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Multimorbidity patterns in patients with heart failure: an observational population study based on electronic health records.

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Manuscripts

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3 **1 Multimorbidity patterns in patients with heart failure: an observational population study**
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5 **2 based on electronic health records.**
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2
3 **23 Abstract**
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6 **24 Objectives:** To characterize the comorbidities of heart failure (HF), to explore their clustering
7
8 **25** into multimorbidity patterns, and to measure the impact of such patterns on the risk of
9
10 **26** hospitalization and mortality.

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13 **27 Design:** Observational retrospective population study based on electronic health records.
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16 **28 Setting:** EpiChron Cohort (Aragón, Spain).
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19 **29 Participants:** All primary and hospital care patients of the EpiChron Cohort with a diagnosis of
20
21 **30** HF in 2011 (i.e., 14,670). We considered all their chronic diseases registered in patients'
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23 **31** electronic health records until the end of 2011.
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26 **32 Primary outcome:** We applied an exploratory factor analysis to identify the multimorbidity
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28 **33** patterns, and logistic and Cox proportional-hazards regressions to investigate the association
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30 **34** between the patterns and the risk of hospitalization in 2012 and of three-year mortality,
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32 **35** respectively.
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34

35 **36 Results:** Almost all HF patients (98%) had multimorbidity, with an average of 7.8 chronic
36
37 **37** diseases per patient. We identified six different multimorbidity patterns, named cardiovascular,
38
39 **38** neurovascular, coronary, metabolic, degenerative, and respiratory. The most prevalent patterns
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41 **39** were the degenerative (64.0%) and cardiovascular (29.9%) in women, and the metabolic
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43 **40** (49.3%) and cardiovascular (43.2%) in men. All patterns were associated with higher risk of
44
45 **41** hospitalization; and the cardiovascular, neurovascular and respiratory patterns significantly
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47 **42** increased the likelihood of three-year mortality.
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50
51 **43 Conclusions:** Multimorbidity is by far the norm rather than the exception in patients with heart
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53 **44** failure, whose comorbidities tend to cluster together beyond simple chance in the form of
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55 **45** multimorbidity patterns that have different impact on health outcomes. This knowledge could
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57 **46** be useful to better understand common pathophysiological pathways underlying this condition
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3 47 and its comorbidities, and factors influencing the prognosis of these patients. Further large scale
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5 48 longitudinal studies are encouraged to confirm the existence of these patterns as well as their
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7 49 differential impact on health outcomes.
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13 51 **Keywords:** Heart failure; Multimorbidity; Comorbidity; Patterns; Hospitalization
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19 53 **Word count:** 3182
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26 55 **Article Summary**
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29 56 *Strengths and limitations of the study*
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32 57 - This is a large-scale population-based study including all primary and hospital care real life
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34 58 patients of the reference population with a diagnosis of HF.
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37 59 - Data in the cohort continuously undergo quality control check-ups that ensure their accuracy
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39 60 and reliability for use in research.
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42 61 - The cross-sectional characterization of the multimorbidity patterns makes it impossible to
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44 62 understand the chronological relationship between the different risk factors and chronic
45
46 63 diseases.
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50 64 - Diagnoses were extracted from electronic health records that were not originally designed for
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52 65 research, thus leading to a potential over or under-reporting of specific diseases.
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55 66 - The estimation of the effect of multimorbidity patterns on health outcomes did not consider
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57 67 the potential confounding role of socioeconomic factors or clinical parameters like the ejection
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59 68 fraction, which were not available in the study cohort.
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70 **Introduction**

71 Improvements in diagnostic and therapeutic procedures have decreased mortality rates
72 associated to heart failure (HF), transforming this condition into a chronic disease with a high
73 burden of comorbidity, as confirmed by European HF registries.¹ The population affected by HF
74 is complex and presents with different phenotypes depending on age, sex, comorbidity, and
75 pathophysiological and prognostic aspects.² Both cardiovascular and non-cardiovascular
76 comorbidity are determining factors in the differentiation of these phenotypes and their impact
77 on health outcomes. In fact, HF patients with non-cardiovascular comorbidity show increased
78 disease burden, severity, risk of hospitalization and death.^{3,4}

79 Recent studies have examined the most prevalent comorbidities in HF patients and their
80 prognostic impact on mortality rates and hospital readmissions.^{2,5,6} However, although the
81 existence of non-random associations among chronic HF comorbidities and their clustering into
82 multimorbidity patterns has already been demonstrated,⁷ most studies still focus on isolated
83 comorbidities, without considering the interrelations among them. Among the few studies
84 addressing multimorbidity in HF patients, some restrict their analyses to the most frequently co-
85 occurring combinations of two and three comorbidities,⁸ others are conducted in relatively small
86 samples,⁹ and the methodological approaches in terms of data source, studied comorbidities, and
87 applied statistical technique vary considerably.^{3,8-10} Moreover, there is a need to perform studies
88 on real life patients from primary care, the level of care where multimorbidity is most frequently
89 dealt with.

90 The Academy of Medical Sciences recently highlighted the importance of investigating
91 which multimorbidity patterns cause the greatest burden, and what are the determinants of the
92 most common clusters of conditions.¹¹ Improving our knowledge on the systematic associations
93 among HF comorbidities is of great interest because some of them are known to share common
94 biological and socioeconomic risk factors on which prevention strategies could be based.

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3 95 Further, the identification and clinical characterization of multimorbidity patterns in patients
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5 96 with HF and the study of their potential impact on negative health outcomes (e.g., risk of death
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7 97 and hospitalization) could shed light on new pathophysiological pathways that may guide the
8
9 98 development of clinical practice guidelines better adapted to patients with HF.¹²
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12 99 This large-scale population study based on electronic health records from real life
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14 100 primary and hospital care patients aimed to characterize the comorbidities of HF, to explore
15
16 101 their clustering into multimorbidity patterns, and to measure the impact of such patterns on
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18 102 negative health outcomes.
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23 24 25 104 **Methods**

26 27 28 105 *Design and study population*

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30
31 106 We conducted a retrospective observational study based on data from the EpiChron Cohort that
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33 107 links demographic, clinical and health outcomes information for all public health system users
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35 108 of the Spanish region of Aragón. A description of the cohort profile and of the data sources was
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37 109 published elsewhere.¹³ This cohort was conformed in 2011 and it included 1,253,292 people at
38
39 110 baseline (approximately 95% of total inhabitants of Aragón). For this study, we selected and
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41 111 followed up for three years all patients with a diagnosis of HF in their primary or hospital
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43 112 electronic health records on 31st January 2011.
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46 47 113 *Outcome variables*

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50 114 For each patient, we analysed data on demographics (i.e., age, sex, area of residence, immigrant
51
52 115 status), healthcare use during 2012 (i.e., use of primary care, specialized care, hospital and
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54 116 emergency services), diagnoses of chronic conditions registered in both primary and hospital
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56 117 care, and all-cause mortality until 31st December 2014. Diagnoses were originally coded
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58 118 according to the International Classification of Primary Care (ICPC) or the International
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3 119 Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and
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5 120 subsequently grouped in Expanded Diagnostic Clusters (EDCs) through the Johns Hopkins
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7 121 ACG® System (version 11.0, The Johns Hopkins University, Baltimore, MD, US). We
8
9 122 considered for the study all patients with the EDC code CAR05, which includes ICPC and ICD-
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11 123 9-CM codes for HF. We included in the analysis all of the 114 EDCs previously defined as
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13 124 chronic by Salisbury et al.¹⁴

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16 125 This study complies with the Declaration of Helsinki, and the research protocol was
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18 126 approved by the Clinical Research Ethics Committee of Aragón (CEICA, PI18/082). The
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20 127 CEICA waived the requirement to obtain the informed consent from patients since the
21
22 128 information used was anonymised.

23 24 25 26 129 *Statistical analyses*

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29 130 All analyses were stratified by sex. First, we performed a descriptive analysis of demographic
30
31 131 and clinical information of the population with HF. We compared means and frequencies using
32
33 132 the Student t test and the chi-squared test, respectively, with their respective 95% confidence
34
35 133 intervals.

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38 134 Second, we applied an exploratory factor analysis to identify the existence of non-random
39
40 135 associations among chronic diseases. To facilitate the epidemiological and clinical interpretation
41
42 136 of the results, we only included in the analysis those comorbidities with a prevalence $\geq 5\%$. The
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44 137 methodology followed was described elsewhere.⁷ Briefly, EDCs were coded as binary variables
45
46 138 (present/absent), and a factor analysis based on a tetrachoric correlation matrix was performed
47
48 139 to determine which diagnoses comprised each factor. We used the principal factor method for
49
50 140 the extraction of the factors, and a scree plot in combination with clinical criteria to determine
51
52 141 the number of factors to extract. We selected EDCs with factor scores ≥ 0.25 as those belonging
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54 142 to each multimorbidity pattern. Model goodness-of-fit and sample adequacy were calculated
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56 143 through the proportions of cumulative variance and the Kaiser-Meyer-Olkin (KMO) parameter.
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58 144 After performing the factor analysis, three clinical experts (FRL, CCS, and APT) proposed and
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3 145 agreed upon the denomination of the resulting patterns. Individuals were subsequently assigned
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5 146 to one or more of the described patterns of multimorbidity if they had at least two of the
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7 147 diseases that comprised the pattern (in addition to HF), as described by Prados et al.⁷
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10 148 Finally, we applied logistic and Cox proportional-hazards regressions to calculate the
11
12 149 risk of having at least one hospitalization during 2012 and of three-year mortality, respectively,
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14 150 depending on the multimorbidity pattern suffered by the individual. Patients' age (continuous
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16 151 variable) and all multimorbidity patterns were included as independent variables in the models.
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18 152 We used Kaplan-Meier survival curves to represent and compare survival rates of individuals
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20 153 with specific multimorbidity patterns, which were tested for the proportional hazard
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22 154 assumption.
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26 155 We conducted all the statistical analysis in STATA (Version 12.0, StataCorp LLC,
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28 156 College Station, TX, US). Statistical significance was set at $p < 0.05$.
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34 158 **Results**

