COMORBIDITIES AND THEIR IMPLICATIONS IN PATIENTS WITH AND WITHOUT TYPE 2 DIABETES MELLITUS AND HEART FAILURE WITH PRESERVED EJECTION FRACTION. FINDINGS FROM THE RICA REGISTRY

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April 28, 2020

Abstract

AIM: to determine if patients with heart failure and preserved ejection fraction (HFpEF) and type 2 diabetes mellitus (T2DM) have a higher comorbidity burden than those without T2DM, if other comorbidities are preferentially associated with T2DM, and if these conditions confer a worse patient prognosis. METHODS AND RESULTS: Cohort study based on the RICA Spanish Heart Failure Registry, a multicenter, prospective registry that enrolls patients admitted for decompensated HF and follows them for 1 year. We selected only patients with HFpEF, classified as having or not having T2DM, and performed an agglomerative hierarchical clustering based on variables such as the presence of arrhythmia, chronic obstructive pulmonary disease, dyslipidemia, liver disease, stroke, dementia, body mass index (BMI), hemoglobin levels, estimated glomerular filtration rate, and systolic blood pressure. 1,934 patients were analyzed: 907 had T2DM (mean age 78.4+/-7.6 years) and 1,027 did not (mean age 81.4+/- 7.6 years). The analysis resulted in 4 clusters in patients with T2DM, and 3 in the reminder. All clusters of patients with T2DM showed higher BMI, and more kidney disease and anemia than those without T2DM. Clusters of patients without T2DM had neither significantly better nor worse outcomes. However, among the T2DM patients, clusters 2, 3 and 4 all had significantly poorer outcomes, the worst being cluster 3 (HR 2.0, 95% CI 1.36-2.93, p=0.001). CONCLUSIONS: Grouping our patients with HFpEF and T2DM into clusters based on comorbidities revealed a greater disease burden and prognostic implications associated with the T2DM phenotype, compared to those without T2DM.

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ABSTRACT

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CONCLUSIONS: Grouping our patients with HFpEF and T2DM into clusters based on comorbidities revealed a greater disease burden and prognostic implications associated with the T2DM phenotype, compared to those without T2DM.

KEY WORDS: Heart failure with preserved ejection fraction; type 2 diabetes mellitus; comorbidity; kidney disease.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

- Heart Failure with preserved ejection fraction is influenced for comorbidities.
- Diabetes mellitus (DM) is one of the most important comorbidities associated.
- The value of the remainder comorbidities in this setting is not fully understood.

WHAT DOES THIS ARTICLE ADD?

- Patients grouped comorbidities revealed a bigger disease burden in the case of DM.
- Comorbidity groups with DM had prognostic effects compared to those without DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and heart failure (HF) are closely related. Patients with T2DM have an increased risk of developing HF and vice versa. Some studies report that more than one-third of patients who are hospitalized for heart failure without a diagnosis of diabetes mellitus (DM) exhibit impaired fasting glucose or glucose intolerance [1], and that the prevalence of diabetes in patients with heart failure ranges from approximately 25% to 40%, depending on the population studied [1]. However, few of these studies differentiated between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). In a subanalysis of the CHARM program (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity), the prevalence of diagnosed diabetes was higher in patients with HFpEF (40%) than in those with HFrEF (35%) [2]. Furthermore, a number of trials in patients with HF have shown an increased risk of cardiovascular death or hospitalization in men and women with diabetes [3-6]. In the case of HFpEF, patients commonly present other associated comorbidities such T2DM, which may contribute to the pathophysiology of HF and its outcome, since their comorbidities are associated with higher rates of non-cardiovascular hospitalization and death. However, the potential impact of HFpEF on the prognosis of T2DM in these patients is not fully characterized. Although diabetes was associated with a steeper increase in left ventricle mass and wall thickness compared to age and sex-adjusted controls in the Framingham study [7], the overall comorbidity burden in patients with T2DM and HF is usually higher than in patients with HF alone [8]. Our aim in this study was to determine if patients with HFpEF and T2DM have a higher comorbidity burden than those without T2DM, if other comorbidities are preferentially associated with T2DM, and if these conditions confer a worse prognosis.

METHODS

Patients were recruited via the RICA Spanish National Heart Failure Registry, supported by the HF and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine (SEMI-IC-FA). The RICA registry is an ongoing multicenter, prospective, cohort study that has been described elsewhere [9,10]. This registry includes consecutive and unique patients aged 50 years or older with HF according to the criteria of the European Society of Cardiology [11]. Patients were included at discharge after an acute event of decompensated HF between March 2008 and May2017,and followed up for 1 year.

The study protocol was approved by the Ethics Committee of the University Hospital Reina Sofia, Cordoba, Spain, and all patients gave their informed consent before inclusion in the cohort. Data were collected in the database via a website (https://www.registrorica.org) that was accessed with a personal password. Complete registry data are published elsewhere [9].

