypically distinct subgroups (phenogroups 1, 2, and 3). We assessed the impact of WRF on the prognosis of each phenogroup by comparing the incidence of composite endpoints, including all-cause death and re-hospitalization due to heart failure, with those of a propensity score-matched, non-WRF control group. Participants in phenogroup 1 (N = 122) were the youngest (69.3 ± 13.7 years), had relatively preserved estimated glomerular filtration rate (eGFR, 70.0 ± 27.7 mL/min/1.73 m^2), and reduced left ventricular ejection fraction (LVEF) (41.8 ± 13.7%). Conversely, participants in phenogroup 3 (N = 122) were the oldest (81.7 ± 8.5 years), had the worst eGFR (33.0 ± 20.9 mL/min/1.73 m^2), and had preserved LVEF (51.7 ± 14.8%). The characteristics of the participants in phenogroup 2 (N = 239) were between those of phenogroups 1 and 3. The propensity score matching analysis showed that WRF was associated with a higher incidence of composite endpoints in phenogroup 1, whereas this association was not observed in phenogroups 2 and 3.
Conclusions   Using cluster analysis, we revealed three phenotypically distinct subgroups of patients with both AHF and WRF. WRF was associated with worse clinical outcomes in the subgroup of younger patients with reduced LVEF and preserved renal function.

Introduction

Worsening renal function (WRF) during acute management of heart failure is known to affect up to 30–50% of patients with acute heart failure (AHF).[1–4] However, the precise or individual impact of WRF on the prognosis of these patients remains controversial. WRF has been variably associated with worse, neutral, or even improved outcomes.[1–4] This variability is likely a product of different pathophysiologic processes driving alterations in renal function. Simultaneously, the

occurrence of WRF during treatment of AHF may affect important therapeutic decisions, such as continuation of decongestion or introduction of renin-angiotensin-aldosterone system inhibitors (RASI).[5] Therefore, identifying patients who are susceptible to the adverse effects of WRF is clinically important. Several studies have recently shown that phenotypic heterogeneity among patients with AHF, including differing left ventricular ejection fraction (LVEF) and haemodynamic status, exert different effects on the association between WRF and prognosis.[6–13] However, identification of each phenotype within both WRF and AHF remains a challenge.

Subgrouping patients with statistical clustering to reveal hidden phenotypic characteristics may be useful for elucidating this phenotypically heterogenic patient group.[14–16] Cohen et al. have successfully revealed several categorisations that have long been overseen by clinicians in patients with heart failure with preserved ejection fraction by applying the cluster technique.[17,18] To the best of our knowledge, no studies have applied this method to patients with both WRF and AHF. Herein, we aimed to identify phenotypically distinct subgroups in a cohort of individuals with AHF complicated by WRF using unsupervised cluster analysis. Furthermore, we assessed the impact of WRF on the prognosis of each phenogroup by comparing their clinical outcome with that of a propensity score-matched, non-WRF control group.

Methods

Study design

Patient data were obtained from the West Tokyo Heart Failure (WET-HF) Registry. Details of the registry have been previously reported.[19,20] This database is a multicentre, prospective cohort registry that includes data on the clinical backgrounds and outcomes of consecutive patients with acute decompensated heart failure (ADHF) requiring hospitalization from five high-volume hospital centres within the Tokyo metropolitan area (three university hospitals and two tertiary referral community hospitals) during the study period. ADHF was defined according to the Framingham AHF criteria. Patients who refused to participate in the registry and those with acute coronary syndrome were excluded. The treating cardiologists initially diagnosed AHF, and the diagnosis was then confirmed by at least one board-certified cardiologist at each institution. Baseline data and outcomes were collected by dedicated clinical research coordinators from medical records and interviews with treating physicians. Finally, two chief investigators inspected the reported data at least once a year to verify their quality. For this study, the data of patients registered between January 2006 and March

2017 were analysed. The patients were followed-up for a median duration of 724 days. The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by each centre's ethics review committee.[21] Written or oral informed consent was obtained from each participant before study inclusion.

Data collection

Data were collected during enrolment using a web-based form. Age, sex, blood pressure, heart rate, co-morbidities, body mass index (BMI), laboratory data, and echocardiographic data were collected. Within the first 48 h of admission, blood samples were obtained to measure laboratory variables. We used a formula to convert the value of N-terminal prohormone of the brain natriuretic peptide (NT-proBNP) to that of the brain natriuretic peptide (BNP): BNP = $10^{(\log10 \ (NT\text{-}proBNP) \ - \ 0.57/1.1)}$, for patients with only NT-proBNP results ($n = 208$).[22] The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.[23] Chronic kidney disease was defined as an eGFR of <60 mL/min/1.73 m^2. The follow-up duration for this analysis was 3 years after the discharge date from the index hospitalization. The endpoints were all-cause death and a composite of all-cause death and readmission due to worsening heart failure. Follow-up data were obtained from hospital records or by contacting the patients or referring physicians through mail or telephone. To ensure the accuracy of the ascertainment of endpoints, the WET-HF Registry is supported by a central study committee that examines the occurrence of each endpoint.

