JACC: HEART FAILURE VOL. 12, NO. 10, 2024

ORIGINAL RESEARCH

HEART FAILURE

Distinct Comorbidity Clusters in Patients With Acute Heart Failure

Data From RELAX-AHF-2

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ABSTRACT

BACKGROUND Multimorbidity frequently occurs in patients with acute heart failure (AHF). The co-occurrence of comorbidities often follows specific patterns.

OBJECTIVES This study investigated multimorbidity subtypes and their associations with clinical outcomes.

METHODS From the prospective RELAX-AHF-2 (Relaxin for the Treatment of Acute Heart Failure-2) trial, 6,545 patients (26% with HF with preserved ejection fraction, defined as LVEF ≥50%) were classified into multimorbidity groups using latent class analysis. The association between subgroups and clinical outcomes was examined. Validation of these findings was conducted in the RELAX-AHF trial, which comprised 1,161 patients.

RESULTS Five distinct multimorbidity groups emerged: 1) diabetes and chronic kidney disease (CKD) (often male, high prevalence of CKD and diabetes mellitus); 2) ischemic (ischemic HF); 3) elderly/atrial fibrillation (AF) (oldest, high prevalence of AF); 4) metabolic (obese, hypertensive, more often HF with preserved ejection fraction); and 5) young (fewest comorbidities). After adjusting for confounders, patients in the diabetes and CKD (HR: 1.80; 95% CI: 1.50-2.20), elderly/AF (HR: 1.42; 95% CI: 1.20-1.70), and metabolic (HR: 1.40; 95% CI: 1.20-1.80) groups had higher rates of the composite outcome than patients in the young group, primarily driven by differences in rehospitalization. Treatment allocation (placebo or serelaxin) modified these associations ($P_{interaction}$ <0.001). Serelaxin-treated patients in the young group were associated with a lower risk for all-cause mortality (HR: 0.59; 95% CI: 0.40-0.90). Similarly, patients from the RELAX-AHF trial clustered in 5 multimorbidity groups. The clinical characteristics and associations with outcomes could also be validated.

CONCLUSIONS Comorbidities naturally clustered into 5 mutually exclusive groups in RELAX-AHF-2, showing variations in clinical outcomes. These data emphasize that the specific combination of comorbidities can influence adverse outcomes and treatment responses in patients with AHF. (JACC Heart Fail. 2024;12:1762–1774) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2024.04.028

Acute heart failure (AHF) is a common cause of unplanned hospital admission in patients aged >65 years.[1] Prognosis of AHF is poor: the 1-year mortality rate is >20%.[2] Several cardiovascular and noncardiovascular comorbidities, including chronic kidney disease (CKD), anemia, and diabetes mellitus (DM), frequently co-occur with heart failure (HF).[3-5] Among 3,226 patients with chronic HF in the European Society of Cardiology HF pilot survey, 74% had at least 1 additional comorbidity.[6] In the United States, almost 40% of Medicare patients with chronic HF had ≥5 comorbidities.[7] In the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry, more than two-thirds of patients with stable HF had at least 1 additional comorbidity.[8,9]

Multimorbidity, defined as having >2 comorbidities, predicts a worse prognosis and complicates treatment.[3] However, co-occurrence of comorbidities is not random and commonly follows similar patterns due to shared risk factors.[10] Previous studies mainly investigated the impact of individual comorbidities.[7,11] Studies investigating the cumulative impact of multimorbidity focused on ambulatory patients with HF from specific geographical regions.[12-16] A better understanding of the unique multimorbidity patterns in AHF may improve treatment allocation and clinical trial design and help plan health care services.[3,17-19] The aim therefore of the present study was to identify multimorbidity subtypes in patients with AHF and investigate their association with clinical outcomes.

METHODS

STUDY DESIGN, STUDY POPULATION, AND SETTING. We studied comorbidities in 6,545 patients with AHF enrolled in 546 centers from 35 countries in the randomized RELAX-AHF-2 (Relaxin for the Treatment of Acute Heart Failure-2) trial. RELAX-AHF-2 was a multicenter, randomized, placebo-controlled, double-blind, event-driven trial that randomized patients admitted to the hospital for AHF in a 1:1 ratio to receive serelaxin or matching placebo. The effect of the study drug on cardiovascular outcome was neutral.[20] The trial design, patient characteristics, and primary results have been described elsewhere.[20,21]

Briefly, patients (>18 years of age) were eligible for enrollment if they were hospitalized for AHF with symptoms, particularly dyspnea, congestion, evidence of volume overload, systolic blood pressure at least 125 mm Hg, elevation in natriuretic peptide concentrations, and mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] between 25 and 75 mL/min/1.73 m^2). Patients received either serelaxin (30 μg/kg/day) or a matching placebo for up to 48 hours.

The ethics committee at each participating center approved the study, and patients provided written informed consent.

STUDY DEFINITIONS. History of stroke, hypertension, DM, hypothyroidism, hyperthyroidism, chronic obstructive pulmonary disease, peripheral arterial occlusive disease, atrial fibrillation (AF), hyperlipidemia, and depression was interrogated and captured systematically in the medical history at the time that patients were enrolled into the trial. Obesity was defined according to the standard body mass index (BMI) cutoff determined by the World Health Organization (>30 kg/m^2). Coronary artery disease (CAD) was defined as a history of myocardial infarction, ischemic etiology, or prior coronary artery bypass grafting or percutaneous coronary intervention. eGFR was calculated by using the MDRD (Modification of Diet in Renal Disease) equation, and CKD was defined as eGFR <60 mL/min/1.73 m^2. Anemia was defined according to World Health Organization criteria (hemoglobin <13 g/dL for men and <12 g/dL for women). HF with preserved ejection fraction (HFpEF) was defined as a left ventricular ejection fraction (EF) ≥50%. The region of enrollment was used to determine geographic distribution.

STATISTICAL ANALYSIS. We identified clusters of comorbidities by performing a latent class analysis (LCA) using the poLCA package in R.[22] A wide-ranging list of comorbidities (AF, CAD, stroke, CKD, obesity, hypertension, hypothyroidism, hyperthyroidism, chronic obstructive pulmonary disease, anemia, peripheral arterial occlusive disease, hyperlipidemia, depression, and DM) that were systematically

ABBREVIATIONS AND ACRONYMS

AE = adverse event
AHF = acute heart failure
AF = atrial fibrillation
BMI = body mass index
CAD = coronary artery disease
CKD = chronic kidney disease
DM = diabetes mellitus
EF = ejection fraction
eGFR = estimated glomerular filtration rate
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
HHF = rehospitalization for heart failure
LCA = latent class analysis
NT-proBNP = N-terminal pro-B-type natriuretic peptide

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center. * Drs Arevalo and Tromp contributed equally to this work.

Manuscript received November 20, 2023; revised manuscript received April 26, 2024, accepted April 30, 2024.

captured during patients' enrollment into the trial was assessed to identify group membership. Patients with missing information were removed.

Maximum likelihood estimations were used to identify clusters based on multimorbidity type. The range of clusters set was 2 to 10. Because poLCA generates class-conditional response probabilities and the starting values are determined randomly, we completed 10 replications to estimate each model. The lowest Bayesian information criterion delivers the most parsimonious model.[22,23] We therefore selected the first minimum Bayesian information criterion value to identify the optimal number of clusters (Supplemental Table 1). After determining the optimal number of clusters, patients' class membership was derived by using a Bayesian approach. Partial probabilities were averaged over the 10 replications and then used to calculate each group membership[22] (Supplemental Table 2). By multiplying each probability corresponding to each variable, a patient's probability of belonging to a group was determined. Final group selection was based on the patient's highest probability of a group. The label assigned to each cluster was based on the diseases that were most commonly observed within that group.

