

Clustering based on comorbidities in patients with chronic heart failure: an illustration of clinical diversity

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Abstract

Aims It is increasingly recognized that the presence of comorbidities substantially contributes to the disease burden in patients with heart failure (HF). Several reports have suggested that clustering of comorbidities can lead to improved characterization of the disease phenotypes, which may influence management of the individual patient. Therefore, we aimed to cluster patients with HF based on medical comorbidities and their treatment and, subsequently, compare the clinical characteristics between these clusters.

Methods and results A total of 603 patients with HF entering an outpatient HF rehabilitation programme were included [median age 65 years (interquartile range 56–71), 57% ischaemic origin of cardiomyopathy, and left ventricular ejection fraction 35% (26–45)]. Exercise performance, daily life activities, disease-specific health status, coping styles, and personality traits were assessed. In addition, the presence of 12 clinically relevant comorbidities was recorded, based on targeted diagnostics combined with applicable pharmacotherapies. Self-organizing maps (SOMs; www.viscovery.net) were used to visualize clusters, generated by using a hybrid algorithm that applies the classical hierarchical cluster method of Ward on top of the SOM topology. Five clusters were identified: (1) a least comorbidities cluster; (2) a cachectic/implosive cluster; (3) a metabolic diabetes cluster; (4) a metabolic renal cluster; and (5) a psychologic cluster. Exercise performance, daily life activities, disease-specific health status, coping styles, personality traits, and number of comorbidities were significantly different between these clusters.

Conclusions Distinct combinations of comorbidities could be identified in patients with HF. Therapy may be tailored based on these clusters as next step towards precision medicine. The effect of such an approach needs to be prospectively tested.

Keywords Heart failure; Clustering; Comorbidities

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Introduction

Heart failure (HF) is a major and increasing global health concern, causing considerable morbidity and mortality around the world. HF is defined by the presence of cardiac dysfunction together with signs and symptoms of HF.¹ Features such as left ventricular ejection fraction (LVEF), New York Heart

Association (NYHA) class, and N-terminal pro-brain natriuretic peptide (NT-proBNP) are used to grade the degree of HF.^{1–3} Nevertheless, the LVEF poorly correlates with physical performance and outcome in patients with HF,⁴ estimation of NYHA class may be difficult,⁵ and NT-proBNP is influenced by factors other than HF.⁶ Moreover, it is increasingly recognized that the presence of common medical comorbidities, such

as chronic obstructive pulmonary disease (COPD), renal dysfunction, gout, anaemia/iron deficiency, and diabetes, substantially contribute to the burden of HF. Indeed, comorbidities can affect symptom burden, functional performance, and health status in patients with HF and increase the risk of hospitalization and mortality.⁷

Besides the disturbed functional performance and common comorbidities, increased symptoms of anxiety and depression are highly prevalent in patients with HF. Personality traits seem to have bigger impact on quality of life and symptoms of anxiety and depression^{8,9} than the degree of LVEF impairment.¹⁰ Also, coping style is an important feature in HF patients. Older patients with HF generally have an avoidant coping style,¹¹ whereas in younger patients, active behavioural coping or active cognitive coping is chosen more frequently.¹² So patients with HF have multiple physical and psychosocial traits, which go beyond the impaired cardiac function. Several reports have suggested that clustering of patient characteristics may be a first step towards phenotyping and, in turn, an improved understanding of the complexity of patients also with HF.^{13–16} In a recent study by Ahmad *et al.*, cluster analysis identified four distinct phenotypes that differed significantly in outcomes and in response to therapeutics. Outcomes were accurately predicted in a large data set of HF patients.¹⁷ Therefore, the present study investigated the frequency of 12 comorbidities and how these comorbidities co-occurred in a well-characterized cohort of patients with HF. In addition, potential differences in physical and psychosocial traits were explored.

Methods

The current analyses used data from 603 patients entering the specialized HF rehabilitation programme at CIRO, Horn, The Netherlands, between June 2005 and September 2015.¹⁸ Patients were referred by the HF outpatient clinics of Maastricht University Medical Center (MUMC+, Maastricht, The Netherlands) and Laurentius Hospital (Roermond, The Netherlands). Patients had to have stable HF, receive maximal medical treatment [i.e. optimal medication,¹ revascularization, resynchronization, and/or internal cardioverter defibrillator (ICD) therapy if indicated], and be motivated to adhere to the HF integrated management programme. Each patient underwent a comprehensive routine 3 day assessment before starting the patient-tailored, multidisciplinary intervention programme. The medical ethical committee informed the authors that the Medical Research Involving Human Subjects Act (WMO) does not apply to this retrospective study using de-identified, pre-existing data and approved the use of these data for the purpose of this study (METC 2018-0586). The Board of Directors of CIRO did approve the use of de-identified patients' records.

Assessments

Demographics, medications, aetiology of HF, LVEF, dyspnoea [NYHA class and Medical Research Council (MRC) dyspnoea grade¹⁹], smoking status, and hospital admissions in the last 12 months were documented. In addition, the following tests were performed: lung function (post-bronchodilator spirometry, static lung volumes, and carbon monoxide transfer factor); body composition [body mass index (BMI), fat-free mass index (FFMI), and bone mineral density at the hip, lumbar spine, and whole body using dual-energy absorptiometry scan]²⁰; resting ECG; a peripheral blood pressure; exercise capacity [cardiopulmonary exercise test (CPET), constant work rate cycling test (CWRT), and 6 min walk test (6MWT)]^{21,22}; problematic activities of daily life [Canadian Occupational Performance Measure (COPM)]²³; coping styles [Utrecht Coping List (UCL)]²⁴; personality traits (Dutch Personality Questionnaire); and symptoms of anxiety and depression [Hospital Anxiety and Depression Scale (HADS)²⁵ and Beck Depression Inventory (BDI)²⁶] and HF-specific quality of life [Minnesota Living With Heart Failure Questionnaire (MLHFQ)²⁷]. Venous blood was obtained in fasting state for assessment of haematology and chemistry including NT-proBNP, potassium, sodium, urea, creatinine, estimated glomerular filtration rate (eGFR), glucose, thyroid stimulating hormone (TSH), C-reactive protein (CRP), cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and haemoglobin.

Comorbidities

Comorbid conditions were identified in all patients based on predefined cut-offs: renal dysfunction (eGFR < 60 mL/min); anaemia (haemoglobin level < 8.1 mmol/L in men; <7.5 mmol/L in women); obesity (BMI ≥ 30 kg/m²); underweight (BMI < 21 kg/m²); muscle wasting (FFMI < 16 kg/m² for men; <15 kg/m² for women); osteoporosis (*T*-score ≤ 2.5); symptoms of anxiety and depression (HADS-A or HADS-D score ≥ 10 points, respectively); and obstructive lung function (forced expiratory volume in 1 s/vital capacity; FEV1/VC < 70%). Additional risk factors found during pre-rehabilitation assessment were as follows: diabetes mellitus (use of antidiabetic medication and/or fasting glucose level ≥ 7.0 mmol/L); hyperglycaemia (fasting glucose level ≥ 5.6 but <7.0 mmol/L and no antidiabetic medication); and gout (use of medication: xanthine oxidase inhibitor and/or colchicine).

