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

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Abstract

Objectives: To characterize the comorbidities of heart failure (HF), to explore their clustering into multimorbidity patterns, and to measure the impact of such patterns on the risk of hospitalization and mortality.

Design: Observational retrospective population study based on electronic health records.

Setting: EpiChron Cohort (Aragón, Spain).

Participants: All primary and hospital care patients of the EpiChron Cohort with a diagnosis of HF in 2011 (i.e., 14,670). We considered all their chronic diseases registered in patients' electronic health records until the end of 2011.

Primary outcome: We applied an exploratory factor analysis to identify the multimorbidity patterns, and logistic and Cox proportional-hazards regressions to investigate the association between the patterns and the risk of hospitalization in 2012 and of three-year mortality, respectively.

Results: Almost all HF patients (98%) had multimorbidity, with an average of 7.8 chronic diseases per patient. We identified six different multimorbidity patterns, named cardiovascular, neurovascular, coronary, metabolic, degenerative, and respiratory. The most prevalent patterns were the degenerative (64.0%) and cardiovascular (29.9%) in women, and the metabolic (49.3%) and cardiovascular (43.2%) in men. All patterns were associated with higher risk of hospitalization; and the cardiovascular, neurovascular and respiratory patterns significantly increased the likelihood of three-year mortality.

Conclusions: Multimorbidity is by far the norm rather than the exception in patients with heart failure, whose comorbidities tend to cluster together beyond simple chance in the form of multimorbidity patterns that have different impact on health outcomes. This knowledge could be useful to better understand common pathophysiological pathways underlying this condition

and its comorbidities, and factors influencing the prognosis of these patients. Further large scale longitudinal studies are encouraged to confirm the existence of these patterns as well as their differential impact on health outcomes.

Keywords: Heart failure; Multimorbidity; Comorbidity; Patterns; Hospitalization

Word count: 3182

Article Summary

Strengths and limitations of the study

- This is a large-scale population-based study including all primary and hospital care real life patients of the reference population with a diagnosis of HF.

- Data in the cohort continuously undergo quality control check-ups that ensure their accuracy and reliability for use in research.

- The cross-sectional characterization of the multimorbidity patterns makes it impossible to understand the chronological relationship between the different risk factors and chronic diseases.

- Diagnoses were extracted from electronic health records that were not originally designed for research, thus leading to a potential over or under-reporting of specific diseases.

- The estimation of the effect of multimorbidity patterns on health outcomes did not consider the potential confounding role of socioeconomic factors or clinical parameters like the ejection fraction, which were not available in the study cohort.

Introduction

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

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

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

Further, the identification and clinical characterization of multimorbidity patterns in patients with HF and the study of their potential impact on negative health outcomes (e.g., risk of death and hospitalization) could shed light on new pathophysiological pathways that may guide the development of clinical practice guidelines better adapted to patients with HF.[12]

This large-scale population study based on electronic health records from real life primary and hospital care patients aimed to characterize the comorbidities of HF, to explore their clustering into multimorbidity patterns, and to measure the impact of such patterns on negative health outcomes.

Methods

Design and study population

We conducted a retrospective observational study based on data from the EpiChron Cohort that links demographic, clinical and health outcomes information for all public health system users of the Spanish region of Aragón. A description of the cohort profile and of the data sources was published elsewhere.[13] This cohort was conformed in 2011 and it included 1,253,292 people at baseline (approximately 95% of total inhabitants of Aragón). For this study, we selected and followed up for three years all patients with a diagnosis of HF in their primary or hospital electronic health records on 31st January 2011.

Outcome variables

For each patient, we analysed data on demographics (i.e., age, sex, area of residence, immigrant status), healthcare use during 2012 (i.e., use of primary care, specialized care, hospital and emergency services), diagnoses of chronic conditions registered in both primary and hospital care, and all-cause mortality until 31st December 2014. Diagnoses were originally coded according to the International Classification of Primary Care (ICPC) or the International

Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and subsequently grouped in Expanded Diagnostic Clusters (EDCs) through the Johns Hopkins ACG® System (version 11.0, The Johns Hopkins University, Baltimore, MD, US). We considered for the study all patients with the EDC code CAR05, which includes ICPC and ICD-9-CM codes for HF. We included in the analysis all of the 114 EDCs previously defined as chronic by Salisbury et al.[14]

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

Statistical analyses

All analyses were stratified by sex. First, we performed a descriptive analysis of demographic and clinical information of the population with HF. We compared means and frequencies using the Student t test and the chi-squared test, respectively, with their respective 95% confidence intervals.