In this analysis, we included only patients with HFpEF [left ventricular ejection fraction (LVEF) higher than 50% and elevated natriuretic peptides], and we excluded patients with either reduced or mid-range ejection fraction and HF caused by valvular heart disease (figure 1). Data analyzed comprise past medical history related to HF, Charlson comorbidity index (CCI), Barthel index (BI), Pfeiffer index (PfI), acute HF episode admission clinical data [blood pressure, heart rate (HR), body mass index (BMI)] and blood chemistry values, including kidney function defined by estimated glomerular filtration rate (eGFR) based on the MDRD equation (Modification of Diet in Renal Disease [12]), blood sugar profile, hemoglobin, serum sodium and potassium levels, and natriuretic peptides.

HF was characterized using the New York Heart Association (NYHA) scale and the evaluation of left ventricular ejection fraction (LVEF) by 2-D echocardiography. We also recorded the etiology of HF (ischemic, hypertensive, alcoholic, toxic, hypertrophic, and others) and the potential cause of decompensation when the patients were included. We excluded patients whose clinical or laboratory data were not fully completed, patients without an echocardiographic examination, and patients who either died during hospitalization or did not complete follow-up.

To analyze differences between patients with and without diabetes, we first divided the sample into two groups according to the diagnosis of T2DM (based on patient history and prescription of hypoglycemic agents). In a second step, we sub-divided the patients according to clusters based on the following variables: arrhythmia, chronic obstructive pulmonary disease (COPD), dyslipidemia, liver disease, stroke, dementia (all defined according to investigators' criteria), BMI, hemoglobin, eGFR, LVEF, and systolic blood pressure (SBP). The primary endpoint was to analyze comorbidities in patients with both HFpEF and T2DM and in patients with HFpEF but without T2DM. Secondary endpoints were to analyze the outcomes of the clusters, firstly in terms of HF mortality and readmissions, and secondly in terms of all-cause mortality and readmissions.

Statistical analysis

We performed an agglomerative hierarchical clustering with the Ward minimum-variance method to group comorbidity variables and identify aggregated conditions. We used the hclust function in R with the dissimilarity matrix defined by the Kendall distance, assuming variables were not parametric (Figure 2) [13]. The previously pre-specified dichotomous variables (COPD, dyslipidemia, liver disease, dementia, and stroke) were assigned a value of one when a given comorbidity was present and zero when it was absent. Categorical variables, such as stroke and arrhythmia, took their values depending on their respective categories. In the case of stroke, the following values were assigned: absent = 0, transitory ischemic accident = 1, hemorrhagic stroke = 2, cardioembolic stroke = 3 and atherothrombotic stroke = 4. In the case of arrhythmia, they were: sinus rhythm = 0, atrial fibrillation or flutter (AF/flutter) = 1, atrioventricular block = 2, and other = 3. Finally, the quantitative pre-specified variables (BMI, eGFR, LVEF, hemoglobin and SBP) retained their numerical value.

Bootstrap resampling techniques (n = 1000) were used to assess reproducibility for each hierarchical cluster,

applying the pvclust function in R [14]. We computed the bootstrap probability (BP) value which corresponds to the frequency with which the cluster is identified in bootstrap copies, and the approximately unbiased (AU) probability values by multiscale bootstrap resampling (Figure 2). Clusters with AU [?] 95% are considered to be strongly supported by data.

Once the clusters were built, we performed univariate comparisons between them. Quantitative variables were expressed as mean +/- standard deviation if normal, and median +/- interquartile range if not normal. The clusters were compared for various numeric parameters by one-way analysis of variance and by the post hoc Tukey's test for multiple comparisons. If the variables were not normal, we used the Kruskal-Wallis test. Qualitative variables were expressed as absolute number and percentage. Study groups were compared using the Chi-squared test.

Finally, a Cox proportional-hazard model was used to examine the association between the clusters and time to hospitalization and death. The model covariates were selected a priori based on previous prognostic reports and clinical experience, and variables which were significant in the initial univariate comparisons were also included. Cumulative curves were estimated by the Kaplan-Meier method and compared by log-rank testing. A p value of < 0.05 was considered significant. Analyses were performed using the SPSS and R programs.

RESULTS

A total of 1,934 patients were analyzed: 907 had T2DM (39.1% men, mean age 78.4+/-7.6 years) and 1,027 did not (39.9% men, mean age 81.4+/- 7.6 years). The most prevalent comorbidities were dyslipidemia (52.4%), AF/flutter (67.4%), and COPD (24.9%). The similarity matrix and significance by variable in the clusters are shown in figure 2.

Clusters

The analysis resulted in 7 significant clusters, 4 in the case of patients with T2DM, and 3 in the non-diabetic patients. Dendrograms portraying patients with and without T2DM are shown in supplementary figure 1.

