THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2020, Vol. 75, No. 10, 1981–1988
doi:10.1093/gerona/glz285
Advance Access publication December 9, 2019

OXFORD

Research Article

Noncardiac-Related Morbidity, Mobility Limitation, and Outcomes in Older Adults With Heart Failure

Mayra Tisminetzky, MD, PhD,[1,2,3] Jerry H. Gurwitz, MD,[1,2,3] Dongjie Fan, MSPH,[4] Kristi Reynolds, MPH, PhD,[5] David H. Smith, PhD, RPh,[6] Hassan Fouayzi, MS, PhD,[1] Sue Hee Sung, MPH,[4] Robert Goldberg, PhD,[1,3] and Alan S. Go, MD[4,7,8,9,10,11]

[1]Meyers Primary Care Institute, A Joint Endeavor of University of Massachusetts Medical School, Reliant Medical Group, and Fallon Health, Worcester, Massachusetts. [2]Division of Geriatric Medicine, Department of Medicine and [3]Department of Population and Quantitative Health Sciences, University of Massachusetts Medical School, Worcester. [4]Division of Research, Kaiser Permanente Northern California, Oakland. [5]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena. [6]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon. [7]Department of Epidemiology, [8]Department of Biostatistics and [9]Department of Medicine, University of California, San Francisco. [10]Department of Medicine and [11]Department of Health Research and Policy, Stanford University, California.

*Address correspondence to: Mayra Tisminetzky, MD, PhD, Division of Geriatric Medicine, University of Massachusetts Medical School, 365 Plantation Street Office Suite 100, Worcester, MA 01605. E-mail: mayra.tisminetzky@umassmed.edu

Received: August 28, 2019; Editorial Decision Date: December 4, 2019

Decision Editor: Anne Newman, MD, MPHS

Abstract

Background: To examine the individual and combined associations of noncardiac-related conditions and mobility limitation with morbidity and mortality in adults with heart failure (HF).

Methods: We conducted a retrospective cohort study in a large, diverse group of adults with HF from five U.S. integrated healthcare delivery systems. We characterized patients with respect to the presence of noncardiac conditions (<3 vs ≥3) and/or mobility impairment (defined by the use/nonuse of a wheelchair, cane, or walker), categorizing them into four subgroups. Outcomes included all-cause death and hospitalizations for HF or any cause.

Results: Among 114,553 adults diagnosed with HF (mean age: 73 years old, 46% women), compared with <3 noncardiac conditions/no mobility limitation, adjusted hazard ratios (HR) for all-cause death among those with <3 noncardiac conditions/mobility limitation, ≥3 noncardiac conditions/no mobility limitation, ≥3 noncardiac conditions/mobility limitation (vs) were 1.40 (95% CI, 1.31–1.51), 1.72 (95% CI, 1.69–1.75), and 1.93 (95% CI, 1.85–2.01), respectively. We did not observe an increased risk of any-cause or HF-related hospitalization related to the presence of mobility limitation among those with a greater burden of noncardiac multimorbidity. Consistent findings regarding mortality were observed within groups defined according to age, gender, and HF type (preserved, reduced, mid-range ejection fraction), with the most prominent impact of mobility limitation in those <65 years of age.

Conclusions: There is an additive association of mobility limitation, beyond the burden of noncardiac multimorbidity, on mortality for patients with HF, and especially prominent in younger patients.

Keywords: Multimorbidity, Mobility impairment, Mortality

The burden of multiple chronic conditions, or multimorbidity, and mobility limitation are interrelated and each independently affects clinical outcomes in older patients with cardiovascular disease (1–10). Among patients with heart failure (HF), multimorbidity increases the risk of adverse outcomes, and it has been suggested that noncardiac-related conditions may have a greater impact than cardiac-related conditions (6). In addition, it has been reported that approximately one out of every two older adults has some degree of mobility limitation (6–8). Even though few studies have investigated the prognostic role of mobility limitation in patients with HF, the lit-

erature suggests that mobility limitation is an important risk factor for the development of adverse outcomes in this vulnerable population (6–8). Data on the interplay between multimorbidity, mobility limitation, and the risk of hospitalization and/or dying in older patients with HF are very sparse, however, and very few studies have examined these associations in this population in clinical settings (6–8). Gaining additional insight into these relationships may help guide care and inform clinical decision-making in the growing population of older adults with HF.