Second, we applied an exploratory factor analysis to identify the existence of non-random associations among chronic diseases. To facilitate the epidemiological and clinical interpretation of the results, we only included in the analysis those comorbidities with a prevalence ≥5%. The methodology followed was described elsewhere.[7] Briefly, EDCs were coded as binary variables (present/absent), and a factor analysis based on a tetrachoric correlation matrix was performed to determine which diagnoses comprised each factor. We used the principal factor method for the extraction of the factors, and a scree plot in combination with clinical criteria to determine the number of factors to extract. We selected EDCs with factor scores ≥0.25 as those belonging to each multimorbidity pattern. Model goodness-of-fit and sample adequacy were calculated through the proportions of cumulative variance and the Kaiser-Meyer-Olkin (KMO) parameter. After performing the factor analysis, three clinical experts (FRL, CCS, and APT) proposed and

agreed upon the denomination of the resulting patterns. Individuals were subsequently assigned to one or more of the described patterns of multimorbidity if they had at least two of the diseases that comprised the pattern (in addition to HF), as described by Prados et al.[7]

Finally, we applied logistic and Cox proportional-hazards regressions to calculate the risk of having at least one hospitalization during 2012 and of three-year mortality, respectively, depending on the multimorbidity pattern suffered by the individual. Patients' age (continuous variable) and all multimorbidity patterns were included as independent variables in the models. We used Kaplan-Meier survival curves to represent and compare survival rates of individuals with specific multimorbidity patterns, which were tested for the proportional hazard assumption.

We conducted all the statistical analysis in STATA (Version 12.0, StataCorp LLC, College Sation, TX, US). Statistical significance was set at $p<0.05$.

Results

A total of 14,670 patients from the EpiChron Cohort had a diagnosis of HF in 2011, representing around 1.1% of the total population in Aragón. The study population is described in Table 1. A predominance of women was observed (57.9% vs 42.1%, $p<0.001$), who were on average older than men (79.9 vs 75.2 years, $p<0.001$) mainly due to a higher proportion of people aged ≥85 years. The cumulative mortality rate throughout the three-year follow-up was higher in men compared with women (36.5% vs 33.3 %, $p<0.001$), and the same pattern was observed for hospital admissions.

In our study, almost all patients with HF (98%) suffered from multimorbidity, with an average of 7.8 chronic diseases per patient. The most prevalent HF comorbidities were similar in women and in men, as hypertension (71.2% vs 65.0%), dyslipidemia (36.9% vs 37.6%), arthropathy (36.8% vs 23.9%), cardiac arrhythmia (35.5% vs 42.6%) and diabetes (30.3% vs

32.3%). Except for hypertension, which was more frequent in women, cardiovascular comorbidities (i.e., ischemic heart disease and arrhythmias) were more prevalent in men, as well as COPD. Arthropathy, varicose veins of lower extremities, obesity, osteoporosis, dementia and depression were also highly prevalent in HF patients, especially in women.

As a result of the factorial analysis, six multimorbidity patterns were identified and described in women, named cardiovascular, respiratory, metabolic, coronary-ischemic, degenerative, and neurovascular. In men, we only identified five patterns, which were similar to those observed in women with the exception of the respiratory pattern. The composition of the patterns of multimorbidity in women and men is detailed in Tables 2 and 3, respectively. In women, these patterns explained up to 40.5% of the cumulative total variance, with a KMO of 0.753. In men, the patterns explained up to 37.3% of the cumulative total variance, with a KMO of 0.761.

A high proportion of the study population was assigned to these patterns, with prevalence rates ranging from 13.5% (neurovascular) to 64.0% (degenerative) in women, and from 22.2% (neurovascular) to 49.3% (metabolic) in men. The prevalence and impact on health outcomes of such multimorbidity patterns is described in Table 4. In general, all patterns were associated with increased risk of hospitalization during the following year (by 12-86%) in both men and women compared with the absence of the pattern, except for the degenerative pattern in women. The cardiovascular, neurovascular and respiratory patterns significantly increased the likelihood of three-year mortality (by 45-74%) in both sexes. The Kaplan-Meier survival curves of population with HF according to different multimorbidity patterns are presented in Figure 1.

Discussion

Comorbidity of Heart Failure

The population with HF of our study suffered a higher morbidity burden than that found in the general population of the EpiChron Cohort.[13] Regarding comorbidity of HF, cardiovascular comorbidities (i.e., ischemic heart disease and arrhythmias), except for hypertension that was more frequent in women, were more prevalent in men, as previously seen in the literature.[1]

The higher prevalence of COPD in men compared to women was probably due to the higher rates of smoking among Spanish men. While the estimated prevalence of COPD in the general Spanish population is 15% in men and 6% in women, these figures were almost doubled in our HF cohort, approaching the 25.6% described in the EAHFE-COPD Study on acute HF patients.[15] This higher prevalence of COPD might be explained because a) both COPD and HF share similar symptoms; b) beta-blockers (indicated for HF) and bronchodilators (indicated for COPD) exert an effect on both pathologies; and c) heart congestion alters pulmonary function tests, among others. The fact that 80% of COPD cases are associated with smoking but close to 50% of HF patients have never smoked makes some authors think that COPD could be over-diagnosed in HF patients.[16]