Statistical analysis

All statistical analyses were performed using SPSS version 24.0 (IBM, Corp, Armonk, NY). First, we conducted a two-step cluster analysis to determine phenogroups among patients with both AHF and WRF. We performed pre-clustering, where the programme used a sequential clustering approach to compress the sub-clusters to determine the desired number of clusters.[24] The programme then used the Bayesian information criterion (BIC) to determine the number of clusters. Finally, the programme grouped the sub-clusters from the first step into the determined number of clusters using the agglomerative hierarchical clustering method. Twenty-five continuous variables were considered potential candidates for clustering. Age, BMI, systolic blood pressure, diastolic blood pressure, heart rate, haemoglobin (Hb) concentration, blood urea nitrogen (BUN), serum sodium concentration, serum potassium concentration, plasma BNP concentration, and eGFR at admission and discharge were considered candidates for the cluster variables. Among the echocardiographic

parameters, we included the LVEF, left ventricular end-diastolic diameter, left ventricular end-systolic diameter (LVESD), and left atrial diameter. Among them, eight pairs with correlation coefficients >0.6 were filtered. In each pair, variables with larger numbers of missing values were excluded from the cluster analysis (BUN at discharge and admission, BMI at discharge, diastolic blood pressure at discharge, Hb concentration at discharge, eGFR at discharge, BNP at discharge, and LVESD). Ultimately, 17 variables were used for clustering. A heat map with standardized values of the phenotypic features across each phenogroup was generated for the hierarchical cluster analysis. Because the standardized values of the characteristics included in the study ranged mainly from −0.9 SD-1.2 SD, the key colour range was set from −1.2 SD-1.2 SD.

Second, to compare the prognosis in each phenogroup with that of patients without WRF who had similar phenotypes, the propensity score (PS) for WRF was calculated for each patient, including those without WRF, using a logistic regression model that included 17 covariates as independent variables and the occurrence of WRF as the dependent variable. A PS-matched cohort of patients without WRF was generated for each WRF phenogroup using 1:1 matching.

Lastly, we compared the differences in demographics, clinical characteristics at admission and discharge, echocardiographic findings, and long-term outcomes between the phenogroups, and between each phenogroup and the PS-matched, non-WRF control group.

The primary outcome for long-term prognosis was the incidence of composite endpoints, including both all-cause death and readmission due to worsening heart failure. The secondary outcome was the incidence of all-cause death. To compare long-term outcomes, we used the Kaplan–Meier curve, log-rank test, and the univariate and multivariate Cox proportional hazards model. Independent variables for the Cox proportional hazard analysis were defined according to the clinical characteristics and medications at discharge, which were not entered into the PS matching analysis. We conducted a power analysis to confirm the statistical power for the comparison of outcomes between the phenogroups, and between each phenogroup and its PS-matched, non-WRF cohort. The statistical power was calculated by fixing the total number according to the study population and assuming an event rate of 0.4 for composite endpoints and 0.3 for all-cause mortality, which were derived from the total event rate in previous publications from the WET-HF. A difference of 30% in these outcomes was defined as significant.

Continuous variables are presented as means ± standard deviations or medians and interquartile ranges (IQR), according to their distribution. Categorical variables are expressed as percentages. *P*-values <0.05 were considered significant for all analyses.

Results

For the present analysis, data from 4000 consecutive patients enrolled in the WET-HF Registry (registered from 1 January 2006 to 31 March 2017) were analysed (*Figure 1*). We excluded patients without available eGFR data at admission or discharge (*n* = 4), cases of in-hospital deaths (*n* = 164), and those without long-term follow-up data, including heart failure readmission and all-cause death (*n* = 244). Among the remaining 3588 patients, 632 had WRF, defined as a > 20% reduction in eGFR at discharge,[25] and 483 with no missing data on the designated 17 clinical variables were included in the cluster analysis.

Phenogroups according to the cluster analysis and their impact on prognosis

The optimal number of clusters identified by the BIC analysis was three (Supporting Information, *Figure S1*), and the two-step cluster analysis revealed three phenotypically different groups. The participants in phenogroup 1 (*n* = 122) were younger (mean age, 69.3 ± 13.7 years), had higher systolic blood pressure and heart rate at admission (170 ± 28.4 mmHg and 119.4 ± 17.6 bpm, respectively), relatively preserved eGFR and Hb concentration at admission (69.9 ± 27.7 mL/min/1.73 m^2 and 13.5 ± 1.8 g/dL, respectively), and reduced LVEF (41.8 ± 13.7%) than those in the other groups. The participants in phenogroup 3 (*n* = 122) were characterized as older (mean age, 81.7 ± 8.5 years) and had preserved ejection fraction (EF) (51.7 ± 13.1%), the worst eGFR (48.2 ± 30.5 mL/min/1.73 m^2), and the highest BNP level (median, 824 pg/mL; IQR, 418–1921 pg/mL). Phenogroup 2 (*n* = 239) generally exhibited phenotypes that were between those of phenogroups 1 and 3; this group included middle-aged individuals with moderate renal dysfunction (eGFR, 56.0 ± 21.7 mL/min/1.73 m^2) and mid-range LVEF (45.8 ± 15.3%). Changes in body weight during the index hospitalization did not differ significantly among the three groups (*Table 1*). The phenotypic characteristics across each phenogroup are shown in a heatmap (*Figure 2*).