We examined the individual and combined associations of noncardiac conditions and mobility limitation on overall and HF-related hospital readmissions and all-cause mortality in a large community-based cohort of patients with HF identified through the Cardiovascular Research Network (11,12).

Method

Source Population

The study population was derived from five integrated healthcare delivery systems within the Cardiovascular Research Network, namely Kaiser Permanente Northern California, Kaiser Permanente Colorado, Kaiser Permanente Northwest, Kaiser Permanente Southern California, and the Fallon Health/Reliant Medical Group in Massachusetts. These healthcare systems provide care to an ethnically and socioeconomically diverse population across varying practice settings and geographically diverse areas. Each site also develops and maintains a Virtual Data Warehouse, which served as the primary data source for individual identification and characterization (11,12). The Virtual Data Warehouse is a distributed standardized data resource comprised of electronic data sets at each Cardiovascular Research Network site, populated with individually linked demographic, administrative, ambulatory pharmacy, outpatient laboratory test results, and healthcare utilization (ambulatory visits and network and non-network hospitalizations with diagnoses and procedures) data for members receiving care at participating sites (11,12).

Institutional review boards at participating sites have reviewed and approved this study and a waiver of consent has been obtained due to the nature of this observational retrospective study.

Study Sample

Persons aged ≥21 and older with diagnosed HF based on either having been hospitalized with a primary discharge diagnosis of HF and/or having ≥3 ambulatory visits coded for HF between January 1, 2005 and December 31, 2012 were included in this investigation. The following *International Classification of Diseases, Ninth Edition* (ICD-9) codes were used to identify patients with HF: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, and 428.9. Previous studies have shown a positive predictive value of >95% for admissions with a primary discharge diagnosis of HF based on these codes when compared against chart review using Framingham clinical criteria (11,12). For the outpatient HF definition, we required ≥3 ambulatory visits with associated HF diagnoses, with ≥1 of the visits being to a cardiologist to enhance specificity for having HF.

Assessment of Noncardiac-Related Conditions

The 18 chronic conditions that were included in our analysis were anemia, arthritis, asthma, atrial fibrillation, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, coronary heart disease, dementia, depression, diabetes mellitus, dyslipidemia, hearing impairment, hypertension, osteoporosis, thyroid disease, and ventricular tachycardia or fibrillation. All conditions were identified employing previously described methods and were included in the analysis based on their high prevalence or association with poor outcomes in the setting of HF (13–16) using data from inpatient, emergency and ambulatory diagnoses and procedures, dispensed prescription medications, and laboratory test results found in the Virtual Data Warehouse. These 18 conditions were further characterized into 5 cardiac (atrial fibrillation, coronary heart disease, dyslipidemia, hypertension, and ventricular tachycardia or fibrillation) or 13 noncardiac-related conditions (ie, all others). Mobility limitation was defined by Healthcare Common Procedure Coding System (HCPCS) codes related to the receipt of healthcare claims for canes, walkers, or wheelchairs. The receipt of any of these HCPCS codes at any time qualified the individual as having mobility impairment (9).

Consistent with the approach used by Manemann and colleagues (6,8), and using the median number of noncardiac conditions as a cut point, individuals with HF were stratified into four groups according to the presence of noncardiac-related conditions and mobility limitation as follows: <3 noncardiac-related conditions and no mobility limitation; <3 noncardiac-related conditions and mobility limitation; ≥3 noncardiac-related conditions and no mobility limitation; and ≥3 noncardiac-related conditions and mobility limitation.

Outcomes

Follow-up ascertainment of the outcomes of interest occurred from the index date through December 31, 2013. Patients were censored if they disenrolled from their health plan or reached the end of the study follow-up (median follow-up 1.8 years, interquartile range: 0.8; 3.1). Hospitalizations were identified from each site's Virtual Data Warehouse, and admissions for HF were based on a primary discharge diagnosis for HF using the same ICD-9 inclusion codes. Deaths were identified from hospital and billing claims databases, administrative health plan databases, state death certificate registries, and Social Security Administration files as available at each site. These approaches have yielded >97% vital status information in prior studies (14–16).

