Clinical Profiles in Acute Heart Failure

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Abstract

Background:

Phenotypes could be more frequently related to outcomes than classical classifications of AHF. Our goal was to identify clinical profiles for acute heart failure (AHF) based on clinical variables at the time of the patient arrival to the Emergency Department (ED).

Methods:

Design: Prospective cohort study.

Participants: Patients with symptoms of AHF were recruited at the EDs of seven Spanish National Health Service hospitals between April 2013 and December 2014. Main measures: Information on sociodemographic, baseline functional status, medical history, and time since diagnosis was collected when the patient arrived at the ED. In addition, the MLWHF questionnaire was administered at arrival and at 1 year after discharge from the ED. Change in MLWHF score and mortality, revisits and readmissions during this first year were considered as outcomes. We combined multiple correspondence analysis (MCA) and cluster analysis (CA) to create clinical profiles.

Results:

A total of 1599 subjects were included in the study. Patients were located on two axes: one was defined as duration of HF and the other as cardiovascular comorbidity. Cluster analysis identified three subtypes of patient (A, B, and C), group B being most frequently corresponding to a “de novo” case. Differences in outcome, including mortality, readmissions and changes in MLWHF score, were encountered between group B and the rest of the groups, results being similar in groups A and C.

Conclusions:

The clinical phenotypes found were associated with clinical and patient-reported outcomes. Such clinical phenotypes could be useful in decision making processes in ED settings.

Clinical registration:

ClinicalTrials.gov ID: NCT03512704

Background

Acute heart failure (AHF) is the first cause of attendance and hospitalization in Emergency Departments (EDs) in Spain, with a prevalence of 7% in over-45-year-olds and 16% in over-75-year-olds.[1] Heart failure (HF) being the final stage of numerous diseases, different profiles of patients are expected.

Ejection fraction (EF) is a parameter used to classify patients with HF, with different management and implications depending on percentage of EF.[2] Moreover to EF and disease course (stable or acute: *de novo* vs decompensation), guidelines classify HF based on the severity of the symptoms. Regarding AHF, patients are classified based on clinical presentation at the EDs, that is, arterial blood pressure, precipitants/causes of decompensation and the presence of clinical symptoms/signs of congestion and/or peripheral hypoperfusion. [3]

Other authors have described various different phenotype classifications of patients.[4 5]. When these phenotypes have been correlated with bed side hemodynamic profiles based on signs and symptoms of congestion/hypoperfusion, as the clinical guidelines recommend, the correlation was not good. In fact, phenotypes were related to mortality, while hemodynamic profiles were not.

Other author suggests the need for a new approach to define clinical profiles in AHF which could stratify patients based on their underlying etiology and their response to novel interventions.[6]

OBJECTIVE

Identify clinical profiles for AHF based on EF, clinical course, symptoms, clinical presentation, etiology/precipitating factors, clinical signs and symptoms of congestion/hypoperfusion and also comorbidities at the time of the arrival to the ED. Such profiles would be associated with different short- and medium-term mortality, readmissions and patient-reported outcomes.

Design

This was a prospective cohort study that recruited patients with symptoms of AHF who attended the EDs of seven Spanish National Health Service hospitals between April 2013 and December 2014 (ClinicalTrials.gov ID: NCT03512704).

PARTICIPANTS:

Patients over 18 years of age were eligible for inclusion in the study if their main diagnosis was AHF based on (i) symptoms (dyspnea) and signs (i.e., rales, hypotension, hypoperfusion, right ventricular HF) of HF and (ii) lung congestion on chest X-ray or elevation of NT-proBNP or HF confirmed by echocardiography.[7] The diagnosis was confirmed by natriuretic peptide measurement or echocardiography in 92% of patients with a first episode of HF.[3]

Patients were excluded if they were unable to complete the questionnaires even with external help, due to sensorineural impairments, dementia or lack of knowledge of the language, or if they were unwilling to participate. The Ethics Committee of the Basque Country approved the study. All patients or caregivers gave their consent to participate in the study. The study was carried out in accordance with the relevant guidelines and regulations.

MEASURES

Information was collected at the time patients arrived at the ED by trained research assistants supervised by clinical researchers. Data were collected on sociodemographic characteristics (age and sex); baseline functional status classified in terms of New York Heart Association (NYHA) functional class; medical history (previous myocardial infarction, cerebrovascular disease, peripheral arterial disease, hypertension, atrial fibrillation/flutter, diabetes, chronic lung disease/chronic obstructive pulmonary disease, depression treated with medication, active smoker, anemia, and the other comorbidities included in the Charlson Comorbidity Index;[8] signs and symptoms of congestion/hypoperfusion at ED arrival (NYHA functional class at ED arrival, rales over more than a third of lung fields, peripheral edema and jugular venous distention); precipitating factors (infections, recent changes in treatments, increase in metabolic demand, pulmonary embolism, acute coronary syndrome, non-controlled arterial blood pressure, arrhythmias, toxicity, myocarditis, or comorbidities)[1]; echocardiographic parameters at admission, or in the case of patients discharged or in whom no echocardiogram was performed during admission, parameters of an echocardiogram performed up to 1 month after the index episode[3]; etiology (ischemic, hypertensive, cardiomyopathy, valvular or congenital disease, arrhythmia, toxic HF, high-output HF, pericardium diseases or primary right ventricular failure); baseline treatments; vital signs and laboratory findings (including hs-TnT and Nt-ProBNP). Date of initial HF diagnosis was prospectively recorded by local site investigators and was allowed to be obtained using any available method (e.g., medical records or patient-reported history) at the discretion of the local investigator. Time between HF diagnosis and the index AHF hospital admission was then calculated. For descriptive purposes, patients were assigned to one of five categories of HF duration : first episode (*de novo*), first 12 months after index episode, duration of 13-24 months, duration ≥ 25 and ≤ 60 months, and ≥ 61 months.[9]