Regarding clinical characteristics other than those entered into the cluster analysis, the prevalence of patients with a history of atrial fibrillation, hypertension, and diabetes mellitus was highest in phenogroup 1, whereas the prevalence of these conditions was lowest in phenogroup 3. In contrast, the prevalence of ischaemic heart disease did not significantly differ among the groups. Each phenogroup exhibited a nearly 30% reduction in eGFR during the index hospitalization. Compared with the participants in phenogroup 1 (young patients with heart failure with reduced ejection [HFrEF] with high blood pressure and preserved renal function), those in phenogroups 3 (older patients with heart failure with

Figure 1 Selection of study population and cluster analysis. BP, blood pressure; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection; HR, heart rate; PS, propensity score; WRF, worsening renal function.
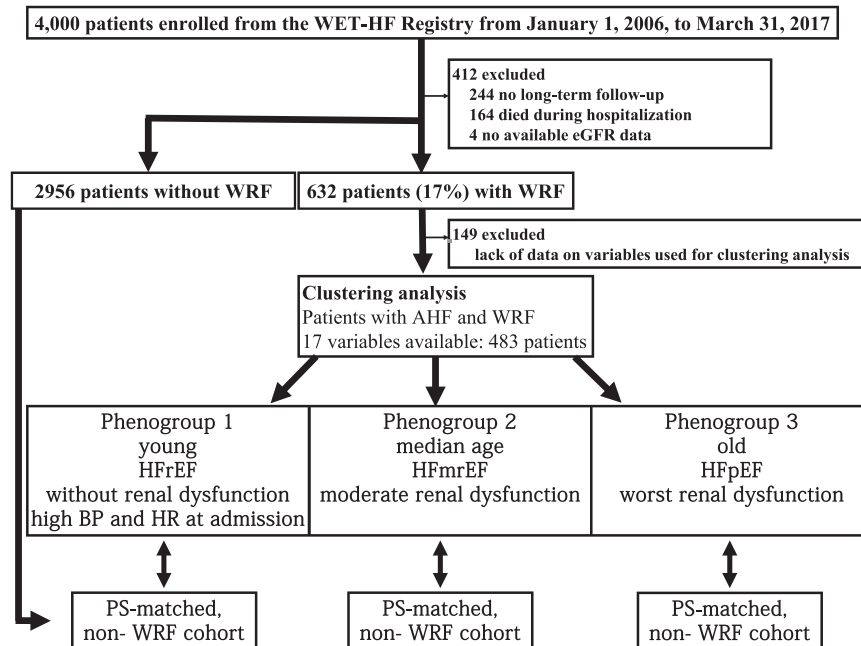
preserved ejection fraction [HFpEF] with impaired renal function) and 2 (patients with variable EF with moderate renal dysfunction) had higher risks of both composite endpoints and all-cause mortality ($P < 0.05$) (*Figure 3*). These outcomes did not differ significantly between phenogroups 2 and 3. The power analysis indicated insufficient statistical power to confirm equality in the prognosis between phenogroups 2 and 3 (Supporting Information, *Table S1*).

Medications at admission, discharge, and those added during hospitalization are summarized in *Table 1*. Addition and prescription rates for beta-blockers and RASIs at discharge were higher in phenogroup 1 compared with the other groups.

Prognosis of the worsening renal function and non-worsening renal function cohorts within each phenogroup

To analyse the effect of WRF on the prognosis of each phenogroup, we compared the clinical outcomes of patients with WRF in each phenogroup with those of the propensity-matched, non-WRF cohort patients. Among the 2956 patients without WRF during the index hospitalization, a cohort of patients for each phenogroup with WRF was generated with 1:1 PS matching using the 17 covariates from the cluster analysis. PS matching resulted in well-balanced cohorts of each WRF

phenogroup (115 in phenogroup 1, 233 in phenogroup 2, and 116 in phenogroup 3) and non-WRF matched controls (115 in matched phenogroup 1, 233 in matched phenogroup 2, and 116 in matched phenogroup 3). Most characteristics entered into the cluster analysis were similar between each phenogroup and its PS-matched cohort, except for diastolic blood pressure and heart rate at admission in phenogroup 3 and its control group (*Table 2*).

In the comparison of composite endpoints between WRF and non-WRF in each phenogroup using univariate Cox proportional hazards analysis, WRF was associated with a higher risk of composite endpoints in phenogroup 1 than in the PS-matched non-WRF cohorts (HR, 1.81; 95% confidence interval (95% CI), 1.07–3.08; $P = 0.03$). In the other two phenogroups, WRF was not associated with the composite endpoints (HR, 1.16; 95% CI, 0.88–1.53; $P = 0.29$ in phenogroup 2, and HR, 1.13; 95% CI, 0.77–1.65; and $P = 0.55$ in phenogroup 3; *Figure 4*). WRF was not associated with the incidence of all-cause death in each phenogroup (*Figure 5*). The negative effect of WRF on the prognosis in phenogroup 1 was consistent after adjusting for clinical characteristics and medications at discharge, which were not entered into the cluster analysis or PS matching (Supporting Information, *Tables S3* and *3*). The power analysis indicated insufficient statistical power to detect significant differences in the composite endpoints and all-cause mortality in phenogroups 2 and 3 (Supporting Information, *Table S2*).