Statistical Analysis

Proportions for categorical variables, means (standard deviation) for normally distributed continuous variables, and medians (interquartile range) for continuous variables with a skewed distribution were used to describe the baseline characteristics of the study cohort. Chi-square tests for categorical variables and analysis of variance for continuous variables were used to test trends in various demographic and clinical characteristics across the four comparison groups. Life-table analyses were performed separately for the risk of dying or having a hospitalization (any-cause or HF-related), further stratified according to the four exposure groups specified above. The log-rank test was used to compare the significance of observed differences in the risk of developing any of the adverse outcomes among comparison groups. Cox proportional hazards regression was used to examine the association between noncardiac conditions/mobility limitation and the risk of dying or having a subsequent hospitalization (any-cause or HF-related). Models were initially performed unadjusted and then conducted controlling for age, gender, and race/ethnicity. Other covariates included cardiac-related conditions and the receipt of relevant cardiac medications

within 120 days before the index date based on dispensed outpatient prescriptions (Angiotensin-converting enzyme (ACE) inhibitors [ACEi], angiotensin II receptor blockers [ARB], ß-blockers, and statins). We also performed additional subgroup analyses stratified by HF type [HF with preserved ejection fraction (HFpEF); HF with reduced ejection fraction (HFrEF), and HF with mid-range ejection (HFmrEF)], by age group (<65, 65–74, 75–84, and ≥85 years), and by gender.

Results

Study Population

We identified 114,553 eligible adults with HF in whom left ventricular systolic function data were available, with mean age of 72.8 years old, 45.9% women, and 73.5% white (Table 1). Patients had a median number of noncardiac-related conditions of 3, with 53,022 patients having <3 noncardiac-related conditions and no mobility limitation; 1,447 patients who presented with <3 noncardiac-related conditions and mobility limitation; 56,292 who presented with ≥3 noncardiac-related conditions and no mobility limitation; and 3,792 who presented with ≥3 noncardiac-related conditions and mobility limitation at the time of study entry. With regard to type of HF, 31.8% had HFpEF, 21.3% had HFrEF, and 8.9% had HFmrEF.

The frequency distribution of the 13 noncardiac conditions examined according to the presence/absence of noncardiac-related conditions/mobility limitation are summarized in Table 1. The two most prevalent noncardiac-related conditions in those with <3 noncardiac conditions and no mobility limitation were chronic kidney disease and diabetes. For the other three groups, similar patterns were found, where the most prevalent noncardiac conditions were chronic kidney disease and arthritis.

Association Between Noncardiac-Related Conditions/Mobility Limitation and Clinical Outcomes

Overall, the highest risk of death was observed in individuals with ≥3 noncardiac conditions and mobility impairment (Table 2). Compared to patients with <3 noncardiac-related conditions and no mobility limitation, patients with greater noncardiac-related burden plus mobility limitation were at a significantly higher risk of death in unadjusted analyses. After adjustment for demographic characteristics, presence of cardiac-related conditions, HF-type, and use of cardiac medications, compared to persons with <3 noncardiac-related conditions and no mobility limitation, there remained a graded increased risk of death with greater noncardiac morbidity burden and mobility limitation: adjusted hazard ratio (HR) 1.40 (95% CI: 1.31–1.51) for those with <3 noncardiac-related conditions and mobility limitation, HR 1.72 (95% CI: 1.69–1.75) for those with ≥3 noncardiac-related conditions and no mobility limitation, and HR 1.93 (95% CI: 1.85–2.01) for those with ≥3 noncardiac-related conditions and mobility limitation (Table 2).

The risk of hospitalization for any cause was the highest, and followed similar trends, in individuals with ≥3 noncardiac conditions with and without mobility impairment (Table 2). Greater noncardiac morbidity burden and mobility impairment remained associated with a graded higher risk of any-cause hospitalization in adjusted analyses: adjusted HR 1.15 (95% CI: 1.08–1.22) for those with <3 noncardiac-related conditions and mobility limitation, HR 1.46 (95% CI: 1.44–1.48) for those with ≥3 noncardiac-related conditions and no mobility limitation, and HR 1.52 (95% CI: 1.47–1.58) for those with ≥3 noncardiac-related conditions and mobility