The Minnesota Living with Heart Failure (MLWHF) questionnaire was administered at baseline and at 1 year after the index episode. MLWHF scores range from 0 to 100, with higher scores reflecting a greater impact of the HF on the patient's quality of life.[10]

Definition of outcomes

Mortality, revisits to the ED and readmissions at 1 year after index episode were recorded. Changes in MLWHF questionnaire assessed at baseline, and 1 year after index episode.

Statistical analyses

The unit of analysis was the patient with symptoms of HF who attended the ED. Frequencies and percentages of sociodemographic characteristics and clinical data were calculated as descriptive statistics. MCA synthesizes information on the original variables into a few components and is designed for categorical variables, whereas CA classifies information into relatively homogeneous groups based on the values of different variables, like the components in the MCA. Active variables were those listed in the *Methods* section, those eventually selected being: sex,, age (≤80 years, >80 years), hypertension, history of anemia, etiology of coronary disease, toxic habits and drugs and atrial arrhythmia; comorbidities of

myocardial infarction, congestive HF, peripheral vascular disease and renal disease; EF at the ED or 1 month earlier or after the ED episode (not reduced, reduced, not specified), HF duration (de novo; 0 years; chronic, 1 year; chronic, 1-5 years; chronic, >5 years), NYHA functional class (I, II, III, IV), precipitating factors such as atrial fibrillation and sinus rhythm loss; presence of bilateral edema; laboratory findings at ED, such as hemoglobin (< 10 g/dl, ≥ 10 g/dl) and blood urea nitrogen (BUN; <17.5 mg/dl, ≥17.5 mg/dl). Mortality, revisits to the ED and readmissions at 1 year after the index episode were used as illustrative or outcomes.

By MCA, information on the original active variables was transformed into continuous factors. For interpretation of the MCA, a number and a positive/negative sign was used to represent each category of active variables, as well as a graphical display of the factors, the relative position of the categories on the graph indicating the association between the categories: the closer the categories, the stronger the association. Based on factors derived from the MCA, CA was performed. The number of groups was selected based on considering which achieved the minimum loss of inertia.[11]

The association between all the active variables as well as illustrative variables or outcomes, and the different groups derived from the combination of MCA and CA was evaluated using the chi-square test. In addition, differences between groups according to MLWHF scores were measured and evaluated using the non-parametric Kruskal-Wallis test.

The statistical analyses were performed using R v.3.5.2 and SAS 9.4 software. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. (Cary, NC, USA.)

Results

A total of 1599 patients were included in the study. Results from the MCA show that two factors explain 62% of the variability in the data. Figure 1 shows the maps created by the first and second factors. The horizontal axis represents the first factor and the vertical axis the second factor. Variables well represented in the first factor were hypertension, anemia, toxic habits and drugs, atrial arrhythmia, congestive HF, renal disease, atrial fibrillation, sinus rhythm, edemas, EF, type of HF and NYHA functional class. The following categories were related to the positive side (right): having hypertension, having anemia, not having toxic habits, having congestive HF and renal disease, having neither atrial fibrillation nor sinus rhythm as precipitating factors, having edema as a symptom, having non-specified EF, BUN≥17.5 mg/dl, being a chronic patient with different follow-ups and being NYHA class IV. In contrast, categories on the negative side (left) were: having neither hypertension nor anemia, having toxic habits, having neither congestive HF nor renal disease, having atrial fibrillation or sinus rhythm as precipitating factors, not having edema, and having non-reduced EF, BUN<17.5 mg/dl, *de novo* HF and NYHA class I. This axis was defined as “Duration of HF”, from *de novo* (left side of the graph) to chronic >5 years (right side of the graph). In addition, the relative position of the outcomes on the graph shows that deaths up to

1 year, as well as readmissions and revisits to ED up to 1 year were well represented by this factor. Positive responses were located on the right side of the axis and negative responses on the left side.

Variables well represented in the second factor were: gender, age, coronary disease, myocardial infarction, atrial fibrillation and EF. Being female, aged >80 years, having neither coronary disease nor myocardial infarction and having atrial fibrillation were the categories related to the positive part (top), whereas being male, aged ≤ 80 years, having coronary disease or myocardial infarction and reduced EF and not having atrial fibrillation were related to the lower part of the graph (bottom). Therefore, this axis was interpreted as “Cardiovascular comorbidity”. EF was well represented in both factors: preserved (left part) and not available EF (right part) was well represented in the first factor whereas reduced EF was well represented in the bottom part of the second factor.