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37 159 A total of 14,670 patients from the EpiChron Cohort had a diagnosis of HF in 2011,
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39 160 representing around 1.1% of the total population in Aragón. The study population is described
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41 161 in Table 1. A predominance of women was observed (57.9% vs 42.1%, $p < 0.001$), who were on
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43 162 average older than men (79.9 vs 75.2 years, $p < 0.001$) mainly due to a higher proportion of
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45 163 people aged ≥ 85 years. The cumulative mortality rate throughout the three-year follow-up was
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47 164 higher in men compared with women (36.5% vs 33.3 %, $p < 0.001$), and the same pattern was
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49 165 observed for hospital admissions.
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53 166 In our study, almost all patients with HF (98%) suffered from multimorbidity, with an
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55 167 average of 7.8 chronic diseases per patient. The most prevalent HF comorbidities were similar
56
57 168 in women and in men, as hypertension (71.2% vs 65.0%), dyslipidemia (36.9% vs 37.6%),
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59 169 arthropathy (36.8% vs 23.9%), cardiac arrhythmia (35.5% vs 42.6%) and diabetes (30.3% vs
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3 170 32.3%). Except for hypertension, which was more frequent in women, cardiovascular
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5 171 comorbidities (i.e., ischemic heart disease and arrhythmias) were more prevalent in men, as well
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7 172 as COPD. Arthropathy, varicose veins of lower extremities, obesity, osteoporosis, dementia and
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9 173 depression were also highly prevalent in HF patients, especially in women.
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11

12 174 As a result of the factorial analysis, six multimorbidity patterns were identified and
13
14 175 described in women, named cardiovascular, respiratory, metabolic, coronary-ischemic,
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16 176 degenerative, and neurovascular. In men, we only identified five patterns, which were similar to
17
18 177 those observed in women with the exception of the respiratory pattern. The composition of the
19
20 178 patterns of multimorbidity in women and men is detailed in Tables 2 and 3, respectively. In
21
22 179 women, these patterns explained up to 40.5% of the cumulative total variance, with a KMO of
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24 180 0.753. In men, the patterns explained up to 37.3% of the cumulative total variance, with a KMO
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26 181 of 0.761.
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30 182 A high proportion of the study population was assigned to these patterns, with
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32 183 prevalence rates ranging from 13.5% (neurovascular) to 64.0% (degenerative) in women, and
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34 184 from 22.2% (neurovascular) to 49.3% (metabolic) in men. The prevalence and impact on health
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36 185 outcomes of such multimorbidity patterns is described in Table 4. In general, all patterns were
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38 186 associated with increased risk of hospitalization during the following year (by 12-86%) in both
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40 187 men and women compared with the absence of the pattern, except for the degenerative pattern
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42 188 in women. The cardiovascular, neurovascular and respiratory patterns significantly increased
43
44 189 the likelihood of three-year mortality (by 45-74%) in both sexes. The Kaplan-Meier survival
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46 190 curves of population with HF according to different multimorbidity patterns are presented in
47
48 191 Figure 1.
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55 193 **Discussion**

58 194 *Comorbidity of Heart Failure*

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3 195 The population with HF of our study suffered a higher morbidity burden than that found in the
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5 196 general population of the EpiChron Cohort.¹³ Regarding comorbidity of HF, cardiovascular
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7 197 comorbidities (i.e., ischemic heart disease and arrhythmias), except for hypertension that was
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9 198 more frequent in women, were more prevalent in men, as previously seen in the literature.¹
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12 199 The higher prevalence of COPD in men compared to women was probably due to the
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14 200 higher rates of smoking among Spanish men. While the estimated prevalence of COPD in the
15
16 201 general Spanish population is 15% in men and 6% in women, these figures were almost doubled
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18 202 in our HF cohort, approaching the 25.6% described in the EAHFE-COPD Study on acute HF
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20 203 patients.¹⁵ This higher prevalence of COPD might be explained because a) both COPD and HF
21
22 204 share similar symptoms; b) beta-blockers (indicated for HF) and bronchodilators (indicated for
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24 205 COPD) exert an effect on both pathologies; and c) heart congestion alters pulmonary function
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26 206 tests, among others. The fact that 80% of COPD cases are associated with smoking but close to
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28 207 50% of HF patients have never smoked makes some authors think that COPD could be over-
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30 208 diagnosed in HF patients.¹⁶
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34 209 Comorbid depression, which was predominantly observed in women, presented a
35
36 210 prevalence 2-3 times higher than that observed in the general population.¹³ Its prevalence is
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38 211 consistent with that reported in the meta-analytic review by Rutledge et al,¹⁷ where the mean
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40 212 prevalence of depression in HF patients was 21.5%. Depression has been associated to worse
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42 213 prognosis in patients with cardiovascular disease in terms of mortality, hospital admissions and
43
44 214 functional status.¹ However, its role as a potential risk factor for the development of HF is less
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46 215 consistent; so far, this has only been proved in women and in older patients with systolic
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48 216 hypertension.¹⁸ The greater prevalence of hypothyroidism observed in HF patients compared to
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50 217 the general population, especially in women, could be partially explained by the structural and
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52 218 hemodynamic secondary effects of thyroid hormones on the heart. The higher prevalence of
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54 219 hypothyroidism observed in women compared to men is congruent with the results from the
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56 220 Euro Heart Failure Survey II.¹⁹
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3 221 The cumulative mortality rate throughout the three-year follow-up, which was higher in
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5 222 men, is in line with the results obtained by Levy et al²⁰ who described greater survival of
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7 223 women with HF compared to men based on the Framingham Heart Study. The clinical
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9 224 composition of the multimorbidity patterns found in the study and their impact on mortality and
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11 225 hospitalization is discussed below.

14 226 *Cardiovascular pattern*

17 227 Almost half of men (43.2%) and one third of women (29.9%) were affected by this pattern. It
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19 228 mainly included cardiac arrhythmia, cardiac valve disorders and hematologic disorders (e.g.,
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21 229 anticoagulant therapy), as well as chronic renal failure and anemia. Kidney and heart diseases
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23 230 share common risk factors and they are interrelated through adaptive mechanisms. Moreover,
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25 231 chronic failure of both organs, volume overload, increased levels of cytokines, malabsorption
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27 232 syndrome, suppression of the bone marrow and anticoagulation treatment increase the
28
29 233 frequency of anemia in HF patients.²¹ The presence of these comorbidities in the cardiovascular
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31 234 but not the coronary-ischemic pattern could imply a greater deterioration in HF patients
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33 235 suffering from the former pattern. In fact, patients presenting with the cardiovascular pattern
34
35 236 showed significantly higher risk of both studied health outcomes in both sexes. This pattern
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37 237 showed the strongest association with hospitalization, increasing the risk by more than 80%,
38
39 238 probably due to the hemodynamic dysfunction produced by cardiac arrhythmias and anemia,
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41 239 which often leads to decompensation and subsequent hospitalization.²²

46 240 *Respiratory pattern*

49 241 This pattern, which was present in 16.9% of women, had COPD and asthma as the most
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51 242 strongly associated diseases. The absence of a specific respiratory pattern in men is remarkable,
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53 243 as it is the absence of COPD in the rest of patterns, considering the acknowledged association
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55 244 between COPD and ischemic heart disease,²³ both related to HF, and the high prevalence of
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57 245 COPD particularly in men. Ahmad et al²⁴ found that COPD appeared in several clusters of
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59 246 patients with HF, especially in those with higher morbidity burden, which also clustered with

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3 247 ischemic heart disease, cerebrovascular disease, smoking and male sex. In our study, COPD did
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5 248 not come up as part of any pattern in men, suggesting a lack of discriminative power of this
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7 249 disease in terms of disease clustering in men with HF. Nevertheless, this pattern had the second-
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9 250 highest impact on both mortality and hospitalization in women.

12 251 *Metabolic pattern*

15 252 This pattern was the most prevalent in both sexes, affecting half of men and women.
17
18 253 The metabolic pattern included obesity, hypertension, diabetes and dyslipidemia; all risk factors
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20 254 conforming the so-called metabolic syndrome. This pattern has been consistently identified
21
22 255 across studies carried out in the general population, and in 18% of patients with HF, with no
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24 256 gender differences.²⁵ This higher prevalence of the pattern observed in our study could be due to
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26 257 the fact that only two diseases had to be present to assign patients to this pattern. When this
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28 258 condition was restricted to present three or more conditions, the prevalence decreased to 21.3%
29
30 259 in women and 22.1% in men, which are closer to previously published rates. Suffering from this
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32 260 pattern was not associated with increased three-year mortality either in men or women, which is
33
34 261 in line with the literature, probably due to reverse epidemiology whereby HF patients with
35
36 262 cardiovascular risk factors have better prognosis.²⁶ However, patients presenting with this
37
38 263 pattern did show a significantly higher risk of hospitalization; 37% in men and 26% in women.