Table 1. Population Characteristics According to the Presence of Noncardiac-Related Conditions and Mobility Limitation

Characteristic	<3 noncardiac no mobility limitation *n* = 53,022	<3 noncardiac mobility limitation *n* = 1,447	≥3 noncardiac no mobility limitation *n* = 56,292	≥3 noncardiac mobility limitation *n* = 3,792
Age, mean, years	69.0	77.2	75.8	78.4
Age category, years %				
<65	35.4	14.1	15.9	10.4
65–74	26.4	20.1	24.6	20.3
75–84	26.1	38.4	36.7	39.0
85 and older	12.2	27.4	22.8	30.3
Men, %	61.5	48.7	48.3	39.1
White	71.0	68.9	76.2	68.4
Black	12.6	4.4	10.6	4.3
Asian	7.3	1.2	5.9	1.0
Noncardiac chronic condition, %				
Diabetes mellitus	25.0	27.4	55.1	54.8
CKD	28.3	35.0	70.8	71.9
Anemia	14.0	18.2	55.6	58.9
Arthritis	19.2	30.4	55.8	60.7
COPD	11.6	15.6	38.5	41.6
Asthma	6.5	3.5	23.3	18.7
Cancer	1.9	3.0	8.4	10.0
Chronic liver disease	1.4	0.9	4.6	3.4
Osteoporosis	4.1	7.6	20.3	26.5
Dementia	1.3	2.6	7.8	10.6
Depression	5.0	5.7	23.1	26.1
Hearing impairment	7.1	7.4	27.1	27.3
Stroke	1.8	2.3	8.1	7.7

Note: CHD = coronary heart disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

limitation, when compared with persons with <3 noncardiac-related conditions and no mobility limitation (Table 2).

The risk of an HF-related hospitalization was the highest and followed similar trends in individuals with ≥3 noncardiac conditions with and without mobility impairment (Table 2). In adjusted analyses, compared to persons with <3 noncardiac-related conditions and no mobility limitation, there were higher adjusted risks with greater noncardiac-related burden and mobility limitation: adjusted HR 1.09 (95% CI: 0.99–1.21) for those with <3 noncardiac-related conditions and mobility limitation, HR 1.46 (95% CI: 1.43–1.49) for those with ≥3 noncardiac-related conditions and no mobility limitation, and HR 1.42 (95% CI, 1.34–1.51) for those with ≥3 noncardiac-related conditions and mobility limitation (Table 2).

Association Between Noncardiac-Related Conditions/Mobility Limitation and Outcomes by Gender

In men, compared to those with <3 noncardiac-related conditions and no mobility limitation, adjusted HRs for all-cause mortality for persons with <3 noncardiac-related conditions and mobility limitation, ≥3 noncardiac-related conditions and no mobility limitation, or ≥3 noncardiac-related conditions and mobility limitation were 1.58 (95% CI: 1.43–1.75), 1.81 (95% CI: 1.76–1.86), and 2.26 (95% CI: 2.11–2.41), respectively (Table 3). In women, compared to persons with those with <3 noncardiac-related conditions and no mobility limitation, adjusted HRs were 1.24 (95% CI: 1.12–1.37) for those with <3 noncardiac-related conditions and mobility limitation, 1.60 (95% CI: 1.56–1.65) for those with ≥3 noncardiac-related conditions and no mobility limitation, and 1.69 (95% CI: 1.60–1.79) for those with ≥3 noncardiac-related conditions and mobility limitation, respectively (Table 3).

Similar trends were found in the multivariable adjusted associations of greater noncardiac conditions/mobility limitation with HF-specific and any-cause hospitalization among both men and women (Table 3).

Association Between Noncardiac-Related Conditions Burden/Mobility Limitation and Outcomes by Age

Across a wide age range, there was a consistent association between higher burden of noncardiac-related conditions/mobility limitation and worse clinical outcomes. However, the relative impact of noncardiac morbidity burden/mobility limitation on outcomes was greater in younger versus older patients (Table 4). For example, among individuals aged <65 years old, compared to patients with <3 noncardiac-related conditions and no mobility limitation, greater noncardiac morbidity burden/mobility limitation (<3 noncardiac-related conditions and mobility limitation, ≥3 noncardiac-related conditions and no mobility limitation, or ≥3 noncardiac-related conditions and mobility limitation) was associated with a notably higher risk of dying from any cause (adjusted HRs 2.21 [95% CI: 1.72–2.83], 2.23 [95% CI: 2.12–2.35], and 3.57 [95% CI: 3.05–4.16], respectively). These relative associations were less prominent in the oldest age group of persons ≥85 years (adjusted HRs 1.12 [95% CI: 1.00–1.26], 1.41 [95% CI: 1.36–1.46], and 1.44 [95% CI: 1.34–1.55], respectively); Table 4.