After applying CA to these results, three subtypes of AHF patient were identified (Figure 2). Group C had the most severe AHF and group B the least severe, in terms of mortality. Patients are represented in Figure 1 using different colors for these three subtypes. Figure 3 shows the two-dimensional distribution created by plotting the first and second components. The relative positions of the three outcome variables are projected onto the graph. The right side of the graph contains the most severe outcomes: deaths, readmissions, and revisits to ED.

Table 1 summarizes the data collected upon arrival at the ED for all patients and across the three subtypes of AHF as a function of the classification of their HF. Statistically significant differences between subtypes were observed in duration of HF, EF, NYHA functional class, etiology, presentation at the ED, precipitants and signs and symptoms of congestion. They also differed in age, gender, comorbidities, laboratory signs and health service use. (Table 2)

Table 1
Distribution of the main variables related to the classifications of heart failure

	Total	**Groups**			**p-value**
		A	B	C	
		N (%)	N (%)	N (%)	
Total	**1599**	**377 (23.58)**	**597 (37.34)**	**625 (39.09)**	
Duration of HF*		bc	ac	ab	<0.0001
De novo	646 (40.40)	69 (18.30)	508 (85.09)	69 (11.04)	
Chronic, 0 years	62 (3.88)	22 (5.84)	6 (1.01)	34 (5.44)	
Chronic, 1 year	273 (17.07)	99 (26.26)	27 (4.52)	147 (23.52)	
Chronic, 1-5 years	407 (25.45)	91 (24.14)	43 (7.20)	273 (43.68)	
Chronic, >5 years	211 (13.20)	96 (25.46)	13 (2.18)	102 (16.32)	
Ejection fraction*		bc	ac	ab	<0.0001
Preserved	547 (34.21)	78 (20.69)	279 (46.73)	190 (30.40)	
Reduced	232 (14.51)	69 (18.30)	148 (24.79)	15 (2.40)	
Not known	820 (51.28)	230 (61.01)	170 (28.48)	420 (67.20)	
NYHA class*		b	ac	b	<0.0001
I	189 (11.82)	26 (6.90)	135 (22.61)	28 (4.48)	
II	429 (26.83)	88 (23.34)	177 (29.65)	164 (26.24)	
III	541 (33.83)	127 (33.69)	183 (30.65)	231 (36.96)	
IV	440 (27.52)	136 (36.07)	102 (17.09)	202 (32.32)	
Etiology					
Coronary disease *	407 (25.45)	268 (71.09)[bc]	93 (15.58)[ac]	46 (7.36)[ab]	<0.0001

	Total	Groups			p-value
High arterial blood pressure	613 (38.34)	126 (33.42)[c]	202 (33.84)[c]	285 (45.60)[ab]	<0.0001
Cardiomyopathy	387 (24.20)	101 (26.79)[c]	165 (27.64)[c]	121 (19.36)[ab]	0.0014
Valvular or congenital disease	388 (24.27)	62 (16.45)[c]	129 (21.61)[c]	197 (31.52)[ab]	<0.0001
Arrhythmia	315 (19.70)	43 (11.41)[bc]	161 (26.97)[ac]	111 (17.76)[ab]	<0.0001
Toxic habits and drugs*	31 (1.94)	3 (0.80)[b]	27 (4.52)[ac]	1 (0.16)[b]	<0.0001
Primary right ventricular failure	58 (3.63)	8 (2.12)[c]	14 (2.35)[c]	36 (5.77)[ab]	0.0012
Presentation at the emergency department					
Systolic blood pressure		b	ac	b	0.0069
Low <90 mmHg	24 (1.52)	8 (2.14)	3 (0.51)	13 (2.11)	
Normal ≥ 90 mmHg-≤140 mmHg	814 (51.68)	214 (57.37)	288 (49.23)	312 (50.57)	
Elevated >140 mmHg	737 (46.79)	151 (40.48)	294 (50.26)	292 (47.33)	
Precipitants					
Acute myocardial infarction	20 (1.25)	9 (2.39)[c]	9 (1.51)	2 (0.32)[a]	0.0133
Hypertension	94 (5.88)	19 (5.04)	39 (6.53)	36 (5.76)	0.6198
Concurrent diseases	152 (9.51)	50 (13.26)[b]	44 (7.37)[a]	58 (9.28)	0.0092
Atrial fibrillation*	270 (16.89)	15 (3.98)[bc]	168 (28.14)[ac]	87 (13.92)[ab]	<0.0001
Other arrhythmias*	60 (3.75)	6 (1.59)[b]	38 (6.37)[ac]	16 (2.56)[b]	<0.0001
Signs and symptoms of congestion					
Edema*	904 (56.54)	235 (62.33)[b]	284 (47.57)[ac]	385 (61.60)[b]	<0.0001

	Total	Groups			p-value
Rales	1167 (73.49)	287 (76.74)	417 (69.97)	463 (74.92)	0.0393
Oliguria	331 (20.91)	84 (22.34)[b]	90 (15.23)[ac]	157 (25.49)[b]	<0.0001
*Illustrative variables					

Table 2
Differences between the three groups identified from the MCA and the CA, with respect to the active variables of the MCA and some others.