42 264 *Coronary-ischemic pattern*

45 265 Although this pattern appeared in both sexes, it was much more prevalent in men (24.7% vs
46
47 266 6.6%). It clustered together ischemic heart disease and acute myocardial infarction, and along
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49 267 with the metabolic pattern, it was one of the most consistent patterns from the clinical point of
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51 268 view. The evolution from micro and macrovascular endothelial damage caused by
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53 269 arteriosclerosis to myocardial injury represents the pathophysiological continuum underlying
54
55 270 this pattern. However, this hypothesis could not be tested in our study since the medical history
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57 271 of HF patients was unknown. Previous studies have corroborated the late appearance of
58
59 272 ischemic heart disease in women with diabetes and hypertension, whereas, in men, this

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3 273 condition appears earlier and in association to myocardial infarction and smoking.²⁷ This pattern
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5 274 increased the risk of hospitalization in both men and women, but it was not associated with
6
7 275 greater three-year mortality in either sex. This may be explained by the effectiveness of beta-
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9 276 blockers, aldosterone antagonists and angiotensin-converting enzyme inhibitors on reducing the
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11 277 risk of sudden death and prolonging survival in patients with HF,²⁸ although this hypothesis
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13 278 needs further investigation based on longer follow-ups.

16 279 *Neurovascular pattern*

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19
20 280 This pattern was identified in both men (22.2%) and women (13.6%), and included conditions
21
22 281 related to arteriosclerotic damage in target organs of (i.e., kidney, extremities and brain) and
23
24 282 thromboembolism secondary to cardiac arrhythmia. The presence of dementia in this pattern
25
26 283 does not come unexpected. A well-known relationship exists between cognitive impairment and
27
28 284 HF, due to low cerebral perfusion, atrial fibrillation, and brain changes secondary to the neuro-
29
30 285 hormonal adaptation mechanisms underlying HF.²⁹ Patients with this pattern had among the
31
32 286 highest risk of three-year mortality. However, its effect on the risk of hospitalization differed by
33
34 287 sex. Whereas it had no effect in women, it increased the risk of hospitalization by 62% in men.
35
36 288 This finding was unexpected, especially bearing in mind that both women and men suffering
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38 289 from this pattern were considerably older.

41 290 *Degenerative pattern*

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44
45 291 This pattern was predominantly described in women (64.0% vs 29.2%) and it included
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47 292 degenerative conditions such as arthropathy, cataract, aphakia, and deafness and hearing loss.
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49 293 Although this pattern would be expected to entail a greater degree of dependency than others, in
50
51 294 the longitudinal nine-year study of Jackson et al,³⁰ the neurological and cardiovascular patterns
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53 295 derived in greater limitations on activities of daily living compared to the degenerative pattern
54
55 296 identified by these authors. The co-occurrence in this pattern of venous disease,
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57 297 thrombophlebitis, osteoporosis and dermatitis may be conditioned by the consequent physical
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59 298 activity restriction in patients with HF. Regarding the risk of hospitalization, this pattern was

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3 299 associated with a low but significant increased risk in women but it had no effect in men. The
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5 300 degenerative pattern was the only one associated to a decreased risk of three-year mortality in
6
7 301 both men and women. This could be due to the lower clinical severity of the conditions
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9 302 conforming this pattern, some of which are typical of older age.
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12 303

15 304 **Conclusion**

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18 305 This study confirmed that multimorbidity is by far the norm rather than the exception in patients
19
20 306 with heart failure, and that comorbidities tend to cluster together beyond simple chance in the
21
22 307 form of multimorbidity patterns that have different impact on health outcomes. This knowledge
23
24 308 could be useful to better understand common pathophysiological pathways underlying this
25
26 309 disease and its comorbidities, and factors influencing the prognosis of these patients. Further
27
28 310 large scale longitudinal studies are encouraged to confirm the existence of these patterns as well
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30 311 as their differential impact on health outcomes.
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33 312

36 313 **Author Contributions**

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40 314 APT and FJRL were the Principal Investigators of the study. AGM, AGG, APT, and FJRL
41
42 315 contributed to the design of the research. AGM and BPP performed the statistical analyses.
43
44 316 APT, FJRL, AGG, and CCS interpreted and discussed the results. AGM and AGG prepared the
45
46 317 first draft of the manuscript. ACL, MJD, and JIPC made important contributions to the revision
47
48 318 of the manuscript. All authors read and approved the final version of the manuscript.
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9 324 manuscript.

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29 331 **Competing interests**

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32 332 None declared.
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36 334 **Patient consent for publication**

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39 335 Not required.
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44 337 **Ethics approval**

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47 338 This study was approved by the Clinical Research Ethics Committee of Aragón (CEICA,
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55 341 **Availability of data**
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3 342 The dataset generated and analyzed during the current study is not publicly available, but is
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5 343 available from the corresponding author on reasonable request.
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437 **Table 1.** Demographic, health services use, and clinical description of patients with heart failure
 438 (n= 14,670).

Characteristics	Women (n= 8488)	Men (n= 6182)	p value
Demographics			
Sex (%)	57.9 (57.1–58.7)	42.1 (41.3–42.9)	<0.001
Mean age (years)	79.9 (79.6–80.1)	75.2 (74.8–75.5)	<0.001
Age interval (%)			
≤44 years	2.34 (2.02–2.67)	3.87 (3.39–4.35)	
45–64 years	6.03 (5.53–6.54)	13.2 (12.3–14.0)	
65–84 years	52.6 (51.5–53.6)	58.7 (57.4–59.9)	
≥85 years	39.0 (38.0–40.1)	24.3 (23.2–25.3)	
Urban area (vs rural) (%)	55.7 (54.6–56.7)	52.3 (51.0–53.5)	<0.001
Immigrants (%)	0.95 (0.74–1.16)	1.38 (1.08–1.67)	0.017
Health services use during 2012			
Visit to family physician			
≥1 visits (%)	91.9 (91.3–92.5)	90.0 (89.2–90.7)	<0.001
Mean number of visits	16.6 (16.3–16.9)	16.5 (16.1–16.8)	0.717
Visit to specialists			
≥1 visits (%)	78.9 (78.0–79.7)	84.6 (83.7–85.5)	<0.001
Mean number of visits	6.45 (6.29–6.61)	8.05 (7.83–8.26)	<0.001
Hospital admissions			
≥1 admissions (%)	39.9 (38.9–41.0)	49.4 (48.1–50.6)	<0.001
Mean number of admissions	0.65 (0.63–0.68)	0.90 (0.87–0.93)	<0.001
Visit to emergency room			
≥1 visits (%)	50.5 (49.4–51.6)	54.8 (53.6–56.0)	<0.001
Mean number of visits	1.05 (1.02–1.09)	1.23 (1.19–1.28)	<0.001
Clinical information			
3-year all-cause mortality (%)	33.3 (32.3–34.3)	36.5 (35.3–37.7)	<0.001
Multimorbidity* (%)	98.2 (97.9–98.4)	97.7 (97.3–98.1)	0.068
Mean number of diseases	7.77 (7.69–7.85)	7.87 (7.77–7.97)	0.114
Prevalence of comorbidities (%)			
Hypertension	71.2 (70.2–72.1)	65.0 (63.8–66.2)	<0.001
Cardiac arrhythmia	35.5 (34.4–36.5)	42.6 (41.4–43.9)	<0.001
Disorders of lipid metabolism	36.9 (35.8–37.9)	37.6 (36.4–38.8)	0.388
Arthropathy	36.8 (35.8–37.8)	23.9 (22.8–25.0)	<0.001
Diabetes	30.3 (29.4–31.3)	32.3 (31.2–33.5)	0.010
Varicose veins of lower extremities	29.4 (28.4–30.4)	11.8 (11.0–12.6)	<0.001
Emphysema, chronic bronchitis, COPD	13.3 (12.6–14.0)	32.8 (31.6–34.0)	<0.001
Cardiovascular disorders, other	19.2 (18.4–20.0)	24.0 (22.9–25.0)	<0.001
Ischemic heart disease (excluding AMI†)	15.3 (14.5–16.0)	24.6 (23.5–25.7)	<0.001
Obesity	20.3 (19.4–21.1)	17.6 (16.7–18.5)	<0.001
Depression	24.8 (23.8–25.7)	10.9 (10.1–11.7)	<0.001
Cataract, aphakia	19.7 (18.9–20.6)	16.9 (15.9–17.8)	<0.001
Surgical aftercare	15.8 (15.0–16.6)	19.3 (18.3–20.2)	<0.001
Cardiac valve disorders	17.0 (16.2–17.8)	17.5 (16.6–18.4)	0.394
Iron deficiency, other deficiency anemias	17.3 (16.5–18.1)	15.6 (14.7–16.5)	0.007
Osteoporosis	23.1 (22.2–24.0)	3.69 (3.22–4.16)	<0.001

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3	Cerebrovascular disease	13.9 (13.2–14.7)	14.3 (13.4–15.1)	0.604
4	Respiratory disorders, other	12.5 (11.8–13.2)	16.1 (15.2–17.1)	<0.001
5	Hypothyroidism	17.6 (16.8–18.4)	6.44 (5.83–7.05)	<0.001
6	Dementia and delirium	13.3 (12.6–14.0)	8.44 (7.75–9.14)	<0.001
7	Prostatic hypertrophy	-	24.6 (23.5–25.7)	-
8	Dermatitis and eczema	9.80 (9.17–10.4)	10.3 (9.58–11.1)	0.287
9	Chronic renal failure	8.19 (7.60–8.77)	12.3 (11.5–13.1)	<0.001
10	Glaucoma	10.4 (9.76–11.1)	8.61 (7.91–9.30)	<0.001
11	Deafness, hearing loss	9.57 (8.94–10.2)	9.17 (8.45–9.89)	0.419
12	AMI	5.84 (5.34–6.34)	13.8 (12.9–14.6)	<0.001
13	Chronic ulcer of the skin	10.2 (9.58–10.9)	7.40 (6.74–8.04)	<0.001
14	Hematologic disorders, other	7.94 (7.37–8.52)	9.43 (8.70–10.2)	0.002
15	Asthma	10.6 (10.0–11.3)	4.69 (4.16–5.22)	<0.001
16	Low back pain	6.54 (6.01–7.06)	6.10 (5.50–6.69)	0.280
17	Gout	2.70 (2.35–3.04)	10.5 (9.75–11.3)	<0.001
18	Neurologic disorders, other	6.63 (6.10–7.16)	5.10 (4.55–5.64)	<0.001
19	Diverticular disease of colon	5.75 (5.25–6.24)	4.82 (4.29–5.35)	0.014
20	Other endocrine disorders	5.96 (5.46–6.47)	3.80 (3.32–4.28)	<0.001

24 439 95% confidence intervals are displayed within brackets. Only comorbidities with a mean

25 440 prevalence equal to or greater than 5% are displayed.