For all comorbidities—except gout—severity degrees were calculated. The following formula is based on the underlying parameter *x* with cut-off x_{cutoff} and standard deviation $\sigma(x)$ and was used for obesity, anxiety, depression, and hyperglycaemia:

$$\text{degree}(x) = \frac{x - x_{\text{cutoff}}}{\sigma(x)}$$

For renal dysfunction, anaemia, underweight, muscle wasting, and COPD, the sign had to be alternated, because lower values indicate a worse state:

$$\text{degree}(x) = (-1) \cdot \frac{x - x_{\text{cutoff}}}{\sigma(x)}$$

By this definition, the severity degrees are comparable across different comorbidities: a value of 0 means that the value is at the cut-off, a value above 0 indicates that the comorbidity is present, a value of 1 means the degree of severity is one standard deviation above the cut-off, and so on.

Data analysis and statistics

Viscovery SOMine 7.2 by Viscovery Software GmbH (www.viscovery.net; Vienna, Austria) was used to create a self-organizing map (SOM) to represent the patients in an ordered manner on a two-dimensional map and to cluster them into several groups with distinct comorbidity patterns.

Self-organizing maps represent multidimensional data on a grid of topologically linked micro-clusters (also called nodes). Each node consists of very similar patients—in terms of the patients overall similarity across all variables of interest—and neighbouring nodes correspond to rather similar patients as well. This approach allows for a consistent visualization of all patients across multiple variables and easy clustering of them. For further information on SOMs, we refer to the supporting information and the primary source book on SOMs by Kohonen.²⁸

Viscovery SOMine offers the possibility to weight the variables that are used for the ordering in the SOM algorithm. In our model, patients have been ordered by the presence/absence of the following comorbidities and the corresponding degrees of their severity: renal dysfunction, diabetes mellitus, hyperglycaemia, anaemia, obesity, underweight, muscle wasting, osteoporosis, COPD, anxiety, depression, and gout. A higher weight was given to the severity degrees and a lower weight to the comorbidity flags. See *Table 3* for the exact values.

Based on the created SOM model, clusters were generated using the SOM-Ward Cluster algorithm, which applies the classical hierarchical cluster method of Ward on top of the SOM topology (Viscovery SOMine 7.2 user's manual, A.6 Ward and SOM-Ward Clustering, Viscovery, 2018). Cluster aggregates are presented with median and interquartile range for continuous variables and as percentages for categorical variables.

R 3.5.1 (www.R-project.org) was used to test all attributes for significant deviations on the clusters. First, all variables were analysed to decide which statistical tests are appropriate for each of them. Then, all variables were tested for

significant differences across all the clusters. After a Benjamini–Hochberg multiple testing correction, variables with adjusted *P*-values < 0.05 were considered to have statistically significant differences across the clustering. Those variables were then further tested for differences of individual clusters against the rest of the data. Again, variables with adjusted *P*-values < 0.05 were considered statistically significant for the individual cluster. Further details about the testing procedure can be found in the supporting information.

Results

Whole sample

In total, 603 patients with HF (71% male) were included. Median age was 65 (56–71) years, 57% had ischaemic origin of HF, with a median LVEF 35% (26–45) (*Table 1*). Patients were pharmacologically treated according to the European Society of Cardiology guidelines²⁹: angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ACE-I/ARB) were used in 91%, beta-blockers in 87%, and mineralocorticoid-receptor antagonists (MRA) in 41%.

Frequency of objectively identified comorbidities

The frequencies of the objectified comorbidities ranged from 3.7% up to 60.2% (*Figure 1*). Renal dysfunction was the most common comorbidity, followed by COPD, obesity, hyperglycaemia, anaemia, and diabetes mellitus.

Number of comorbidities

Almost all subjects (97.6%) had one or more comorbidities, and 64.7% of the patients had three or more comorbidities (*Figure 2*). The co-occurrences of individual comorbidities in patients with each of the 12 specific comorbidities are shown in *Figure 3*. For example, in obese patients, gout was highly prevalent (20%), but not in patients with muscle wasting (2%) or underweight (5%). The distribution of various continuous markers of comorbidities in the clusters is shown in *Figure 4*.

Clustering based on comorbidities

Five clusters were identified (*Figure 5*). *Tables 1–3* provide a detailed description of demographics and comorbidities per cluster. Patients in Cluster 1 (*the least comorbidities cluster*, *n* = 183) had significantly fewer comorbidities compared with patients in other clusters. Cluster 2 (*the cachectic/impulsive*

Table 1 Demographics and cardiac-related attributes

Attribute	Whole sample N = 603	C1 N = 183	C2 N = 103	C3 N = 107	C4 N = 103	C5 N = 107
Male, % patients	71	76	52	81	76	68
Age, years	65 (56–72)	64 (54–70)	65 (55–73)	68 (60–74)	69 (60–76)	59 (49–67)
Ischaemic underlying cause, % patients	57	48	49	78	67	49
LVEF, %	35 (26–45)	35 (26–45)	38 (26–47)	30 (25–39)	33 (26–44)	40 (31–50)
Resting heart rate, b.p.m.	73 (64–82)	73 (64–82)	75 (67–83)	74 (66–88)	70 (61–82)	74 (64–82)
QRS, ms	104 (90–138)	100 (90–130)	98 (84–131)	114 (92–147)	110 (91–158)	106 (91–138)
LBBB, % patients	18	19	25	14	19	13
RBBB, % patients	11	7	6	17	14	12
IVCD, % patients	38	36	33	45	44	35
Cardiac support device, % patients						
ICD	20	24	11	26	19	19
Biventricular ICD	21	22	15	23	26	17
Pacemaker	4	2	3	7	4	5
Resting blood pressure, mmHg						
Systolic	120 (110–135)	120 (110–140)	125 (110–140)	125 (113–140)	117 (105–126)	125 (110–135)
Diastolic	75 (68–80)	80 (70–84)	73 (60–80)	75 (70–80)	70 (60–78)	75 (69–80)
Toilet visits at night, <i>n</i>	1 (0–2)	1 (0–1.5)	1 (0–2)	1 (0.5–2)	1 (1–2)	1 (0–2)
Pillows to sleep on, <i>n</i>	1 (1–2)	1 (1–2)	1 (1–1.8)	1 (1–2)	1 (1–2)	1 (1–2)
MRC dyspnoea scale, grade	2 (2–3)	2 (1–3)	2 (2–3)	2 (1.8–3)	2.5 (2–3)	2 (2–3)
NYHA class	2 (2–3)	2 (2–2)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)
NYHA class, % patients						
I	6	11	3	6	5	1
II	64	68	66	58	55	68
III	30	21	28	36	40	31
IV	1	0	3	0	0	0
Smoking pack years, <i>n</i>	20 (4–35)	20 (5–39)	20 (3–35)	25 (10–40)	20 (6–30)	10 (0–25)
Hospital admissions last 12 months, <i>n</i>	1 (0–1)	0 (0–1)	1 (0–1)	1 (0–1.3)	1 (0–2)	1 (0–2)
NT-proBNP, pmol/L	84 (30–216)	62 (19–168)	82 (32–244)	96 (37–209)	214 (72–307)	61 (21–157)
Potassium, mmol/L	4.2 (4–4.6)	4.2 (3.9–4.6)	4.3 (4–4.7)	4.3 (4–4.6)	4.2 (4–4.7)	4.2 (3.9–4.6)
Sodium, mmol/L	141 (140–143)	141 (140–143)	141 (140–143)	141 (140–143)	142 (140–143)	141 (140–142)
Urea, mmol/L	7.8 (5.9–10.5)	7.3 (5.7–8.9)	6.4 (4.9–8.3)	9.3 (6.7–13.2)	11.1 (8.1–15.2)	6.9 (5.7–8.9)
Creatinine, μ mol/L	110 (91–138)	101 (89–118)	96 (77–113)	130 (104–167)	146 (129–173)	103 (90–125)
TSH, mIU/L	2.3 (1.5–3.9)	2.3 (1.3–3.1)	2.3 (1.5–4.3)	2.2 (1.8–4)	2.7 (1.4–4.4)	2.8 (1.5–3.9)
CRP, mg/L	2.4 (0.9–6.8)	2 (0.8–5)	2 (0.7–7.1)	2.8 (0.8–6.6)	4 (1.5–11)	2.6 (1.1–6.2)
Haemoglobin, mmol/L	8.3 (7.7–9)	8.6 (8.2–9.2)	8.4 (7.6–9)	8.2 (7.6–9.1)	7.4 (6.9–7.9)	8.5 (7.9–9.1)
Glucose, mmol/L	5.9 (5.3–6.8)	5.7 (5.3–6.2)	5.6 (5.2–6.2)	8 (7.3–8.9)	5.4 (5.1–6)	6.1 (5.5–7.6)
Medication, % patients	61	54	50	82	64	57
Statins						
Beta-blocker	87	89	80	94	84	87
Diuretics	74	68	67	87	85	66
MRA	41	35	43	44	47	38
ACE inhibitor	59	61	63	53	54	64
ARB	32	34	27	39	31	27
Diabetes	19	7	5	57	13	21
Gout	15	5	0	23	39	13