The resulting clusters are shown in table 1 and figure 3 (above). Clusters 1, 2, 3 and 4 pertain to patients with T2DM. Cluster number 1 (n: 201) included predominantly female patients with high cardiovascular risk without arrhythmia (only 1% had AF/flutter). They had high systolic blood pressure (SBP) and high prevalence of both dyslipidemia and atherothrombotic stroke. Cluster number 2 (n: 303) included older patients, also predominantly women, with no dyslipidemia, lower SBP, and a prevalence of AF/flutter greater than 50%. Cluster number 3 (n: 140) included mostly male patients with COPD, dyslipidemia, and liver disease. Although the presence of AF/flutter was 58.6%, this cluster showed the lowest rate of cerebrovascular disease (92.1% patients without any stroke). Cluster number 4 (n: 263) was similar to number 1. However, the prevalence of AF/flutter (93.9%), TIA (7.2%), and cardioembolic stroke (3.4%) was much higher. Clusters 5, 6 and 7 pertain to patients without T2DM. On average, these clusters portrayed older patients, with lower SBP and BMI and better eGFR than those with T2DM. Overall, the associations among the variables included are less significant (figure 2). However, variables such as hemoglobin and eGFR are more significant in defining the clusters, whereas the presence of arrhythmia is not. Cluster 5 contains predominantly men (66.5%) with COPD and a high prevalence of AF/flutter (64.8%). They also have the highest levels of eGFR (62.3 +/- 32.7ml/min, p=0.0001) and hemoglobin (12.8 +/- 2.9 gr/dl, p=0.01). Cluster 6 again contains mainly women (69.6%) with excess weight and a high prevalence of dyslipidemia (97.1%) and stroke, both hemorrhagic and cardioembolic or atherothrombotic (p=0.003). Approximately half have AF/flutter (55.1%) and of the three clusters without T2DM, patients in cluster 6 have the lowest levels of eGFR (p=0.0001) and hemoglobin (p=0.01). Finally, cluster 7, with a 67% predominance of women, is quite undifferentiated, with a slightly higher SBP than the other clusters without T2DM, and a notable prevalence of AF/flutter (63.2%) and TIA (4%).

Some additional findings by clusters are shown in Table 2. Patients with T2DM had more history of hypertension, mainly clusters 3 and 4. Charlson comorbidity index is similarly higher in these patients, the

highest levels being found in cluster 3. Regarding etiology of HF, ischemic cardiomyopathy was significantly prevalent in patients with T2DM (p=0.001), particularly in cluster 3 (40%). Finally, significant differences in treatment were detected among the clusters. Overall, patients with T2DM were more often treated with angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) (p=0.004), beta-blockers (p=0.003), loop diuretics (p=0.007), and thiazides (p=0.009).

Outcomes

Table 3 shows the results according to the multivariate Cox regression analysis, and figure 3 (below) shows the Kaplan-Meier curves. Regarding HF mortality and readmissions, age, comorbidity (CCI), Barthel index, eGFR and serum sodium were significantly related to the endpoint. In the analysis of the clusters, the clusters of patients without T2DM had neither significantly better nor worse outcomes than those of cluster 1 (patients with T2DM). However, significantly worse outcomes were detected among the patients with T2DM in clusters 2, 3 and 4, the worst being in number 3 (HR 2.0, 95% CI 1.36-2.93, p=0.001). As for total mortality and readmissions, again age, comorbidity (CCI), Barthel index, eGFR, and serum sodium were significantly related to this endpoint. Furthermore, in terms of clusters, clusters of patients without T2DM were again not significantly associated with an increase in total mortality and readmissions. Nevertheless, cluster 3 and 4, showed this association, and once more cluster 3 was the worst (HR 1.6, 95% CI 1.22-2-16, p=0.001).

DISCUSSION

Our cluster analysis of patients with and without T2DM revealed a greater number of defined groups among patients with T2DM and, moreover, a worse prognosis in the majority of these patients compared with the clusters of patients without T2DM.

Composite connections between comorbidities themselves and between comorbidities and the cardiovascular system lead to the establishment of HF, whether HFpEF or HFrEF. Conversely, HF may cause comorbidities, which, in turn, adversely influence outcomes [15]. It is known that HFpEF is associated with more comorbidities than HFrEF [16] and thus, HFpEF emerges as a model with proinflammatory cardiovascular and non-cardiovascular coexisting comorbidities, resulting in systemic inflammation and later fibrosis and different clinical HFpEF phenotypes. DM is a prevalent comorbidity in HF and has a significantly adverse impact on prognosis. About 45% of patients with HFpEF have DM, and the prevalence of comorbid DM is growing most markedly in those with new-onset HFpEF [17]. Although the characteristics and outcomes of this population are poorly understood, some previous reports suggest that DM is associated with increased morbidity and long-term mortality in HFpEF [18,19]. Furthermore, patients with DM and HFpEF have already been described as a unique phenotype within HFpEF [19]. In this study, we show how other additional pathologies can form new sub-clusters resulting in different outcomes within the group of patients with T2DM, while this influence is not observed in patients without T2DM.