	Total	Group			p-value
		A	B	C	
		N (%)	N (%)	N (%)	
Total	1599	377 (23.58)	597 (37.34)	625 (39.09)	
Age (>80 years)*	781 (48.84)	152 (40.32)[c]	223 (37.35)[c]	406 (64.96)[ab]	<0.0001
Gender (Female)*	805 (50.34)	88 (23.34)[bc]	291 (48.74)[ac]	426 (68.16)[ab]	<0.0001
Comorbidities					
Charlson index†	2 [1–3]	3 [2–5][bc]	1 [0-2][ac]	2 [1–3][ab]	<0.0001
Myocardial infarction*	271 (16.95)	203 (53.85)[cb]	47 (7.87)[ac]	21 (3.36)[ab]	<0.0001
Congestive heart failure*	945 (59.10)	301 (79.84)[b]	115 (19.26)[ac]	529 (84.64)[b]	<0.0001
Peripheral vascular disease*	243 (15.20)	120 (31.83)[cb]	63 (10.55)[a]	60 (9.60)[a]	<0.0001
Peptic ulcer	120 (7.50)	38 (10.08)[b]	34 (5.70)[a]	48 (7.68)	0.0399
Diabetes with organ damage	126 (7.88)	52 (13.79)[cb]	34 (5.70)[a]	40 (6.40)[a]	<0.0001
Malignant tumor	189 (11.82)	57 (15.12)[b]	56 (9.38)[a]	76 (12.16)	0.0245
Moderate or severe kidney disease*	132 (8.26)	89 (23.61)[cb]	18 (3.02)[a]	25 (4.00)[a]	<0.0001
Hypertension*	1295(80.99)	316 (83.82)[b]	425 (71.19)[ac]	554 (88.64)[b]	<0.0001
Auricular arrhythmia *	959 (59.97)	188 (49.87)[c]	262 (43.89)[c]	509 (81.44)[ab]	<0.0001
Diabetes	624 (39.02)	178 (47.21)[b]	195 (32.66)[ac]	251 (40.16)[b]	<0.0001
Chronic obstructive pulmonary disease	305 (19.10)	94 (25.00)[cb]	99 (16.61)[a]	112 (17.92)[a]	0.0033

	Total	Group			p-value
Depression	159 (9.94)	24 (6.37)[c]	48 (8.04)[c]	87 (13.92)[ab]	<0.0001
Smoking*	113 (7.07)	26 (6.90)[cb]	80 (13.40)[ac]	7 (1.12)[ab]	<0.0001
Anemia*	471 (29.46)	169 (44.83)[cb]	70 (11.73)[ac]	232 (37.12)[ab]	<0.0001
Laboratory test results					
Low hemoglobin* (12 women, 13 men)	851 (53.22)	284 (75.33)[cb]	203 (34.00)[ac]	364 (58.24)[ab]	<0.0001
Low sodium (<135 mEq/L)	221 (13.86)	61 (16.18)[b]	58 (9.73)[ac]	102 (16.40)[b]	0.0011
High BUN (≥17.5 mg/dl)*	293 (18.32)	124 (32.89)[cb]	41 (6.87)[ac]	128 (20.48)[ab]	<0.0001
High blood glucose (≥173.5 mg/dL)	312 (19.61)	89 (23.73)[cb]	120 (20.17)[a]	103 (16.59)[a]	0.0206
Potassium*	4.48 (1.61)	4.66 (2.07)[cb]	4.48 (1.93)[a]	4.37 (0.61)[a]	<0.0001
Troponin†	25 [12-45]	31 [15-53][b]	19 [9-40][ac]	29 [14-42][b]	0.0003
Nt-proBNP (x1000)†	3.85 [2.02-7.72]	5.81 [2.94-11.06][cb]	3.37 [1.75-5.45][a]	3.80 [2.02-8.49][a]	<0.0001
Health service use					
Previous admission (yes)	564 (35.52)	212 (56.38)[b]	36 (6.04)[ac]	316 (51.30)[b]	<0.0001
Previous emergency department attendance (yes)	311 (19.62)	101 (27.01)[b]	17 (2.85)[ac]	193 (31.38)[b]	<0.0001
*Illustrative variables †Data are expressed as medium [interquartile range]					

The percentage of patients with a *de novo* diagnosis was higher in group B than in the rest of the groups, while the percentage of patients in whom HF was diagnosed more than 5 years earlier was higher in group A. There were significant differences between groups A and C in etiology: group A patients were

more likely to have coronary disease or cardiomyopathy, and acute myocardial infraction as a precipitant, whereas hypertension, valve disease and right ventricular HF were the most common etiologies in group C. Further, the rates of arrhythmia as an etiology and toxic habits were higher in group B than in the other groups. The median of the Charlson comorbidity index was highest in group A.