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRP, C-reactive protein; GFR, glomerular filtration rate; ICD, internal cardioverter defibrillator; IVCD, interventricular conduction delay; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; mMRC, modified Medical Research Council; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RBBB, right bundle branch block; TSH, thyroid stimulating hormone.

Data are shown as median (interquartile range) or % patients.

Green cell: value is significantly lower (adjusted $P < 0.05$) compared with whole sample; red cell: value is significantly higher (adjusted $P < 0.05$) compared with whole sample, where each variable was tested with the appropriate tests and a multiple testing correction was applied; see Statistics section. Missing data: ischaemic underlying cause, $n = 213$; left ventricular ejection fraction (LVEF), $n = 132$; resting heart rate, $n = 15$; QRS, $n = 158$; left bundle branch block (LBBB), $n = 245$; right bundle branch block (RBBB), $n = 260$; cardiac support device, $n = 23$; resting blood pressure, $n = 99$; toilet visits at night, $n = 59$; pillows to sleep, $n = 43$; Medical Research Council (MRC), $n = 131$; New York Heart Association (NYHA), $n = 33$; pack years, $n = 195$; hospital admissions, $n = 272$; NT-proBNP, $n = 374$; potassium, $n = 9$; sodium, $n = 9$; urea, $n = 12$; creatinine, $n = 16$; TSH, $n = 413$; CRP, $n = 22$; and medication, $n = 28$.

Figure 1 Frequencies of objectively identified comorbidities. The total number of subjects with a present comorbidity always refers to the number of subjects with known information concerning the respective comorbidity; this is shown in *Figure 3*. FFMI, fat-free mass index.

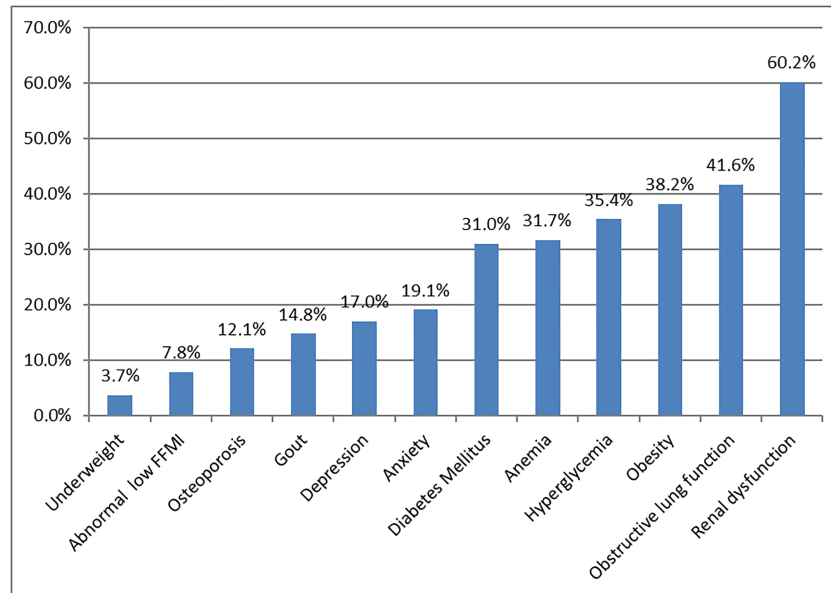
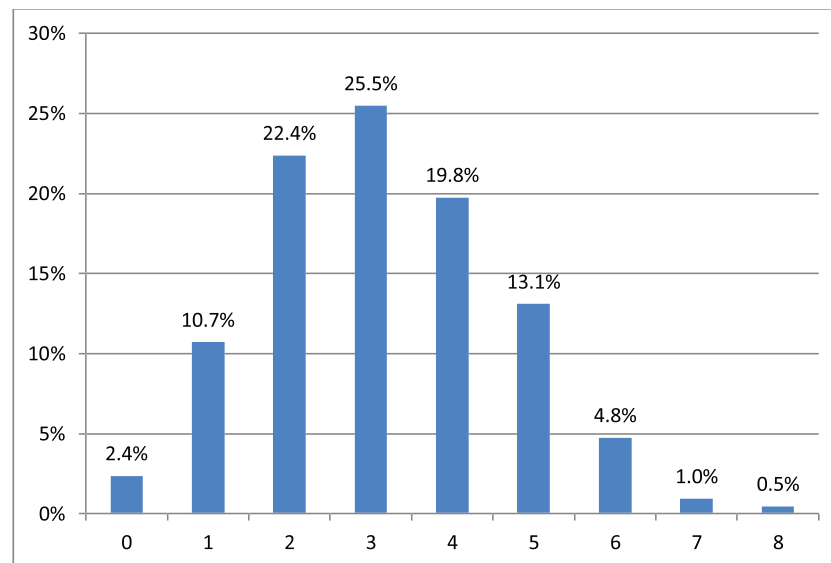


Figure 2 Number of comorbidities per patient*. *of 420 patients with all comorbidity information available.



cluster, $n = 103$) had significantly more patients with underweight, low FFMI, osteoporosis, and obstructive lung function and significantly fewer with gout, anxiety, obesity, and diabetes mellitus. Cluster 3 (*the metabolic diabetes cluster*, $n = 107$) had significantly more patients with gout, obstructive lung function, diabetes mellitus, and renal dysfunction and significantly fewer with anxiety, depression, low FFMI, and hyperglycaemia. Cluster 4 (*the metabolic renal cluster*,

$n = 103$) had significantly more patients with gout, osteoporosis, anaemia, and renal dysfunction and significantly fewer with anxiety, depression, low FFMI, and diabetes mellitus. Cluster 5 (*the psychological cluster*, $n = 107$) had significantly more patients with anxiety, depression, obesity, and diabetes mellitus, worse quality of life, and significantly fewer patients with low FFMI, osteoporosis, obstructive lung function, anaemia, and renal dysfunction.

Figure 3 The frequencies of objectively identified comorbidities in patients with chronic heart failure with each of the 12 selected specific comorbidities. In subjects in whom the comorbidity mentioned in the row is present, the prevalence of the other comorbidities mentioned in the column is shown. Note that the information about the presence or absence of a comorbidity was not known for all patients. Therefore, the total number of subjects with a present comorbidity always refers to the number of subjects with known information concerning the respective comorbidity. For interpretation, the table is coloured: blue, less than 20% prevalence; green, 20–40% prevalence; yellow, 40–60% prevalence; and red, more than 60% prevalence. FFMI, fat-free mass index.

