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Multimorbidity in Heart Failure: Impact on Outcomes

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Abstract

OBJECTIVES—To investigate the impact of the number and type of comorbid conditions on death and hospitalizations among patients with incident heart failure (HF).

DESIGN—Population-based cohort study.

SETTING—Olmsted County, Minnesota.

PARTICIPANTS—Olmsted County, MN residents with incident HF from 2000–2010.

MEASUREMENTS—The prevalence of 16 chronic conditions obtained at HF diagnosis; further classified into 3 groups: cardiovascular (CV)-related, other physical and mental.

RESULTS—1,714 incident HF patients (mean±SD age 76±14, 56% female) were identified. The mean number of conditions per patient was 2.6 ± 1.5, 1.3 ± 1.1 and 0.30 ± 0.61 for CV-related, other physical and mental conditions, respectively. After a mean follow-up of 4.2 years, 1,073 deaths and 6,306 hospitalizations occurred. An increase of 1 other physical or mental condition was associated with a 14% (HR: 1.14; 95% CI: 1.08–1.20) and 31% (HR: 1.31; 95% CI:

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Study concept and design: Manemann, Roger.

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1.19–1.44) higher risk of death, respectively, and a 26% (HR: 1.26; 95% CI: 1.20–1.32) and 18% (HR: 1.18; 95% CI: 1.07–1.29) increased risk of hospitalization after adjustment for age, sex, ejection fraction, in- or outpatient status, and number of other conditions. In contrast, an increase of 1 CV-related condition was not associated with increased risk of death and was associated with a 10% (HR: 1.10; 95% CI: 1.06–1.15) increased risk of hospitalization.

CONCLUSION—CV-related conditions are the most common type of comorbid conditions among HF patients, however other physical and mental conditions are more strongly associated with death and hospitalizations. This underscores the impact of non-CV conditions on outcomes in HF.

Keywords

heart failure; epidemiology; population; multimorbidity; outcomes

INTRODUCTION

Multimorbidity, defined as the co-occurrence of 2 or more chronic conditions,¹ is a common condition in adults.¹ More than 1 in 4 adults in the US has multimorbidity^{2–4} and the prevalence increases with age, with nearly 3 of 4 adults over the age of 65 years having multiple chronic conditions.² Multimorbidity increases the risk of adverse outcomes such as declining functional status, hospitalizations and death.^{2, 5–9} Indeed, two-thirds of total health care spending is used to care for the 27% of Americans with multimorbidity.²

Multimorbidity is particularly burdensome in heart failure (HF), one of the most costly health care conditions in the US,¹⁰ with reports of between two-fifths and two-thirds of HF patients having 5 or more additional chronic conditions.^{11–14} The most common comorbid conditions in HF are cardiovascular (CV)-related,¹¹ however over half of hospitalizations¹⁵ and a large proportion of deaths among HF patients are due to non-CV causes.¹⁶ Furthermore, it was recently reported that some psychological conditions co-occur more frequently than expected in HF patients.¹¹ These findings raise the question of which set of comorbid conditions are most likely to adversely impact outcomes in HF. Therefore, we undertook this study to investigate, in a geographically-defined community, the impact of the number and types of co-morbid conditions (CV-related, other physical and mental) on death and hospitalizations in HF.

METHODS

Study Setting

This study was conducted in Olmsted County, Minnesota (2010 population: 144,243). Olmsted County has similar age, sex and ethnic characteristics as the state of Minnesota and the Upper Midwest region of the US.¹⁷ Furthermore, age- and sex-specific mortality rates are similar for Olmsted County, the state of Minnesota and the entire US.¹⁷

Our study utilized the resources of the Rochester Epidemiology Project (REP), a records-linkage system allowing nearly complete capture of health care utilization and outcomes in county residents.¹⁸ The retrieval of nearly all health care related events occurring in Olmsted

County is possible because this area is relatively isolated from other urban centers and only a few providers (mainly Mayo Clinic, Olmsted Medical Center, and their affiliated hospitals) deliver most health care to local residents.

Identification of the Incident Heart Failure Patients

Possible HF diagnoses among Olmsted County residents 21 years of age and older between 2000 and 2010 were identified using *International Classification of Diseases-9th Revision, Clinical Modification* (ICD-9-CM) code 428 assigned during either an outpatient visit or a hospitalization.^{15, 19} A random sample of 50% of HF diagnoses between 2000 and 2006 and 100% of potential HF cases from 2007 to 2010 were manually reviewed. HF diagnoses were validated by experienced nurse abstractors using the Framingham Criteria.²⁰ The event was classified as incident if after review of the entire medical record there was no history of prior HF.