Compared to the other groups, a reduced EF was more common in group B, and the percentage of NYHA class I patients was the highest in this group while the percentage of patients with hypotension at arrival at the ED was the lowest. Further, in group B, the percentage of patients with atrial fibrillation and other arrhythmias was higher and congestion was less common. (Table 1)

Regarding other variables (Table 2), the percentages of females and patients older than 80 years were highest in group C. Group A had the highest scores in the Charlson comorbidity index and the highest percentages of patients with low levels of hemoglobin and high levels of BUN and potassium and Nt-proBNP.

Associations between subtypes and outcomes are shown in Table 3. Group B was the less likely to present poor outcomes during the first year after the index episode. The distribution of patients across the subtypes was significantly associated with the five outcomes (p<0.001).

Table 3
Distribution of the outcomes, by subtype

	Total	**Group**			**p-value**
		A N (%)	B N (%)	C N (%)	
Total	1599	377 (23.58)	597 (37.34)	625 (39.09)	
2-month mortality	123 (7.69)	39 (10.34)[b]	28 (4.69)[ac]	56 (8.96)[b]	0.0017
1-year readmission	857 (53.60)	229 (60.74)[b]	256 (42.88)[ac]	372 (59.52)[b]	<0.0001
1-year revisits to emergency department	453 (28.33)	130 (34.48)[b]	126 (21.11)[ac]	197 (31.52)[b]	<0.0001
1-year mortality	372 (23.57)	120 (32.26)[b]	95 (16.05)[ac]	157 (25.57)[b]	<0.0001

Group B were those who showed the greatest improvement in total and physical MLWHF scores and significant differences were detected between them and group C. (Figure4)

Discussion

The goal of assessment in AHF, as in other decompensations of chronic diseases, should be determined the level of injury (in this case, of the heart), its impact on the patient's health status and the risk of future events (readmission or death).[12]

In 2015, Kao et al. published a set of phenotypes derived from a cohort in a trial including patients with an EF of at least of 45%, and symptoms of NYHA class II-IV, who were older than 60 years and had been hospitalized in the previous 6 months.[13] Unlike these authors, however, our phenotypes are based on a representative sample of patients with HF including all forms of presentation of AHF in the ED, and hence, we believe that they are more useful in this setting. On the other hand, we have related these phenotypes to changes in patient quality of life, including self-reported outcomes in their evaluation.

In our hierarchy, patients were first classified based on duration of HF, followed by the presence of cardiovascular comorbidities.

- Type A patients were mainly men and less likely to have preserved EF, with a longer history of HF, and worse functional status. The most common etiology was coronary disease, patients presenting at the ED with acute myocardial infarction or concurrent pathologies. They had higher levels of comorbidity, obtained worse results in laboratory tests, and were more likely to have a reduced EF than other chronic patients (Type C)
- Type B patients were more frequently recently diagnosed with HF, with preserved EF with lower levels of comorbidities, no signs of congestion and arrhythmia as the main precipitant together with toxic habits and drugs.
- Type C patients had chronic HF, were mainly women and older than those with types A or B, with lower levels of comorbidity than type A and more levels than type B, but a higher rate of depression. The etiology, in this case, was more frequently related to valve disease and primary right ventricular failure.

Note that main predictor of poor outcome is related to disease duration (measured as time since diagnosis), more than NYHA functional class or EF, which have, until now, been the most widely used classifications for making decision about management including treatment of AHF. Greene et al.[9] found that the influence of HF duration on mortality was potentially more pronounced among women but did not differ with age, history of ischemic heart disease, or EF. Previous research has demonstrated the existence of different subgroups based on *de novo* or pre-existing episode(s) of AHF [14]. Our study has identified another two groups within acute decompensated HF, one composed basically of men with cardiovascular disease (type A) and the other of women with valve disease as the main etiology (type C). When we explored associations between these patient profiles and outcomes, we encountered differences between de novo and acute decompensated HF, and not between types A and C, either in mortality and health service use or in change in quality of life, in spite of differences in age, EF and etiology.

Recently, Choi K et al [15] have associated EF with prognosis in *de novo* and acute decompensated HF, and concluded that preserved EF may indicate better prognosis in acute decompensated HF but not in *de novo* cases. In relation to this, our results are different, the highest percentage of patients with preserved EF being in type C and the percentage with reduced EF highest in Type A, while both types had a similar prognosis.

Unfortunately, we had much missing information concerning EF. We identified that the profile of patients without this information included chronic disease, and it is likely that, in such cases, echocardiography is not repeated at the time of the index episode for the study. They usually have poorer functional status. In any case, though we recognize this as one of the limitations of this study, our statistical approach allows to consider missing information in one variable as another category of the variable, and in our case, they have been included in the final analysis. This useful feature of MCA allowed us to conclude that the missingness pattern was not significantly related either to the other variables considered in the study or to the outcomes.[16] In spite of the properties of MCA, we performed a sensitivity analysis including data on EF up to 2 years prior to the index episode.[17] We found that patients were differently classified and we believe that the information collected from parameters of an echocardiogram performed up to 1 month after the index episode is more precise, as used in this work, considering not available information as another category.