26 441 *Defined as having two or more chronic conditions from a list of 114 chronic diagnoses.

27 442 †Acute myocardial infarction.

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452 **Table 2.** Multimorbidity patterns identified in women with heart failure (n= 8488). Each pattern
 453 is represented by the comorbidities and their loading factors in the pattern.

Patterns	Comorbidities	Loading factors
Cardiovascular	Cardiac arrhythmia	0.80
	Cardiac valve disorders	0.62
	Cardiovascular disorders, other	0.58
	Hematologic disorders, other	0.52
	Surgical aftercare	0.33
	Cardiomyopathy	0.32
	Chronic renal failure	0.29
Respiratory	Respiratory disorders, other	0.47
	Emphysema, chronic bronchitis, COPD	0.47
	Asthma	0.42
	Other endocrine disorders	0.37
	Chronic renal failure	0.30
	Surgical aftercare	0.25
Metabolic	Diabetic retinopathy	0.74
	Diabetes	0.73
	Obesity	0.40
	Hypertension	0.36
	Disorders of lipid metabolism	0.26
Coronary-ischemic	Acute myocardial infarction	0.76
	Ischemic heart disease (excluding AMI*)	0.66
	Surgical aftercare	0.30
Degenerative	Varicose veins of lower extremities	0.53
	Arthropathy	0.53
	Cataract, aphakia	0.45
	Osteoporosis	0.34
	Thrombophlebitis	0.29
	Deafness, hearing loss	0.26
	Obesity	0.25
	Hypertension	0.25
Neurovascular	Dementia and delirium	0.76
	Chronic ulcer of the skin	0.48
	Cerebrovascular disease	0.41
	Chronic renal failure	0.28
	Respiratory disorders, other	0.25

454 *Acute myocardial infarction.

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459 **Table 3.** Multimorbidity patterns identified in men with heart failure (n= 6182). Each pattern is
 460 represented by the comorbidities and their loading factors in the pattern.

Patterns	Comorbidities	Loading factors
Cardiovascular	Cardiovascular disorders, other	0.66
	Cardiac arrhythmia	0.64
	Cardiac valve disorders	0.58
	Cardiomyopathy	0.55
	Surgical aftercare	0.46
	Hematologic disorders, other	0.39
	Respiratory disorders, other	0.39
	Chronic renal failure	0.33
	Iron deficiency, other deficiency anemias	0.26
Neurovascular	Dementia and delirium	0.54
	Generalized atherosclerosis	0.52
	Peripheral vascular disease	0.46
	Chronic renal failure	0.45
	Cerebrovascular disease	0.43
	Respiratory disorders, other	0.43
	Chronic ulcer of the skin	0.39
	Iron deficiency, other deficiency anemias	0.39
Metabolic	Obesity	0.71
	Diabetes	0.45
	Hypertension	0.45
	Disorders of lipid metabolism	0.40
	Substance use	0.31
Coronary- ischemic	Ischemic heart disease (excluding AMI*)	0.70
	Acute myocardial infarction	0.70
	Surgical aftercare	0.36
	Disorders of lipid metabolism	0.36
Degenerative	Arthropathy	0.43
	Cataract, aphakia	0.42
	Deafness, hearing loss	0.39
	Glaucoma	0.31
	Varicose veins of lower extremities	0.30
	Dermatitis and eczema	0.30
	Prostatic hypertrophy	0.26

461 *Acute myocardial infarction.

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466 **Table 4.** Prevalence of multimorbidity patterns identified in men (n= 6182) and women (n=
 467 8488) with heart failure, and adjusted associations with hospitalization and death.

Multimorbidity pattern	Prevalence (%)	Mean age (years)	Hospitalization (OR)*	p value	Death (HR)†	p value
Women						
Cardiovascular	29.9	80.4	1.86 (1.66-2.08)	<0.001	1.45 (1.33-1.58)	<0.001
Metabolic	49.9	80.1	1.26 (1.13-1.39)	<0.001	1.04 (0.97-1.13)	0.284
Coronary-ischemic	6.60	80.7	1.48 (1.23-1.79)	<0.001	1.13 (0.99-1.30)	0.061
Neurovascular	13.6	84.1	1.12 (0.97-1.30)	0.117	1.62 (1.48-1.78)	<0.001
Degenerative	64.0	81.1	1.19 (1.06-1.32)	0.002	0.70 (0.65-0.76)	<0.001
Respiratory	16.9	81.0	1.71 (1.50-1.97)	<0.001	1.53 (1.39-1.69)	<0.001
Men						
Cardiovascular	43.2	76.8	1.83 (1.62-2.07)	<0.001	1.60 (1.46-1.76)	<0.001
Metabolic	49.3	75.3	1.37 (1.22-1.53)	<0.001	0.98 (0.90-1.07)	0.695
Coronary-ischemic	24.7	76.2	1.25 (1.10-1.43)	0.001	0.99 (0.90-1.09)	0.818
Neurovascular	22.2	79.9	1.62 (1.41-1.86)	<0.001	1.74 (1.58-1.91)	<0.001
Degenerative	29.2	80.2	1.03 (0.91-1.16)	0.687	0.75 (0.68-0.81)	<0.001

468 *Odds ratio for having at least one hospitalization during the following year.

469 †Hazard ratio for all-cause death after three years of follow-up.

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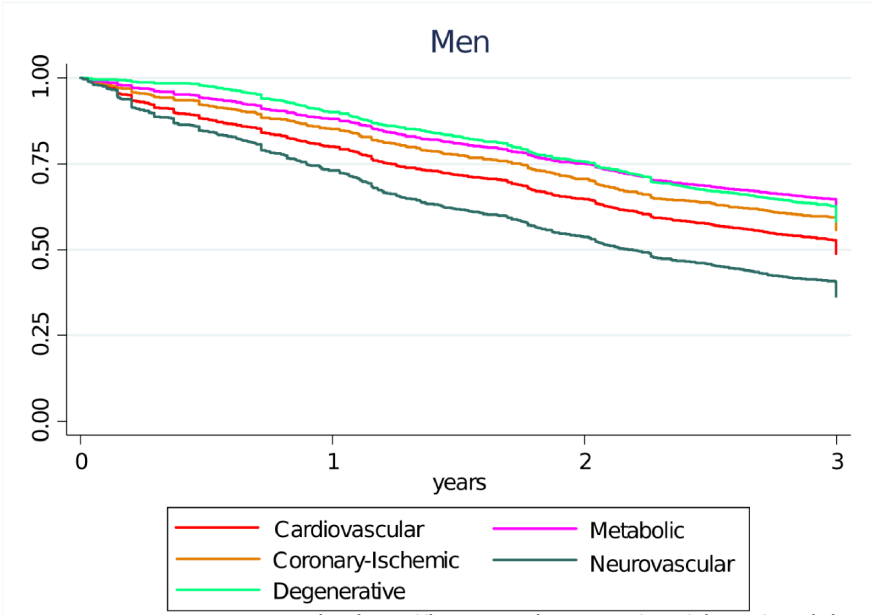
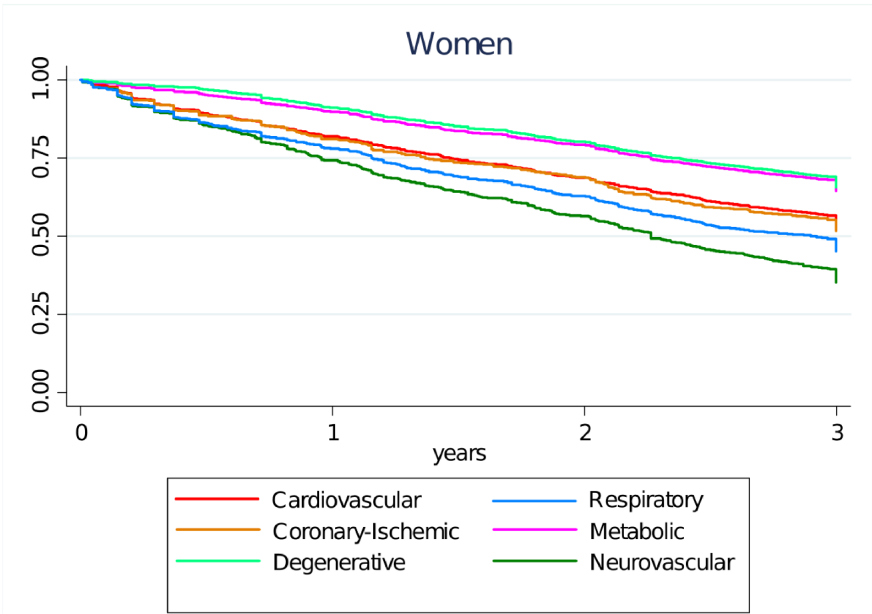
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3 485 **Figure 1.** Kaplan-Meier survival curves in women (n= 8488) and men (n= 6182) with heart
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5 486 failure according to the presence of different patterns of multimorbidity.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	6
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Multimorbidity patterns in patients with heart failure: an observational Spanish study based on electronic health records.