	% Renal dysfunction	% Diabetes Mellitus	% Hyperglycemia	% Anemia	% Obesity	% Underweight	% Abnormal low FFMI	% Osteoporosis	% Obstructive lung function	% Anxiety	% Depression	% Gout
Renal dysfunction (n=296/492)		37%	31%	43%	37%	3%	6%	14%	41%	17%	17%	23%
Diabetes Mellitus (n=184/593)	69%			36%	48%	2%	2%	9%	40%	20%	17%	21%
Hyperglycemia (n=210/593)	54%			29%	41%	3%	10%	12%	44%	19%	20%	10%
Anemia (n=188/593)	75%	35%	32%		32%	5%	11%	12%	45%	18%	17%	21%
Obesity (n=229/599)	58%	39%	38%	27%		0%	1%	9%	32%	23%	19%	20%
Underweight (n=22/599)	62%	18%	27%	41%	0%		50%	22%	55%	25%	20%	5%
Abnormal low FFMI (n=44/561)	62%	9%	44%	44%	2%	25%		23%	39%	10%	20%	2%
Osteoporosis (n=64/530)	70%	22%	38%	33%	28%	6%	14%		59%	14%	24%	19%
Obstructive lung function (n=249/593)	60%	30%	38%	34%	29%	5%	7%	17%		17%	16%	16%
Anxiety (n=110/576)	52%	31%	34%	28%	48%	5%	4%	9%	35%		51%	15%
Depression (n=98/576)	61%	31%	41%	30%	44%	4%	9%	17%	38%	57%		15%
Gout (n=89/603)	79%	43%	24%	44%	51%	1%	1%	15%	45%	20%	17%	

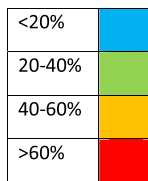


Figure 4 Distribution of various continuous markers of comorbidities in clusters. These values were used to define the severity degrees as noted in the Methods section.

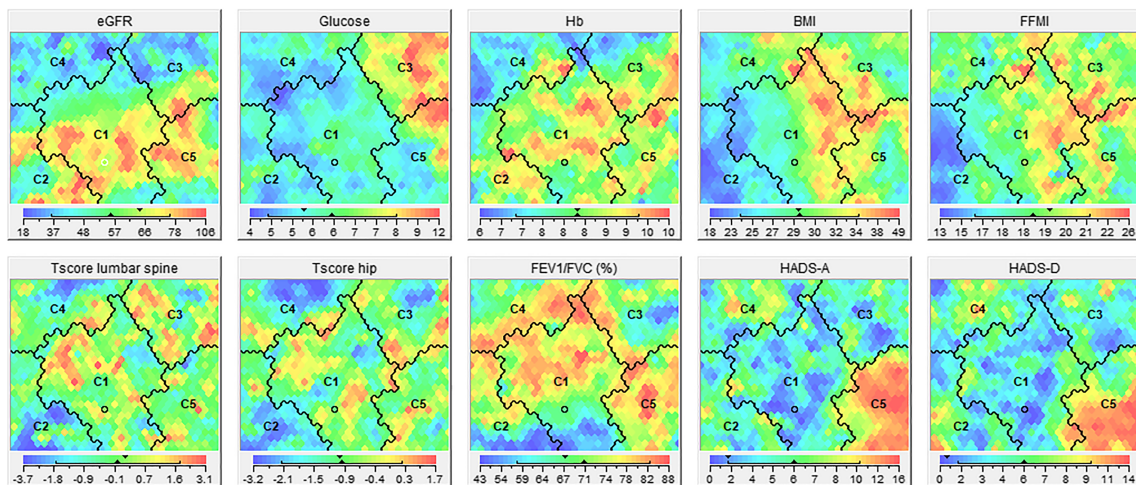
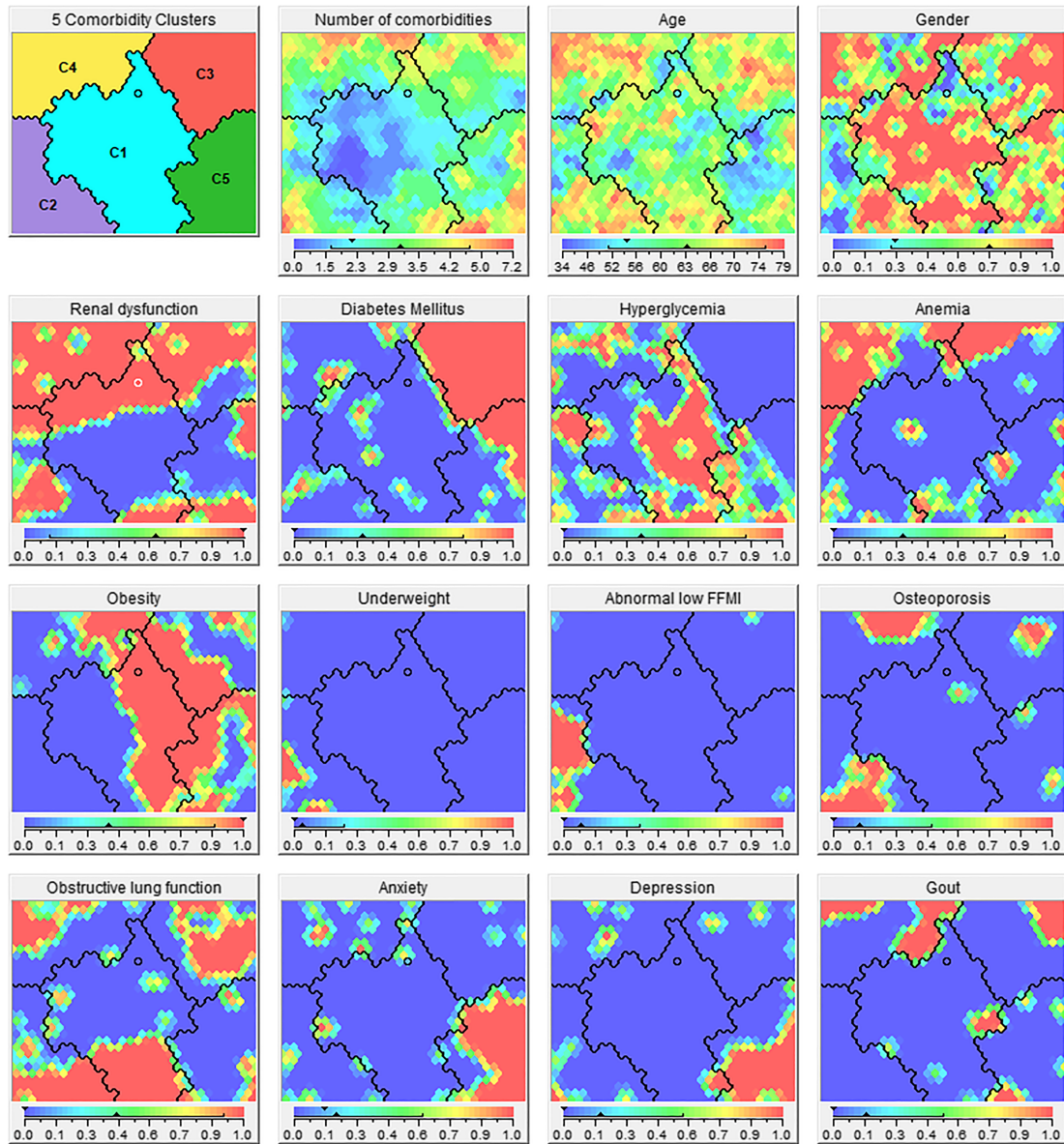


Figure 5 Clusters based on extra-cardiac features in 603 patients with HF. Viscovery SOMine 7.2 placed all subjects on a specific position on the map based on their profile of comorbidities. The more subjects resemble in terms of their comorbidities, the closer they are on the map. When looking at individual comorbidities or characteristics, subjects are coloured red if the comorbidity is present and blue when it is absent. On the maps, males are coloured red and females blue. In this way, the maps can be interpreted. Viscovery SOMine 7.2 identified five different clusters of patients with HF with a significant different profile of comorbidities (95% confidence interval). The cluster borders are drawn as thick lines on the map pictures. Definition of clusters: C1 = least comorbidities, C2 = cachectic/impulsive, C3 = metabolic diabetes, C4 = metabolic renal, C5 = psychologic. FFMI, fat-free mass index.