Similar trends were found in the multivariable associations of greater noncardiac-related conditions burden/mobility limitation with HF-specific and any cause hospitalizations, in which the strength of association was less prominent with older age (Table 4).

Association Between Noncardiac-Related Conditions/Mobility Limitation and Outcomes by Type of HF

For the outcome of all-cause mortality, among patients with confirmed HFpEF, compared to individuals with <3 noncardiac-related conditions and no mobility limitation, adjusted HRs for those with <3 noncardiac-related conditions and mobility limitation, ≥3 noncardiac-related conditions and no mobility limitation, or ≥3 noncardiac-related conditions and mobility limitation were 1.39 (95% CI: 1.22–1.58), 1.68 (95% CI: 1.63–1.74), and 2.11 (95% CI: 1.96–2.26), respectively. The direction and strength of association between higher noncardiac-related morbidity burden/mobility limitation and the risk of death were similar for patients with HFrEF or HFmrEF (Table 5).

Similar trends were observed for greater burden of noncardiac-related conditions/mobility limitation and the outcomes of HF-specific and any-cause hospitalization according to type of HF (Table 5).

Discussion

In this large, population-based study of adults with HF, we found an additive impact of mobility limitation, beyond the burden of

Table 2. Risk of Adverse Events in Patients Diagnosed with HF Between 2005 and 2012 According to the Presence of Noncardiac-Related Conditions and Mobility Limitation: Overall

<3 noncardiac conditions No mobility limitation	<3 noncardiac conditions Mobility limitation HR (95% CI)		≥3 noncardiac conditions No mobility limitation HR (95% CI)		≥3 noncardiac conditions Mobility limitation HR (95% CI)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
All-cause mortality						
Referent	1.99 (1.86; 2.14)	1.40 (1.31; 1.51)	2.00 (1.96; 2.03)	1.72 (1.69; 1.75)	2.75 (2.63; 2.86)	1.93 (1.85; 2.01)
Any-cause hospitalization						
Referent	1.25 (1.18; 1.33)	1.15 (1.08; 1.22)	1.58 (1.56; 1.60)	1.46 (1.44; 1.48)	1.70 (1.64; 1.77)	1.52 (1.47; 1.58)
HF-related hos pitalization						
Referent	1.22 (1.11; 1.35)	1.09 (0.99; 1.21)	1.60 (1.57; 1.64)	1.46 (1.43; 1.49)	1.63 (1.54; 1.73)	1.42 (1.34; 1.51)

Notes: Model covariates: age, gender, race/ethnicity, hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, ventricular tachycardia/fibrillation, ACE inhibitors, angiotensin II receptor blockers, ß-blockers, and statin. ACE = angiotensin-converting enzyme; HF = heart failure; HR = hazard ratios.

Table 3. Risk of Adverse Events in Patients Diagnosed With HF Between 2005 and 2012 According to the Presence of Noncardiac-Related Conditions and Mobility Limitation by Gender