Compared to the set of patients without T2DM, our patients with T2DM shared similar characteristics to those previously described in this phenotype [19]. Patients had higher BMI, more prevalence of both dyslipidemia and ischemic etiology, and all subgroups were similar in terms of impaired renal function and hemoglobin below 12 g/dl. We might hypothesize about the presence of a cardiorenal anemia syndrome in this population, derived from an interaction between diabetic microvascular disease affecting the kidneys and myocardium [20], and other factors such as elevated central venous and intra-abdominal pressure, left ventricular hypertrophy, left ventricular strain, RAAS activation, oxidative injury, pulmonary hypertension, and right ventricular dysfunction [21]. Additionally, it should be noted that AF/flutter can form a separate cluster (cluster 4), very similar to cluster 1 except for the presence of these arrhythmias and older age. It is known that AF/flutter interacts with both DM and HFpEF [22,23]. In our case, the presence of AF/flutter in patients with HFpEF and DM determines a different profile which adds up to a significantly worse outcome. However, the worst profile in terms of outcomes corresponds to cluster 3, the only group of T2DM patients with predominantly men, and the one that is particularly characterized by the presence of COPD (also more than half of the patients had AF/flutter). It is known that COPD is an independent predictor of mortality

in patients with HFpEF and in patients with HFrEF [24]. DM is likewise independently correlated with reduced lung function, while obesity may further worsen ventilatory mechanics [25]. Apart from smoking, which is more prevalent in this group, the comorbidity burden (CCI) is also the highest. All these factors may incorporate a pro-inflammatory state that determines greater cardiovascular disease, and this, along with a worse functional class (the prevalence of NYHA III was the highest in this cluster), could contribute to higher mortality.

In contrast to patients with T2DM, the clusters of patients without T2DM had significant differences in hemoglobin and renal function (eGFR). Renal impairment is not as prevalent as in diabetic patients and determines one group (cluster 6) in which dyslipidemia and cerebrovascular disease is also prevalent. This cluster is comparable with clusters 1 and 4 in patients with T2DM. However, the differences in hemoglobin and eGFR may lead to a lower prevalence of cardiorenal anemia syndrome, and along with the absence of T2DM may contribute to the differences in prognosis among these clusters. Again cluster 5 may have some similarities with cluster 3. The presence of COPD and smoking are decisive in both groups, though, here too, disparities in eGFR, BMI and hemoglobin may play a role in the significant differences in outcomes. Finally clusters 2 and 7, which were the most numerous, encompass the oldest female patients with a high prevalence of AF/flutter and hypertensive myocardiopathy, but with no another differential characteristics. It could be that patients with genuine HFpEF and no other relevant pathologies (their CCI was the lowest among the clusters in their class, with/without T2DM) modify the phenotype, irrespective of the presence or absence of T2DM, which would contribute to the difference in the prognosis between both of them in terms of HF. These clusters should be better defined using other variables that we were unable to analyze, such as exercise capacity or vascular stiffness.

Our study has several limitations. Firstly, mortality during admission was not recorded, and this may have led to a significant selection bias and misleading results. Secondly, the data come from a registry which started to include patients in 2008, so they may not all conform to the current definition of HFpEF. Finally, we have not included in the analysis some discordant comorbidities of T2DM (e.g., depression) that may have a significant clinical impact [26].

In conclusion, the grouping of our patients with HFpEF and T2DM into clusters based on their comorbidities revealed prognostic implications according to the phenotype obtained. All clusters with T2DM presented similar levels of kidney disease and anemia. In contrast, the clusters of patients with HFpEF but without T2DM showed significant differences in renal dysfunction and anemia. However, they did not have a significantly worse outcome compared to the clusters with T2DM. Therefore, comorbidities may play a more important role in determining prognosis in patients with HFpEF and T2DM.

FUNDING

This study received neither grants nor funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1: Characteristics by clusters based on selected comorbidities

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P	Cluster 5	Cluster 6	Cluster 7	P
N	201	303	140	263		236	316	475	
Age	78 (12)	81 (8)	78 (9)	80 (9)	0.0000	82 (9.5)	82.5 (8)	84 (8)	0.0
Sex (male)	55 (27.4%)	124 (40.9%)	91 (65%)	85 (32.3%)	0.00001	157 (66.5%)	96 (30.4%)	157 (33%)	0.0
SBP (mmHg)	148 (38)	140 (36)	141 (35)	140 (37)	0.0005	137 (35)	135 (35)	137 (33)	0.0
eGFR (MDRD)	49.2 (35.6)	51.9 (32.9)	54 (32)	51.7 (35.9)	0.39	62.3 (33.7)	58.2 (38.9)	60 (35)	0.0
Hemoglobin (g/dl)	11.4 (2.5)	11.7 (2.8)	11.1 (2.9)	11.5 (2.7)	0.62	12.8 (2.9)	12.1 (2.7)	12.3 (2.6)	0.0
BMI (kg/m2)	30.5 (8.8)	29.7 (7.2)	31.2 (6.8)	30.9 (7.3)	0.28	28.5 (7.2)	28.9 (7.0)	28.3 (6.6)	0.2
Dyslipidemia	201 (100%)	2 (0.66%)	135 (96.4%)	263 (100%)	0.0001	102 (43.2%)	307 (97.1%)	3 (0.63%)	0.0
COPD	0 (0%)	77 (25.4%)	140 (100%)	0 (0%)	0.0001	236 (100%)	5 (1.6%)	24 (5%)	0.0
Arrhythmia	Arrhythmia	Arrhythmia	Arrhythmia	Arrhythmia	Arrhythmia				
No	199 (99%)	104 (34.3%)	54 (38.6%)	2 (0.76%)	0.0001	76 (32.2%)	130 (41.1%)	167 (35.2%)	0.0