Data Collection

The US Department of Health and Human Services (US-DHHS) recently identified 20 chronic conditions that are considered a public health priority,^{21, 22} and we selected these conditions as comorbidities in our cohort.^{11, 23} These conditions were ascertained electronically by retrieving ICD-9 codes from both inpatient and outpatient encounters at all providers indexed in the REP. Two occurrences of a code (either the same code or two different codes within the code set for a given disease) separated by more than 30 days and occurring within 5 years prior to the incident HF date were required for diagnosis. Since all patients had HF, this condition was not included. Very few individuals in our cohort had autism (N=0), hepatitis (N=9), and human immunodeficiency virus (HIV) (N=0), and thus, these were also not included, leaving 16 chronic conditions. The conditions were further classified into three comorbidity groups: CV-related, other physical and mental. The CV-related conditions included coronary artery disease (CAD), arrhythmia, stroke, hypertension, hyperlipidemia and diabetes. The other physical conditions included arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and cancer, whereas the mental conditions included depression, dementia, schizophrenia and substance abuse.

Ejection fraction (EF) was determined using values collected from any echocardiogram, angiogram, multigated acquisition scan, or sestamibi scan performed within ± 90 days of the incident HF diagnosis. When multiple values were available, the value closest to the HF date was used, and the average value was used when multiple values were measured on the same day. HF with preserved EF was defined as EF $\geq 50\%$, while HF with reduced EF was defined as EF $< 50\%$.²⁴

Outcomes Ascertainment

Participants were followed through 12/31/2013 for death from any cause and all-cause hospitalization. Deaths were obtained from inpatient and outpatient medical records, as well as death certificates received from Olmsted County and the state of Minnesota. All hospitalizations after HF diagnosis were retrieved from the REP which, as described previously, includes information on all hospital care delivered to Olmsted County residents

within the county. Inhospital transfers or transfers between Olmsted Medical Center and Mayo Clinic were counted as one hospitalization.

Statistical Analysis

Baseline characteristics are presented as frequencies (percent), mean (SD) or median (25th, 75th percentile). Cox proportional hazards regression was used to determine associations between each individual condition and the number of conditions within each comorbidity group with death and Andersen-Gill models were used for hospitalizations. There were a limited number of patients who had 5 or 6 physical conditions (n=8); thus they were grouped with those that had 4. Likewise, those who had 3 or 4 mental conditions (n=20) were grouped together with those who had 2. Multiple imputation methodology was used to account for the 20% with missing EF data. Five datasets were created, with missing values replaced by imputed values based on a model that incorporated various demographic and clinical variables. The latter model included variables previously recognized as predictors of missing EF in HF²⁵ and others identified in the present analysis. The results of these datasets were then combined using Rubin's rules.²⁶ All analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, NC). This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

RESULTS

Between 2000 and 2010 1,714 incident HF patients were identified (mean±SD age 76±14, 56% female; Table 1). Of these, 1,377 (80%) had an EF measurement within ±90 days of the incident HF date with 53% categorized as having preserved EF. The proportion of patients who were outpatients at the time of HF diagnosis was 32%. The overall mean number of conditions per patient was 4.2±2.3; the mean number of conditions by comorbidity group was 2.6±1.5, 1.3±1.1 and 0.30±0.6 for CV-related, other physical and mental conditions, respectively. Approximately 90% of patients had at least 1 CV-related comorbid condition, while 69% had at least 1 other physical condition and 27% had at least 1 mental condition. The most common comorbid condition was hypertension (74%), followed by hyperlipidemia (50%) and arrhythmias (50%).

After a mean follow-up of 4.2 years, 1,073 deaths and 6,306 hospitalizations occurred. Individual predictors of death included diabetes, COPD, CKD, cancer, dementia, schizophrenia and substance abuse (Figure 1). After adjustment for age, sex, EF, in- or outpatient status and the number of other physical and mental conditions, the risk of death per increase of 1 CV-related condition was not significantly associated with death (HR 1.03; 95% CI: 0.99–1.08; Table 2). After adjustment, the risk of death per increase in 1 other physical condition was 14% (HR 1.14; 95% CI: 1.08–1.20) and the risk per increase in 1 mental condition was 31% (HR 1.31; 95% CI: 1.19–1.44).