Differences in patient characteristics between clusters (Tables 1 and 2)

Cluster 1 (*least comorbidities cluster*) was characterized by significantly less ischaemic origin of HF, less activity-related dyspnoea, less hospital admissions < 12 months, a higher resting diastolic blood pressure, higher haemoglobin, eGFR, lower glucose, a better physical functioning, a better

disease-specific quality of life, an active coping style, low palliative reaction, avoidance and passive reaction pattern, a dominant personality with high self-esteem, and low inadequacy, rigidity, and resentment.

Cluster 2 (*the cachectic/impulsive cluster*) was characterized by a significantly lower proportion of men, less ICDs, lower glucose, higher eGFR, a lower peak cycling load, and low dominance in personality.

Table 2 Exercise capacity, daily activities, health status, coping styles, and personality traits for each cluster

Attribute	Whole sample N = 603	C1 N = 183	C2 N = 103	C3 N = 107	C4 N = 103	C5 N = 107
Exercise capacity						
6MWD, m	495 (420–566)	524 (461–608)	493 (405–583)	469 (403–540)	462 (385–545)	495 (431–564)
Peak cycling load, W	97 (72–129)	119 (83–151)	82 (54–113)	88 (71–115)	88 (63–106)	109 (77–144)
Cycle endurance time, s	305 (218–470)	347 (247–539)	267 (195–426)	300 (228–425)	277 (199–382)	341 (199–533)
COPM, points						
Performance	4 (3–5)	4 (3–5)	4 (2.8–4.5)	4 (3.3–4.7)	4 (3–5)	3.5 (2.8–4.8)
Satisfaction	3.4 (2.2–4.7)	3.6 (2.4–5)	3.3 (2.2–5)	3.8 (2.3–4.5)	3.5 (2.2–4.7)	3 (1.7–4.1)
Health status						
MLHFQ, points	53 (41–63)	48 (37–58)	51 (41–65)	51 (40–61)	53 (41–64)	67 (55–77)
Total score	22 (17–28)	21 (15–24)	22 (18–28)	21 (16–25)	22 (18–28)	29 (23–33)
Physical	11 (8–14)	10 (7–13)	12 (7–14)	11 (8–13)	11 (7–15)	15 (12–19)
Emotional						
Coping styles						
Utrecht Coping List, points	18 (15–21)	19 (16–21)	18 (14–20)	18 (16–21)	18 (15–20)	16 (14–19)
Active confronting	16 (14–18)	16 (14–18)	17 (15–18)	16 (14–19)	16 (14–19)	17 (16–20)
Palliative reaction	16 (14–18)	15 (13–17)	16 (13–19)	16 (13–18)	16 (13–18)	16 (15–19)
Avoidance	12 (10–14)	12 (10–14)	13 (10–15)	12 (10–14)	13 (11–15)	12 (9–14)
Seeking social support	11 (9–14)	10 (8–13)	12 (9–13)	10 (8–12)	11 (9–13)	15 (13–17)
Passive reaction pattern	6 (5–7)	5 (5–6)	6 (5–7)	6 (5–6)	6 (5–7)	6 (5–7)
Expressing emotions	12 (10–14)	12 (10–14)	12 (11–14)	12 (11–14)	11 (10–14)	12 (10–14)
Reassuring thoughts						
Personality traits						
Dutch Personality Questionnaire, points	15 (11–20)	17 (13–20)	13 (8–17)	16 (13–21)	16 (12–20)	15 (10–19)
Dominance	12 (8–20)	9 (5–14)	12 (9–17)	11 (6–17)	12 (8–20)	24 (17–30)
Inadequacy	29 (24–34)	28 (22–32)	28 (24–34)	30 (26–33)	30 (26–36)	29 (26–34)
Rigidity	9 (4–15)	6 (3–12)	9 (3–15)	9 (4–15)	10 (4–16)	13 (8–18)
Social inadequacy	19 (14–25)	16 (12–22)	17 (11–24)	19 (14–24)	20 (17–25)	24 (18–30)
Resentment	14 (10–18)	13 (10–18)	13 (9–16)	16 (12–20)	14 (10–18)	14 (10–19)
Self-sufficiency	24 (21–29)	26 (23–31)	24 (19–27)	27 (24–30)	24 (21–29)	21 (18–24)
Self-esteem						

6MWD, 6 min walking distance; COPM, Canadian Occupational Performance Measure; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

Data are shown as median (interquartile range) or % patients.

Green cell: value is significantly lower (adjusted $P < 0.05$) compared with whole sample; red cell: value is significantly higher (adjusted $P < 0.05$) compared with whole sample. Missing data: 6 min walk distance (6MWD), $n = 2$; peak cycling load, $n = 19$; Canadian Occupational Performance Measure (COPM-Performance), $n = 7$; Canadian Occupational Performance Measure (COPM-Satisfaction), $n = 78$; Minnesota Living with Heart Failure Questionnaire (MLHFQ), $n = 224$; coping styles, $n = 62$; and personality traits, $n = 227$.

Table 3 Comorbidities

Attribute	Whole sample N = 603	C1 N = 183	C2 N = 103	C3 N = 107	C4 N = 103	C5 N = 107
Number of comorbidities	3 (2-4)	2 (1-3)	3 (2-4)	4 (3-4)	4 (3-5)	4 (3-5)
<i>Psychological symptoms</i>						
HADS, points						
Anxiety	6 (3-9)	4 (2-6)	6 (4-7)	4 (3-7)	5 (3-8)	11 (10-13)
Depression	5 (2-8)	4 (2-6)	5 (2-7)	4 (3-6)	4 (2-7)	11 (8-12)
BDI score, points	11 (6-17)	8 (5-12)	11 (7-17)	8 (6-14)	11 (7-16)	21 (16-27)
Anxiety, % patients	19	4	10	3	10	75
Depression, % patients	17	3	14	6	8	62
<i>Body composition</i>						
BMI, kg/m ²	28.6 (25.7-32.1)	29.5 (26.6-33.4)	23.4 (21.6-25.7)	29.8 (28.2-33.2)	27.8 (25.4-30.2)	31 (28-34.2)
Underweight, % patients	4	0	20	0	1	0
Obesity, % patients	38	47	0	48	29	60
FFMI, kg/m ²	18.7 (17.1-20.4)	19.2 (17.8-20.8)	15.9 (14.8-17.7)	19.8 (18.5-21.1)	18.6 (17.3-19.9)	18.9 (17.8-20.9)
Abnormal low FFMI, % patients	8	0	40	1	1	1
<i>T score</i>						
Lumbar spine	-0.1 (-1.1 to 1)	0.1 (-0.7 to 1.3)	-1.1 (-2.6 to -0.2)	0.5 (-0.5 to 2)	-0.4 (-1.6 to 0.7)	0 (-0.7 to 0.8)
Hip	-1.1 (-1.7 to -0.3)	-0.9 (-1.4 to -0.2)	-1.8 (-2.3 to -1.1)	-0.7 (-1.6 to 0.1)	-1.5 (-2.2 to -0.7)	-0.9 (-1.3 to 0)
Osteoporosis, % patients	12	1	37	9	23	4
<i>Lung function</i>						
FEV1, % predicted	91 (77-106)	96 (78-110)	84 (59-98)	87 (71-99)	92 (76-102)	97 (84-112)
FEV1/VC, %	71 (63-77)	71 (63-77)	67 (53-75)	68 (59-76)	72 (65-78)	74 (70-80)
Obstructive spirometry, % patients [MS1]	42	38	58	55	42	19
TLCO, % predicted	67 (57-78)	73 (62-83)	64 (53-74)	64 (57-75)	61 (50-68)	71 (65-82)
<i>Remaining comorbidities</i>						
Anaemia, % patients	32	11	31	34	77	22
Hyperglycaemia, % patients	35	53	44	0	31	38
Estimated GFR, mL/min/1.73 m ²	55 (42-68)	63 (53-73)	60 (49-74)	46 (33-60)	42 (32-48)	60 (46-73)
Renal dysfunction, % patients	60	43	49	73	95	48