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P	Cluster 5	Cluster 6	Cluster 7	P
AF/flutter	2 (1%)	191 (63%)	82 (58.6%)	247 (93.9%)		153 (64.8%)	174 (55.1%)	300 (63.2%)	
AV block	0 (0%)	5 (1.65%)	1 (0.7%)	9 (3.4%)		5 (2.1%)	6 (1.9%)	6 (1.3%)	
Other	0 (0%)	3 (0.9%)	3 (2.1%)	5 (1.9%)		2 (0.8%)	6 (1.9%)	2 (0.4%)	
Stroke	Stroke	Stroke	Stroke	Stroke	Stroke				
No	179 (89%)	262 (86.5%)	129 (92.1%)	214 (81.4%)	0.002	220 (93.2%)	260 (82.3%)	420 (88.4%)	0.0
TIA	9 (4.5%)	13 (4.3%)	3 (2.1%)	19 (7.2%)		9 (3.8%)	12 (3.8%)	19 (4%)	
Hemorrhagic	0 (0%)	2 (0.6%)	3 (2.1%)	5 (1.9%)		2 (0.8%)	8 (2.5%)	4 (0.8%)	
Cardioembolic	0 (0%)	8 (2.6%)	3 (2.1%)	9 (3.4%)		2 (0.85%)	16 (5.1%)	15 (3.2%)	
Atherothrombotic	13 (6.5%)	18 (5.9%)	2 (1.4%)	16 (6.1%)		3 (1.3%)	20 (6.3%)	17 (3.6%)	
Liver disease	12 (5.9%)	20 (6.6%)	18 (12.9%)	13 (4.9%)	0.02	16 (6.8%)	11 (3.5%)	23 (4.8%)	0.2
Dementia	8 (3.9%)	19 (6.3%)	6 (4.3%)	9 (3.4%)	0.4	10 (4.2%)	16 (5.1%)	28 (5.9%)	0.6
HbA1c (%)	7.2 (2.2)	6.8 (1.3)	7 (1.6)	6.9 (2)	0.29				

Quantitative variables are shown as mean (standard deviation). Qualitative variables are shown as absolute number (percentage).

AF/flutter: atrial fibrillation/flutter; AV block: atrioventricular block; BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration ratio by MDRD formula; HbA1c: glycosylated hemoglobin; SBP: systolic blood pressure; TIA: transitory ischemic attack.

Table 2: Clinical, laboratory and echocardiographic findings by cluster

VARIABLE	Patients with T2DM CLUSTER 1	Patients with T2DM CLUSTER 2	Patients with T2DM CLUSTER 3	Patients with T2DM CLUSTER 4	Patients without T2DM CLUSTER 5	Patients without T2DM CLUSTER 6	Patients without T2DM CLUSTER 7	P
N	201	303	140	263	236	316	475	
History of hypertension	191 (95%)	288 (95%)	137 (98%)	253 (96%)	201 (85%)	286 (91%)	408 (86%)	<0.001
History of smoking	44 (22%)	99 (33%)	86 (61%)	75 (29%)	127 (54%)	71 (22%)	117 (25%)	0.187
History of alcoholism	19 (9.5%)	48 (16%)	35 (25%)	29 (11%)	61 (26%)	37 (12%)	49 (10%)	0.948
CCI	4.17±2.28	3.64±2.45	5.29±2.49	4.06±2.25	2.67±1.87	1.83±1.78	1.65±1.75	<0.001
Barthel index	81.59±24.12	79.59±23.11	84.61±19.39	79.10±22.90	84.51±19.54	81.29±22.75	81.84±22.55	0.113
Pfeiffer index	1.57±2.04	1.69±2.21	1.22±1.54	1.62±1.82	1.50±1.88	1.63±1.99	1.53±1.91	0.914
HR (bpm)	84.97±22.51	85.51±20.76	85.40±19.90	83.88±21.99	88.68±22,19	86.62±22,49	88.93±24.33	0,001