Baseline characteristics were stratified according to the consigned group and are shown as mean ± SD, median (Q1 to Q3), or numbers (percentages), as appropriate. Incidence of the 25 most common adverse events (AEs) stratified according to multimorbidity group and treatment allocation is reported. Differences between multimorbidity clusters were tested with 1-way analysis of variance, Student's *t*-test, Kruskal-Wallis test for continuous variables, or the chi-square test for categorical variables where appropriate.

POSTDISCHARGE OUTCOMES. The present analysis focused on the composite endpoint of all-cause death or adjudicated rehospitalization for HF (HHF) or renal failure through day 180. Impaired renal failure in the RELAX-AHF-2 trial was defined as an eGFR ≤75 mL/min/1.73 m^2. Outcomes were independently adjudicated.

Kaplan-Meier curves stratified according to class membership are presented, with differences between them tested by using the log-rank test for survival through day 180. Multivariable Cox regression analysis was used to test for differences between multimorbidity groups in the composite endpoint of all-cause death or HHF or renal failure and all-cause death alone. To determine the risk of HHF or renal failure through day 180, a competing risk analysis was performed using all-cause mortality as competing risk.[24] The group with the lowest risk (risk nadir) was used as a reference category in multivariable Cox regression and competing risk analyses. In addition, we tested for interactions between group membership and HF type (heart failure with reduced ejection fraction [HFrEF] or HFpEF) as well as treatment allocation (serelaxin or placebo). The likelihood ratio test was performed to compare the outcome models with the interaction terms. Furthermore, the interaction model was adjusted for the number of comorbidities. In the presence of a significant interaction, this analysis was stratified according to group membership, using the placebo allocation as the reference category.

Model correction was performed in a step-wise manner. In model 1, we corrected for age and sex. Model 2 included variables in model 1 and region of origin, previous hospitalization for HF (yes/no), NYHA functional class, HFrEF vs HFpEF, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Because 20% of the NT-proBNP values were missing, the stratified analysis for cluster membership and treatment allocation was not adjusted for this variable.

All tests were performed 2-sided, and values of $P < 0.05$ were considered statistically significant. Statistical analyses were performed by using R version 4.0.3 (R Foundation for Statistical Computing).

VALIDATION. We conducted an independent validation analysis using data from 1,161 patients included in the RELAX-AHF trial. The design and primary results of the RELAX-AHF trial have been previously published.[25] In brief, RELAX-AHF was an international, phase 3, randomized, double-blind, placebo-controlled, parallel-group trial that compared a 48-hour treatment of serelaxin vs. placebo in patients hospitalized for AHF. Cluster membership of RELAX-AHF patients was predicted by applying the calculated posterior probabilities from the RELAX-AHF-2 LCA. In addition, the association between predicted cluster membership and the rate of the trial's secondary outcome, which comprised a combined endpoint of all-cause death or HHF or renal failure up to day 60, were investigated. To determine the risk of HHF or renal failure, a competing risk analysis was performed using all-cause mortality as competing risk.

RESULTS

BASELINE CHARACTERISTICS. In the total population, 60% were male, the mean age was 73 ± 11 years,

TABLE 1 Baseline Characteristics According to Multimorbidity Group

	Metabolic (23.3%, n = 1,525)	Diabetes and CKD (18.16%, n = 1,189)	Young (18.68%, n = 1,223)	Ischemic (14.86%, n = 973)	Elderly/AF (24.98%, n = 1,635)	*P* Value
Placebo/serelaxin	50.4/49.6 (763/751)	50.8/49.2 (598/580)	49.8/50.2 (603/609)	49.0/51.0 (474/493)	49.5/50.5 (803/818)	0.925
Age, y	70.96 ± 10.81	73.74 ± 9.12	69.43 ± 13.32	71.21 ± 10.81	78.01 ± 9.50	<0.001
Female/male	45.3/54.7 (691/834)	36.9/63.1 (439/750)	37.4/62.6 (458/765)	30.1/69.9 (293/680)	46.2/53.8 (756/879)	<0.001
Weight, kg	99.42 ± 18.05	85.98 ± 18.73	82.59 ± 20.65	81.00 ± 18.71	71.66 ± 12.25	<0.001
Height, cm	167.35 ± 10	167.86 ± 8.88	168.33 ± 9.71	168.77 ± 9.44	167.02 ± 9.22	<0.001
BMI, kg/m^2	35.53 ± 5.44	30.50 ± 6.03	29.04 ± 6.28	28.32 ± 5.54	25.56 ± 3.12	<0.001
Comorbidities						
Number of comorbidities	6.00 (5.00-7.00)	8.00 (7.00-9.00)	3.00 (2.00-3.00)	5.00 (4.00-6.00)	5.00 (4.00-6.00)	<0.001
Coronary artery disease	49.1 (636)	92.5 (1,023)	37.5 (287)	99.9 (855)	62.7 (855)	<0.001
Myocardial ischemia	37.6 (561)	77.6 (912)	19.6 (236)	78.4 (755)	46.7 (753)	<0.001
Myocardial infarction	22.1 (334)	54.5 (639)	11.4 (138)	58.4 (564)	29.0 (469)	<0.001
Aortic valve incompetence	17.8 (265)	22.8 (266)	15.3 (183)	23.7 (226)	27.9 (449)	<0.001
Mitral valve incompetence	50.4 (753)	57.7 (673)	41.2 (493)	55.7 (531)	58.5 (940)	<0.001
Mitral valve stenosis	2.7 (40)	2.5 (29)	1.3 (16)	1.9 (18)	4.4 (70)	<0.001
Aortic valve stenosis	8.5 (127)	14.8 (173)	5.4 (65)	9.9 (95)	11.3 (182)	<0.001
Atrial fibrillation or flutter	68.5 (1,039)	46.5 (551)	33.3 (406)	19.3 (188)	78.7 (1,281)	<0.001
Hypertension	98.8 (1,503)	99.2 (1,179)	68.2 (833)	92.8 (903)	89.2 (1,457)	<0.001
Diabetes mellitus	63.9 (974)	93.9 (1,117)	12.7 (155)	46.4 (451)	19.3 (316)	<0.001
Obesity, BMI >30 kg/m^2	97.1 (1,453)	49.2 (569)	38.4 (460)	27.8 (267)	2.1 (33)	<0.001
Hyperlipidemia	56.6 (846)	86.4 (1,013)	1.3 (15)	85.9 (820)	38.3 (617)	<0.001
Chronic kidney disease	77.2 (1,172)	93.9 (1,113)	49.5 (605)	43.6 (423)	80.4 (1,311)	<0.001
Anemia	40.2 (610)	85.6 (1,009)	24.7 (300)	23.7 (229)	56.5 (918)	<0.001
Hypothyroidism	14.2 (216)	15.2 (180)	1.1 (14)	2.9 (28)	16.3 (266)	<0.001
Hyperthyroidism	3.4 (52)	3.1 (37)	0.2 (2)	0.0 (0)	7.9 (129)	<0.001
Stroke	13.8 (210)	28.0 (332)	0.2 (3)	10.8 (105)	21.9 (358)	<0.001
Peripheral arterial occlusive disease	0.8 (12)	39.1 (458)	0.0 (0)	20.9 (201)	12.7 (206)	<0.001
Chronic obstructive pulmonary disease	17.6 (266)	26.6 (313)	6.1 (75)	12.7 (123)	16.2 (264)	<0.001
Depression	8.9 (136)	18.8 (222)	2.3 (28)	5.8 (56)	11.1 (181)	<0.001
Cardiac pacemaker insertion	13.8 (210)	18.3 (217)	5.3 (65)	8.4 (81)	16.5 (269)	<0.001
Cardiac resynchronization therapy	3.4 (52)	6.3 (74)	2.2 (27)	2.4 (23)	4.8 (78)	<0.001
Implantable defibrillator insertion	8.1 (123)	14.0 (166)	4.3 (53)	9.3 (90)	8.8 (144)	<0.001
Percutaneous coronary intervention	16.0 (243)	46.6 (548)	7.1 (86)	40.6 (392)	18.7 (303)	<0.001
Coronary artery bypass	9.0 (137)	30.8 (365)	3.1 (38)	24.1 (234)	11.4 (187)	<0.001
Alcohol consumption	28.7 (434)	26.5 (313)	34.4 (416)	33.6 (327)	27.7 (447)	<0.001
HF history						
NYHA functional class						<0.001
I	3.2 (49)	4.0 (47)	3.0 (37)	3.0 (29)	2.9 (48)	
II	30.6 (466)	28.7 (341)	23.2 (284)	27.6 (269)	29.8 (488)	
III	35.0 (534)	38.9 (462)	25.7 (314)	33.8 (329)	33.3 (545)	
IV	8.7 (133)	9.8 (116)	5.7 (70)	6.2 (60)	7.8 (128)	
EF, %	41.07 ± 14.25	40.74 ± 13.88	35.49 ± 13.03	35.53 ± 12.68	40.28 ± 13.73	<0.001
HFpEF, LVEF ≥50%	32.91 (470)	30.69 (337)	17.74 (205)	16.07 (149)	28.55 (434)	<0.001
History of HF	79.5 (1,211)	82.8 (984)	59.2 (724)	72.3 (703)	75.4 (1,232)	<0.001
Years since diagnosis of HF	2.94 (0.84-6.92)	3.15 (0.88-7.14)	1.73 (0.32-4.78)	2.72 (0.81-6.56)	2.62 (0.68-6.53)	<0.001
Primary HF etiology						<0.001
Ischemic	38 (775)	76.4 (957)	27.5 (700)	85.4 (871)	48.7 (1,002)	
Nonischemic	62.0 (750)	23.6 (232)	72.5 (523)	14.6 (102)	51.3 (633)	
Prior HF hospitalization	58.7 (847)	65.5 (747)	39.1 (423)	49.8 (459)	56.4 (862)	<0.001
Number of HF hospitalizations in the last 12 mo						<0.001
>3 hospitalizations	9.2 (77)	14.0 (103)	8.1 (34)	8.6 (39)	8.9 (75)	
1-2 hospitalizations	59.9 (503)	63.6 (469)	61.9 (260)	57.3 (260)	60.2 (507)	
No hospitalizations	31.0 (260)	22.4 (165)	30.0 (126)	34.1 (155)	30.9 (260)	
Geographic distribution						
Region of enrollment						<0.001
Eastern Europe	47.5 (724)	30.8 (366)	47.4 (580)	47.1 (458)	42.9 (702)	
Latin America	9.4 (144)	5.2 (62)	16.3 (199)	8.4 (82)	9.5 (155)	
North America	12.7 (193)	18.0 (214)	7.3 (89)	9.9 (96)	6.4 (104)	
Western Europe	29.6 (451)	45.2 (538)	27.9 (341)	32.5 (316)	40.1 (656)	
Other	0.9 (13)	0.8 (9)	1.1 (14)	2.2 (21)	1.1 (18)	