Individual predictors of hospitalizations within 1 year were arrhythmia, diabetes, arthritis, COPD, CKD, cancer and depression. The risk of hospitalization per increase of 1 CV-related condition was 10% (adjusted HR 1.10; 95% CI: 1.06–1.15; Table 2). The risk of hospitalization was 26% higher per increase of 1 other physical condition (adjusted HR 1.26; 95% CI: 1.20–1.32) and 18% higher per increase of 1 mental condition (adjusted HR

1.18; 95% CI: 1.07–1.29). Similar results were obtained when analysis were stratified by preserved and reduced EF.

In ancillary analyses we further examined the associations of CV-related conditions with outcomes. First, as there was a suggestion of nonlinearity in the association between the number of CV-related conditions and death, we repeated the analysis grouping 1 to 4 conditions together. The HRs (95% CI) for 1–4, 5 and 6 CV conditions were 1.15 (0.89–1.48), 1.20 (0.88–1.64), 1.85 (1.19–2.90), respectively. Second, we further categorized CV-related conditions into CV risk factors (hyperlipidemia, hypertension and diabetes) and CV diseases (CAD, arrhythmia and stroke). After adjustment for age, sex, EF, in- or outpatient status and the number of other conditions, the risk of death per increase of 1 CV risk factor was not significantly associated with death (HR 0.97; 95% CI: 0.91–1.04) and the risk of death per increase of 1 CV disease was 10% (HR 1.10; 95% CI: 1.02–1.18). After adjustment, the risk of hospitalization per increase of 1 CV risk factor was 8% (HR 1.08; 95% CI: 1.02–1.15) and for CV disease was 13% (HR 1.13; 95% CI: 1.06–1.22).

DISCUSSION

The present contemporary community-based findings indicate that, on average, patients with HF have 4 additional comorbid conditions. While the most common comorbidities are CV in nature, the burden of other physical or mental conditions is more strongly associated with death and hospitalizations, even after adjusting for important confounders including the number of CV-related conditions. Diabetes, COPD, CKD, cancer, dementia, schizophrenia and substance abuse were independent predictors of death, while arrhythmia, diabetes, arthritis, COPD, CKD, cancer and depression predicted hospitalizations. These results have important implications for clinical decision-making and for the management of older adults living with HF.

Multimorbidity and Outcomes

Previous studies have described the major burden of multimorbidity in HF.^{11–14} We previously reported in our validated cohort of HF patients that the majority of HF patients (86%) have 2 or more chronic conditions and that 42% have 5 or more conditions.¹¹ Studies using Medicare, National Health and Nutrition Examination Survey data and data from the Cardiovascular Research Network reported similar results with between 42–58% of HF patients reporting 5 or more conditions^{12–14} While it is known that comorbidities are prevalent in HF patients, less is known about how these conditions impact outcomes and whether the type of condition may play a role in prognosis.

A study of Medicare beneficiaries with HF found that a higher number of comorbidities was associated with mortality in both hospitalized and non-hospitalized patients, and also found that several non-cardiac conditions were associated with death.¹² Another study of Medicare beneficiaries reported that nearly 40% of patients with HF have 5 or more non-cardiac conditions.²⁷ The risk of hospitalization increased with the number of non-cardiac conditions. However, these studies are limited to patients enrolled in Medicare with no validation of heart failure diagnoses and no ejection fraction data.^{12, 27} Furthermore, these studies did not investigate the differential impact of CV-related and non-CV conditions. Our

current study extends these previous findings by studying in a community-based validated HF cohort with EF data, the impact of the types of comorbid conditions on death and hospitalizations. In addition, we separated non-CV conditions into other physical and mental conditions in order to investigate the specific effect of these types of conditions.

Interestingly, we found that an increase in the number of other physical and mental conditions was associated with an increased risk of death among HF patients, even after adjusting for age, sex, EF and the number of conditions in the other comorbidity groups. However, we did not observe an association with CV-related conditions. In ancillary analyses, we did see a modest increased risk of death for CV disease but not for CV risk factors. The independent predictors of death were predominantly non-CV conditions. An increase in each of the 3 comorbidity groups was associated with an increased risk of hospitalization; however the associations were strongest for other physical and mental conditions. The majority of individual predictors of hospitalization were also non-CV related. A recent review reported that many comorbidities increase morbidity and mortality similarly in patients with reduced and preserved EF.²⁸ In the present study herein, results were similar when analyses were stratified by preserved and reduced EF.