	Patients with T2DM	Patients with T2DM	Patients with T2DM	Patients with T2DM	Patients without T2DM	Patients without T2DM	Patients without T2DM	
LVEF	60+10	60+11	60+10	60+10	61.1+10.5	61.3+12	63+13	0.22
LVPWT (mm)	11.67±1.94	11.90±2.42	12.04±1.82	11.66±1.82	12.17±3.52	11.81±7.62	11.44±2.41	0.753
PASP (mmHg)	41.62±13.53	47.01±13.50	46.91±15.93	48.09±15.63	46.57±13.68	44.35±13.03	44.83±14.03	0.122
LAD (mm)	42.67±8.24	45.37±9.65	45.97±8.92	45.89±9.99	47.19±10.03	46.55±9.42	45.07±10.06	0.07
Serum sodium (mEq/L)	138.62±4.67	138.86±4.79	137.79±12.44	138.32±5.11	139.33±4.81	138.70±5.00	139.20±4.94	0.025
Serum potassium (mEq/L)	4.46±0.57	4.37±0.64	4.44±0.54	4.36±0.63	4.30±0.59	4.28±0.61	4.27±0.60	<0.001
Etiology of HF								
Hypertensive	101 (51%)	196 (65%)	84 (61%)	178 (68%)	145 (62%)	197 (63%)	312 (66%)	0.420
Ischemic	80 (40%)	48 (16%)	40 (29%)	54 (21%)	36 (15%)	67 (21%)	60 (13%)	<0.001
Alcoholic	0	1 (0.33%)	1 (0.73%)	0	4 (1.7%)	0	1 (0.21%)	0.459
Toxic	0	0	1 (0.73%)	0	0	0	2 (0.42%)	1.000
Hypertrophic	3 (1.5%)	11 (3.7%)	2 (1.5%)	2 (0.76%)	4 (1.7%)	7 (2.2%)	18 (3.8%)	0.300
Others	14 (7.1%)	44 (15%)	9 (6.6%)	28 (11%)	45 (19%)	44 (14%)	78 (17%)	<0.001
NT-ProBNP	4328.45± 5623.14	5054.05± 6646.79	4774.06± 4989.90	4703.97± 6593.10	4963.54± 6093.54	5155.51± 5689.35	5729.33± 7147.94	0,135
New York Heart Association Class								
I	23 (12%)	12 (4.0%)	9 (6.5%)	12 (4.6%)	16 (6.8%)	37 (12%)	64 (14%)	<0.001
II	118 (59%)	173 (57%)	67 (48%)	158 (61%)	130 (56%)	198 (63%)	277 (59%)	0.353
III	53 (27%)	109 (36%)	56 (40%)	88 (34%)	81 (35%)	72 (23%)	118 (25%)	<0.001
IV	5 (2.5%)	7 (2.3%)	7 (5.0%)	3 (1.1%)	7 (3.0%)	6 (1.9%)	11 (2.3%)	1.000
Medications								
ACEi/ARB	148 (74%)	222 (73%)	92 (66%)	186 (71%)	156 (66%)	190 (60%)	324 (68%)	0.004
Beta-blockers	128 (64%)	172 (57%)	71 (51%)	158 (60%)	94 (40%)	179 (57%)	255 (54%)	0.003
Loop diuretics	176 (88%)	281 (93%)	127 (91%)	229 (87%)	210 (89%)	260 (82%)	409 (86%)	0.007
Thiazides	24 (12%)	37 (12%)	16 (11%)	36 (14%)	16 (6.8%)	33 (10%)	41 (8.6%)	0.009
Potassium-sparing diuretics	34 (17%)	76 (25%)	31 (22%)	62 (24%)	55 (23%)	52 (16%)	99 (21%)	0.220

Quantitative variables are shown as mean (standard deviation). Qualitative variables are shown as absolute number (percentage).

ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCI: Charlson comorbidity index; HR: heart rate; LAD: left atrium diameter; LVEF: Left ventricular ejection fraction; LVPWT: left ventricular posterior wall thickening; NT-ProBNP: N-terminal pro b-type natriuretic peptide; PASP: pulmonary artery systolic pressure.

Table 3: Cox regression analysis

VARIABLE	HR	95% CI	P	HR	95% CI	P
	Heart failure mortality and readmissions	Heart failure mortality and readmissions	Heart failure mortality and readmissions	Overall mortality and readmissions	Overall mortality and readmissions	Overall mortality and readmissions
Age	1.02	(1.01-1.03)	0.001	1.01	(1.01-1.02)	<0.001
CCI	1.11	(1.08-1.14)	<0.001	1.11	(1.08-1.14)	<0.001
Barthel Index	0.99	(0.99-0.99)	<0.001	0.99	(0.99-0.99)	<0.001
LVEF	0.99	(0.98-1.00)	0.157	0.99	(0.99-1.00)	0.076
eGFR	0.99	(0.98-0.99)	<0.001	0.99	(0.99-0.99)	<0.001
Serum sodium	0.98	(0.97-0.99)	<0.001	0.98	(0.97-0.99)	<0.001
ACEi/ARB	0.91	(0.76-1.08)	0.272	0.97	(0.85-1.11)	0.676
Beta-blockers	0.93	(0.79-1.09)	0.361	0.95	(0.84-1.07)	0.398
Loop diuretics	1.3	(0.99-1.71)	0.061	1.19	(0.98-1.44)	0.079
Clusters						
Cluster 1	Ref.		<0.001	Ref.		0.002
Cluster 2	1.42	(1.01-2.02)	0.047	1.16	(0.91-1.49)	0.23
Cluster 3	2	(1.36-2.93)	<0.001	1.62	(1.22-2.16)	<0.001
Cluster 4	1.65	(1.16-2.34)	0.005	1.3	(1.01-1.67)	0.043
Cluster 5	1.3	(0.90-1.88)	0.167	1.11	(0.85-1.44)	0.442
Cluster 6	1.22	(0.86-1.74)	0.267	1	(0.77-1.28)	0.981
Cluster 7	1.1	(0.78-1.54)	0.589	1.05	(0.83-1.32)	0.703

ACEi/ARB: angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker; CCI: Charlson comorbidity index; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction.