BDI, Beck Depression Inventory; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FFMI, fat-free mass index; HADS, Hospital Anxiety and Depression Scale; TLCO, transfer factor of the lung for carbon monoxide; VC, vital capacity.

Data are shown as median (interquartile range) or % patients. Green cell: value is significantly lower (adjusted $P < 0.05$) compared with whole sample; red cell: value is significantly higher (adjusted $P < 0.05$) compared with whole sample, where each variable was tested with the appropriate tests and a multiple testing correction was applied; see Statistics section. Missing data: number of comorbidities, $n = 183$; Hospital Anxiety and Depression Scale (HADS), $n = 27$; Beck Depression Inventory (BDI), $n = 215$; body mass index (BMI), $n = 4$; fat-free mass index (FFMI), $n = 42$; osteoporosis, $n = 73$; forced expiratory volume in the first second (FEV1), $n = 6$; carbon monoxide transfer factor (TLCO), $n = 43$; dyslipidaemia, $n = 22$; anaemia, $n = 10$; hypertension, $n = 99$; hyperglycaemia, $n = 10$; and renal dysfunction, $n = 111$.

Cluster 3 (*the metabolic diabetes cluster*) was characterized by a significantly higher proportion of men, an older age, more ischaemic origin of HF, a lower LVEF, more pack years, higher glucose and lower eGFR, more use of statins, diuretics, anti-diabetics, and anti-gout medication, a lower walking distance, a low passive reaction coping style, and a high self-sufficient personality with high self-esteem.

Patients in Cluster 4 (*the metabolic renal cluster*) had a significantly older age, a lower resting systolic and diastolic blood pressure, more hospital admissions < 12 months, a higher NT-proBNP, higher CRP, lower eGFR, glucose, and haemoglobin, more use of diuretics and anti-gout medication, and a lower physical functioning.

Patients in Cluster 5 (*the psychological cluster*) were characterized by significantly younger age, a higher LVEF, fewer pack years, higher eGFR, glucose, and haemoglobin, a higher peak cycling load, lower score for satisfaction with the performance in ADL, a worse disease-specific quality of life, a passive and avoidance coping style, low active confronting, and a high social inadequacy and resentment personality with lower self-esteem.

Median LVEF was 35%. This was significantly higher in the psychologic cluster and lower in the metabolic diabetes cluster; ischaemic origin of HF was higher in the metabolic cluster and lower in the least comorbidities cluster.

Discussion

In this study, five distinct clusters were identified, each with their own specific combination of comorbidities, extra-cardiac physical traits, emotional traits, coping style, personality traits, and health status. These clusters advance our understanding of the clinical diversity of comorbidities and extra-cardiac traits in patients with HF. Moreover, these findings emphasize the need for a comprehensive assessment of these traits to enable a personalized and integrated care programme for each individual patient with HF, which goes beyond the cardiac abnormalities.

The current analyses and visualizations illustrate the clinical diversity in patients with HF. Common medical comorbidities vary in frequency and co-occur in different patterns. Indeed, a least comorbidities cluster, a cachectic/implosive cluster, a metabolic diabetes cluster, a metabolic renal cluster, and a psychological cluster were identified. These results corroborate, at least partially, the results of Gimeno-Miguel and colleagues,³⁰ who reported multi-morbidity in 98% of their sample and presented six comorbidity-based clusters in patients with an HF diagnosis in primary or hospital electronic health records (e.g. a cardiovascular cluster, a respiratory cluster, a metabolic cluster, a coronary-ischaemic cluster, a degenerative cluster, and a neurovascular cluster).³⁰ They compared

men and women and measured the impact of such patterns on the risk of hospitalization and mortality. The sample of Gimeno-Miguel and colleagues was markedly older (median age 78 years) and had more different comorbidities. However, they did not look at functional status of the patients and also did not combine comorbidities. This may explain the differences in comorbidity-based clusters between their and our study. Degenerative diseases like dementia and delirium were not actively assessed in the current study (median age 63 years, referred for a comprehensive HF rehabilitation programme). Moreover, Triest and colleagues screened for comorbidities in electronic health records, which most probably underestimated the true prevalence of comorbidities.³¹ Tromp *et al.*¹⁶ clustered patients with HF based on comorbidities. The population is different from ours (Asian HF patients, prospectively collected). However, the metabolic cluster and the young cluster with fewer comorbidities are also present. They did not describe a psychologic cluster, which is seen in our population. In the current study, except for gout (which was based on medication use), comorbidities were objectively assessed, as has been done before in patients with COPD.^{14,32} The cachectic/implosive cluster [characterized by a combined loss of muscle tissue (low FFMI), bone tissue (more osteoporosis), and lung tissue (more obstructive lung disease and low mean diffusion capacity)] and the psychological cluster (more anxiety and depression) were also present in patients with COPD.^{14,32} Interestingly, obstructive lung function, in this analysis, does not cluster with anxiety and depression, but is rather less prevalent. The shown physical frailty is of clinical importance as this is known to increase mortality and morbidity.³³ Moreover, frailty is a strong predictor of adverse post-implantation outcome in patients undergoing cardiac re-synchronization therapy³⁴ and cardiac surgery.³³ Remarkably, the patients in the metabolic diabetes cluster reported significantly more pack years smoking. Ahmad and colleagues¹³ clustered patients included in the HF-ACTION trial, on the basis of 45 clinical variables, including age, sex, race, symptoms, comorbidities, HF aetiology, socio-economic status, quality of life, cardiopulmonary exercise test parameters, and biomarker levels. These clusters responded differently to therapy and had a different prognosis. Compared with our analysis, the least comorbidities cluster is also identified. Cluster 4 resembles our least comorbidities cluster. In Clusters 1 and 3, a lot of comorbidities were shown, like in our metabolic clusters, however not at the basis of objectively identified values. Especially body composition and psychological factors leading to the cachectic/implosive and psychologic clusters are not subjects of their analysis.