It is important to highlight that an increasing number of other physical and mental conditions was more strongly associated with an increased risk of death and hospitalization compared to CV-related conditions, even after adjusting for the number of CV-related conditions. Our results underscore that conditions that are unrelated to HF in pathophysiology or management negatively impact outcomes. Furthermore, comorbid conditions may also have a negative impact on management as indicated by a recent study in hypertensive patients.²⁹ In this study of uncontrolled hypertensive patients it was observed that the patients with more unrelated comorbid conditions were less likely to have their hypertension addressed at a primary care visit.²⁹ Patients with multimorbidity involving unrelated conditions indeed are more complex, highlighting the need to better understand the role of non-CV conditions in the management and outcomes in patients with HF.

Limitations, Strengths and Clinical Implications

Some limitations deserve mention. We recognize that additional ailments beyond those studied herein, including in particular geriatric conditions contribute to multimorbidity in HF patients. We focused on the selected chronic conditions considered a public health priority by the US-DHHS as these could be readily retrieved from the medical record. Second, the reliance on ICD-9-CM codes to identify the chronic conditions may have resulted in some errors in the capture of these conditions. However, we required 2 occurrences of a diagnostic code separated by more than 30 days to reduce false positive diagnoses. Our study has several strengths, including the rigorous validation of HF in a community cohort of in-and outpatients with the ability to categorize preserved and reduced EF. The linkage of medical records allowed for complete ascertainment of comorbidities from multiple sources of care. Furthermore, we categorized non-CV related conditions into other physical and mental allowing us to study the impact of these comorbidity groups separately.

Our results provide important evidence that mental and other physical conditions negatively impact outcomes, even more so than CV-related conditions. Thus, it is important to ‘think outside the heart’ and provide a holistic approach to caring for patients with HF. Indeed, as indicated in a recent AHA/ACC/HHS Clinical Practice Guideline for patients with cardiovascular disease and comorbid conditions, the presence of multiple conditions increases challenges for health care providers and patients and can affect patient safety if recommendations for one condition conflict with those of another condition.³⁰ The present data give support to the need to develop guidelines, recommendations and performance measures to specifically address issues pertinent to older adults living with HF and multimorbidity, which in turn could ultimately lead to improved patient-centered care for these complex patients.

CONCLUSION

While cardiovascular conditions are the most common types of comorbid conditions among HF patients, an increase in the number of other physical and mental conditions is more strongly associated with death and hospitalizations. Conditions associated with worse outcomes were predominately non-cardiovascular in nature. This underscores the need for multimorbidity to be effectively integrated into clinical care of older adults with HF.

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Figure 1.

Adjusted* hazard ratios (95% CI) for death and hospitalizations by individual conditions.

*Adjusted for age, sex, ejection fraction, in/outpatient status and all other variables in figure.

Table 1**Baseline Participant Characteristics**

	Overall (N=1714)
Age (years), mean (SD)	76.3 (13.6)
Female	963 (56.2)
EF 50% ^a	734 (53.3)
Outpatient	554 (32.3)
Number of comorbidities, mean (SD)	
Overall	4.2 (2.3)
Cardiovascular	2.6 (1.5)
Other physical	1.3 (1.1)
Mental	0.3 (0.6)
Cardiovascular-related	
Coronary artery disease	680 (39.7)
Arrhythmia	855 (49.9)
Stroke	218 (12.7)
Hypertension	1274 (74.3)
Hyperlipidemia	860 (50.2)
Diabetes	578 (33.7)
Other physical	
Arthritis	588 (34.3)
Osteoporosis	264 (15.4)
Asthma	141 (8.2)
COPD	334 (19.5)
Chronic Kidney Disease	296 (17.3)
Cancer	525 (30.6)
Mental	
Depression	332 (19.4)
Dementia	165 (9.6)
Schizophrenia	49 (2.9)
Substance Abuse	48 (2.8)

Results are presented as n (%) unless otherwise specified.

^a337 patients were missing ejection fraction.

COPD=chronic obstructive pulmonary disease; EF=ejection fraction; SD=standard deviation

Table 2

Hazard Ratios (95%CI)^a for Death and Hospitalizations for an Increase of 1 Condition in Each Comorbidity Group

	CV-related conditions	Other physical conditions	Mental conditions
Death	1.03 (0.99–1.08)	1.14 (1.08–1.20)	1.31 (1.19–1.44)
Hospitalizations	1.10 (1.06–1.15)	1.26 (1.20–1.32)	1.18 (1.07–1.29)

^a Adjusted for age, sex, ejection fraction, in- or outpatient at the time of HF, and the number of conditions in each of the other two comorbidity groups.

CI=confidence interval; CV=cardiovascular