Continued on the next page

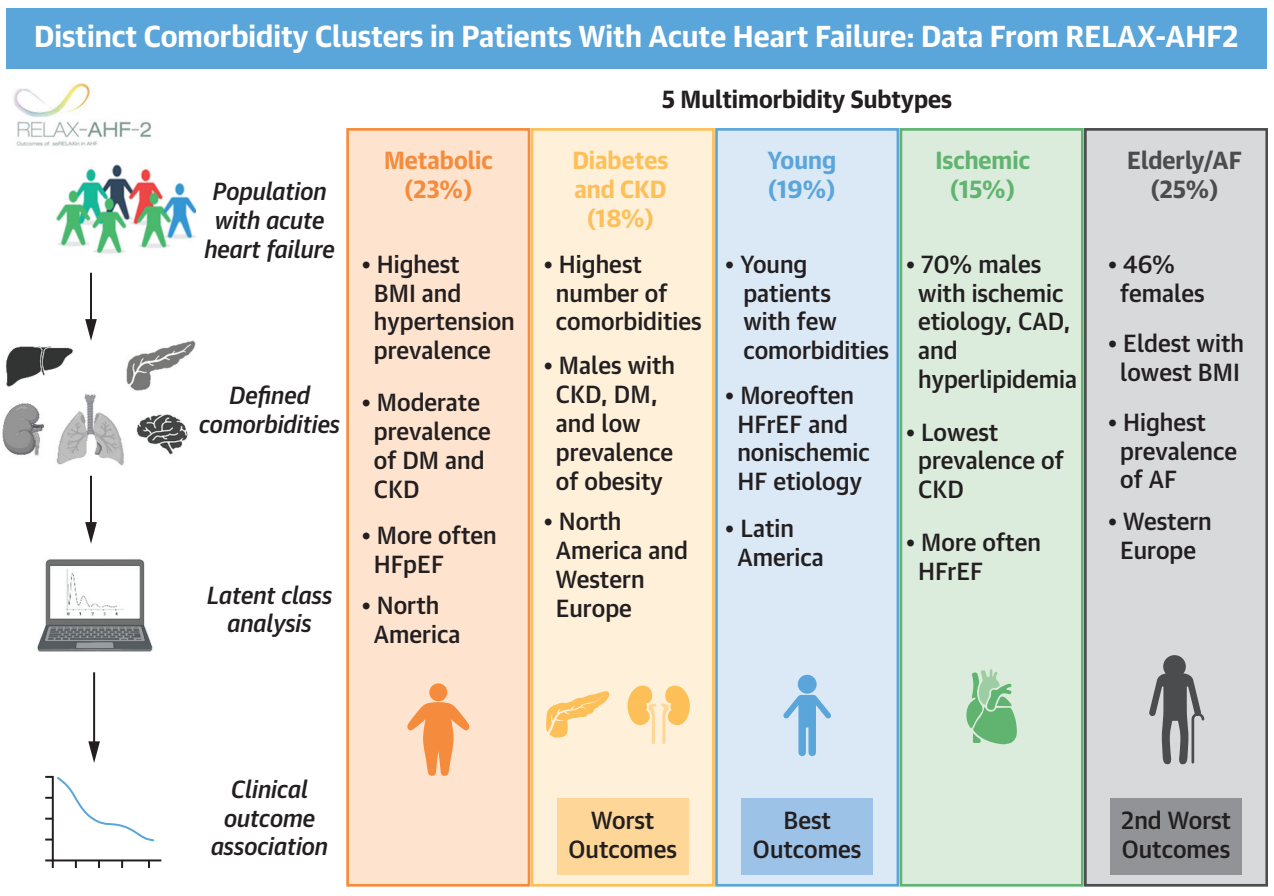
TABLE 1 Continued

	Metabolic (23.3%, n = 1,525)	Diabetes and CKD (18.16%, n = 1,189)	Young (18.68%, n = 1,223)	Ischemic (14.86%, n = 973)	Elderly/AF (24.98%, n = 1,635)	*P* Value
Clinical profile						
Angina pectoris	17.8 (268)	26.1 (304)	9.1 (111)	30.3 (291)	19.5 (315)	<0.001
Edema	91.6 (1,313)	85.9 (953)	82.4 (938)	79.8 (730)	83.5 (1,285)	<0.001
Orthopnea	97.0 (1,390)	95.6 (1,060)	96.1 (1,094)	95.8 (877)	96.4 (1,483)	0.391
Dyspnea on exertion	96.9 (1,384)	94.6 (1,044)	95.8 (1,086)	96.7 (883)	95.5 (1,459)	0.028
Increase jugular venous pressure >10 cm	27.9 (360)	27.8 (283)	24.7 (262)	22.7 (193)	24.0 (337)	0.016
Rales	54.7 (784)	53.6 (594)	55.3 (629)	57.0 (522)	53.3 (820)	0.407
Pulse, beats/min	82.75 ± 16.61	76.48 ± 13.95	86.29 ± 16.19	79.82 ± 14.18	81.02 ± 16.88	<0.001
Respiration rate, breaths/min	21.94 ± 4.58	21.28 ± 4.49	21.92 ± 4.64	21.19 ± 4.33	21.30 ± 4.29	<0.001
Systolic blood pressure, mm Hg	142.50 ± 15.35	143.63 ± 16.73	140.92 ± 15.09	141.64 ± 14.55	140.02 ± 14.46	<0.001
Diastolic blood pressure, mm Hg	80.92 ± 13.62	74.50 ± 13.28	83.93 ± 14.13	80.44 ± 13.34	78.03 ± 13.45	<0.001
Medication						
ACE inhibitor or ARB	71.6 (1,092)	71.5 (850)	51.9 (635)	69.3 (674)	63.2 (1,033)	<0.001
Beta-blockers	73.3 (1,118)	81.5 (969)	52.7 (644)	74.5 (725)	72.5 (1,185)	<0.001
MRA	31.5 (480)	26.8 (319)	24.3 (297)	31.8 (309)	27.6 (451)	<0.001
Loop diuretic agents	70.1 (1,069)	78.3 (931)	47.6 (582)	58.0 (564)	66.8 (1,092)	<0.001
Laboratory						
Hemoglobin, g/L	128.53 ± 19.29	113.46 ± 15.94	135.37 ± 18.81	134.41 ± 17.33	123.09 ± 18.20	<0.001
Hematocrit (ratio)	40 ± 6	35 ± 5	41 ± 6	41 ± 5	38 ± 5	<0.001
Leukocytes (10^9/L)	8.30 (6.80-10.20)	8.30 (6.60-10.40)	8.20 (6.70-9.97)	8.40 (6.92-10.40)	7.71 (6.23-9.70)	<0.001
Lymphocytes (absolute) (10^9/L)	1.36 (0.98-1.84)	1.25 (0.90-1.70)	1.49 (1.10-2.00)	1.49 (1.10-2.03)	1.25 (0.90-1.68)	<0.001
Neutrophils (absolute) (10^9/L)	5.91 (4.67-7.60)	6.03 (4.60-7.80)	5.73 (4.47-7.30)	6.00 (4.61-7.68)	5.54 (4.22-7.37)	<0.001
Basophils (absolute) (10^9/L)	0.02 (0.00-0.05)	0.03 (0.00-0.06)	0.02 (0.00-0.05)	0.02 (0.00-0.05)	0.02 (0.00-0.05)	0.127
Eosinophils (absolute) (10^9/L)	0.10 (0.05-0.19)	0.12 (0.07-0.20)	0.10 (0.03-0.16)	0.10 (0.04-0.20)	0.10 (0.03-0.17)	<0.001
Monocytes (absolute) (10^9/L)	0.64 ± 0.29	0.64 ± 0.30	0.61 ± 0.32	0.62 ± 0.30	0.62 ± 0.36	0.179
Glucose, serum, nonfasting, mmol/L	7.19 (5.90-9.66)	8.83 (6.49-12.00)	6.49 (5.56-8.10)	7.22 (5.88-10.09)	6.50 (5.56-8.10)	<0.001
Hemoglobin A_{1c} (%)	6.30 (5.60-7.20)	6.80 (5.90-7.70)	5.80 (5.30-6.33)	6.00 (5.50-6.90)	5.80 (5.28-6.30)	<0.001