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Manuscripts

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2
3 **1 Multimorbidity patterns in patients with heart failure: an observational Spanish study**
4
5 **2 based on electronic health records.**
6
7

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1
2
3 **23 Abstract**
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5

6 **24 Objectives:** To characterise the comorbidities of heart failure (HF) in men and women, to explore
7
8 **25** their clustering into multimorbidity patterns, and to measure the impact of such patterns on the
9
10 **26** risk of hospitalization and mortality.

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13 **27 Design:** Observational retrospective population study based on electronic health records.
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16 **28 Setting:** EpiChron Cohort (Aragón, Spain).
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18

19 **29 Participants:** All the primary and hospital care patients of the EpiChron Cohort with a diagnosis
20
21 of HF on 1 January 2011 (i.e., 8488 women and 6182 men). We analysed all the chronic diseases
22
23 registered in patients' electronic health records until 31 December 2011.
24
25

26 **32 Primary outcome:** We performed an exploratory factor analysis to identify the multimorbidity
27
28 patterns in men and women, and logistic and Cox proportional-hazards regressions to investigate
29
30 the association between the patterns and the risk of hospitalization in 2012, and of three-year
31
32 mortality, respectively.
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34

35 **36 Results:** Almost all HF patients (98%) had multimorbidity, with an average of 7.8 chronic
37
38 diseases per patient. We identified six different multimorbidity patterns, named cardiovascular,
39
40 neurovascular, coronary, metabolic, degenerative, and respiratory. The most prevalent were the
41
42 degenerative (64.0%) and cardiovascular (29.9%) patterns in women, and the metabolic (49.3%)
43
44 and cardiovascular (43.2%) patterns in men. Every pattern was associated with higher
45
46 hospitalization risks; and the cardiovascular, neurovascular and respiratory patterns significantly
47
48 increased the likelihood of three-year mortality.
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50

51 **52 Conclusions:** Multimorbidity is the norm rather than the exception in patients with heart failure,
53
54 whose comorbidities tend to cluster together beyond simple chance in the form of multimorbidity
55
56 patterns that have different impact on health outcomes. This knowledge could be useful to better
57
58 understand common pathophysiological pathways underlying this condition and its
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3 47 comorbidities, and the factors influencing the prognosis of men and women with HF. Further
4
5 48 large scale longitudinal studies are encouraged to confirm the existence of these patterns as well
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7 49 as their differential impact on health outcomes.
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12
13 51 **Keywords:** Heart failure; Multimorbidity; Comorbidity; Chronic disease; Hospitalization;
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15 52 Mortality; Cohort
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21 54 **Word count:** 3483
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27
28 56 **Article Summary**
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30
31 57 ***Strengths and limitations of the study***
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33
34 58 - This is a large-scale population-based study that included the primary and hospital care patients
35
36 59 of the reference population with a diagnosis of HF.
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38
39 60 - The data in the cohort continuously underwent quality control check-ups to ensure its accuracy
40
41 61 and reliability for research purposes.
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44
45 62 - The cross-sectional characterisation of the multimorbidity patterns made it impossible to
46
47 63 understand the chronological relationship between the different risk factors and chronic diseases.
48

49
50 64 - Diagnoses were extracted from electronic health records that were not originally designed for
51
52 65 research, thus leading to a potential over or under-reporting of specific diseases.
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55 66 - The estimation of the effect of multimorbidity patterns on health outcomes did not consider the
56
57 67 potential confounding role of socioeconomic factors or clinical parameters, like the ejection
58
59 68 fraction, which were not available in the study cohort.
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69 Introduction

70 Improvements in diagnostic and therapeutic procedures have decreased heart failure (HF)
71 mortality rates, transforming this previously life-threatening condition into a chronic disease with
72 a high burden of comorbidity, as confirmed by European HF registries.¹ HF patients are complex
73 and present different phenotypes depending on age, sex, comorbidity, and pathophysiological and
74 prognostic aspects.² Both cardiovascular and non-cardiovascular comorbidities are determining
75 factors in the differentiation of these phenotypes and their impact on health outcomes. In fact, HF
76 patients with non-cardiovascular comorbidities show increased disease burdens, severity, risk of
77 hospitalization and death.^{3,4}

78 Recent studies have examined the most prevalent comorbidities in HF patients and their
79 prognostic impact on mortality rates and hospital readmissions.^{2,5,6} However, although the
80 clustering of chronic diseases into multimorbidity patterns has already been demonstrated in the
81 general population,⁷ most studies still focus on isolated comorbidities, without considering the
82 interrelations among them. Some of the few studies addressing multimorbidity in HF patients
83 restrict their analyses to the most frequently co-occurring combinations of two or three
84 comorbidities,⁸ while others are conducted in relatively small samples⁹. Moreover, the
85 methodological approaches in these studies in terms of data sources, studied comorbidities, and
86 statistical analysis techniques vary considerably.^{3,8-10} Thus, there is still a need to perform studies
87 on real patients from primary care, where multimorbidity is most frequently dealt with, and to
88 address the sex/gender perspective of this disease and its comorbidities.

89 The Academy of Medical Sciences recently highlighted the importance of investigating
90 which multimorbidity patterns cause the greatest burden of disease, and the determinants of the
91 most common clusters of conditions.¹¹ Improving our knowledge on the systematic associations
92 among HF comorbidities is of great interest, as some of them are known to share common
93 biological and socioeconomic risk factors on which prevention strategies could be based.
94 Furthermore, the identification and clinical characterisation of multimorbidity patterns in men

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3 95 and women with HF, and the study of their potential impact on negative health outcomes (e.g.,
4
5 96 risk of death and hospitalization) could shed light on new pathophysiological pathways. These
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7 97 pathways could help guide the development of clinical practice guidelines better adapted to
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9 98 patients with HF based on their sex and comorbidities.¹²
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12 99 This large-scale population study based on electronic health records from real primary
13
14 100 and hospital care patients aimed to characterise the comorbidities of HF in men and women, to
15
16 101 explore their clustering into multimorbidity patterns, and to measure the impact of said patterns
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18 102 on negative health outcomes.
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20 21 22 103 **Methods**

23 24 25 104 *Design and study population*

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27
28 105 We conducted a retrospective observational study based on the EpiChron Cohort, which links
29
30 106 demographic, clinical and health-outcome-related information for all public health system users
31
32 107 of the Spanish region of Aragón. A description of the cohort profile and of the data sources was
33
34 108 published elsewhere.¹³ This cohort was conformed in 2011 and it included 1,253,292 people at
35
36 109 baseline (approximately 95% of the total inhabitants of Aragón). For this study, we selected all
37
38 110 patients with HF diagnosis in their primary or hospital electronic health records on 1 January 2011
39
40 111 and followed-up on them for three years.
41

42 43 44 112 *Study variables*

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46
47 113 For each patient, we analysed demographic data (i.e., age, sex, area of residence, immigration
48
49 114 status), hospital admissions during 2012, all chronic condition diagnoses from primary and/or
50
51 115 hospital care, and all-cause mortality until 31 December 2014. Diagnoses were extracted from the
52
53 116 electronic health records of both primary and hospital care levels, and included all active episodes
54
55 117 between 1 January 2011 and 31 December 2011, even if a healthcare professional had recorded
56
57 118 them before the initial date. Diseases were originally coded according to the International
58
59 119 Classification of Primary Care (ICPC) (in primary care settings) or the International Classification
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3 120 of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (in hospital settings), and
4
5 121 subsequently grouped into 260 mutually exclusive Expanded Diagnostic Clusters (EDCs) through
6
7 122 the Johns Hopkins ACG® System (version 11.0, The Johns Hopkins University, Baltimore, MD,
8
9 123 US).¹⁴ We included every patient with the CAR05 EDC code, as well as the ICPC and ICD-9-
10
11 124 CM codes for HF, and considered all 114 possible EDCs previously established as chronic by
12
13 125 Salisbury et al.¹⁵ for the analysis. Multimorbidity was defined as the presence of two or more
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16 126 EDCs from Salisbury's list.

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18
19 127 This study complies with the Declaration of Helsinki, and the Clinical Research Ethics
20
21 128 Committee of Aragón (CEICA) approved the research protocol (PI18/082). The CEICA waived
22
23 129 the requirement to obtain informed consent from patients since all the information was
24
25 130 anonymised.

26 27 28 131 *Statistical analyses*

29
30
31 132 All our analyses were stratified by sex. First, we performed a descriptive analysis on demographic
32
33 133 and clinical information of the population with HF. We compared means and frequencies using
34
35 134 Student's t-test and the chi-squared test, respectively, with their corresponding 95% confidence
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37 135 intervals.