Main strenght of our study is related to the fact that, in contrast to traditional statistical methods, we aimed to create patient typologies that were not strictly related to a specific outcome.(18) Subtypes were identified on the initial evaluation of the AHF patients in the ED. Their statistically significant relationships between them and different outcomes provides a proper validation of the subtypes identified.

Our phenotypes showed differences in outcomes between chronic and *de novo* patients, both in mortality and health service use and in changes in quality of life. To our knowledge, this is the first time that clinical phenotypes have been associated with patient-reported outcomes, this being another strength of the present study.

Conclusion

We hope these clinical phenotypes will be useful in ED and hospital settings, having encountered groups with different prognosis depending on the duration of HF and presence of cardiovascular comorbidity, the two types of chronic patients not differing in terms of prognosis up to a year.

Declarations

- CONFLICT OF INTEREST

Authors declares no conflict of interest.

- ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of the Basque Country (reference PI2012113). All patients or caregivers consented to participate. The study was carried out in accordance with the relevant guidelines and regulations.

- DATA AVAILABILITY

The datasets generated and/or analysed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

- Ethics approval and consent to participate.

The institutional review board of each hospital approved the study, and all patients or caregivers gave their consent to participate in the study.

- Consent for publication

Not applicable

- Availability of data and materials

The study is registered in Clinical trials.gov: NCT03512704. Data and materials are available upon request.

- Competing interests

The authors declare they have no conflict of interest.

- Funding

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- Authors' contributions

Susana García-Gutierrez contributed to the study design, data collection, data analysis, data interpretation, writing of the original draft, review, editing and approval the final version.

José Mª Quintana, contributed to the study design, data analysis, data interpretation, writing of the original draft, review, editing and approval the final version.

Ane Antón-Ladislao y Urko Aguirre contributed to the study design, data analysis, data interpretation, writing of the original draft, review, editing and approval the final version.

Raúl Quirós, Antonio Lara, Irene Rilo, Ibon Rodríguez, Nekane Murga and the ESSIC –REDISSEC Group contributed to the data collection, data interpretation, review, editing and approval the final version.

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Figures

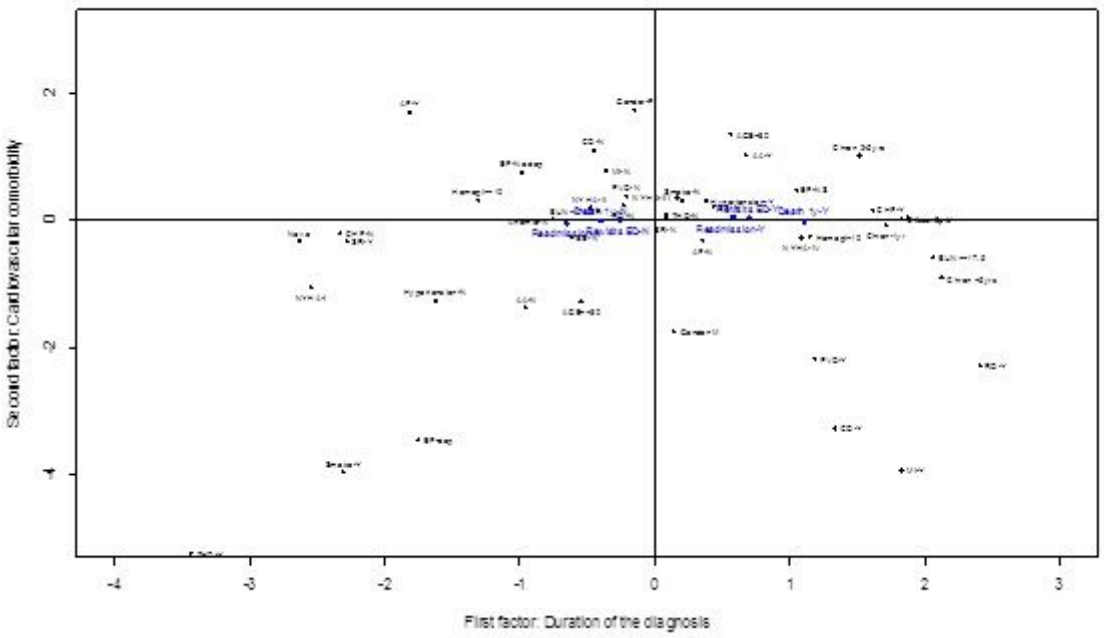

Figure 1

Graphical display created by the two factors derived from the multiple correspondence analysis.