Table 1 Baseline demographics and clinical characteristics of the enrolled patients with acute heart failure and worsening renal function, stratified by phenogroup

	Phenogroup 1 (*n* = 122)	Phenogroup 2 (*n* = 239)	Phenogroup 3 (*n* = 122)	All (*n* = 483)	Missing value
Demographics					
Age, years (SD)	69.3 (13.7)	76.3 (10.1)	81.7 (8.5)	75.9 (11.6)	0
Body mass index, kg/m^2 (SD)	24.4 (4.0)	24.1 (5.5)	21.6 (3.8)	23.5 (4.9)	0
Medical history					
Sex, female %	42.6	47.7	54.9	48.2	0
Atrial fibrillation, %	50.0	47.3	38.5	45.8	0
Diabetes Mellitus, %	41.0	37.2	36.1	37.9	0
Hypertension, %	82.8	66.5	72.1	72.0	0
Ischaemic heart disease, %	27.9	28.9	32.8	29.6	0
Clinical characteristics at admission					
Systolic blood pressure, mmHg (SD)	170.0 (28.4)	133.7 (23.8)	152.3 (32.4)	147.6 (31.1)	0
Diastolic blood pressure, mmHg (SD)	108.7 (18.6)	74.4 (15.3)	81.2 (19.3)	84.8 (22.1)	0
Heart rate, b.p.m. (SD)	119.4 (17.6)	84.9 (20.9)	88.1 (22.0)	94.4 (26.8)	0
Haemoglobin, g/dL (SD)	13.5 (1.8)	11.6 (2.0)	10.5 (1.8)	11.8 (2.2)	0
Na, mEq/L (SD)	139.9 (3.2)	141.0 (2.8)	135.7 (5.9)	139.4 (4.5)	0
K, mEq/L (SD)	4.1 (0.5)	4.1 (0.5)	4.6 (0.6)	4.2 (0.6)	0
eGFR, mL/min/1.73 m^2 (SD)	70.0 (27.7)	56.0 (21.7)	48.2 (30.5)	57.6 (26.8)	0
BNP, pg/mL (IQR)	514 (311 to 900)	544 (272 to 1128)	824 (418 to 1921)	570 (318 to 1221)	0
Clinical characteristics at discharge					
Systolic blood pressure, mmHg (SD)	113.8 (16.1)	109.7 (14.5)	121.5 (19.5)	113.7 (17.0)	0
Heart rate, b.p.m. (SD)	74.0 (13.6)	68.8 (10.9)	69.8 (11.2)	70.4 (11.9)	0
Na, mEq/L (SD)	138.9 (2.9)	138.8 (3.4)	136.3 (4.9)	138.2 (3.9)	0
K, mEq/L (SD)	4.5 (0.5)	4.4 (0.5)	4.6 (0.6)	4.5 (0.6)	0
eGFR, mL/min/1.73 m^2 (SD)	49.3 (20.6)	38.1 (15.7)	33.0 (20.9)	39.7 (19.4)	0
Body weight change, % (IQR)	−6.1 (−10.5 to −3.3)	−6.9 (−11.1 to −3.4)	−6.4 (−12.6 to −1.0)	−6.6 (−11.1 to −2.6)	5
Echocardiographic findings					
LVDd, mm (SD)	53.3 (8.7)	52.6 (10.1)	45.7 (8.7)	51.1 (9.9)	0
LVEF, % (SD)	41.8 (13.7)	45.8 (15.3)	51.7 (13.1)	46.3 (14.8)	0
LAd, mm (SD)	43.3 (7.2)	45.5 (9.8)	41.2 (7.6)	43.8 (8.8)	0
Medications at discharge					
Beta-blockers, *n* (%)	109 (89.3)	172 (72.0)	91 (74.6)	372 (77.0)	0
RASIs, *n* (%)	85 (69.7)	159 (66.5)	68 (55.7)	312 (64.6)	0
MRAs, *n* (%)	41 (27.5)	103 (43.3)	29 (23.8)	182 (37.8)	1
Loop diuretics, *n* (%)	87 (71.3)	190 (79.8)	90 (73.8)	367 (76.1)	1
CCBs, *n* (%)	45 (37.5)	79 (33.5)	61 (50.4)	185 (38.3)	6
Medications at admission					
Beta-blockers, *n* (%)	36 (29.5)	117 (49.0)	58 (47.5)	211 (43.6)	0
RASIs, *n* (%)	38 (31.1)	114 (47.7)	48 (39.3)	200 (41.4)	0
MRAs, *n* (%)	15 (12.3)	41 (17.2)	12 (9.8)	68 (16.5)	27
Loop diuretics, *n* (%)	35 (28.7)	121 (50.6)	47 (38.5)	203 (42.0)	1
CCBs, *n* (%)	36 (30.0)	82 (35.2)	46 (38.0)	164 (34.0)	9
Medications added during hospitalization					
Beta-blockers, *n* (%)	74 (60.7)	65 (27.2)	37 (30.3)	176 (36.4)	0
RASIs, *n* (%)	51 (41.8)	64 (26.8)	32 (26.2)	147 (30.4)	0
MRAs, *n* (%)	35 (29.9)	65 (29.5)	17 (14.3)	176 (38.6)	27
Loop diuretics, *n* (%)	55 (45.1)	78 (32.8)	51 (41.8)	184 (38.2)	1
CCBs, *n* (%)	9 (7.3)	2 (0.8)	15 (12.3)	26 (5.5)	9