Comorbid depression, which was predominantly observed in women, presented a prevalence 2-3 times higher than that observed in the general population.[13] Its prevalence is consistent with that reported in the meta-analytic review by Rutledge et al,[17] where the mean prevalence of depression in HF patients was 21.5%. Depression has been associated to worse prognosis in patients with cardiovascular disease in terms of mortality, hospital admissions and functional status.[1] However, its role as a potential risk factor for the development of HF is less consistent; so far, this has only been proved in women and in older patients with systolic hypertension.[18] The greater prevalence of hypothyroidism observed in HF patients compared to the general population, especially in women, could be partially explained by the structural and hemodynamic secondary effects of thyroid hormones on the heart. The higher prevalence of hypothyroidism observed in women compared to men is congruent with the results from the Euro Heart Failure Survey II.[19]

The cumulative mortality rate throughout the three-year follow-up, which was higher in men, is in line with the results obtained by Levy et al[20] who described greater survival of women with HF compared to men based on the Framingham Heart Study. The clinical composition of the multimorbidity patterns found in the study and their impact on mortality and hospitalization is discussed below.

Cardiovascular pattern

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

Respiratory pattern

This pattern, which was present in 16.9% of women, had COPD and asthma as the most strongly associated diseases. The absence of a specific respiratory pattern in men is remarkable, as it is the absence of COPD in the rest of patterns, considering the acknowledged association between COPD and ischemic heart disease,[23] both related to HF, and the high prevalence of COPD particularly in men. Ahmad et al[24] found that COPD appeared in several clusters of patients with HF, especially in those with higher morbidity burden, which also clustered with

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

Metabolic pattern

This pattern was the most prevalent in both sexes, affecting half of men and women. The metabolic pattern included obesity, hypertension, diabetes and dyslipidemia; all risk factors conforming the so-called metabolic syndrome. This pattern has been consistently identified across studies carried out in the general population, and in 18% of patients with HF, with no gender differences.[25] This higher prevalence of the pattern observed in our study could be due to the fact that only two diseases had to be present to assign patients to this pattern. When this condition was restricted to present three or more conditions, the prevalence decreased to 21.3% in women and 22.1% in men, which are closer to previously published rates. Suffering from this pattern was not associated with increased three-year mortality either in men or women, which is in line with the literature, probably due to reverse epidemiology whereby HF patients with cardiovascular risk factors have better prognosis.[26] However, patients presenting with this pattern did show a significantly higher risk of hospitalization; 37% in men and 26% in women.

Coronary-ischemic pattern

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

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

Neurovascular pattern

This pattern was identified in both men (22.2%) and women (13.6%), and included conditions related to arteriosclerotic damage in target organs of (i.e., kidney, extremities and brain) and thromboembolism secondary to cardiac arrhythmia. The presence of dementia in this pattern does not come unexpected. A well-known relationship exists between cognitive impairment and HF, due to low cerebral perfusion, atrial fibrillation, and brain changes secondary to the neuro-hormonal adaptation mechanisms underlying HF.[29] Patients with this pattern had among the highest risk of three-year mortality. However, its effect on the risk of hospitalization differed by sex. Whereas it had no effect in women, it increased the risk of hospitalization by 62% in men. This finding was unexpected, especially bearing in mind that both women and men suffering from this pattern were considerably older.

Degenerative pattern

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

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

Conclusion

This study confirmed that multimorbidity is by far the norm rather than the exception in patients with heart failure, and that comorbidities tend to cluster together beyond simple chance in the form of multimorbidity patterns that have different impact on health outcomes. This knowledge could be useful to better understand common pathophysiological pathways underlying this disease and its comorbidities, and factors influencing the prognosis of these patients. Further large scale longitudinal studies are encouraged to confirm the existence of these patterns as well as their differential impact on health outcomes.

Author Contributions

APT and FJRL were the Principal Investigators of the study. AGM, AGG, APT, and FJRL contributed to the design of the research. AGM and BPP performed the statistical analyses. APT, FJRL, AGG, and CCS interpreted and discussed the results. AGM and AGG prepared the first draft of the manuscript. ACL, MJD, and JIPC made important contributions to the revision of the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Clinical Research Ethics Committee of Aragón (CEICA, PI18/082).

Availability of data

The dataset generated and analyzed during the current study is not publicly available, but is available from the corresponding author on reasonable request.

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Table 1. Demographic, health services use, 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
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

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
Neurologic disorders, other	6.63 (6.10–7.16)	5.10 (4.55–5.64)	<0.001
Diverticular disease of colon	5.75 (5.25–6.24)	4.82 (4.29–5.35)	0.014
Other endocrine disorders	5.96 (5.46–6.47)	3.80 (3.32–4.28)	<0.001

95% confidence intervals are displayed within brackets. Only comorbidities with a mean prevalence equal to or greater than 5% are displayed.

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

†Acute myocardial infarction.

Table 2. Multimorbidity patterns identified in women with heart failure (n= 8488). Each pattern 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

*Acute myocardial infarction.

Table 3. Multimorbidity patterns identified in men with heart failure (n= 6182). Each pattern is 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

*Acute myocardial infarction.