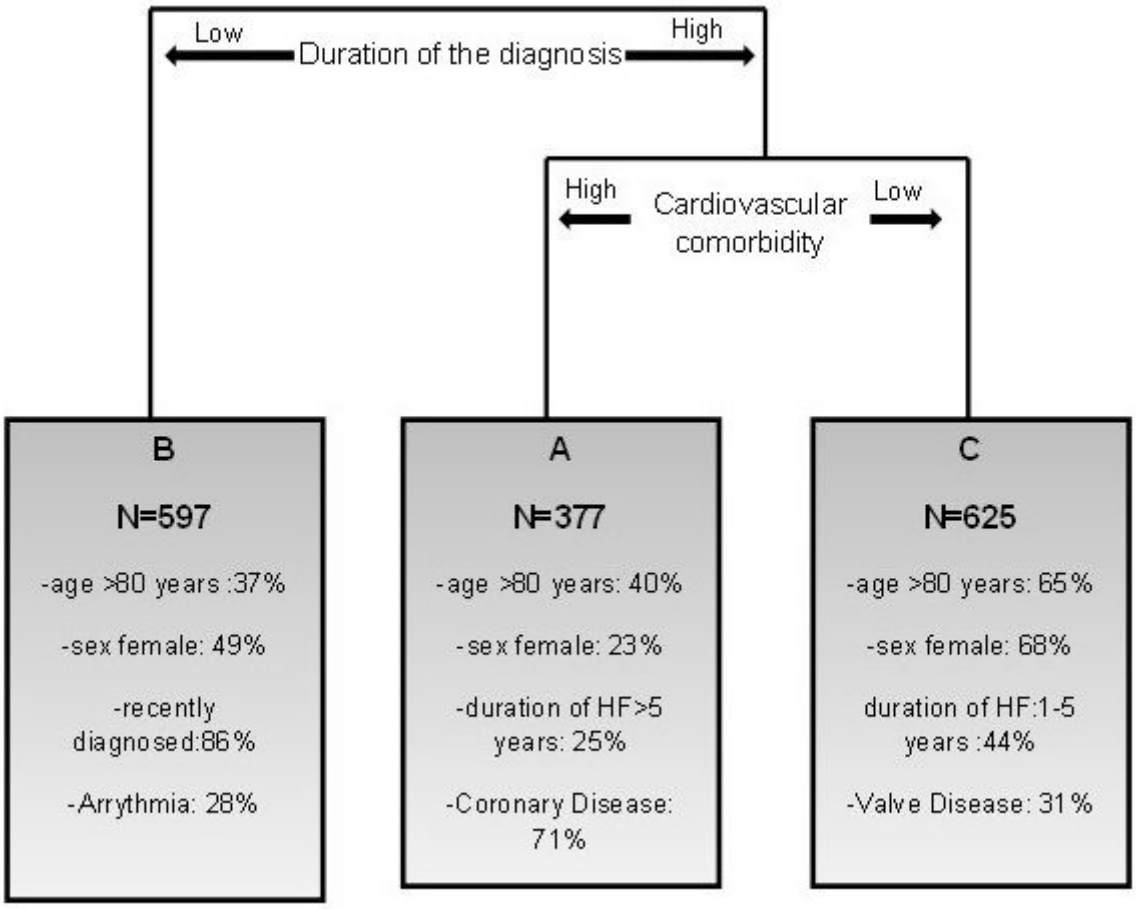

Figure 2

Groups of patients obtained from the cluster analysis.