Sodium, mmol/L	139.70 ± 4.15	139.09 ± 4.25	139.77 ± 4.10	139.49 ± 3.89	139.27 ± 4.71	<0.001
Potassium, mmol/L	4.32 ± 0.61	4.40 ± 0.61	4.26 ± 0.57	4.32 ± 0.57	4.33 ± 0.61	<0.001
Creatinine, μmol/L	122.06 ± 33.12	137.63 ± 34.65	109.43 ± 29.73	109.85 ± 29.81	121.27 ± 34.38	<0.001
Urea, mmol/L	8.82 (6.78-11.65)	10.20 (8.00-13.79)	7.60 (6.00-9.66)	7.70 (6.13-9.72)	8.99 (6.88-11.90)	<0.001
Cystatin C, mg/L	1.57 (1.27-1.89)	1.77 (1.50-2.16)	1.31 (1.11-1.58)	1.33 (1.11-1.62)	1.61 (1.32-2.04)	<0.001
Blood urea nitrogen, mg/dL	24.73 (18.99-32.67)	28.87 (22.42-38.68)	21.30 (16.99-27.07)	21.58 (17.27-27.41)	25.00 (19.13-33.24)	<0.001
eGFR, mL/min/1.73 m^2	50.01 ± 13.66	43.55 ± 11.41	57.94 ± 14.19	58.45 ± 14.01	48.90 ± 13.40	<0.001
Alkaline phosphatase, U/L	95.00 (74.23-131.00)	99.00 (76.00-132.75)	91.80 (71.00-135.00)	90.00 (69.70-123.50)	96.00 (74.40-135.00)	<0.001
Alanine aminotransferase, U/L	22.00 (16.00-34.88)	20.00 (15.00-31.00)	27.00 (19.00-43.00)	24.00 (16.00-37.00)	23.00 (15.00-36.00)	<0.001
Aspartate aminotransferase, U/L	25.00 (19.00-34.00)	23.00 (18.00-33.00)	29.00 (22.00-40.00)	26.00 (20.00-36.00)	28.00 (21.00-39.00)	<0.001
Gamma-glutamyltransferase, U/L	50.00 (26.00-84.00)	41.00 (21.50-95.50)	42.00 (22.00-83.00)	44.00 (25.00-81.00)	49.00 (27.00-90.25)	0.645
Bilirubin, μmol/L	13.85 (9.56-21.00)	11.12 (7.81-17.00)	16.42 (10.90-23.94)	13.68 (9.06-19.00)	14.26 (10.09-22.06)	<0.001
NT-proBNP, pg/mL	4,804.57 (3,118.99-8,675.55)	6,033.86 (3,538.26-9,809.27)	6,696.28 (3,804.78-11,462.83)	5,831.23 (3,392.67-9,008.01)	7,308.67 (4,237.71-13,508.64)	<0.001
Troponin T, μg/L	0.03 (0.02-0.06)	0.04 (0.03-0.06)	0.03 (0.02-0.06)	0.04 (0.02-0.07)	0.04 (0.02-0.06)	0.008
Fibroblast growth factor-23, RU/mL	409.00 (199.50-1,214.75)	441.00 (232.00-1,104.00)	335.50 (160.25-1,082.75)	255.00 (124.50-605.00)	481.00 (204.00-1,597.00)	<0.001
GDF-15, ng/L	2,967.50 (2,188.25-4,093.00)	3,657.00 (2,637.50-4,534.50)	2,647.50 (1,827.25-3,625.50)	2,505.00 (1,881.75-3,572.25)	3,155.50 (2,338.00-4,716.50)	<0.001
Procalcitonin, ng/mL	0.05 (0.05-0.12)	0.05 (0.05-0.15)	0.05 (0.05-0.10)	0.05 (0.05-0.12)	0.05 (0.05-0.13)	0.229

Values are % (n), mean ± SD or median (Q1-Q3), unless otherwise indicated.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body max index; CKD = chronic kidney disease; EF = ejection fraction; eGFR = estimated glomerular filtration rate; freq = frequency; GDF = growth differentiation factor; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

CENTRAL ILLUSTRATION Multimorbidity in Acute Heart Failure



Gomez KA, et al. JACC Heart Fail. 2024;12(10):1762–1774.