	<3 Noncardiac No mobility limitation	<3 noncardiac conditions Mobility limitation HR (95% CI)		≥3 Noncardiac conditions No mobility limitation HR (95% CI)		≥3 Noncardiac conditions Mobility limitation HR (95% CI)	
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
All-cause mortality							
Men	Referent	2.22 (2.01; 2.45)	1.58 (1.43; 1.75)	2.18 (2.13; 2.23)	1.81 (1.76; 1.86)	3.26 (3.05; 3.47)	2.26 (2.11; 2.41)
Women		1.76 (1.60; 1.95)	1.24 (1.12; 1.37)	1.80 (1.75; 1.85)	1.60 (1.56; 1.65)	2.37 (2.24; 2.51)	1.69 (1.60; 1.79)
Any-cause hospitalization							
Men	Referent	1.34 (1.23; 1.46)	1.23 (1.13; 1.34)	1.60 (1.57; 1.63)	1.47 (1.44; 1.50)	1.85 (1.74; 1.96)	1.63 (1.54; 1.74)
Women		1.17 (1.07; 1.27)	1.08 (0.99; 1.18)	1.55 (1.52; 1.58)	1.45 (1.42; 1.48)	1.60 (1.52; 1.68)	1.46 (1.38; 1.53)
HF-related hospitalization							
Men	Referent	1.43 (1.25; 1.64)	1.30 (1.14; 1.49)	1.64 (1.60; 1.69)	1.49 (1.45; 1.54)	1.66 (1.51; 1.82)	1.43 (1.30; 1.58)
Women		1.03 (0.89; 1.19)	0.92 (0.80; 1.07)	1.55 (1.50; 1.60)	1.42 (1.38; 1.47)	1.57 (1.46; 1.70)	1.40 (1.30; 1.52)

Notes: Model covariates: Age, gender, race/ethnicity, hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, ventricular tachycardia/fibrillation, ACE inhibitors, angiotensin II receptor blockers, ß-blockers, and statin. ACE = angiotensin-converting enzyme; HF = heart failure; HR = hazard ratios.

noncardiac multimorbidity, on all-cause mortality in adults with HF. We did not observe an increased risk of any-cause or HF-related hospitalization in relation to the presence of mobility limitation among those with a greater burden of noncardiac multimorbidity. Consistent findings related to the presence of mobility limitation and adverse outcomes, namely an incremental increased risk for death and more attenuated association with hospitalization, were seen according to patient age, gender, and HF type (preserved, reduced, mid-range ejection fraction), with a more prominent relative impact of mobility limitation on outcomes in those aged <65 years old. These findings highlight the fact that the clinical implications of mobility limitation are not limited just to older adults with HF (9). Similar trends were found in men and women and among those with preserved, reduced, and mid-range ejection fraction.

Numerous studies have examined the individual and combined associations of noncardiac conditions and mobility limitation burden with clinical outcomes in older adults (8,9,17–20). The Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) included 3,500 individuals with HF (mean age 71 years; 70% men) and eight noncardiac conditions (17). The authors reported an increased risk of all-cause death and subsequent hospitalizations according to the presence of noncardiac conditions, particularly among individuals who presented with either chronic kidney disease and anemia who were at the greatest risk of death whereas those who presented with chronic obstructive pulmonary disease and anemia were at higher risk of hospitalization when compared with those without these conditions (17). Researchers from the ambulatory clinics in the Veterans Affairs system examined the association of 15 noncardiac comorbidities with hospitalization and death in individuals with HFpEF and HFrEF during up to 2 year follow-up (n = 9,442; mean age 70 years old, 95% men) (20). In contrast to our findings, that study reported an association between noncardiac comorbidity burden and increased risk for non-HF-related hospitalizations in individuals with HFpEF compared to those with HFrEF, while there was a similar association of noncardiac conditions and mortality in persons with HFpEF and HFrEF (20). Among >72,000 Medicare beneficiaries aged ≥65 and older hospitalized with an acute myocardial infarction, mobility limitation (defined by the use of canes, wheelchairs, or walkers) was associated with modestly higher adjusted odds of death during the first year postdischarge (adjusted odds ratio 1.14, 95% CI 1.09; 1.20) (9). In examining the combined effects of noncardiac conditions and mobility limitation on healthcare utilization and mortality among 2,692 adults (mean age 74 years, 54% men) with presumed incident HF, those with both multimorbidity (≥2 noncardiac conditions) and functional limitation (ie, mobility limitation and/or activities of daily living and/or instrumental activities of daily living) experienced the highest risk of death and excess healthcare utilization, whereas those with only functional limitation had similar rates of hospitalization and emergency department visits as those with only multimorbidity (8). Even though these studies were carried out in slightly different patient population and geographic settings than ours, and only one of the studies examined the combined effects of noncardiac conditions and mobility limitation on selected outcomes, together with our findings, these results highlight the importance of considering both noncardiac burden and mobility limitation when managing adults with any form of HF.