BNP, brain natriuretic peptide; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LAd, left atrium diameter; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; RASIs, renin-angiotensin-system inhibitors; SD, standard deviation.
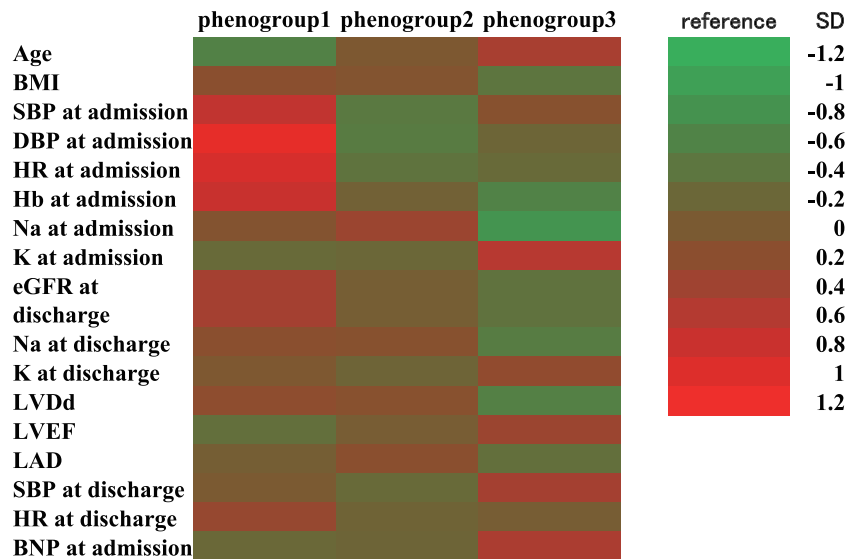
Discussion

The impact of WRF on the prognosis of patients with AHF is unclear, as WRF reflects both the treatment strategy and underlying phenotypic heterogeneity. WRF in the setting of aggressive and effective decongestive therapy in AHF is a result of effective decongestion and is not associated with acute tubular necrosis or poor prognosis. In addition, some cases of WRF may be attributed to appropriate clinical interventions such as administration of RASIs, and thus, may be associated with better clinical outcomes. Therefore, identifying subgroups of patients who are more susceptible to the

unfavourable effect of WRF among patients with AHF according to their clinical phenotype will allow more tailored treatment for each patient. In this cluster analysis of the WET-HF Registry, we identified three phenogroups according to their clinical features. Further, WRF was associated with increased adverse outcomes in phenogroup 1, which was characterized by younger age, heart failure with reduced ejection fraction (LVEF), preserved renal function, and higher blood pressure/tachycardia at admission. These results indicated the utility of cluster analysis for the subgrouping of patients with both WRF and AHF.

Clinical characteristics and outcomes in each subgroup

Phenogroup 1 experienced the most favourable outcome during the follow-up among the three phenogroups with both WRF and AHF. The participants in phenogroup 1 were characterized by younger age, high blood pressure, preserved renal function, and non-anaemic status, all of which are known to be preferable prognostic factors for patients with AHF.[26] Therefore, these factors may have contributed to the decreased mortality in phenogroup 1. Moreover, high blood

Table 2 Baseline characteristics of WRF and PS-matched, non-WRF cohorts in each phenogroup