FIGURE LEGENDS

Figure 1: Study flowchart

Figure 2: Dissimilarity matrix defined by Kendall distance and multiscale bootstrap resampling. In the matrix square, the color level is proportional to the similarity value between the observations. If it is red, the distance between the variables is 0 (high similarity) and if it is green, the distance is the highest (low similarity). In the multiscale bootstrap resampling [approximately unbiased probability (AU) in red; bootstrap probability (BP) in green]. The greater the value of both, the more significantly representative the grouping of the variables included.

Panel A: Patients with HFpEF and T2DM. Panel B: Patients with HFpEF and without T2DM.

BMI: body mass index; COPD: Chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration ratio by MDRD formula; HB: hemoglobin; SBP: systolic blood pressure.

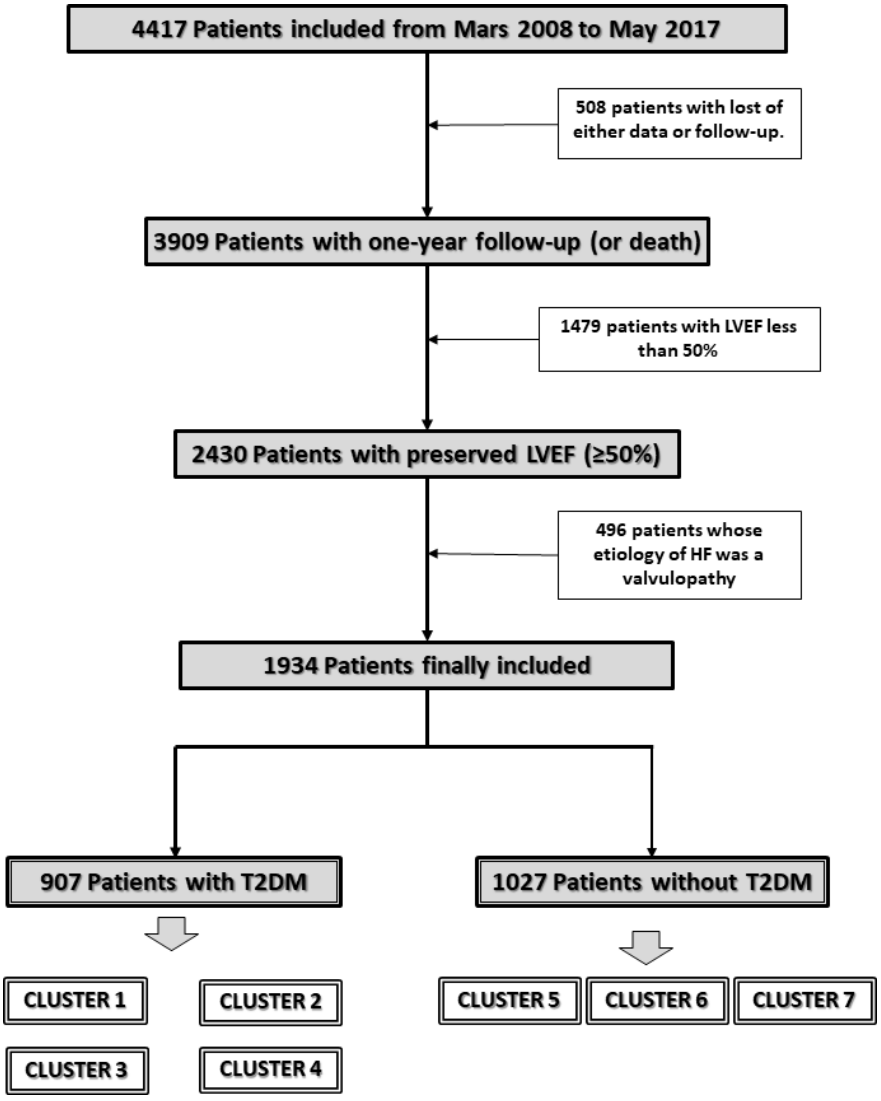
Figure 3: Descriptive figure of the clusters (above) and Kaplan Meier curves (below).

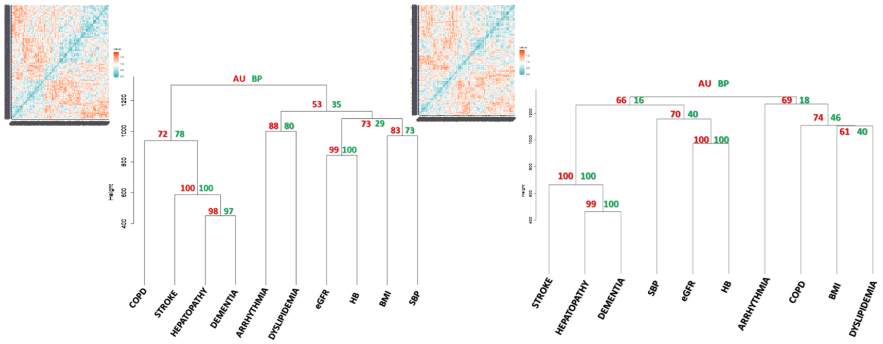
Supplementary figure 1: Dendrograms of patients with and without type 2 diabetes mellitus, with their corresponding clusters.