Comorbidities naturally cluster in 5 distinct subgroups in patients with acute heart failure (AHF), which show differences in clinical outcomes. The graphic presents the aims, methods, and most important findings of this study. Created with BioRender.com. AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

and 26% had HFpEF. The median number of comorbidities was 5 (Q1-Q3: 4-7). Hypertension (90%) was the most prevalent comorbidity, followed by CKD (71%) and CAD (68%).

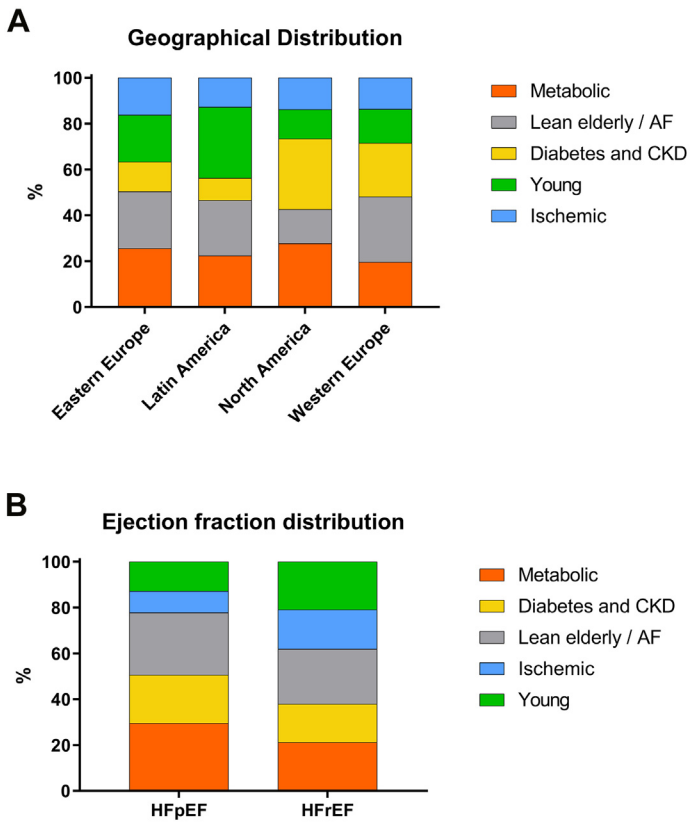
LCA identified 5 multimorbidity groups (Supplemental Table 1) of relatively equal size (N = 973-1,635). Each group had a distinct combination of comorbidities and was labeled based on the diseases most frequently observed within that cluster: metabolic (n = 1), diabetes and CKD (n = 2), young (n = 3), ischemic (n = 4), and elderly/AF (n = 5). Table 1 shows the baseline characteristics according to multimorbidity groups, and the Central Illustration summarizes the results. The distribution of patients between the serelaxin and placebo groups was similar ($P = 0.92$).

"The metabolic group" had the highest prevalence of obesity, hypertension, and HFpEF (Figure 1) and a high prevalence of DM (64%). These patients were more likely from North America.

"The diabetes and CKD group" had the highest number of comorbidities (8; Q1-Q3: 7-9), and a high prevalence of DM (94%) and CKD (94%), despite only 49% of patients being obese. Patients enrolled in North America and Western Europe were more likely to belong to this group.

"The young group" were youngest (mean age 69.4 years) and had fewer comorbidities, more

FIGURE 1 Distribution of Multimorbidity Groups



Bar graphs showing the distribution of multimorbidity groups across geographical regions (A) and according to type of heart failure (B). Heart failure with preserved ejection fraction (HFpEF) defined as left ventricular ejection fraction ≥50%. AF = atrial fibrillation; CKD = chronic kidney disease; HFrEF = heart failure with reduced ejection fraction.

likely HFrEF (mean EF 36%), and had the highest prevalence of nonischemic HF etiology (73%). The young group had the least HF medications prescribed especially, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers. These patients were more likely from Latin America.

"The ischemic group" were more likely male, had a high prevalence of CAD and hyperlipidemia, the lowest CKD prevalence, and the highest prevalence of ischemic etiology (85%). These patients more likely had HFrEF. The ischemic pattern was evenly spread among geographical regions.

"The elderly/AF group" was the largest group (N = 1,635 [24%]). Patients from the elderly/AF group were more likely female, were the oldest, had the lowest BMI, and had the highest prevalence of AF. Elderly/AF patients had the highest NT-proBNP concentrations. These patients were more likely from Western Europe.

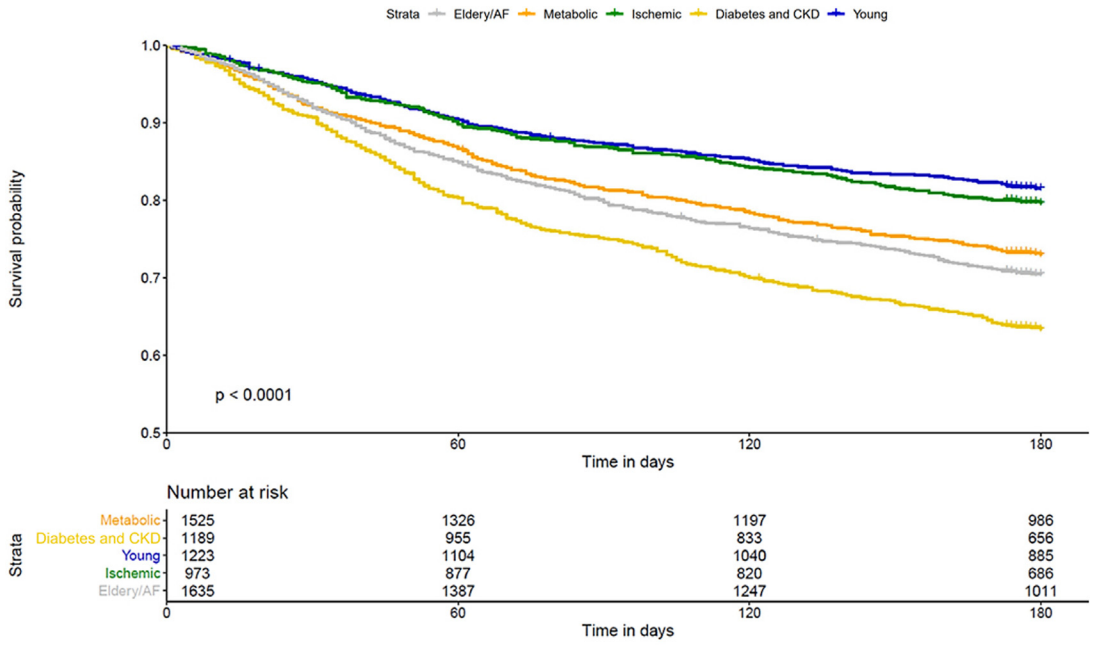
MULTIMORBIDITY GROUPS DRIVE PREVALENCE OF AEs. In the total population, 60% (n = 3,922) experienced at least 1 of the 25 most frequent AEs in the first 5 days. The incidence of AEs between the serelaxin and placebo groups was similar (49.3% and 50.6%, respectively). The ischemic group reported the fewest AEs in both the serelaxin (13.8%) and placebo (12.8%) subgroups (Supplemental Tables 3 and 4). Notably, the metabolic group (26%) in serelaxin-treated patients and the elderly/AF group (26%) in patients receiving placebo had the highest AE incidences.