In the current analysis, each comorbidity-based cluster had a distinct pattern of extra-cardiac physical traits, emotional traits, coping style, personality traits, and health status. For example, the least comorbidity cluster had a significantly better physical functioning and disease-specific quality of life compared with the other clusters, which was different from

the psychological cluster. Moreover, coping styles, personality traits, and psychological traits were completely opposite between these two clusters, while the cardiac characteristics were very similar.

The current study found clear differences in coping styles between the five clusters. For example, the psychological cluster seems to have completely opposite coping styles and personality traits than Cluster 1 (the least comorbidity cluster). So the HF patients from these two clusters have clearly different styles to master, minimize, or tolerate stress and daily life challenges, which may be of clinical importance on how to achieve best clinical outcome in these patients. Li and Shun describe that patients use different coping strategies, which have impact on physical and psychological self-care. Experiencing social support from spouses as well as socio-demographic characteristics, such as personality, are playing a role in coping and self-care.³⁵

The psychological cluster has significantly higher inadequacy, social inadequacy and resentment, and lower self-esteem. Moreover, they show higher scores on coping style palliative reaction, avoidance, and passive reaction pattern. They are more depressed and anxious. Remarkable, their health status is worse, but their exercise tolerance and ADL performance is not. This may deserve extra attention by healthcare professionals, including psychological care. According to Widdershoven *et al.*,³⁶ there is a clear relationship between depression and poor health status in patients with HF and between Type D personality and poor mental status. Both psychological risk factors seem to be associated with poor self-care and inadequate health behaviours, potentially mediated via inadequate coping, poor social support, and lower self-efficacy.³⁷ Moreover, coping style is known to be linked to the emotional responses of patients with HF. Avoidance coping may not serve HF patients well in terms of facilitating their response to the difficult physical and psychological challenges, posed by their disease.¹² Indeed, patients often need to adhere to complex medication regimes. Moreover, they often have to change their behaviour towards a healthy lifestyle, including smoking cessation, adjusting eating habits, and increasing their physical activities.¹ It is reasonable to assume that an active confronting coping style is more beneficial than an avoidance, passive reaction, or palliative reaction coping style. The avoidance coping style was associated with significantly higher anxiety, anger, depression, confusion, and fatigue in patients with advanced HF.³⁸ To introduce changes may therefore require a different approach in the psychological cluster.³⁵

Healthcare professionals involved in HF care need to be aware that patients may suffer from specific clusters of comorbidities that are not reflected by the regular cardiac function test. Additional assessment of the different aspects needs to be considered, in best practice, integrated in regular care or at the start of rehabilitation programmes. Comorbid-

ity patterns can occur, irrespective of the underlying primary organ failure. So the index disease (i.e. HF) is part of a multimorbidity syndrome, instead of HF-specific comorbidity patterns. Consequently, HF care should also involve allied healthcare professionals and possible other medical specialists to adequately deal with all extra-cardiac features, such as lower-limb muscle weakness and exercise intolerance (physiotherapist), abnormal body composition (dietician), problematic ADLs (occupational therapist), impaired lung function (chest physician), comorbidities (geriatrician or internal medicine specialist), and psychological symptoms and inadequate coping styles (psychologist). In order to involve them in the most appropriate way, clustering of patients and identifying their specific needs may be of great value.

Strengths and weaknesses

This study using SOMs illustrates the clinical diversity of the comorbidities in patients with HF. Patients included in this study were entering a specialized rehabilitation programme and do not reflect the entire HF population. Moreover, our sample consists of only a small part of patients with preserved EF, 29% were female, and the average age was relatively low. This may limit the external validity of our findings. Still, our sample consisted of a considerable number of HF patients with a clinically representative disease severity. Although we have assessed multiple non-cardiac features, not all relevant characteristics for development of optimal integrated care were included. For example, cognitive functioning and presence of social support were not, which may limit application particularly in very elderly HF patients. In addition, because the inclusion to this study was before 2015, patients were not treated with sacubitril/valsartan or SGLT-2 inhibitors.

An important limitation of this study is the fact that possible clinical consequences have not been tested. This needs to be done in future studies. However, the analysis not only highlights the need for such specific intervention trials but also provides evidence how such interventions could look like. This may result in significant improvement of managed care in HF to possibly improve outcomes, quality of life, and cost-effectiveness.

In the current analysis, the unbiased approach to identify these comorbidity clusters is a major strength. We use SOMs to represent the data distribution, because data dependency can be understood easily when observing the map.

Whether tailoring therapy according to disease subtypes is possible or necessary should be tested in future studies. Still, it may be speculated that, for example, patients in Cluster 5 could take advantage from psychological interventions next to exercise training; patients in Clusters 3 and 4, besides exercise training, from attention to the metabolic disruption; and patients in Cluster 2, from nutritional intervention as well as

strength training. Furthermore, patients could take advantage of an intervention by the occupational therapist. Patients in Cluster 1, the biggest cluster, are in general doing well and they show a limited number of comorbidities. Accordingly, no additional interventions that may be costly but of little added value could be advised in these patients.

Conclusions

Distinct combinations of comorbidities could be identified in patients with HF. They have very diverse combinations of comorbidities, leading to five different clusters of phenotypes. Therapy may be tailored based on these clusters as next step towards precision medicine. Still, the effect of such an approach needs to be prospectively tested.

Conflict of interest

Dr Franssen reports grants and personal fees from AstraZeneca, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Chiesi, personal fees from GlaxoSmithKline, personal fees from Novartis, and non-financial support from TEVA, outside the submitted work. Dr Vanfleteren reports grants and personal fees from AstraZeneca, personal fees from Novartis, GSK, Chiesi, Menarini, Pulmonx, Resmed, Boehringer, Verona Pharma,

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Supporting information

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

Data S1. Supporting information.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
2. Ghashghaei R, Arbit B, Maisel AS. Current and novel biomarkers in heart failure: Bench to bedside. *Curr Opin Cardiol* 2016; **31**: 191–195.
3. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J* 2006; **27**: 65–75.
4. Gosker HR, Lencer NH, Franssen FM, van der Vusse GJ, Wouters EF, Schols AM. Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest* 2003; **123**: 1416–1424.
5. Bennett JA, Riegel B, Bittner V, Nichols J. Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. *Heart Lung* 2002; **31**: 262–270.
6. Maeder MT, Mueller C, Pfisterer ME, Buser PT, Brunner-La Rocca HP. Use of B-type natriuretic peptide outside of the emergency department. *Int J Cardiol* 2008; **127**: 5–16.
7. Metra M, Zaca V, Parati G, Agostoni P, Bonadies M, Ciccone M, Zacà V, Parati G, Agostoni P, Bonadies M, Ciccone M, Cas AD, Iacoviello M, Lagioia R, Lombardi C, Maio R, Magri D, Musca G, Padeletti M, Perticone F, Pezzali N, Piepoli M, Sciacqua A, Zanolla L, Nodari S, Filardi PP, Dei Cas L, Heart Failure Study Group of the Italian Society of Cardiology. Cardiovascular and noncardiovascular comorbidities in patients with chronic heart failure. *J Cardiovasc Med (Hagerstown)* 2011; **12**: 76–84.
8. Damen NL, Versteeg H, van Helmond SJ, de Jaegere PP, van Geuns RJ, Meine MM et al. The distressed (Type D) personality mediates the relationship between remembered parenting and psychological distress in cardiac patients. *Psychol Health* 2014; **29**: 318–333.
9. Samartzis L, Dimopoulos S, Manetos C, Agapitou V, Tasoulis A, Tseliou E, Pozios I, Kaldara E, Terrovitis J, Nanas S. Neuroticism personality trait is associated with quality of life in patients with chronic heart failure. *World J Cardiol* 2014; **6**: 1113–1121.
10. Feola M, Garnero S, Vallauri P, Salvatico L, Vado A, Leto L, Testa M. Relationship between cognitive function, Depression/Anxiety and functional parameters in patients admitted for congestive heart failure. *Open Cardiovasc Med J*. 2013; **7**: 54–60.
11. Buetow S, Goodyear-Smith F, Coster G. Coping strategies in the self-management of chronic heart failure. *Fam Pract* 2001; **18**: 117–122.
12. Doering LV, Dracup K, Caldwell MA, Moser DK, Erickson VS, Fonarow G, Hamilton M. Is coping style linked to