Our findings suggest an important relative impact of mobility limitation on the risk of adverse outcomes in those aged <65 years old. These findings are in contrast with the results of other studies that have examined the association between mobility limitation and clinical outcomes in patients with cardiovascular disease across

Table 4. Risk of Adverse Events in Patients Diagnosed with HF Between 2005 and 2012 According to the Presence of Noncardiac-Related Conditions and Mobility Limitation by Age Group

<3 Noncardiac conditions No mobility limitation		<3 Noncardiac conditions Mobility limitation HR (95% CI)		≥3 Noncardiac conditions No mobility limitation HR (95% CI)		≥3 Noncardiac conditions Mobility limitation HR (95% CI)	
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
All-cause mortality							
<65	Referent	2.27 (1.77; 2.91)	2.21 (1.72; 2.83)	2.25 (2.15; 2.36)	2.23 (2.12; 2.35)	3.61 (3.10; 4.21)	3.57 (3.05; 4.16)
65–74		1.57 (1.32; 1.87)	1.51 (1.27; 1.80)	1.77 (1.70; 1.84)	1.86 (1.79; 1.94)	2.46 (2.23; 2.71)	2.45 (2.21; 2.70)
75–84		1.48 (1.33; 1.65)	1.35 (1.21; 1.51)	1.57 (1.53; 1.62)	1.65 (1.60; 1.70)	1.95 (1.82; 2.08)	1.86 (1.73; 1.99)
≥85		1.19 (1.05; 1.33)	1.12 (1.00; 1.26)	1.32 (1.27; 1.37)	1.41 (1.36; 1.46)	1.47 (1.37; 1.58)	1.44 (1.34; 1.55)
Any-cause hospitalization							
<65	Referent	1.54 (1.31; 1.81)	1.49 (1.27; 1.75)	1.74 (1.69; 1.79)	1.64 (1.59; 1.69)	2.37 (2.12; 2.65)	2.23 (2.00; 2.49)
65–74		1.27 (1.11; 1.44)	1.27 (1.11; 1.44	1.54 (1.50; 1.58)	1.50 (1.46; 1.54)	1.88 (1.74; 2.04)	1.82 (1.68; 1.97)
75–84		1.09 (0.99; 1.20)	1.07 (0.97; 1.18)	1.42 (1.39; 1.45)	1.40 (1.37; 1.44)	1.40 (1.32; 1.49)	1.36 (1.28; 1.45)
≥85		0.89 (0.79; 1.02)	0.89 (0.79; 1.01)	1.26 (1.22; 1.31)	1.26 (1.22; 1.31)	1.21 (1.12; 1.31)	1.22 (1.13; 1.32)
HF-related hospitalization							
<65	Referent	1.06 (0.79; 1.43)	1.12 (0.83; 1.51)	1.71 (1.63; 1.79)	1.66 (1.58; 1.74)	1.96 (1.65; 2.32)	2.00 (1.68; 2.38)
65–74		1.27 (1.03; 1.56)	1.27 (1.03; 1.57	1.64 (1.57; 1.71)	1.60 (1.53; 1.67)	2.00 (1.78; 2.25)	1.99 (1.77; 2.24)
75–84		1.03 (0.88; 1.20)	1.01 (0.86; 1.18	1.38 (1.33; 1.43)	1.37 (1.32; 1.42)	1.30 (1.18; 1.43)	1.27 (1.16; 1.40)
≥85		0.94 (0.78; 1.14)	0.95 (0.78; 1.15)	1.21 (1.15; 1.27)	1.19 (1.13; 1.26)	1.00 (0.89; 1.13)	1.01 (0.89; 1.14)

Notes: Model covariates: Gender, race/ethnicity, hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, ventricular tachycardia/fibrillation, ACE inhibitors, angiotensin II receptor blockers, ß-blockers, and statin. ACE = angiotensin-converting enzyme; HF = heart failure.

different age groups. The "Pulmonary Edema and Stiffness of the Vascular System" study (21), examined whether increased cardiovascular stiffness was associated with disability in more than 400 middle-aged and older adults with HF. In this cohort of middle-aged and elderly men with HF, cardiovascular stiffness was associated with decreased mobility and increased the likelihood of overall disability; decreased mobility was shown to be an independent predictor of mortality in this vulnerable population (21). A sample of 100 adults with HF, 71 years and older, from the three communities of the Established Populations for Epidemiologic Studies of the Elderly were assessed for the impact of mobility impairment with the risk of all-cause hospitalizations. Mobility impairment was measured by standing balance, a timed 2.4 m walk, and a timed test of rising from a chair five times (22). Mobility impairment was significantly associated with the risk of being hospitalized over a 4 year follow-up period. An increased hospitalization risk was particularly found for older individuals who presented with other geriatric conditions including dementia, hip fracture, and decubitus ulcer (22).