MULTIMORBIDITY GROUPS DRIVE PROGNOSIS AND TREATMENT RESPONSE. In total, 1,725 (26%) patients experienced death, HHF, or renal failure within 180 days. Specifically, 755 (11%) patients died, and 1,236 (18%) patients were hospitalized for HF or renal failure. **Figure 2** illustrates the crude outcome differences between clusters, with the young group being the least likely (17%) to experience a primary event, while the diabetes and CKD cluster was the most likely (34%) to experience a primary event. **Table 2** indicates that, compared with the young group, the diabetes and CKD (HR: 1.80; 95% CI: 1.50-2.20), elderly/AF (HR: 1.42; 95% CI: 1.20-1.70), and metabolic (HR: 1.4; 95% CI: 1.20-1.80) groups were more likely to have a primary combined event. The diabetes and CKD group had the highest risk (HR: 1.80; 95% CI: 1.40-2.40) for all-cause death.

Nevertheless, the results of the competing risk analysis for HHF or renal failure revealed that not only did the diabetes and CKD cluster experience the highest HR (HR: 1.70; 95% CI: 1.30-2.30) but that the metabolic (HR: 1.60; 95% CI 1.20-2.00) and elderly/AF (HR: 1.60, 95% CI: 1.20-2.10) groups also had an increased risk compared with the young group (**Table 2**).

The type of heart failure (HFrEF or HFpEF) did not influence the associations of multimorbidity clusters with the composite outcome ($P_{interaction}$ = 0.29) (Supplemental Table 5). However, there was a significant interaction between multimorbidity groups and treatment allocation (placebo or serelaxin) ($P_{interaction}$ < 0.001) for the composite primary outcome and all-cause death alone. This interaction remained significant ($P_{interaction}$ < 0.001) after adjusting for the number of comorbidities (Supplemental Table 6). **Table 3** presents the stratified analysis of treatment allocation with serelaxin according to cluster membership. Serelaxin was associated with a reduced risk of all-cause mortality in the young group (HR: 0.60; 95% CI: 0.40-0.90)

FIGURE 2 **Multimorbidity Groups Drive Prognosis**



Kaplan-Meier curves showing differences for the combined outcome of all-cause mortality or rehospitalization for heart failure or renal failure through day 180 across multimorbidity groups. Abbreviations as in Figure 1.

(Supplemental Figure 1). Nevertheless, serelaxin allocation showed no significant association with the composite primary outcome in the young group (HR: 0.90; 95% CI: 0.68-1.20).

VALIDATION IN RELAX-AHF. In the total population of the RELAX-AHF trial, 63% were male, the mean age was 72 years, and 24% had HFpEF. For the most part, these participants had clinical and laboratory characteristics that were similar to those of the RELAX-AHF-2 cohort. The median number of comorbidities was 5 (Q1-Q3: 4-7). Hypertension (87%) was the most prevalent comorbidity, followed by CKD (70%), AF (54%), and CAD (53%).

The posterior probabilities derived from the RELAX-AHF-2 analysis predicted class membership of patients from the RELAX-AHF trial. Patients were effectively allocated into 5 mutually exclusive multimorbidity groups of relatively equal size (N = 214-267) (Supplemental Table 7). Following the pattern of the RELAX-AHF-2 analysis, we identified similar multimorbidity groups: a metabolic group with the highest prevalence of obesity (98%), hypertension (97%), and HFpEF (32%); a diabetes and CKD group with the highest number of comorbidities (median 7; Q1-Q3: 6.8-8.0) and a high prevalence of diabetes (99%) and CKD (94%); a young group characterized by few comorbidities (median 3; Q1-Q3: 2-3), a higher likelihood of HFrEF (mean EF 33%), and the highest prevalence of nonischemic HF etiology (78%); an ischemic group with the lowest prevalence of CKD (48%) and the highest prevalence of ischemic etiology (81%) and hyperlipidemia (85%); an elderly/AF group, which was the largest among them (N = 267 [23%]), had the lowest BMI (mean 26 kg/m^2 [± 24.6-28 kg/m^2]) and the highest prevalence of AF (84%).

In line with our initial analysis, the young group had the lowest likelihood (6%) and the diabetes and CKD group (20%) was the most likely to experience the combined endpoint through day 60. Crude outcome differences ($P = 0.001$) between clusters are depicted in Supplemental Figure 2. Compared with the young group, the diabetes and CKD (HR: 3.26; 95% CI: 1.30-8.20) and the metabolic (HR: 2.62; 95% CI: 1.0-6.60) groups more likely had a combined event. Consistent with our primary analysis, the competing risk analysis revealed that the diabetes and CKD (HR: 6.57; 95% CI: 1.50-28.60) and metabolic (HR: 5.37; 95% CI: 1.20-23.50) groups had increased risk compared with the young group for HHF or renal failure through day 60 (Supplemental Table 8).

TABLE 2 Multimorbidity Groups Drive Clinical Outcomes

		Model 1		Model 2		Model 3	
	Event	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All cause death or adjudicated HHF or renal failure through day 180 (24.6%)							
Young	207/1,223 (16.9%)	Ref.		Ref.		Ref.	
Metabolic	400/1,189 (33.6%)	1.54 (1.31-1.81)	**<0.001**	1.54 (1.31-1.81)	**<0.001**	1.43 (1.17-1.75)	**<0.001**
Diabetes and CKD	378/1,525 (24.8%)	2.23 (1.90-2.62)	**<0.001**	2.15 (1.83-2.53)	**<0.001**	1.80 (1.46-2.20)	**<0.001**
Ischemic	434/1,635 (26.5%)	1.11 (0.92-1.34)	0.283	1.09 (0.90-1.31)	0.402	1.06 (0.84-1.33)	0.63
Elderly/AF	188/973 (19.3%)	1.71 (1.46-2.01)	**<0.001**	1.6 (1.36-1.88)	**<0.001**	1.42 (1.16-1.73)	**<0.001**
All-cause death through day 180 (11.5%)							
Young	107/1,223 (8.7%)	Ref.		Ref.		Ref.	
Metabolic	181/1,189 (15.3%)	1.21 (0.95-1.55)	0.12	1.16 (0.89-1.53)	0.275	1.27 (0.94-1.71)	0.114
Diabetes and CKD	161/1,525 (10.6%)	1.78 (1.40-2.27)	**<0.001**	1.73 (1.32-2.27)	**<0.001**	1.81 (1.35-2.44)	**<0.001**
Ischemic	220/1,635 (13.5%)	1.00 (0.76-1.33)	0.98	1.06 (0.78-1.44)	0.707	1.10 (0.79-1.54)	0.569
Elderly/AF	86/973 (8.8%)	1.57 (1.25-1.98)	**<0.001**	1.26 (0.97-1.64)	0.084	1.21 (0.91-1.60)	0.197
Adjudicated HHF or renal failure through day 180 (18.88%)							
Young	140/1,223 (11.4%)	Ref.		Ref.		Ref.	
Metabolic	330/1,189 (27.8%)	1.77 (1.42-2.20)	**<0.001**	1.80 (1.44-2.24)	**<0.001**	1.55 (1.17-2.04)	**0.002**
Diabetes and CKD	298/1,525 (19.5%)	2.37 (1.91-2.95)	**<0.001**	2.45 (1.97-3.06)	**<0.001**	1.69 (1.26-2.25)	**<0.001**
Ischemic	327/1,635 (20.0%)	1.20 (0.93-1.55)	0.17	1.21 (0.94-1.57)	0.14	1.04 (0.75-1.43)	0.83
Elderly/AF	141/973 (14.5%)	1.72 (1.38-2.14)	**<0.001**	1.84 (1.47-2.30)	**<0.001**	1.59 (1.20-2.11)	**0.001**

Results of Cox regression analysis for the combined outcome of all-cause mortality or rehospitalization due to heart failure (HHF) or renal failure and all-cause death alone through day 180, and competing risk analysis for adjudicated HHF or renal failure through day 180. Model 1 was the univariate analysis. Model 2 adjusted for model 1 plus age and sex. Model 3 adjusted for model 2 plus NYHA functional class 1 month before inclusion, region of origin, previous hospitalization for HF, and NT-proBNP levels. **Bold** indicates significant *P* values.