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

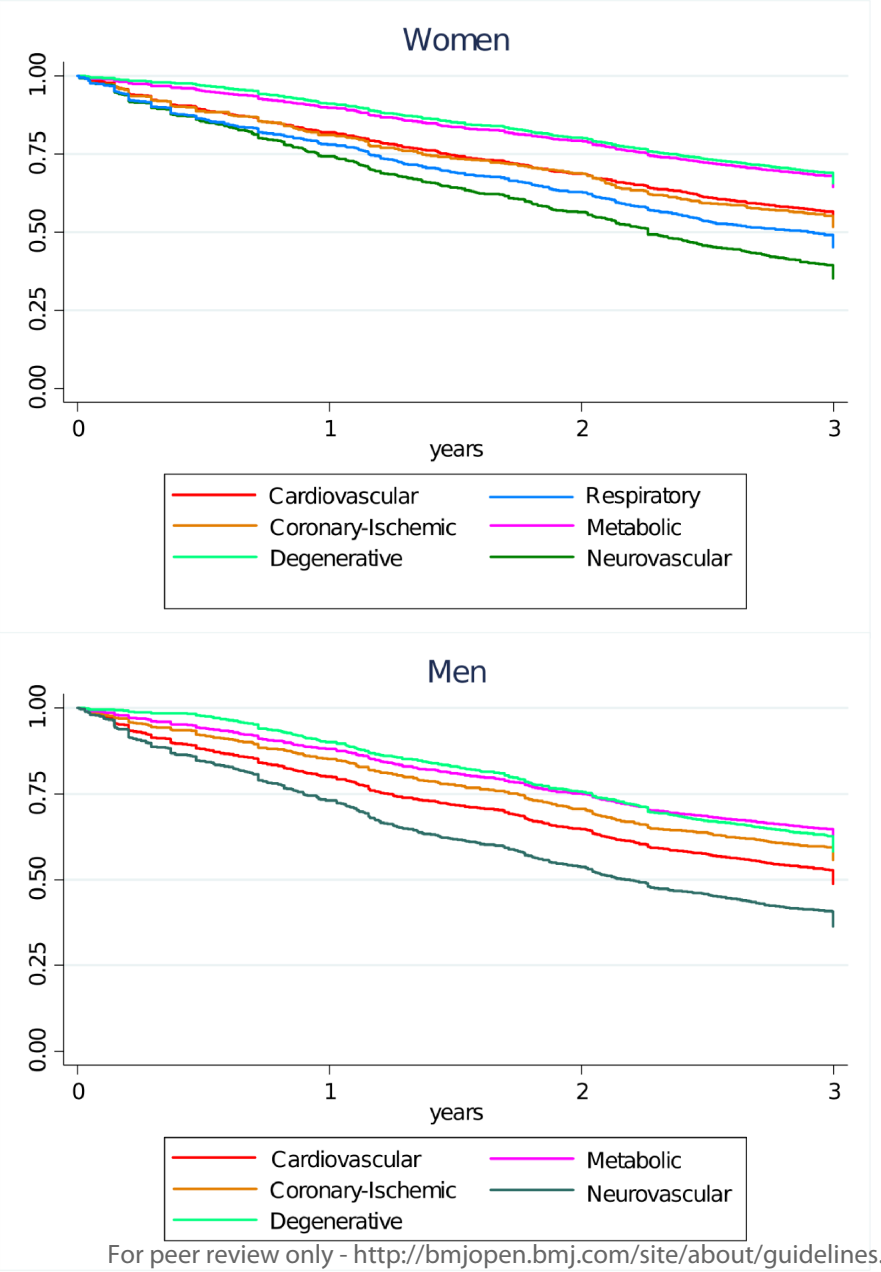
Multimorbidity pattern	**Prevalence** (%)	**Mean age** (years)	**Hospitalization** (OR)*	**p value**	**Death** (HR)†	**p value**
Women						
Cardiovascular	29.9	80.4	1.86 (1.66-2.08)	<0.001	1.45 (1.33-1.58)	<0.001
Metabolic	49.9	80.1	1.26 (1.13-1.39)	<0.001	1.04 (0.97-1.13)	0.284
Coronary-ischemic	6.60	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

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

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

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

[Attached as pptx file]



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	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	
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	7-8
		(*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	
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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Abstract

Objectives: To characterise the comorbidities of heart failure (HF) in men and women, to explore their clustering into multimorbidity patterns, and to measure the impact of such patterns on the risk of hospitalization and mortality.

Design: Observational retrospective population study based on electronic health records.

Setting: EpiChron Cohort (Aragón, Spain).

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

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

Results: Almost all HF patients (98%) had multimorbidity, with an average of 7.8 chronic diseases per patient. We identified six different multimorbidity patterns, named cardiovascular, neurovascular, coronary, metabolic, degenerative, and respiratory. The most prevalent were the degenerative (64.0%) and cardiovascular (29.9%) patterns in women, and the metabolic (49.3%) and cardiovascular (43.2%) patterns in men. Every pattern was associated with higher hospitalization risks; and the cardiovascular, neurovascular and respiratory patterns significantly increased the likelihood of three-year mortality.