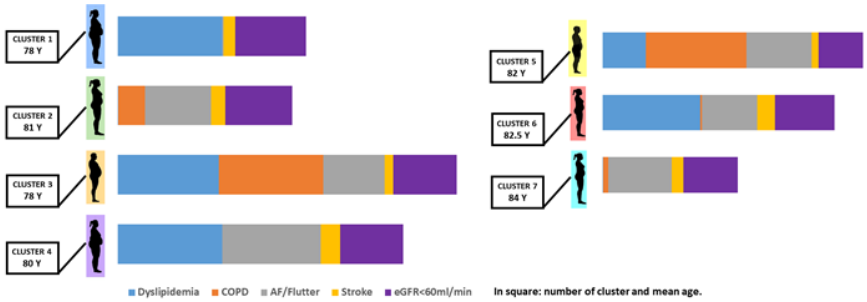
APPENDIX 1

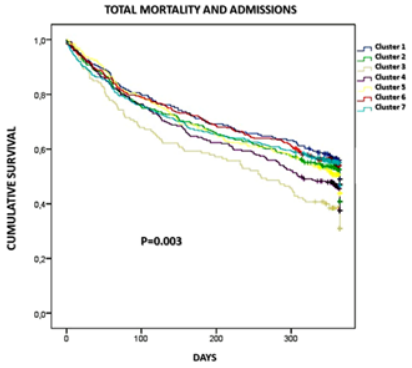
Membership of RICA registry:

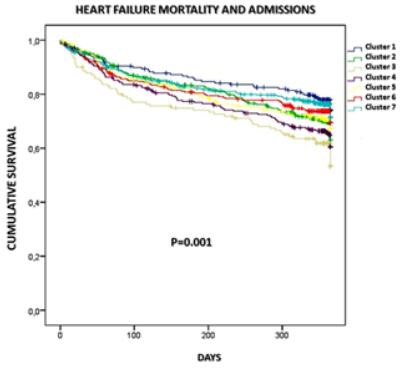
Álvarez Rocha P, Anarte L, Arévalo-Lorido JC, Carrascosa S, Carretero-Gómez J, Cepeda JM, Díez-Manglano J, Epelde F, Fabra Juana S, García Escrivá D, García López P, Gómez Huelgas R, González Franco A, León Acuña A, Llàcer P, López-Castellanos G, Manzano L, Montero-Pérez-Barquero M, Ormaechea G, Pérez Silvestre J, Quesada Simón MA, Roca Villanueva B, Ruiz Ortega R, Soler Rangel ML, Suárez Pedreira I, Trullàs JC.

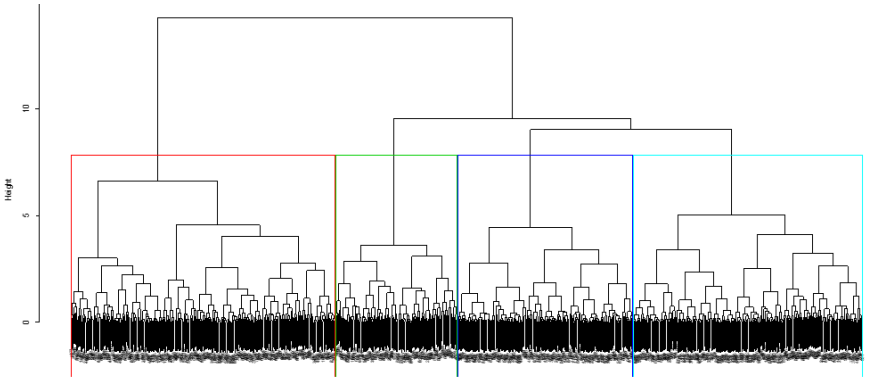




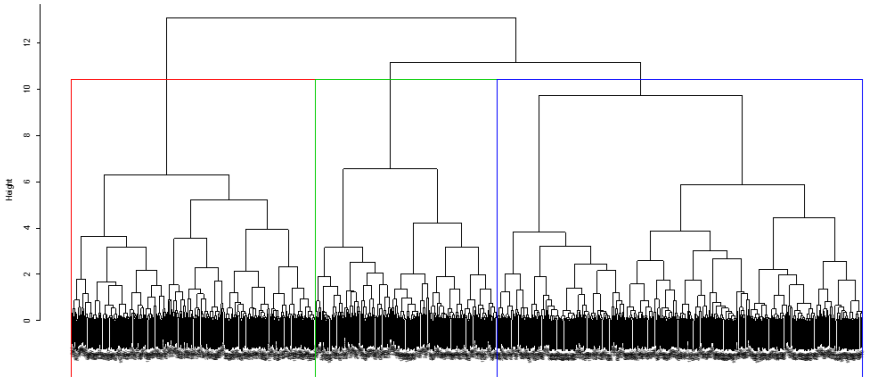








Patients with heart faiure and preserved ejection fraction and with type 2 diabetes mellitus



Patients with heart faiure and preserved ejection fraction and without type 2 diabetes mellitus