	Phenogroup 1			Phenogroup 2			Phenogroup 3		
	WRF patients (n = 115)	Non-WRF Controls (n = 115)	P value	WRF patients (n = 233)	Non-WRF Controls (n = 233)	P value	WRF patients (n = 116)	Non-WRF Controls (n = 116)	P value
Demographics									
Age, years (SD)	69.7 (12.2)	69.2 (13.5)	0.77	76.8 (11.8)	76.3 (9.9)	0.58	80.7 (9.4)	81.8 (8.5)	0.66
Body mass index, kg/m² (SD)	24.2 (4.0)	24.5 (3.9)	0.71	23.8 (4.6)	23.8 (5.0)	0.85	21.8 (3.3)	21.7 (3.8)	0.81
Clinical characteristics at admission									
Systolic blood pressure, mmHg (SD)	169.5 (36.7)	169.5 (28.6)	<0.001	140.7 (34.1)	133.4 (23.6)	0.006	144.5 (33.8)	152.7 (32.7)	0.73
Diastolic blood pressure, mmHg (SD)	109.1 (24.7)	107.9 (17.3)	0.67	81.2 (22.8)	73.4 (15.0)	<0.001	78.5 (19.8)	81.7 (19.0)	0.49
Heart rate, b.p.m. (SD)	122.2 (29.7)	117.6 (23.9)	0.20	92.2 (28.9)	85.2 (20.8)	0.003	91.3 (27.5)	88.8 (22.1)	0.42
Haemoglobin, g/dL (SD)	13.7 (2.3)	13.5 (1.8)	0.41	11.6 (2.0)	11.6 (2.0)	0.97	10.1 (2.2)	10.5 (1.8)	0.14
Na, mEq/L (SD)	140.2 (3.2)	140.0 (3.3)	0.38	140.8 (3.1)	140.9 (2.8)	0.61	136.8 (5.1)	135.9 (5.6)	0.46
K, mEq/L (SD)	4.09 (0.52)	4.08 (0.48)	0.60	4.11 (0.45)	4.10 (0.53)	0.97	4.56 (0.66)	4.55 (0.63)	0.96
eGFR, mL/min/1.73 m² (SD)	64.2 (24.9)	67.5 (24.7)	0.90	54.4 (20.6)	55.8 (21.8)	0.47	47.0 (25.6)	47.5 (28.1)	0.89
BNP, pg/mL (IQR)	559 (296 to 965)	526 (318 to 875)	0.80	563 (283 to 952)	545 (273 to 1134)	0.73	571 (304 to 1617)	793 (417 to 1900)	0.36
Clinical characteristics at discharge									
Systolic blood pressure, mmHg (SD)	114.4 (17.1)	113.9 (16.4)	0.44	110.8 (16.4)	110.0 (14.4)	0.54	121.8 (19.9)	121.4 (19.1)	0.61
Diastolic blood pressure, mmHg (SD)	76.0 (14.9)	73.4 (13.8)	0.98	67.8 (11.4)	68.7 (10.9)	0.97	69.9 (10.1)	69.8 (11.3)	0.43
Na, mEq/L (SD)	139.4 (3.0)	138.8 (2.9)	0.86	138.6 (4.6)	138.8 (3.4)	0.85	136.7 (4.6)	136.4 (4.9)	0.55
K, mEq/L (SD)	4.40 (0.57)	4.47 (0.54)	0.56	4.38 (0.55)	4.36 (0.50)	0.87	4.53 (0.59)	4.56 (0.65)	0.55
eGFR, mL/min/1.73 m² (SD)	47.6 (18.8)	66.0 (28.6)	<0.001	38.1 (15.8)	54.3 (19.9)	<0.001	32.5 (19.2)	49.8 (25.6)	<0.001
Body weight change[a], % (IQR)	−6.0 (−10.5 to −3.6)	−6.6 (−10.2 to −3.7)	0.46	−6.8 (−10.7 to −3.3)	−7.1 (−11.5 to −4.0)	0.40	−6.6 (−12.3 to −1.2)	−6.9 (−11.8 to −2.7)	0.75
Echocardiographic findings									
LVDd, mm (SD)	52.7 (8.9)	53.3 (8.7)	0.53	52.4 (9.7)	52.6 (10.1)	0.77	46.2 (8.2)	45.9 (8.6)	0.78
LVEF, % (SD)	42.7 (13.9)	41.6 (13.5)	0.59	46.0 (15.1)	45.6 (15.3)	0.57	52.3 (12.8)	51.4 (13.1)	0.99
LAd, mm (SD)	43.3 (7.8)	43.4 (7.3)	0.76	46.0 (10.1)	45.6 (9.7)	0.73	40.9 (8.7)	41.1 (7.6)	0.24
Medications at discharge									
Beta-blockers, n (%)	102 (88.7)	103 (89.6)	0.83	169 (72.5)	173 (74.2)	0.68	86 (74.1)	79 (68.1)	0.31
RASIs, n (%)	79 (68.7)	77 (67.0)	0.78	154 (66.1)	171 (73.4)	0.09	66 (56.9)	72 (62.1)	0.42
MRAs, n (%)	47 (40.9)	45 (39.1)	0.79	101 (43.5)	92 (39.5)	0.38	28 (24.1)	37 (31.9)	0.19
Loop diuretics, n (%)	81 (70.4)	89 (77.4)	0.23	187 (80.6)	179 (76.8)	0.32	87 (75.0)	86 (74.1)	0.88
CCBs, n (%)	41 (35.7)	38 (33.0)	0.71	77 (33.0)	82 (35.2)	0.58	58 (50.0)	47 (40.5)	0.15

BNP, brain natriuretic peptide; CCBs, calcium channel blockers; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LAd, left atrium diameter; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; PS, propensity score; RASIs, renin-angiotensin-system inhibitors SD, standard deviation; WRF, worsening renal function;
[a]Body weight change indicates the % decrease in body weight during hospitalization.

Figure 4 Comparison of 3 year composite endpoints between the worsening renal function (WRF) and non-WRF subgroups in each phenogroup. WRF was associated with higher incidence of composite endpoints including all-cause death and heart failure re-admission in phenogroup 1, whereas in the other two phenogroups the association was not observed.
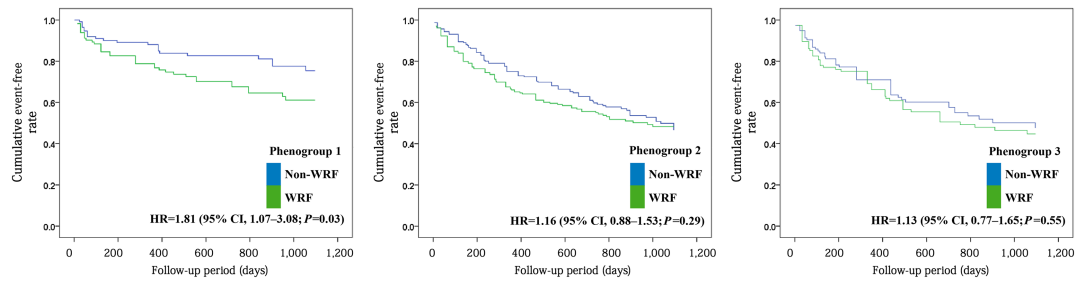

Figure 5 Comparison of 3 year all-cause death between the worsening renal function (WRF) and non-WRF subgroups in each phenogroup. WRF was not associated with all-cause mortality in all three phenogroups.
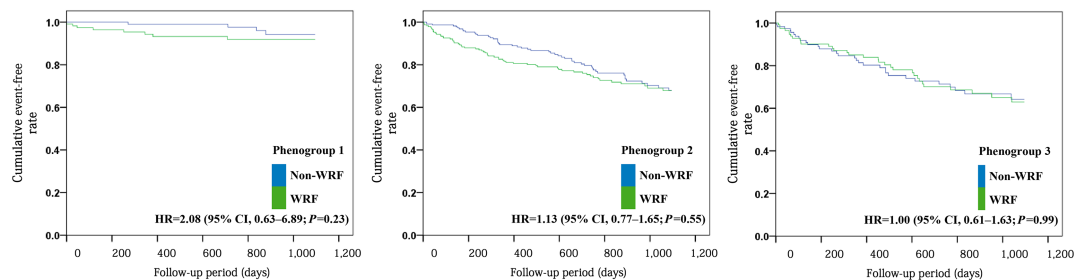