Conclusions: Multimorbidity is the norm rather than the exception in patients with heart failure, whose comorbidities tend to cluster together beyond simple chance in the form of multimorbidity patterns that have different impact on health outcomes. This knowledge could be useful to better understand common pathophysiological pathways underlying this condition and its

comorbidities, and the factors influencing the prognosis of men and women with HF. Further large scale longitudinal studies are encouraged to confirm the existence of these patterns as well as their differential impact on health outcomes.

Keywords: Heart failure; Multimorbidity; Comorbidity; Chronic disease; Hospitalization; Mortality; Cohort

Word count: 3483

Article Summary

Strengths and limitations of the study

- This is a large-scale population-based study that included the primary and hospital care patients of the reference population with a diagnosis of HF.

- The data in the cohort continuously underwent quality control check-ups to ensure its accuracy and reliability for research purposes.

- The cross-sectional characterisation of the multimorbidity patterns made it impossible to understand the chronological relationship between the different risk factors and chronic diseases.

- Diagnoses were extracted from electronic health records that were not originally designed for research, thus leading to a potential over or under-reporting of specific diseases.

- The estimation of the effect of multimorbidity patterns on health outcomes did not consider the potential confounding role of socioeconomic factors or clinical parameters, like the ejection fraction, which were not available in the study cohort.

Introduction

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

Recent studies have examined the most prevalent comorbidities in HF patients and their prognostic impact on mortality rates and hospital readmissions.[2,5,6] However, although the clustering of chronic diseases into multimorbidity patterns has already been demonstrated in the general population,[7] most studies still focus on isolated comorbidities, without considering the interrelations among them. Some of the few studies addressing multimorbidity in HF patients restrict their analyses to the most frequently co-occurring combinations of two or three comorbidities,[8] while others are conducted in relatively small samples[9]. Moreover, the methodological approaches in these studies in terms of data sources, studied comorbidities, and statistical analysis techniques vary considerably.[3,8–10] Thus, there is still a need to perform studies on real patients from primary care, where multimorbidity is most frequently dealt with, and to address the sex/gender perspective of this disease and its comorbidities.

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

and women with HF, and the study of their potential impact on negative health outcomes (e.g., risk of death and hospitalization) could shed light on new pathophysiological pathways. These pathways could help guide the development of clinical practice guidelines better adapted to patients with HF based on their sex and comorbidities.[12]

This large-scale population study based on electronic health records from real primary and hospital care patients aimed to characterise the comorbidities of HF in men and women, to explore their clustering into multimorbidity patterns, and to measure the impact of said patterns on negative health outcomes.

Methods

Design and study population

We conducted a retrospective observational study based on the EpiChron Cohort, which links demographic, clinical and health-outcome-related information for all public health system users of the Spanish region of Aragón. A description of the cohort profile and of the data sources was published elsewhere.[13] This cohort was conformed in 2011 and it included 1,253,292 people at baseline (approximately 95% of the total inhabitants of Aragón). For this study, we selected all patients with HF diagnosis in their primary or hospital electronic health records on 1 January 2011 and followed-up on them for three years.

Study variables

For each patient, we analysed demographic data (i.e., age, sex, area of residence, immigration status), hospital admissions during 2012, all chronic condition diagnoses from primary and/or hospital care, and all-cause mortality until 31 December 2014. Diagnoses were extracted from the electronic health records of both primary and hospital care levels, and included all active episodes between 1 January 2011 and 31 December 2011, even if a healthcare professional had recorded them before the initial date. Diseases were originally coded according to the International Classification of Primary Care (ICPC) (in primary care settings) or the International Classification

of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (in hospital settings), and subsequently grouped into 260 mutually exclusive Expanded Diagnostic Clusters (EDCs) through the Johns Hopkins ACG® System (version 11.0, The Johns Hopkins University, Baltimore, MD, US).[14] We included every patient with the CAR05 EDC code, as well as the ICPC and ICD-9-CM codes for HF, and considered all 114 possible EDCs previously established as chronic by Salisbury et al.[15] for the analysis. Multimorbidity was defined as the presence of two or more EDCs from Salisbury's list.

This study complies with the Declaration of Helsinki, and the Clinical Research Ethics Committee of Aragón (CEICA) approved the research protocol (PI18/082). The CEICA waived the requirement to obtain informed consent from patients since all the information was anonymised.

Statistical analyses

All our analyses were stratified by sex. First, we performed a descriptive analysis on demographic and clinical information of the population with HF. We compared means and frequencies using Student's t-test and the chi-squared test, respectively, with their corresponding 95% confidence intervals.