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40 136 Second, we applied an exploratory factor analysis to identify the existence of non-random
41
42 137 associations among chronic diseases in men and women. To facilitate the epidemiological and
43
44 138 clinical interpretation of the results, we only included in the analysis those chronic comorbidities
45
46 139 from Salisbury's list with a prevalence $\geq 5\%$ in each sex. The methodology followed was
47
48 140 described elsewhere.⁷ Briefly, EDCs were coded as binary variables (present/absent), and a factor
49
50 141 analysis based on a tetrachoric correlation matrix was performed to determine which diagnoses
51
52 142 comprised each factor. We used the principal factor method for the extraction of the factors, and
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54 143 a scree plot in combination with clinical criteria to determine the number of factors to extract.
55
56 144 The EDCs with factor scores ≥ 0.25 within a pattern were considered to be part of that
57
58 145 multimorbidity pattern, so that the same EDC could be present in more than one cluster. Model

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3 146 goodness-of-fit and sample adequacy were calculated through the proportions of cumulative
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5 147 variance and the Kaiser-Meyer-Olkin (KMO) parameter. After performing the factor analysis,
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7 148 three clinical experts (FRL, CCS, and APT) proposed and agreed upon the denomination of the
8
9 149 resulting patterns according to the most relevant diseases and those with the highest loading factor
10
11 150 within each pattern. Individuals were subsequently assigned to one or more of the described
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13 151 patterns of multimorbidity if they had at least two of the diseases that comprised the pattern (in
14
15 152 addition to HF), as described by Prados et al.⁷
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18

19 153 Finally, we applied logistic and Cox proportional-hazards regressions to calculate the risk
20
21 154 of having at least one hospitalization during 2012 and of three-year mortality, respectively,
22
23 155 depending on the multimorbidity pattern suffered by the individual (compared to having no
24
25 156 patterns). Patient age (continuous variable) and all the multimorbidity patterns were included as
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27 157 independent variables in the models. We used Kaplan-Meier survival curves to represent and
28
29 158 compare survival rates of individuals with specific multimorbidity patterns, which were also used
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31 159 to test for the proportional hazard assumption.
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34 160 We conducted all statistical analyses using STATA (Version 12.0, StataCorp LLC,
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36 161 College Station, TX, US). Statistical significance was set at $p < 0.05$.
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39 162 *Patient and Public Involvement*

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43 163 Patients and public were not involved in this study.
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46 164 **Results**

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48
49 165 A total of 14,670 patients from the EpiChron Cohort had a HF diagnosis in 2011, representing
50
51 166 around 1.1% of the total population of Aragón. The study population is described in Table 1.
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53 167 Women predominated over men (57.9% vs 42.1%, $p < 0.001$) and were older on average (79.9 vs
54
55 168 75.2 years, $p < 0.001$) mainly due to a higher proportion of people aged ≥ 85 years. The cumulative
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57 169 mortality rate throughout the three-year follow-up was higher in men than in women (36.5% vs
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59 170 33.3 %, $p < 0.001$), and the same pattern was observed for hospital admissions.
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2
3 171 In our study, almost all patients with HF (98%) suffered from multimorbidity, with an
4
5 172 average disease burden of 7.8 chronic diseases per patient (HF included). These figures are higher
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7 173 than those observed in the reference cohort (38% and 1.7 chronic diseases/patient, respectively).
8
9 174 The most prevalent HF comorbidities were similar in women and in men, and specifically were
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11 175 hypertension (71.2% vs 65.0%), dyslipidemia (36.9% vs 37.6%), arthropathy (36.8% vs 23.9%),
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13 176 cardiac arrhythmia (35.5% vs 42.6%) and diabetes (30.3% vs 32.3%). Except for hypertension,
14
15 177 which was more frequent in women, cardiovascular comorbidities (i.e., ischemic heart disease
16
17 178 and arrhythmias) as well as COPD, were more prevalent in men. Arthropathy, varicose veins of
18
19 179 lower extremities, obesity, osteoporosis, dementia and depression were also highly prevalent in
20
21 180 HF patients, especially in women.
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25 181 We identified and described six multimorbidity patterns in women, which resulted from
26
27 182 the factorial analysis, namely cardiovascular, respiratory, metabolic, coronary-ischemic,
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29 183 degenerative, and neurovascular patterns. Men only showed five patterns, which were similar to
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31 184 those observed in women with the exception of the respiratory pattern. Tables 2 and 3 detail the
32
33 185 compositions of the multimorbidity patterns in women and men, respectively. In women, these
34
35 186 patterns explained up to 40.5% of the cumulative total variance, with a KMO of 0.753. In men,
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37 187 the patterns explained up to 37.3% of the cumulative total variance, with a KMO of 0.761.
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41 188 A high proportion of the study population was assigned to these patterns, with prevalence
42
43 189 rates ranging from 13.5% (neurovascular) to 64.0% (degenerative) in women, and from 22.2%
44
45 190 (neurovascular) to 49.3% (metabolic) in men. The prevalence and impact on health outcomes of
46
47 191 such multimorbidity patterns is described in Table 4. In general, all the multimorbidity patterns
48
49 192 were associated with an increased risk of hospitalization during the following year (12-86%
50
51 193 increase) in both men and women compared with the absence of the pattern, except for the
52
53 194 degenerative pattern in women. The cardiovascular, neurovascular and respiratory patterns
54
55 195 significantly increased the likelihood of three-year mortality (45-74% increase) in both sexes. The
56
57 196 Kaplan-Meier survival curves of population with HF according to different multimorbidity
58
59 197 patterns are presented in Figure 1.
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1
2
3 198 **Discussion**

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6 199 ***Comorbidity of Heart Failure***

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9 200 The higher morbidity burden found in our population with HF when compared with the general
10
11 201 population of the EpiChron Cohort¹³ could probably be explained by the differences in their age
12
13 202 and sex distributions (mean age of 77.9 vs 44.2 years, and 57.9% vs 50.5% of women,
14
15 203 respectively). The fact that almost the entire population with HF suffered from multimorbidity
16
17 204 (i.e., at least one comorbidity in addition to HF) could be due in part to our operationalization of
18
19 205 multimorbidity, whereby an exceptionally comprehensive list of chronic conditions was
20
21 206 considered. Although most studies agree in defining multimorbidity as the co-occurrence of two
22
23 207 or more chronic conditions, different classification systems are frequently used and the number
24
25 208 of diseases considered varies considerably from 5 to 335 conditions among studies.^{16,17} This lack
26
27 209 of international consensus regarding the definition of multimorbidity hinders the comparison of
28
29 210 results among studies, and the estimations on its prevalence and health impact.

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32
33 211 In our study, ischemic heart disease and arrhythmias were the most prevalent HF
34
35 212 comorbidities in men, and hypertension was the most frequent in women, as previously
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37 213 described.¹ The higher prevalence of COPD in men compared to women was probably due to the
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39 214 higher rates of smoking among Spanish men.¹⁸ While the estimated prevalence of COPD in the
40
41 215 general Spanish population is 15% in men and 6% in women,¹⁹ these figures were almost doubled
42
43 216 in our HF cohort, approaching the 25.6% described in the EAHFE-COPD Study on acute HF
44
45 217 patients.²⁰ The higher COPD prevalence might be explained because a) both COPD and HF share
46
47 218 similar symptoms; b) beta-blockers (indicated for HF) and bronchodilators (indicated for COPD)
48
49 219 have an effect on both pathologies; and c) heart congestion alters pulmonary function tests, among
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51 220 others. In this regard, a study found that congestive heart failure is strongly associated with
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53 221 comorbidities that may lead to the misdiagnosis, and more specifically over-diagnosis of COPD
54
55 222 in these patients.²¹

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3 223 Comorbid depression, which was predominantly observed in women, presented a
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5 224 prevalence 2-3 times higher than that observed in the general population.¹³ Its prevalence is
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7 225 consistent with that reported in the meta-analytic review by Rutledge et al,²² where the mean
8
9 226 prevalence of depression in HF patients was 21.5%. Depression has been associated to worse
10
11 227 prognosis in patients with cardiovascular disease in terms of mortality, hospital admissions and
12
13 228 functional status.¹ However, its role as a potential risk factor for the development of HF is less
14
15 229 consistent; so far, this has only been proven in women and in older patients with systolic
16
17 230 hypertension.²³ The greater prevalence of hypothyroidism observed in HF patients compared to
18
19 231 that of the population aged ≥ 65 years from the same reference cohort (3.1% in men; 12.7% in
20
21 232 women)¹³ could be partially explained by the structural and hemodynamic secondary effects of
22
23 233 the lack of thyroid hormones on the heart. The higher prevalence of hypothyroidism observed in
24
25 234 women compared to men is congruent with the results from the Euro Heart Failure Survey II.¹⁹

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29 235 The clinical composition of the multimorbidity patterns found in the study and their
30
31 236 impact on mortality and hospitalization is discussed below. In general, the number and type of
32
33 237 patterns obtained in men and women were very similar, although their prevalence, composition,
34
35 238 and impact on health outcomes differed moderately.

38 39 239 ***Cardiovascular pattern***

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41
42 240 This pattern mainly included cardiac arrhythmia, cardiac valve disorders and hematologic
43
44 241 disorders (e.g., anticoagulant therapy), as well as chronic renal failure and anemia. Kidney and
45
46 242 heart diseases share common risk factors and they are interrelated through adaptive mechanisms.
47
48 243 Moreover, chronic failure of both organs, volume overload, increased levels of cytokines,
49
50 244 malabsorption syndrome, suppression of the bone marrow and anticoagulant therapy increase the
51
52 245 frequency of anemia in HF patients.²⁴ The presence of these comorbidities in the cardiovascular
53
54 246 but not in the coronary-ischemic pattern could imply a greater deterioration in HF patients
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56 247 suffering from the former pattern. In fact, patients presenting the cardiovascular pattern showed
57
58 248 significantly higher risk of hospitalization and mortality in both sexes. The strong association of
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1
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3 249 this pattern with hospitalization could probably be due to the hemodynamic dysfunction produced
4
5 250 by cardiac arrhythmias and anemia, which often leads to decompensation and subsequent
6
7 251 hospitalization.²⁵
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9

10 252 ***Respiratory pattern***

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12
13 253 The absence of a specific respiratory pattern in men is remarkable, as is the absence of COPD in
14
15 254 the rest of patterns, considering the acknowledged association between COPD and ischemic heart
16
17 255 disease,²⁶ both related to HF, and the high prevalence of COPD particularly in men. Ahmad et
18
19 256 al²⁷ found that COPD appeared in several clusters of patients with HF, especially in those with
20
21 257 higher morbidity burden, which also clustered with ischemic heart disease, cerebrovascular
22
23 258 disease, smoking and male sex. In our study, COPD did not come up as part of any pattern in
24
25 259 men, suggesting a lack of discriminative power of this disease in terms of disease clustering in
26
27 260 men with HF. Nevertheless, this pattern had the second-highest impact on both mortality and
28
29 261 hospitalization in women.
30
31