Ref. = Reference; other abbreviations as in Table 1.

DISCUSSION

Novel unsupervised statistical techniques such as LCA allow through comprehensive categorization of various clinical features to identify distinct subgroups within a heterogeneous population such as AHF.[26] Utilizing a broad range of clinical features, LCA has previously been used to identify subgroups of HFpEF[27] and nonischemic HFrEF.[28] In both studies, the combination of high-dimensional phenotyping and unsupervised statistical techniques allowed identification of patient subgroups with significantly different prognoses and responses to specific therapies.

Our retrospective analysis permitted us to highlight the following: first, we identified 5 mutually exclusive multimorbidity groups in patients with AHF with a distinct geographic distribution. Second, multimorbidity groups had differences in risks for rehospitalization and death. Third, these associations were modified according to treatment allocation. Furthermore, these findings were validated in an independent cohort. Our results highlight the importance of the unique co-occurrence of comorbidities in determining patients' postdischarge outcomes and treatment responses.

FIVE DISTINCT MULTIMORBIDITY GROUPS IN PATIENTS WITH AHF. Patients with AHF naturally clustered into 5 multimorbidity subgroups (metabolic, diabetes and CKD, young, ischemic, and elderly/AF). Previous studies on multimorbidity patterns in patients with HF were limited to specific regions (Sweden, Spain, the Netherlands, Asia, or the United States) and included patients with ambulatory HF.[12-16] A study from Asia[13] identified similar comorbidity clusters, except for a lean diabetic subtype not found in our cohort. This can be explained by the low proportion of Asian patients enrolled in RELAX-AHF-2. A study from the United States[12] in patients with ambulant HFrEF and HFpEF likewise identified 5 comorbidity clusters (low-burden, metabolic-vascular, anemic, ischemic, and metabolic). These clusters also had differential risks of hospital admission, death, and health care resource use. The ischemic, metabolic subtypes, and a low comorbidity subgroup seem to be similar to the subgroups identified in our study. Our diabetes and CKD cluster partially resembles that of

TABLE 3 Stratified Analysis Within Multimorbidity Groups by Treatment Allocation (Serelaxin vs Placebo)

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All cause death or adjudicated rehospitalization due to HF/renal failure through day 180						
Metabolic	0.96 (0.79-1.17)	0.69	0.96 (0.79-1.16)	0.68	1.01 (0.82-1.24)	0.94
Diabetes and CKD	1.00 (0.82-1.20)	0.96	0.99 (0.82-1.20)	0.94	0.94 (0.76-1.14)	0.52
Young	0.86 (0.66-1.12)	0.28	0.86 (0.66-1.12)	0.26	0.90 (0.68-1.20)	0.49
Ischemic	1.13 (0.85-1.50)	0.39	1.12 (0.85-1.48)	0.43	1.09 (0.81-1.46)	0.58
Elderly/AF	0.89 (0.74-1.06)	0.20	0.88 (0.74-1.06)	0.17	0.88 (0.72-1.07)	0.20
All-cause death through day 180						
Metabolic	0.78 (0.57-1.06)	0.11	0.76 (0.56-1.04)	0.09	0.86 (0.62-1.21)	0.40
Diabetes and CKD	1.13 (0.84-1.52)	0.41	1.13 (0.84-1.51)	0.42	1.02 (0.75-1.40)	0.88
Young	0.63 (0.43-0.94)	**0.02**	0.62 (0.42-0.91)	**0.02**	0.59 (0.38-0.92)	**0.02**
Ischemic	0.98 (0.64-1.50)	0.93	0.97 (0.63-1.48)	0.88	1.01 (0.65-1.58)	0.95
Elderly/AF	1.07 (0.82-1.39)	0.63	1.03 (0.79-1.35)	0.81	1.00 (0.75-1.34)	0.99

Results of Cox regression for the combined outcome of all-cause mortality or HHF or renal failure and all-cause mortality through day 180. Model 1 stratified analysis within multimorbidity groups according to their treatment allocation (serelaxin or placebo). Model 2 adjusted for model 1 plus age and sex. Model 3 adjusted for model 2 plus NYHA functional class 1 month before inclusion, region of origin, previous hospitalization for HF (yes/no), and HFrEF vs. HfpEF. **Bold** indicates significant *P* values.

Abbreviations as in Tables 1 and 2.

the Gulea et al[12] metabolic-vascular cluster by having the highest number of comorbidities, high prevalence of DM, CAD, hypertension, and CKD and worse clinical outcomes. The anemic cluster did not have a direct equivalence in our study, suggesting that this cluster might be specific to a U.S. population with ambulant HF. Although the multimorbidity analysis conducted by Uszko-Lencer et al[15] and Gimeno-Miguel et al[16] in a Dutch and Spanish ambulatory HF cohort show similarities with the groups identified in our analysis, differences between the analyses may arise from variations in study definitions, population characteristics (higher percentage of women), the inclusion of different comorbidities, and statistical approaches. Notably, Uszko-Lencer et al[15] incorporated the corresponding degrees of disease severity into their model, whereas Gimeno-Miguel et al[16] did not combine comorbidities. We extend previous studies by including more countries from world regions and studying patterns of multimorbidity in patients hospitalized for acute HF.

MULTIMORBIDITY GROUPS HAVE DIFFERENCES IN CLINICAL OUTCOMES. Our results emphasize that multimorbidity groups can affect outcomes differently. Significant differences in AE incidence were observed among subgroups, particularly with the metabolic cluster having the highest incidence only within the serelaxin subgroup. In addition, our findings highlight variations in the prescription of HF medications among subgroups. Notably, the young group received limited HF medications, especially angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers. These observations underscore that the combination of multiple comorbidities, along with the likely influence of concomitant therapies prescribed, can affect the likelihood of experiencing AEs in clinical trials. However, these results are only hypothesis-generating and should be validated in an independent prospective cohort.

In our study, multimorbidity pattern was additionally a stronger predictor for HHF than mortality. This might suggest that optimizing comorbidity care will more likely prevent HHF than mortality. Consistent with earlier studies,[12,13] the young class had the lowest risk of the composite endpoint all-cause death or HHF or renal failure. The diabetes and CKD cluster, in contrast, had the worst prognosis for all clinical outcomes studied. Indeed, evidence from recent analysis such as FIDELITY (Finerenone in Chronic Kidney Disease and Type 2 Diabetes: Combined FIDELIO-DKD and FIGARO-DKD trial program analysis),[29] and clinical trials including FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease),[30] FIGARO-DKD (Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease),[31] and EMPEROR-Pooled (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure-Combined Reduced and Preserved Trials),[32,33] among others, have stressed the significant interaction between diabetes and kidney disease and HF. These studies have shown a significant reduction in cardiovascular disease events and a consistent benefit for slowing renal disease progression, confirming that the

interplay between diabetes and kidney disease and HF modifies the overall burden of disease morbidity and mortality.[34]

In contrast to previous studies,[12,13] the ischemic cluster did not have an increased mortality risk compared with that of the young group. This might be explained by the inclusion criteria for RELAX-AHF-2, which resulted in the enrollment of a population that was at lower risk than patients with AHF included in registry-based studies.[35] These criteria in particular excluded patients with AHF with clinical evidence of acute coronary syndrome.[21]

To validate our results, we used the calculated posterior probabilities and applied them to an independent cohort of 1,161 patients with AHF. The 5 predicted multimorbidity groups followed the same baseline characteristics pattern and associations with outcome as our RELAX-AHF-2 analysis.