Second, we applied an exploratory factor analysis to identify the existence of non-random associations among chronic diseases in men and women. To facilitate the epidemiological and clinical interpretation of the results, we only included in the analysis those chronic comorbidities from Salisbury's list with a prevalence ≥5% in each sex. The methodology followed was described elsewhere.[7] Briefly, EDCs were coded as binary variables (present/absent), and a factor analysis based on a tetrachoric correlation matrix was performed to determine which diagnoses comprised each factor. We used the principal factor method for the extraction of the factors, and a scree plot in combination with clinical criteria to determine the number of factors to extract. The EDCs with factor scores ≥0.25 within a pattern were considered to be part of that multimorbidity pattern, so that the same EDC could be present in more than one cluster. Model

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

Finally, we applied logistic and Cox proportional-hazards regressions to calculate the risk of having at least one hospitalization during 2012 and of three-year mortality, respectively, depending on the multimorbidity pattern suffered by the individual (compared to having no patterns). Patient age (continuous variable) and all the multimorbidity patterns were included as independent variables in the models. We used Kaplan-Meier survival curves to represent and compare survival rates of individuals with specific multimorbidity patterns, which were also used to test for the proportional hazard assumption.

We conducted all statistical analyses using STATA (Version 12.0, StataCorp LLC, College Sation, TX, US). Statistical significance was set at $p<0.05$.

Patient and Public Involvement

Patients and public were not involved in this study.

Results

A total of 14,670 patients from the EpiChron Cohort had a HF diagnosis in 2011, representing around 1.1% of the total population of Aragón. The study population is described in Table 1. Women predominated over men (57.9% vs 42.1%, $p<0.001$) and were older on average (79.9 vs 75.2 years, $p<0.001$) mainly due to a higher proportion of people aged ≥85 years. The cumulative mortality rate throughout the three-year follow-up was higher in men than in women (36.5% vs 33.3 %, $p<0.001$), and the same pattern was observed for hospital admissions.

In our study, almost all patients with HF (98%) suffered from multimorbidity, with an average disease burden of 7.8 chronic diseases per patient (HF included). These figures are higher than those observed in the reference cohort (38% and 1.7 chronic diseases/patient, respectively). The most prevalent HF comorbidities were similar in women and in men, and specifically were hypertension (71.2% vs 65.0%), dyslipidemia (36.9% vs 37.6%), arthropathy (36.8% vs 23.9%), cardiac arrhythmia (35.5% vs 42.6%) and diabetes (30.3% vs 32.3%). Except for hypertension, which was more frequent in women, cardiovascular comorbidities (i.e., ischemic heart disease and arrhythmias) as well as COPD, were more prevalent in men. Arthropathy, varicose veins of lower extremities, obesity, osteoporosis, dementia and depression were also highly prevalent in HF patients, especially in women.

We identified and described six multimorbidity patterns in women, which resulted from the factorial analysis, namely cardiovascular, respiratory, metabolic, coronary-ischemic, degenerative, and neurovascular patterns. Men only showed five patterns, which were similar to those observed in women with the exception of the respiratory pattern. Tables 2 and 3 detail the compositions of the multimorbidity patterns in women and men, respectively. In women, these patterns explained up to 40.5% of the cumulative total variance, with a KMO of 0.753. In men, the patterns explained up to 37.3% of the cumulative total variance, with a KMO of 0.761.

A high proportion of the study population was assigned to these patterns, with prevalence rates ranging from 13.5% (neurovascular) to 64.0% (degenerative) in women, and from 22.2% (neurovascular) to 49.3% (metabolic) in men. The prevalence and impact on health outcomes of such multimorbidity patterns is described in Table 4. In general, all the multimorbidity patterns were associated with an increased risk of hospitalization during the following year (12-86% increase) in both men and women compared with the absence of the pattern, except for the degenerative pattern in women. The cardiovascular, neurovascular and respiratory patterns significantly increased the likelihood of three-year mortality (45-74% increase) in both sexes. The Kaplan-Meier survival curves of population with HF according to different multimorbidity patterns are presented in Figure 1.

Discussion

Comorbidity of Heart Failure

The higher morbidity burden found in our population with HF when compared with the general population of the EpiChron Cohort[13] could probably be explained by the differences in their age and sex distributions (mean age of 77.9 vs 44.2 years, and 57.9% vs 50.5% of women, respectively). The fact that almost the entire population with HF suffered from multimorbidity (i.e., at least one comorbidity in addition to HF) could be due in part to our operationalization of multimorbidity, whereby an exceptionally comprehensive list of chronic conditions was considered. Although most studies agree in defining multimorbidity as the co-occurrence of two or more chronic conditions, different classification systems are frequently used and the number of diseases considered varies considerably from 5 to 335 conditions among studies.[16,17] This lack of international consensus regarding the definition of multimorbidity hinders the comparison of results among studies, and the estimations on its prevalence and health impact.