32
33 262 ***Metabolic pattern***

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35
36 263 This pattern, which was the most prevalent in both sexes, included risk factors for the so-called
37
38 264 metabolic syndrome. This pattern has been consistently identified across studies carried out in the
39
40 265 general population, and in 18% of patients with HF, with no gender differences.²⁸ The fact that
41
42 266 only two diseases had to be present to assign patients to the metabolic pattern could justify its
43
44 267 higher prevalence. When this pattern was restricted to presenting three or more conditions, its
45
46 268 prevalence decreased to 21.3% in women and 22.1% in men, which is closer to previously
47
48 269 published prevalence rates. The absence of an association of this pattern with increased three-
49
50 270 year mortality both in men and women is in line with existing literature, probably due to reverse
51
52 271 epidemiology whereby HF patients with cardiovascular risk factors have better prognosis.²⁹
53
54
55

56 272 ***Coronary-ischemic pattern***

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2
3 273 This pattern was, along with the metabolic pattern, one of the most consistent patterns from a
4
5 274 clinical standpoint. The evolution from micro- and macro-vascular endothelial damage caused by
6
7 275 arteriosclerosis to myocardial injury represents a pathophysiological continuum underlying this
8
9 276 pattern. However, our study could not test this hypothesis since the medical history of HF patients
10
11 277 was unknown. Previous studies have corroborated the late appearance of ischemic heart disease
12
13 278 in women with diabetes and hypertension, whereas, in men, this condition appears earlier and in
14
15 279 association to myocardial infarction and smoking.³⁰ The absence of association with three-year
16
17 280 mortality may be explained by the effectiveness of beta-blockers, aldosterone antagonists and
18
19 281 angiotensin-converting enzyme inhibitors on reducing the risk of sudden death and prolonging
20
21 282 survival in patients with HF,³¹ although this hypothesis needs further investigation based on
22
23 283 longer follow-up periods.

27 284 *Neurovascular pattern*

285 This pattern included conditions related to arteriosclerotic damage in target organs (i.e., kidneys,
286
287 extremities and brain) and thromboembolisms secondary to cardiac arrhythmia. The presence of
288
289 dementia in this pattern is not unexpected. The relationship between cognitive impairment and
290
291 HF is well known, and is secondary to low cerebral perfusion, atrial fibrillation, and brain changes
292
293 consequence of the neuro-hormonal adaptation mechanisms underlying HF.³² Patients with this
294
295 pattern had among the highest risks of three-year mortality. However, the lack of impact on
296
297 women's hospitalization risk was unexpected, especially bearing in mind that women suffering
298
299 from this pattern were considerably older.

293 294 *Degenerative pattern*

295 This pattern, predominantly described in women, included degenerative conditions such as
296
297 arthropathy, cataracts, aphakia, and hearing loss. Although this pattern would be expected to
298
299 entail a greater degree of dependency than others, in the longitudinal nine-year study of Jackson
300
301 et al,³³ the neurological and cardiovascular patterns derived in greater limitations on activities of
302
303 daily living compared to the degenerative pattern identified by these authors. The co-occurrence

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2
3 299 of venous disease, thrombophlebitis, osteoporosis and dermatitis in this pattern could be
4
5 300 conditioned by the physical activity restrictions of patients with HF. This pattern was the only one
6
7 301 associated to a decreased risk of three-year mortality in both men and women, maybe due to the
8
9 302 lower clinical severity of the conditions conforming it, some of which are typical of older age.
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11

12 303 Overall, our results reflect the importance of taking the complete constellation of diseases
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14 304 that surrounds HF into account in both the study and its clinical management. Comorbidities have
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16 305 been found to cluster similarly in both sexes; however, some relevant differences have emerged
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18 306 in the composition of the patterns and its impact on health outcomes. Although exploratory, these
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20 307 findings could give us important clues on which specific comorbidities or disease combinations
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22 308 should be given more attention in men and women with HF in order to better direct disease
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24 309 prevention and control strategies. Specifically, it seems that clinicians should pay particular
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26 310 attention to the appearance of neurovascular and other cardiovascular comorbidities in both men
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28 311 and women, and to respiratory diseases in the case of women, to try to minimize their impact on
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30 312 health outcomes.
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33 313 *Strengths and limitations of the study*

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37 314 The main strength of this study is that it represents a large-scale population including real primary
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39 315 and hospital care patients with a diagnosis of HF. Moreover, HF comorbidities were
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41 316 comprehensively studied by using an exhaustive list of chronic conditions, and not only the most
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43 317 prevalent or severe ones.
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47 318 One of the main limitations of the study is the cross-sectional characterisation of the
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49 319 multimorbidity patterns that makes it impossible to understand the chronological relationship
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51 320 between the different risk factors and chronic diseases. Furthermore, this work is exploratory in
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53 321 its approach and methodology. The estimation of the effect of multimorbidity patterns on health
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55 322 outcomes did not consider the potential confounding role of socioeconomic factors or clinical
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57 323 parameters, like the ejection fraction, which were not available in the study cohort. Other
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59 324 variables such as lifestyle habits (e.g., smoking and drinking behaviours) were also unavailable,
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3 325 and diagnoses were based on real data extracted from electronic health records that were not
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5 326 originally designed for research, thus leading to a potential over or under-reporting of specific
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7 327 diseases. In this regard, data in the EpiChron cohort undergoes continuous quality control check-
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9 328 ups that ensure its accuracy and reliability for research purposes.

12 329 **Conclusion**

15 330 This study confirmed that multimorbidity is the norm rather than the exception in patients with
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17 331 heart failure, and that comorbidities tend to cluster together beyond simple chance in the form of
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19 332 multimorbidity patterns that have different impact on health outcomes in men and women. This
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21 333 knowledge could be useful to better understand common pathophysiological pathways underlying
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23 334 this disease and its comorbidities, and the factors that influence the prognosis of these patients.
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25 335 Further large scale longitudinal studies are encouraged to confirm the existence of these patterns
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27 336 as well as their differential impact on health outcomes.

31 337 **Author Contributions**

34 338 APT and FJRL were the Principal Investigators of the study. AGM, AGG, APT, and FJRL
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36 339 contributed to the design of the research. AGM and BPP performed the statistical analyses. APT,
37
38 340 FJRL, AGG, and CCS interpreted and discussed the results. AGM and AGG prepared the first
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40 341 draft of the manuscript. ACL, MJD, and JIPC made important contributions to the revision of the
41
42 342 manuscript. All authors read and approved the final version of the manuscript.

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8 351 **Competing interests**
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11 352 None declared.
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14 353 **Patient consent for publication**
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17 354 Not required.
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20 355 **Ethics approval**
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24 356 This study was approved by the Clinical Research Ethics Committee of Aragón (CEICA,
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26 357 PI18/082).
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29 358 **Availability of data**
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32 359 The dataset generated and analysed during the current study is not publicly available, but is
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34 360 available from the corresponding author on reasonable request.
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457 **Table 1.** Demographic and clinical description of patients with heart failure (n= 14,670).

Characteristics	Women (n= 8488)	Men (n= 6182)	p value
Demographics			
Sex (%)	57.9 (57.1–58.7)	42.1 (41.3–42.9)	<0.001
Mean age (years)	79.9 (79.6–80.1)	75.2 (74.8–75.5)	<0.001
Age interval (%)			
≤44 years	2.34 (2.02–2.67)	3.87 (3.39–4.35)	
45–64 years	6.03 (5.53–6.54)	13.2 (12.3–14.0)	
65–84 years	52.6 (51.5–53.6)	58.7 (57.4–59.9)	
≥85 years	39.0 (38.0–40.1)	24.3 (23.2–25.3)	
Urban area (vs rural) (%)	55.7 (54.6–56.7)	52.3 (51.0–53.5)	<0.001
Immigrants (%)	0.95 (0.74–1.16)	1.38 (1.08–1.67)	0.017
Clinical information			
3-year all-cause mortality (%)	33.3 (32.3–34.3)	36.5 (35.3–37.7)	<0.001
Multimorbidity* (%)	98.2 (97.9–98.4)	97.7 (97.3–98.1)	0.068
Mean number of diseases	7.77 (7.69–7.85)	7.87 (7.77–7.97)	0.114
Prevalence of comorbidities (%)			
Hypertension	71.2 (70.2–72.1)	65.0 (63.8–66.2)	<0.001
Cardiac arrhythmia	35.5 (34.4–36.5)	42.6 (41.4–43.9)	<0.001
Disorders of lipid metabolism	36.9 (35.8–37.9)	37.6 (36.4–38.8)	0.388
Arthropathy	36.8 (35.8–37.8)	23.9 (22.8–25.0)	<0.001
Diabetes	30.3 (29.4–31.3)	32.3 (31.2–33.5)	0.010
Varicose veins of lower extremities	29.4 (28.4–30.4)	11.8 (11.0–12.6)	<0.001
Emphysema, chronic bronchitis, COPD	13.3 (12.6–14.0)	32.8 (31.6–34.0)	<0.001
Cardiovascular disorders, other	19.2 (18.4–20.0)	24.0 (22.9–25.0)	<0.001
Ischemic heart disease (excluding AMI†)	15.3 (14.5–16.0)	24.6 (23.5–25.7)	<0.001
Obesity	20.3 (19.4–21.1)	17.6 (16.7–18.5)	<0.001
Depression	24.8 (23.8–25.7)	10.9 (10.1–11.7)	<0.001
Cataract, aphakia	19.7 (18.9–20.6)	16.9 (15.9–17.8)	<0.001
Surgical aftercare	15.8 (15.0–16.6)	19.3 (18.3–20.2)	<0.001
Cardiac valve disorders	17.0 (16.2–17.8)	17.5 (16.6–18.4)	0.394
Iron deficiency, other deficiency anemias	17.3 (16.5–18.1)	15.6 (14.7–16.5)	0.007
Osteoporosis	23.1 (22.2–24.0)	3.69 (3.22–4.16)	<0.001
Cerebrovascular disease	13.9 (13.2–14.7)	14.3 (13.4–15.1)	0.604
Respiratory disorders, other	12.5 (11.8–13.2)	16.1 (15.2–17.1)	<0.001
Hypothyroidism	17.6 (16.8–18.4)	6.44 (5.83–7.05)	<0.001
Dementia and delirium	13.3 (12.6–14.0)	8.44 (7.75–9.14)	<0.001
Prostatic hypertrophy	-	24.6 (23.5–25.7)	-
Dermatitis and eczema	9.80 (9.17–10.4)	10.3 (9.58–11.1)	0.287
Chronic renal failure	8.19 (7.60–8.77)	12.3 (11.5–13.1)	<0.001
Glaucoma	10.4 (9.76–11.1)	8.61 (7.91–9.30)	<0.001
Deafness, hearing loss	9.57 (8.94–10.2)	9.17 (8.45–9.89)	0.419
AMI	5.84 (5.34–6.34)	13.8 (12.9–14.6)	<0.001
Chronic ulcer of the skin	10.2 (9.58–10.9)	7.40 (6.74–8.04)	<0.001
Hematologic disorders, other	7.94 (7.37–8.52)	9.43 (8.70–10.2)	0.002
Asthma	10.6 (10.0–11.3)	4.69 (4.16–5.22)	<0.001
Low back pain	6.54 (6.01–7.06)	6.10 (5.50–6.69)	0.280
Gout	2.70 (2.35–3.04)	10.5 (9.75–11.3)	<0.001