Altogether, these results emphasize that the clinical prognosis of patients with AHF may be dependent on the cumulative effect of unique combinations of comorbidities.

MULTIMORBIDITY GROUP MEMBERSHIP MODIFIED THE EFFECT OF TREATMENT ON CLINICAL OUTCOME. There was a significant interaction between treatment allocation and multimorbidity group for clinical outcome. This interaction remained significant after adjustment for the number of comorbidities, indicating that indeed it is the combination of comorbidities, rather than the quantity of them, that influences treatment response.

Multimorbidity group membership modified the effect of treatment allocation on all- cause mortality such that the young group showed a potential benefit of treatment with serelaxin. A trend for reduced risk for cardiovascular death for younger patients treated with serelaxin has been shown in the primary subgroup analysis of this trial.[20] These results highlight the importance of comorbidities in potentially determining treatment benefit. However, these results should be prospectively validated.

A multitude of AHF clinical trials, including the RELAX-AHF-2 trial, have yielded neutral or negative results when assessing the impact of novel treatments on symptom relief and survival.[36,37] Given the heterogeneous nature of AHF, clinical profiling could prove beneficial for the improved classification of these patients, potentially leading to the development of personalized treatment options. Although we were able to show that the presence of multiple comorbidities is an important and independent predictor of differential outcomes, our study was not primarily aimed at creating a new classification or risk stratification tool. Instead, the primary objective of the present study was to illustrate that the existence of multiple comorbidities is not random, adds clinical value, amplifies the disease burden, and affects the outcomes and treatment responses of patients with AHF. Our data highlight that the distinct combination of multiple comorbidities influences the treatment response of patients with AHF. Given the heterogeneous nature of AHF, improved patient classification may lead to personalized therapy guidelines. Furthermore, consideration of multimorbidity groups could help inform the design and conduct of future clinical trials and may be used to identify responders to therapies.

STUDY LIMITATIONS. The present study is based on a post hoc analysis of a clinical trial. Inherent to clinical trials, there is likely bias in patient selection. In particular, inclusion criteria for RELAX-AHF-2 resulted in the enrollment of a population that was at lower in-hospital mortality risk than patients with AHF included in registry-based studies.[35] Although the RELAX-AHF-2 was an international trial that included patients from 35 countries, 90% of the patients were White. Rehospitalization causes (HF or renal failure) were not independently recorded, preventing assessment of the impact of renal failure on outcomes. Also, comorbidities included in the LCA analysis were mostly interrogated in different geographical regions, which could drive some of the findings described. Finally, although every effort has been made to correct for potential confounders in survival analyses, some uncaptured factors might have influenced differences in survival between groups.

CONCLUSIONS

Comorbidities naturally cluster in 5 distinct groups in patients with AHF: diabetes and CKD, ischemic, elderly/AF, metabolic, and young. Multimorbidity groups were associated with different composite outcomes of all-cause mortality or HHF or renal failure as well as all-cause death and HHF or renal failure alone. Treatment allocation modified the associations with clinical outcome. These data highlight that the distinct combination of multiple comorbidities carries additional clinical value, increasing the disease burden and affecting the outcome and treatment response of patients with AHF.

ACKNOWLEDGMENTS Artificial intelligence programs were used to proofread the final version of the manuscript.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by the PROMINENT project (funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement number 754425). Dr Tromp is supported by the National University of Singapore Start-up grant, the tier 1 grant from the ministry of education, and the CS-IRG New Investigator Grant from the National Medical Research Council; has received consulting or speaker fees from Daiichi Sankyo, Boehringer Ingelheim, Roche Diagnostics, and Us2.ai; and owns patent US-10702247-B2 unrelated to the present work. Drs Cotter and Davison are employees of Momentum Research, Inc, which has received grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics Inc, Corteria Pharmaceuticals, Roche Diagnostics Inc, Sanofi, Windtree Therapeutics Inc, and XyloCor Therapeutics. Dr Felker has received research grants from the National Heart, Lung, and Blood Institute, the American Heart Association, Amgen, Bayer, BMS, Merck, Cytokinetics, and CSL-Behring; has acted as a consultant to Novartis, Amgen, BMS, Cytokinetics, Medtronic, Cardionomic, Boehringer Ingelheim, American Regent, Abbott, AstraZeneca, Reprieve, Myovant, Sequana, Windtree Therapeutics, and Whiteswell; and has served on clinical endpoint committees/data safety monitoring boards for Amgen, Merck, Medtronic, EBR Systems, V-Wave, LivaNova, Siemens, and Rocket Pharma. Dr Gimpelewicz is an employee of Novartis. Dr Greenberg is a consultant for or on the advisory board of AstraZeneca, Bayer, Ionis, Merck, Mesoblast, and Tenaya; and has been on the Data Safety Monitoring Board of ACI, Axon, AstraZeneca, Bayer, Cytokinetics, Boehringer Ingelheim, EBR Systems, Faraday, Inventiva, Impulse Dynamics, Ionis, Salubris, Vifor, Viking, and Windtree. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc, EchoNous Inc, Eli Lilly, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, ProSciento Inc, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and Us2.ai; and serves as co-founder and nonexecutive director of Us2.ai. Dr Voors has received research support and/or has been a consultant for Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Cytokinetics, Merck, MyoKardia, Novo Nordisk, Novartis, and Roche Diagnostics. Dr Metra received personal fees of minimal amounts in the last 3 years from Actelion, Amgen, LivaNova, and Vifor pharma as a member of Executive or Data Monitoring Committees of sponsored clinical trials; and from AstraZeneca, Abbott Vascular, Bayer, Boehringer Ingelheim, and Edwards Therapeutics for participation on advisory boards and/or speeches at sponsored meetings. Dr Teerlink has received research support and/or has been a consultant for Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Medtronic, Merck, Novartis, Servier, and Windtree Therapeutics. Dr van der Meer received grant support and/or consultancy fees from Novartis, Pharma Nord, Pfizer, Ionis, Astra Zeneca, Vifor Pharma, Pharmacosmos, BridgeBio, and Novo Nordisk. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

HF frequently co-occurs with multiple comorbidities. Multimorbidity is not random. A better understanding of the unique multimorbidity patterns in AHF may improve personalized treatment allocation, clinical trial design, and help plan health care services. We performed an LCA to delineate multimorbidity groups. The aim of this analysis was not to create a novel prediction model for outcomes in AHF. This method is unbiased and data-driven and can identify novel, potentially "hidden" patterns that are obscured due to the broad constellation of characteristics of these patients. Altogether, the results observed highlight that the distinct combination of multiple comorbidities follows a pattern and affects the outcome and treatment response of patients with AHF.

TRANSLATIONAL OUTLOOK:

The present study delves into the complexities of multimorbidity groups and their implications on the outcome and treatment response of patients with AHF. Our results are based on a post hoc analysis of a clinical trial, which inherently may introduce biases. Although efforts have been made to validate the results using an independent cohort, it remains imperative to prospectively validate these findings in a clinical trial setting, in which the impact of comorbidities on patient outcomes is a critical consideration in the study design and planning. By considering such factors in future trials, we may potentially identify effective therapeutic interventions for specific populations of patients. Conducting further research in this direction can pave the way for a more nuanced understanding of multimorbidity and its role in identifying responders to therapies, thereby advancing both personalized medicine and scientific inquiry.

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KEY WORDS acute heart failure, cluster, multimorbidity, RELAX-AHF-2, poLCA

APPENDIX For supplemental figures and tables, please see the online version of this paper.