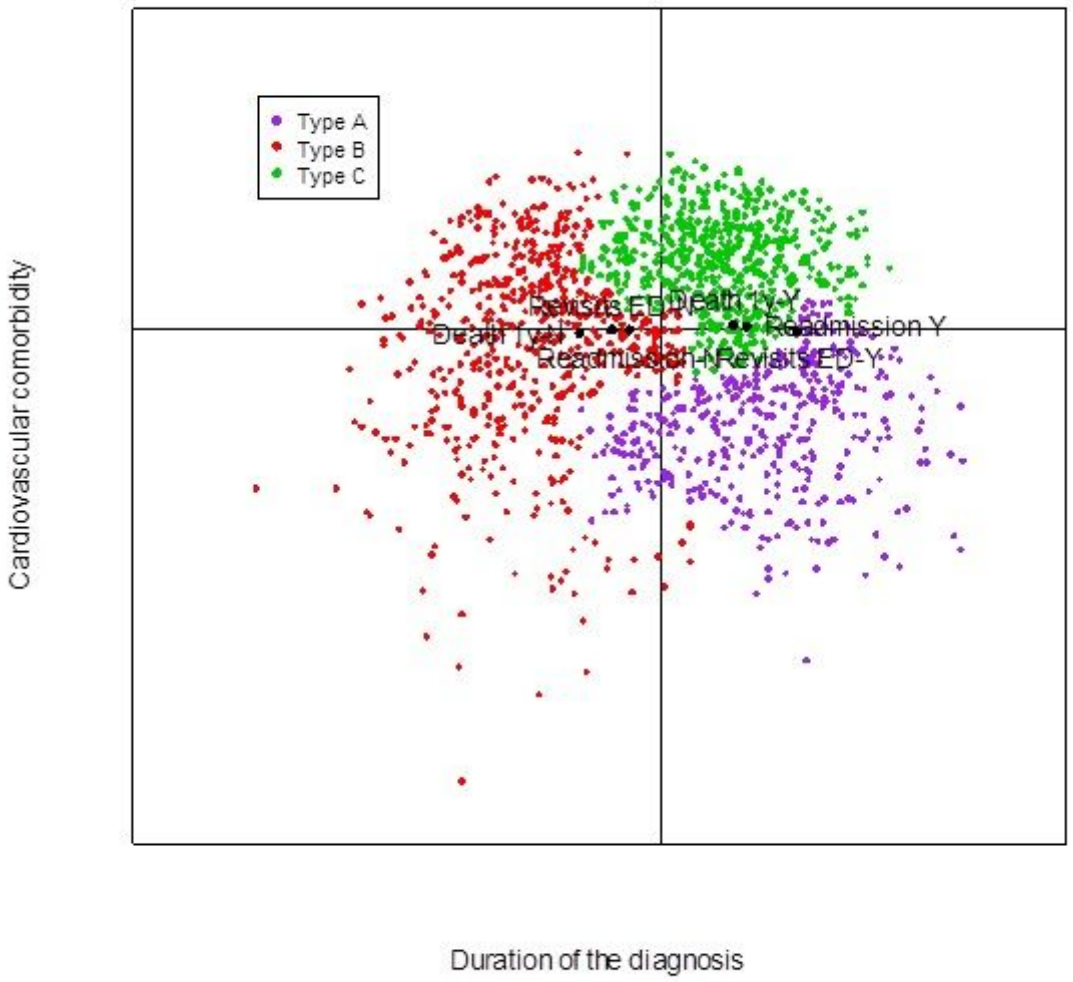

Figure 3

Graphic display of the plane created by the two factors with the different groups of patients and illustrative variables.

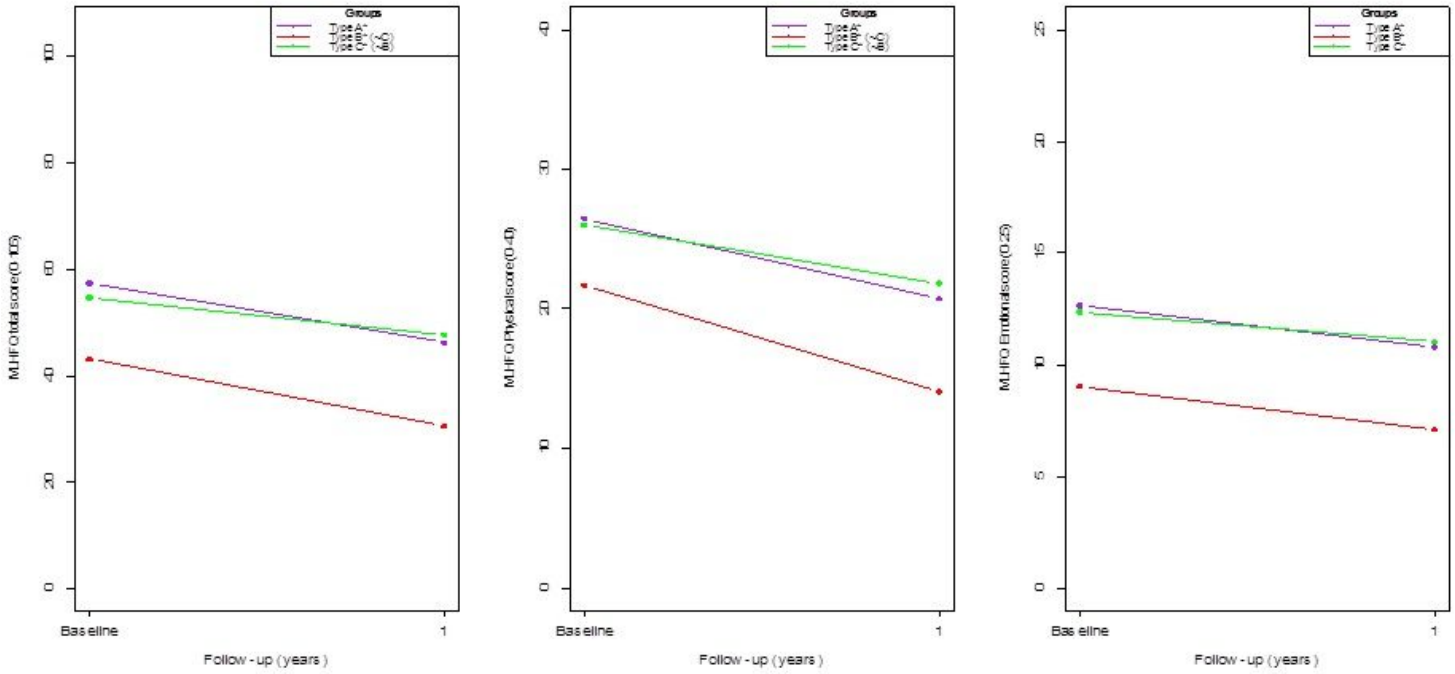

Figure 4

MLHFQ measures (global, physical and emotional score) at baseline and at 1 year after index episode, according to types of patients derived from the combination of MCA and CA. *indicates statistical significance differences between baseline and 1 year's scores. ~A indicates statistical significance differences with respect type A patients in change from baseline to 1 year MLHFQ measures. ~B indicates statistical significance differences with respect type B patients in change from baseline to 1 year MLHFQ measures. ~C indicates statistical significance differences with respect type C patients in change from baseline to 1 year MLHFQ measures.