In our study, ischemic heart disease and arrhythmias were the most prevalent HF comorbidities in men, and hypertension was the most frequent in women, as previously described.[1] The higher prevalence of COPD in men compared to women was probably due to the higher rates of smoking among Spanish men.[18] While the estimated prevalence of COPD in the general Spanish population is 15% in men and 6% in women,[19] these figures were almost doubled in our HF cohort, approaching the 25.6% described in the EAHFE-COPD Study on acute HF patients.[20] The higher COPD prevalence might be explained because a) both COPD and HF share similar symptoms; b) beta-blockers (indicated for HF) and bronchodilators (indicated for COPD) have an effect on both pathologies; and c) heart congestion alters pulmonary function tests, among others. In this regard, a study found that congestive heart failure is strongly associated with comorbidities that may lead to the misdiagnosis, and more specifically over-diagnosis of COPD in these patients.[21]

Comorbid depression, which was predominantly observed in women, presented a prevalence 2-3 times higher than that observed in the general population.[13] Its prevalence is consistent with that reported in the meta-analytic review by Rutledge et al,[22] where the mean prevalence of depression in HF patients was 21.5%. Depression has been associated to worse prognosis in patients with cardiovascular disease in terms of mortality, hospital admissions and functional status.[1] However, its role as a potential risk factor for the development of HF is less consistent; so far, this has only been proven in women and in older patients with systolic hypertension.[23] The greater prevalence of hypothyroidism observed in HF patients compared to that of the population aged ≥65 years from the same reference cohort (3.1% in men; 12.7% in women)[13] could be partially explained by the structural and hemodynamic secondary effects of the lack of thyroid hormones on the heart. The higher prevalence of hypothyroidism observed in women compared to men is congruent with the results from the Euro Heart Failure Survey II.[19]

The clinical composition of the multimorbidity patterns found in the study and their impact on mortality and hospitalization is discussed below. In general, the number and type of patterns obtained in men and women were very similar, although their prevalence, composition, and impact on health outcomes differed moderately.

Cardiovascular pattern

This pattern mainly included cardiac arrhythmia, cardiac valve disorders and hematologic disorders (e.g., anticoagulant therapy), as well as chronic renal failure and anemia. Kidney and heart diseases share common risk factors and they are interrelated through adaptive mechanisms. Moreover, chronic failure of both organs, volume overload, increased levels of cytokines, malabsorption syndrome, suppression of the bone marrow and anticoagulant therapy increase the frequency of anemia in HF patients.[24] The presence of these comorbidities in the cardiovascular but not in the coronary-ischemic pattern could imply a greater deterioration in HF patients suffering from the former pattern. In fact, patients presenting the cardiovascular pattern showed significantly higher risk of hospitalization and mortality in both sexes. The strong association of

this pattern with hospitalization could probably be due to the hemodynamic dysfunction produced by cardiac arrhythmias and anemia, which often leads to decompensation and subsequent hospitalization.[25]

Respiratory pattern

The absence of a specific respiratory pattern in men is remarkable, as is the absence of COPD in the rest of patterns, considering the acknowledged association between COPD and ischemic heart disease,[26] both related to HF, and the high prevalence of COPD particularly in men. Ahmad et al[27] found that COPD appeared in several clusters of patients with HF, especially in those with higher morbidity burden, which also clustered with ischemic heart disease, cerebrovascular disease, smoking and male sex. In our study, COPD did not come up as part of any pattern in men, suggesting a lack of discriminative power of this disease in terms of disease clustering in men with HF. Nevertheless, this pattern had the second-highest impact on both mortality and hospitalization in women.

Metabolic pattern

This pattern, which was the most prevalent in both sexes, included risk factors for the so-called metabolic syndrome. This pattern has been consistently identified across studies carried out in the general population, and in 18% of patients with HF, with no gender differences.[28] The fact that only two diseases had to be present to assign patients to the metabolic pattern could justify its higher prevalence. When this pattern was restricted to presenting three or more conditions, its prevalence decreased to 21.3% in women and 22.1% in men, which is closer to previously published prevalence rates. The absence of an association of this pattern with increased three-year mortality both in men and women is in line with existing literature, probably due to reverse epidemiology whereby HF patients with cardiovascular risk factors have better prognosis.[29]

Coronary-ischemic pattern

This pattern was, along with the metabolic pattern, one of the most consistent patterns from a clinical standpoint. The evolution from micro- and macro-vascular endothelial damage caused by arteriosclerosis to myocardial injury represents a pathophysiological continuum underlying this pattern. However, our study could not test this hypothesis since the medical history of HF patients was unknown. Previous studies have corroborated the late appearance of ischemic heart disease in women with diabetes and hypertension, whereas, in men, this condition appears earlier and in association to myocardial infarction and smoking.[30] The absence of association with three-year mortality may be explained by the effectiveness of beta-blockers, aldosterone antagonists and angiotensin-converting enzyme inhibitors on reducing the risk of sudden death and prolonging survival in patients with HF,[31] although this hypothesis needs further investigation based on longer follow-up periods.

Neurovascular pattern

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

Degenerative pattern

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

of venous disease, thrombophlebitis, osteoporosis and dermatitis in this pattern could be conditioned by the physical activity restrictions ofpatients with HF. This pattern was the only one associated to a decreased risk of three-year mortality in both men and women, maybe due to the lower clinical severity of the conditions conforming it, some of which are typical of older age.