Table 3 Multivariate Cox proportional hazard analysis comparing the effect of co-morbidities, medications at discharge, and worsening renal function (WRF) on composite endpoints in phenogroup 1 and its propensity-matched (PSM) non-WRF cohort

	HR (95% CI)	P value
Model 1. WRF and clinical characteristics		
WRF	1.87 (1.08–3.22)	0.03
Sex	0.84 (0.49–1.46)	0.54
Diabetes	1.02 (0.59–1.77)	0.94
Atrial fibrillation	2.02 (1.18–3.45)	0.01
Hypertension	1.03 (0.53–2.02)	0.92
Ischaemic heart disease	1.94 (1.13–3.35)	0.02
Model 2. WRF and medications at discharge		
WRF	1.94 (1.12–3.36)	0.02
RASIs	1.28 (0.71–2.31)	0.41
Beta-blockers	0.82 (0.37–1.82)	0.63
MRAs	0.62 (0.35–1.10)	0.10
CCBs	0.94 (0.54–1.65)	0.84

CCBs, calcium channel blockers; CI, confidence interval; HR, hazard ratio; MRAs, mineralocorticoid receptor antagonists; PSM, propensity score matched; RASIs, renin-angiotensin-system inhibitors; WRF, worsening renal function.

pressure and rapid heart rate at admission were observed in phenogroup 1, implying that the underlying pathophysiology of congestion in these patients is a central volume shift induced by sympathetic nerve activation, rather than volume overload.[27,28] In contrast, individuals in phenogroup 2, which mainly consisted of patients with heart failure with mid-range ejection fraction (HFmrEF), and phenogroup 3, which mainly consisted of participants with HFpEF, demonstrated a worse prognosis than those in phenogroup 1. These two groups had an older population with a relatively preserved LVEF and impaired kidney function. In particular, phenogroup 3 had the oldest participants, the lowest serum sodium and Hb levels, the highest BNP, and the worst renal function at admission, which have been linked to an adverse prognosis for AHF in previous reports. These characteristics may have led to increased mortality in phenogroup 3. Interestingly, a cluster study on a cohort of individuals with HFpEF proposed that a subgroup sharing the features of phenogroup 3 had a poor prognosis, suggesting the possible existence of a phenogroup 3-like population in the real-world heart failure setting.[14,17] In summary, phenogroup 1 may be defined as 'young patients with HFrEF presenting with high blood pressure and preserved renal function', phenogroup 2 as 'patients with variable EF with moderate renal dysfunction', and phenogroup 3 as 'older patients with HFpEF with impaired renal function'.

Prognostic impact of worsening renal function between each subgroup and its propensity score-matched non-worsening renal function control group

Our PS-matched cohort analysis suggested that WRF was associated with a poor prognosis compared with the PS-matched non-WRF control patients in phenogroup 1. This tendency was not observed in patients from phenogroups 2 and 3 and their matched cohorts. The association observed in phenogroup 1 remained significant after adjusting for clinical characteristics and medications at discharge. This result corresponds to those of previous studies, which indicated that WRF may be a predictor of adverse outcomes in patients with HFrEF and HFmrEF. Using a prospective cohort registry, Lofman *et al.* evaluated the impact of WRF based on LVEF and reported that WRF was associated with an increased risk for mortality in the HFrEF group, which had a similar age (66.3 ± 14.7 years), lower kidney function (average creatinine, 1.51 mg/dL), and higher BNP levels (1600 pg/mL) compared with phenogroup 1.[9] Additionally, a large observational study from Korea demonstrated that WRF was an independent predictor of adverse outcomes among the HFrEF population, which had a similar background to phenogroup 1 in terms of age and renal function at admission.[10] Furthermore, in a meta-analysis, WRF predicted higher mortality and hospitalization rates in patients with HFrEF.[3] Their population in the HFrEF group was also similar to that of phenogroup 1, with regard to age (64 ± 11 years) and basically preserved kidney function (BNP data unknown). In contrast, a sub-analysis from the randomised control study called the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial showed that WRF may be associated with favourable outcomes in patients with HFrEF.[29] However, the baseline characteristics of the patients in the registry were different from those of our WET-HF Registry; the participants were younger than ours (56.0 ± 13.6 years) and had a more severely impaired LVEF (19.3 ± 6.7%). This difference in baseline parameters may be responsible for the discrepancy in the effect of WRF. Overall, WRF may be associated with worse outcomes in patients with HFrEF and HFmrEF, and our results were consistent with this tendency.

Effect of therapeutic interventions

The effects of therapeutic interventions, including the degree of decongestion and introduction of RASIs, were not negligible in terms of the clinical impact of WRF in this study. These interventions might have had an effect on the cluster analysis itself, on the prognostic difference between the phenogroups, and between each phenogroup and its PS-matched, non-WRF cohort. For example, the RASI prescription rate was significantly different between the phenogroups. These differences might have stemmed from the difference in the LVEF among the three subgroups, as several patients in phenogroup 1 were considered to be HFrEF. In contrast, the difference in the RASI prescription rate at discharge was not significantly different between each phenogroup and its PS-matched, non-WRF cohort.