- emotional states in heart failure patients? *J Card Fail* 2004; **10**: 344–349.
13. Ahmad T, Pencina MJ, Schulte PJ, O'Brien E, Whellan DJ, Pina IL, O'Brien E, Whellan DJ, Piña IL, Kitzman DW, Lee KL, O'Connor CM, Felker GM. Clinical implications of chronic heart failure phenotypes defined by cluster analysis. *J Am Coll Cardiol* 2014; **64**: 1765–1774.
 14. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, Rutten EP, Op't Roodt J, Wouters EF, Franssen FM Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; **187**: 728–735.
 15. Erro R, Vitale C, Amboni M, Picillo M, Moccia M, Longo K, Santangelo G, de Rosa A, Allocca F, Giordano F, Orefice G, de Michele G, Santoro L, Pellicchia MT, Barone P. The heterogeneity of early Parkinson's disease: A cluster analysis on newly diagnosed untreated patients. *PLoS One* 2013; **8**: e70244.
 16. Tromp J, Tay WT, Ouwerkerk W, Teng TK, Yap J, MacDonald MR, Leineweber K, McMurray J, Zile MR, Anand IS, Richards AMR, Lam CSP, ASIAN-HF authors. Multimorbidity in patients with heart failure from 11 asian regions: A prospective cohort study using the ASIAN-HF registry. *PLoS Med* 2018; **15**: e1002541.
 17. Ahmad T, Lund LH, Rao P, Ghosh R, Warier P, Vaccaro B, Dahlström U, O'Connor CM, Felker GM, Desai NR. Machine learning methods improve prognostication, identify clinically distinct phenotypes, and detect heterogeneity in response to therapy in a large cohort of heart failure patients. *J Am Heart Assoc* 2018; **7**. <https://doi.org/10.1161/JAHA.117.008081>
 18. Spruit MA, Vanderhoven-Augustin I, Janssen PP, Wouters EF. Integration of pulmonary rehabilitation in COPD. *Lancet* 2008; **371**: 12–13.
 19. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; **54**: 581–586.
 20. Graat-Verboom L, van den Borne BE, Smeenk FW, Spruit MA, Wouters EF. Osteoporosis in COPD outpatients based on bone mineral density and vertebral fractures. *J Bone Miner Res* 2011; **26**: 561–568.
 21. Uszko-Lencer N, Mesquita R, Janssen E, Werter C, Brunner-La Rocca HP, Pitta F, Wouters EFM, Spruit MA Reliability, construct validity and determinants of 6-minute walk test performance in patients with chronic heart failure. *Int J Cardiol* 2017; **240**: 285–290.
 22. Andrianopoulos V, Wagers SS, Groenen MT, Vanfleteren LE, Franssen FM, Smeenk FW, Vogiatzis I, Wouters EF, Spruit MA, CIRO Rehabilitation Network. Characteristics and determinants of endurance cycle ergometry and six-minute walk distance in patients with COPD. *BMC Pulm Med* 2014; **14**: 97.
 23. Nakken N, Janssen DJ, van den Bogaart EH, van Vliet M, de Vries GJ, Bootsma GP, Gronenschild MH, Delbressine JM, Muris JW, Wouters EF, Spruit MA. Patient versus proxy-reported problematic activities of daily life in patients with COPD. *Respirology* 2017; **22**: 307–314.
 24. Stoilkova A, Janssen DJ, Franssen FM, Spruit MA, Wouters EF. Coping styles in patients with COPD before and after pulmonary rehabilitation. *Respir Med* 2013; **107**: 825–833.
 25. Smid DE, Franssen FM, Houben-Wilke S, Vanfleteren LE, Janssen DJ, Wouters EF, Spruit MA. Responsiveness and MCID Estimates for CAT, CCQ, and HADS in Patients with COPD Undergoing Pulmonary Rehabilitation: A Prospective Analysis. *J Am Med Dir Assoc* 2017; **18**: 53–58.
 26. Cleutjens F, Spruit MA, Ponds R, Vanfleteren L, Franssen FME, Gijzen C, Dijkstra JB, Wouters EFM, Janssen DJA. Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease. *Chron Respir Dis* 2017 1479972317709651.
 27. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota living with heart failure questionnaire: Reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan multicenter research group. *Am Heart J* 1992; **124**: 1017–1025.
 28. Kohonen T. *Self-organizing maps*. edition r, editor: Springer; 2001.
 29. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Rev Esp Cardiol (Engl Ed)* 2016; **69**: 1167.
 30. Gimeno-Miguel A, Gracia Gutierrez A, Poblador-Plou B, Coscollar-Santaliestra C, Perez-Calvo JI, Divo MJ, Gracia Gutiérrez A, Poblador-Plou B, Coscollar-Santaliestra C, Pérez-Calvo JI, Divo MJ, Calderón-Larrañaga A, Prados-Torres A, Ruiz-Laiglesia FJ. Multimorbidity patterns in patients with heart failure: An observational spanish study based on electronic health records. *BMJ Open* 2019; **9**: e033174.
 31. Triest FJ, Franssen FM, Spruit MA, Groenen MT, Wouters EF, Vanfleteren LE. Poor agreement between chart-based and objectively identified comorbidities of COPD. *Eur Respir J* 2015; **46**: 1492–1495.
 32. Triest FJJ, Franssen FME, Reynaert N, Gaffron S, Spruit MA, Janssen DJA, Rutten EPA, Wouters EFM, Vanfleteren LEGW. Disease-specific comorbidity clusters in COPD and accelerated aging. *J Clin Med* 2019; **8**. <https://doi.org/10.3390/jcm8040511>
 33. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014; **63**: 747–762.
 34. Dominguez-Rodriguez A, Abreu-Gonzalez P, Jimenez-Sosa A, Gonzalez J, Caballero-Estevéz N, Martin-Casanas FV, Lara-Padron A, Aranda JM. The impact of frailty in older patients with non-ischaemic cardiomyopathy after implantation of cardiac resynchronization therapy defibrillator. *Europace* 2015; **17**: 598–602.
 35. Li CC, Shun SC. Understanding self care coping styles in patients with chronic heart failure: A systematic review. *Eur J Cardiovasc Nurs* 2016; **15**: 12–19.
 36. Widdershoven J, Kessing D, Schiffer A, Denollet J, Kupper N. How are depression and type D personality associated with outcomes in chronic heart failure patients? *Curr Heart Fail Rep* 2013; **10**: 244–253.
 37. Reynolds NA, Ski CF, McEvedy SM, Thompson DR, Cameron J. Construct validity of the heart failure screening tool (Heart-FaST) to identify heart failure patients at risk of poor self-care: Rasch analysis. *J Adv Nurs* 2018; **74**: 1412–1422.
 38. Nahlen Bose C, Elfstrom ML, Bjorling G, Persson H, Saboonchi F. Patterns and the mediating role of avoidant coping style and illness perception on anxiety and depression in patients with chronic heart failure. *Scand J Caring Sci* 2016; **30**: 704–713.