Overall, our results reflect the importance of taking the complete constellation of diseases that surrounds HF into account in both the study and its clinical management. Comorbidities have been found to cluster similarly in both sexes; however, some relevant differences have emerged in the composition of the patterns and its impact on health outcomes. Although exploratory, these findings could give us important clues on which specific comorbidities or disease combinations should be given more attention in men and women with HF in order to better direct disease prevention and control strategies. Specifically, it seems that clinicians should pay particular attention to the appearance of neurovascular and other cardiovascular comorbidities in both men and women, and to respiratory diseases in the case of women, to try to minimize their impact on health outcomes.

Strengths and limitations of the study

The main strength of this study is that it represents a large-scale population including real primary and hospital care patients with a diagnosis of HF. Moreover, HF comorbidities were comprehensively studied by using an exhaustive list of chronic conditions, and not only the most prevalent or severe ones.

One of the main limitations of the study is the cross-sectional characterisation of the multimorbidity patterns that makes it impossible to understand the chronological relationship between the different risk factors and chronic diseases. Furthermore, this work is exploratory in its approach and methodology. The estimation of the effect of multimorbidity patterns on health outcomes did not consider the potential confounding role of socioeconomic factors or clinical parameters, like the ejection fraction, which were not available in the study cohort. Other variables such as lifestyle habits (e.g., smoking and drinking behaviours) were also unavailable,

and diagnoses were based on real data extracted from electronic health records that were not originally designed for research, thus leading to a potential over or under-reporting of specific diseases. In this regard, data in the EpiChron cohort undergoes continuous quality control check-ups that ensure its accuracy and reliability for research purposes.

Conclusion

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

Author Contributions

APT and FJRL were the Principal Investigators of the study. AGM, AGG, APT, and FJRL contributed to the design of the research. AGM and BPP performed the statistical analyses. APT, FJRL, AGG, and CCS interpreted and discussed the results. AGM and AGG prepared the first draft of the manuscript. ACL, MJD, and JIPC made important contributions to the revision of the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Clinical Research Ethics Committee of Aragón (CEICA, PI18/082).

Availability of data

The dataset generated and analysed during the current study is not publicly available, but is 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

Neurologic disorders, other	6.63 (6.10–7.16)	5.10 (4.55–5.64)	<0.001
Diverticular disease of colon	5.75 (5.25–6.24)	4.82 (4.29–5.35)	0.014
Other endocrine disorders	5.96 (5.46–6.47)	3.80 (3.32–4.28)	<0.001

95% confidence intervals are displayed within brackets. Only comorbidities with a mean prevalence equal to or greater than 5% are displayed.

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

†Acute myocardial infarction.

Table 2. Multimorbidity patterns identified in women with heart failure (n= 8488). Each pattern 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

*Acute myocardial infarction.

Table 3. Multimorbidity patterns identified in men with heart failure (n= 6182). Each pattern is 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

*Acute myocardial infarction.

Table 4. Prevalence of multimorbidity patterns identified in men (n= 6182) and women (n= 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

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

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

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.

[Attached as TIFF file]

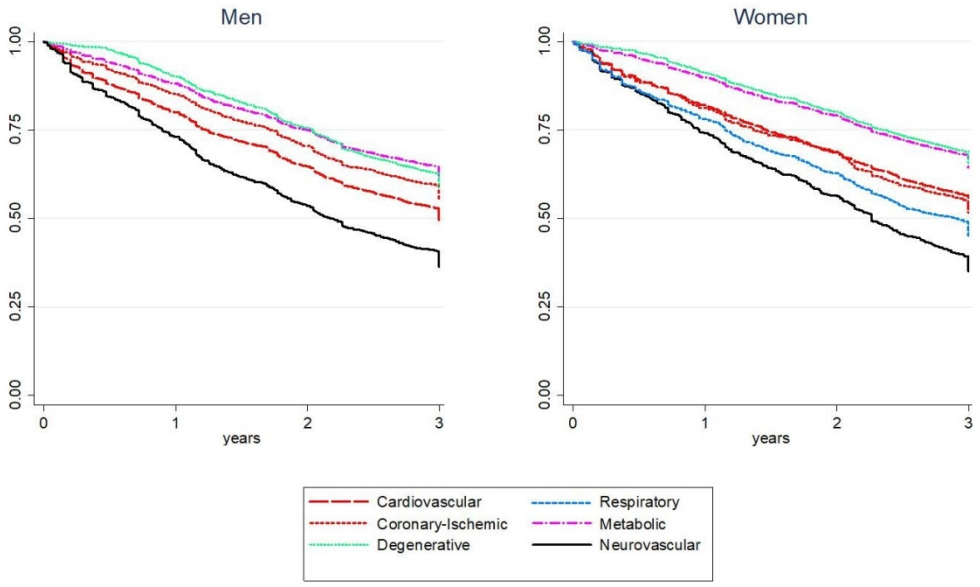

Figure 1. Kaplan-Meier survival curves in men (n= 6182) and women (n= 8488) with heart failure according to the presence of different patterns of multimorbidity.

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	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	
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	7-8
		(*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	
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.