We also analysed the body weight change (as a surrogate of clinical decongestion) during hospitalization. The results shown in *Tables 1* and *2* suggested that the difference in the degree of body weight change was not significant between the phenogroups or between each phenogroup and its PS-matched, non-WRF cohort, suggesting that the effect of the degree of decongestion might have been negligible in our analysis.

Taken together, the effects of these interventions might have been negligible or minimal when comparing each phenogroup and its PS-matched, non-WRF cohort. Further, the Cox proportional hazards analysis between each phenogroup and its PS-matched, non-WRF cohort, adjusted for the medications at discharge, demonstrated consistent results, suggesting that the negative effect of WRF in phenogroup 1 might have been independent of the therapeutic interventions. These results may be explained by the fact that our cluster analysis stems largely from the demographic features and characteristics at the time of admission (i.e. factors determined prior to the initiation of treatment).

Interpretation of the phenogrouping from a clinical standpoint

Given the nature of the analysis (observational, data-driven) and the classification using unsupervised machine learning, we were unable to present a concrete pathophysiological background to explain the classification. Therefore, the essential aim of this study was to investigate whether there are categories of patients with WRF with differentiated clinical outcomes. This classification may help physicians develop tailored treatment strategies. Nonetheless, we tried to interpret this phenogrouping system from a clinical standpoint. We propose that the classification may be based on both the clinical characteristics and haemodynamic condition at admission. As shown in the heatmap in *Figure 2*, clinical characteristics such as age, LVEF, Hb concentration, and eGFR gradually changed between the phenogroups, suggesting their significance in the classification. Additionally, these differences may explain the differences in the prognosis among the three groups, as they are known outcome predictors in patients with AHF.

In contrast, phenogroup 1 had significant differences from the other two groups in that the patients exhibited elevated systolic and diastolic blood pressure and heart rate at

admission. This may explain why WRF was only associated with a worse prognosis among the patients in phenogroup 1. These vital signs at admission imply that the pathophysiological cause of congestion in phenogroup 1 was a central volume shift associated with sympathetic nerve activation rather than volume overload. Because the amount of body fluid may not increase in this type of congestion, excessive diuresis might have led to potential renal injury in phenogroup 1.

Selection of the cluster variables

We selected 25 continuous variables as the cluster candidates and introduced 17 variables from among them into the cluster analysis based on the independence between each variable and the number of missing values. Although patient characteristics such as history of hypertension, diabetes mellitus, or medications used during the hospitalization are important contributors to both the development and consequence of WRF, we did not enter these binary variables into the cluster analysis for two reasons. First, including these variables may have violated the inter-independency among the variables (e.g. history of hypertension and blood pressure at admission were not independent). Second, the phenogroups revealed from the cluster analysis including both continuous and binary variables might have been strongly skewed and affected by binary variables. These skewed phenogroups deviated from our intention, as they were largely defined by the presence or absence of specific binary characteristics and thus, diminished the strength of the cluster analysis.

Limitations

Our study has several limitations other than those discussed above. First, patients with missing variables required for the cluster analysis were excluded from the analysis. We did not employ multiple imputation methods for missing values because the methods may enhance the effect of the variables with more missing data because the presumed imputed values were calculated based on the existing data. Thus, we selected variables with fewer missing values for our analysis; however, this manner of analysis possibly reduced the generalisability of the study findings. Ideally, validation of our results using other heart failure registries may support the existence of our hypothetical phenogroups. Additionally, the power analysis suggested that there was insufficient power to detect differences in the prognosis, suggesting that the lack of significant differences in some outcomes might have been due to an underpowered analysis. Further studies with larger populations are needed to provide more information regarding this point.

Conclusion

Using cluster analysis, we revealed three phenotypically distinct subgroups of patients hospitalized for AHF experiencing WRF. Among them, possible interactions between WRF and worse clinical outcomes were observed in phenogroup 1, a subgroup of younger patients with reduced LVEF, preserved renal function, higher blood pressure, and rapid heart rate at admission. This analysis provides additional data to suggest that HFrEF increases the risk of a poor prognostic impact of WRF. Further studies using a cluster analysis to reveal subgroups from both WRF and AHF may provide additional information to better understand this heterogeneous condition.

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Conflict of interest

Dr. Shiraishi is affiliated with a department endowed by Nippon Shinyaku Co., Ltd., Medtronic Japan Co., Ltd., and BIOTRONIK JAPAN Inc. and received research grants from the SECOM Science and Technology Foundation and the Uehara Memorial Foundation and honoraria from Otsuka Pharmaceuticals Co., Ltd. and Ono Pharmaceuticals Co., Ltd. Dr. Kohsaka received an unrestricted research grant from the Department of Cardiology, Keio University School of Medicine, Bayer Pharmaceuticals Co., Ltd., Daiichi Sankyo Co., Ltd., and Novartis Pharma Co., Ltd. These funders were not involved in the design and conduct of the study; in the collection, analysis, and interpretation of the data; nor in the preparation, review, or approval of the manuscript. The other authors have no conflicts of interest to disclose. There are no patents, products in development, or marketed products to declare.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Power calculations for comparisons among phegnogroups.

Table S2. Power calculations for comparison between each phenogroup with WRF and its propensity score-matched non-WRF cohort.

Table S3. Cox proportional hazard analysis comparing the effect of comorbidities, medications at discharge and worsening renal function (WRF) on prognosis in each phenogroup and its propensity-matched (PSM) non-WRF cohort.

Figure S1. BIC change according to each cluster numbers. BIC: Bayesian information criteria.

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