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3	Neurologic disorders, other	6.63 (6.10–7.16)	5.10 (4.55–5.64)	<0.001
4	Diverticular disease of colon	5.75 (5.25–6.24)	4.82 (4.29–5.35)	0.014
5	Other endocrine disorders	5.96 (5.46–6.47)	3.80 (3.32–4.28)	<0.001
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7 458 95% confidence intervals are displayed within brackets. Only comorbidities with a mean

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9 459 prevalence equal to or greater than 5% are displayed.

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11 460 *Defined as having two or more chronic conditions from a list of 114 chronic diagnoses.

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13 461 †Acute myocardial infarction.

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477 **Table 2.** Multimorbidity patterns identified in women with heart failure (n= 8488). Each pattern
 478 is represented by the comorbidities and their loading factors in the pattern.

Patterns	Comorbidities	Loading factors
Cardiovascular	Cardiac arrhythmia	0.80
	Cardiac valve disorders	0.62
	Cardiovascular disorders, other	0.58
	Hematologic disorders, other	0.52
	Surgical aftercare	0.33
	Cardiomyopathy	0.32
	Chronic renal failure	0.29
Respiratory	Respiratory disorders, other	0.47
	Emphysema, chronic bronchitis, COPD	0.47
	Asthma	0.42
	Other endocrine disorders	0.37
	Chronic renal failure	0.30
	Surgical aftercare	0.25
Metabolic	Diabetic retinopathy	0.74
	Diabetes	0.73
	Obesity	0.40
	Hypertension	0.36
	Disorders of lipid metabolism	0.26
Coronary-ischemic	Acute myocardial infarction	0.76
	Ischemic heart disease (excluding AMI*)	0.66
	Surgical aftercare	0.30
Degenerative	Varicose veins of lower extremities	0.53
	Arthropathy	0.53
	Cataract, aphakia	0.45
	Osteoporosis	0.34
	Thrombophlebitis	0.29
	Deafness, hearing loss	0.26
	Obesity	0.25
Hypertension	0.25	
Neurovascular	Dementia and delirium	0.76
	Chronic ulcer of the skin	0.48
	Cerebrovascular disease	0.41
	Chronic renal failure	0.28
	Respiratory disorders, other	0.25

479 *Acute myocardial infarction.

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481 **Table 3.** Multimorbidity patterns identified in men with heart failure (n= 6182). Each pattern is
 482 represented by the comorbidities and their loading factors in the pattern.

Patterns	Comorbidities	Loading factors
Cardiovascular	Cardiovascular disorders, other	0.66
	Cardiac arrhythmia	0.64
	Cardiac valve disorders	0.58
	Cardiomyopathy	0.55
	Surgical aftercare	0.46
	Hematologic disorders, other	0.39
	Respiratory disorders, other	0.39
	Chronic renal failure	0.33
	Iron deficiency, other deficiency anemias	0.26
Neurovascular	Dementia and delirium	0.54
	Generalized atherosclerosis	0.52
	Peripheral vascular disease	0.46
	Chronic renal failure	0.45
	Cerebrovascular disease	0.43
	Respiratory disorders, other	0.43
	Chronic ulcer of the skin	0.39
	Iron deficiency, other deficiency anemias	0.39
Metabolic	Obesity	0.71
	Diabetes	0.45
	Hypertension	0.45
	Disorders of lipid metabolism	0.40
	Substance use	0.31
Coronary- ischemic	Ischemic heart disease (excluding AMI*)	0.70
	Acute myocardial infarction	0.70
	Surgical aftercare	0.36
	Disorders of lipid metabolism	0.36
Degenerative	Arthropathy	0.43
	Cataract, aphakia	0.42
	Deafness, hearing loss	0.39
	Glaucoma	0.31
	Varicose veins of lower extremities	0.30
	Dermatitis and eczema	0.30
	Prostatic hypertrophy	0.26

483 *Acute myocardial infarction.

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485 **Table 4.** Prevalence of multimorbidity patterns identified in men (n= 6182) and women (n= 8488)
 486 with heart failure, and adjusted associations with hospitalization and death.

Multimorbidity pattern	Prevalence (%)	Mean age (years)	Hospitalization (OR)*	p value	Death (HR)†	p value
Women						
Cardiovascular	29.9	80.4	1.86 (1.66-2.08)	<0.001	1.45 (1.33-1.58)	<0.001
Metabolic	49.9	80.1	1.26 (1.13-1.39)	<0.001	1.04 (0.97-1.13)	0.284
Coronary-ischemic	6.60	80.7	1.48 (1.23-1.79)	<0.001	1.13 (0.99-1.30)	0.061
Neurovascular	13.6	84.1	1.12 (0.97-1.30)	0.117	1.62 (1.48-1.78)	<0.001
Degenerative	64.0	81.1	1.19 (1.06-1.32)	0.002	0.70 (0.65-0.76)	<0.001
Respiratory	16.9	81.0	1.71 (1.50-1.97)	<0.001	1.53 (1.39-1.69)	<0.001
Men						
Cardiovascular	43.2	76.8	1.83 (1.62-2.07)	<0.001	1.60 (1.46-1.76)	<0.001
Metabolic	49.3	75.3	1.37 (1.22-1.53)	<0.001	0.98 (0.90-1.07)	0.695
Coronary-ischemic	24.7	76.2	1.25 (1.10-1.43)	0.001	0.99 (0.90-1.09)	0.818
Neurovascular	22.2	79.9	1.62 (1.41-1.86)	<0.001	1.74 (1.58-1.91)	<0.001
Degenerative	29.2	80.2	1.03 (0.91-1.16)	0.687	0.75 (0.68-0.81)	<0.001

487 *Odds ratio for having at least one hospitalization during the following year (compared to not
 488 having the pattern).

489 †Hazard ratio for all-cause death after three years of follow-up (compared to not having the
 490 pattern).

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492 **Figure 1.** Kaplan-Meier survival curves in men (n= 6182) and women (n= 8488) with heart failure
493 according to the presence of different patterns of multimorbidity.
494 [Attached as TIFF file]

For peer review only

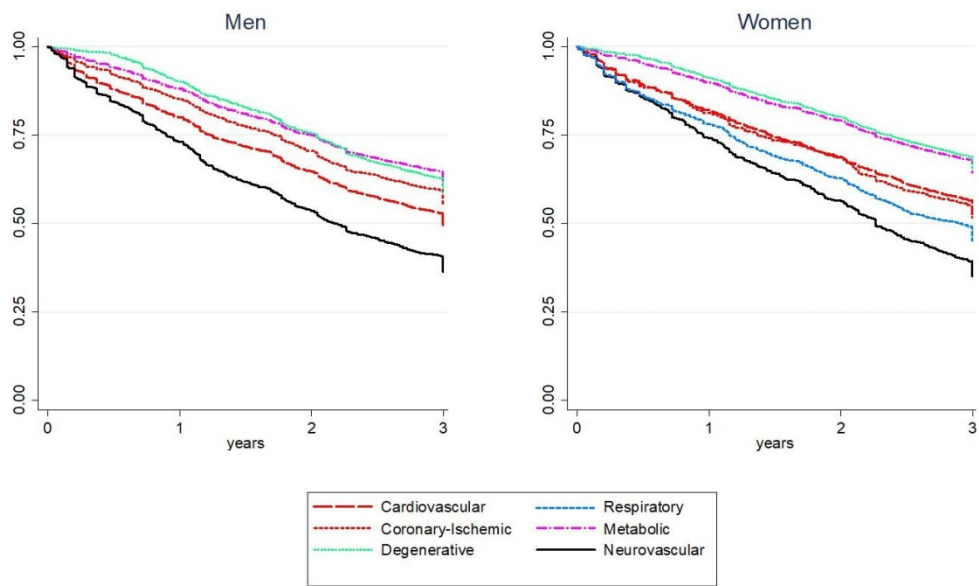


Figure 1. Kaplan-Meier survival curves in men (n= 6182) and women (n= 8488) with heart failure according to the presence of different patterns of multimorbidity.

228x146mm (150 x 150 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	6
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13-14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.