Some potential explanations for our unexpected findings of a particularly marked impact of mobility in persons <65 years old in the present study might be due to the different approach that we used to define mobility limitation using HCPCS codes instead of more traditional measures of factors such as exercise capacity that require a formal evaluation of the patient. Another potential explanation is "survival bias." Patients in our 85 years and older group might be different from other older adults by virtue of having survived to this older age. Although we found that the associations of greater mobility impairment with death and hospitalization were strongest in individuals aged ≤65 years, the impact of mobility impairment at population-level is largest among older patients with HF since the prevalence of mobility impairment is highest in the oldest patients.

Study Strengths and Limitations

Our study had several strengths and limitations. A limitation of our study was the use of HCPCS codes to identify mobility limitation, which does not include direct observation of patients to assess mobility limitation but has been used and validated in different populations to characterize the association with adverse outcomes (eg, death after myocardial infarction, hospitalizations, functional decline, and drug-related side effects) (9,18,19). As mentioned before mobility limitation was defined based on the approach by Chrischilles and colleagues (9). These researchers developed patient function-related indicators, which were derived from claims records in a cohort of U.S. Medicare beneficiaries aged 65 years and older who were hospitalized with an acute myocardial infarction. One of the function-related indicators was labeled mobility limitation and it was defined by claims (HCPCS codes) for the use of a cane, walker, or a wheelchair. In their article, the investigators reported that persons with mobility limitation were at increased risk for dying over the subsequent 12 months (adjusted OR = 1.14 (95% CI 1.09; 1.20)) and were less likely to undergo a cardiac catheterization during the hospitalization (adjusted OR = 0.85 (95% CI 0.81; 0.89)) (9). These findings suggest that the mobility limitation indicator employed by Chrischilles and colleagues did predict an outcome (mortality) and health service utilization/clinical decision-making (receipt of a cardiac catheterization) consistent with what would be expected in relation to the functional status of older acute myocardial infarction patients. Other investigators have examined the association between mobility limitation (using the same indicator described by Chrischilles et al.), clinical decision-making, and clinical outcomes across a range of conditions

Table 5. Risk of Adverse Events in Patients Diagnosed with HF Between 2005 and 2012 According to the Presence of Noncardiac-Related Conditions and Mobility Limitation by HF-type

<3 noncardiac conditions No mobility limitation		<3 noncardiac conditions Mobility limitation HR (95% CI)		≥3 noncardiac conditions No mobility limitation HR (95% CI)		≥3 noncardiac conditions Mobility limitation HR (95% CI)	
		Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
All-cause mortality							
HFpEF	Referent	1.89 (1.66; 2.14)	1.39 (1.22; 1.58)	1.89 (1.83; 1.95)	1.68 (1.63; 1.74)	2.72 (2.54; 2.91)	2.11 (1.96; 2.26)
HFrEF		2.41 (2.12; 2.75)	1.55 (1.36; 1.77)	2.22 (2.14; 2.31)	1.75 (1.68; 1.82)	3.41 (2.12; 2.75)	2.01 (1.83; 2.21)
HFmrEF		2.18 (1.68; 2.84)	1.60 (1.23; 2.09)	2.09 (1.98; 2.21)	1.75 (1.65; 1.86)	3.57 (3.05; 4.16)	2.49 (2.12; 2.92)
Any cause hospitalization							
HFpEF	Referent	1.12 (1.01; 1.25)	1.06 (0.95; 1.17)	1.54 (1.51; 1.57)	1.47 (1.43; 1.50)	1.62 (1.53; 1.72)	1.52 (1.44; 1.62)
HFrEF		1.40 (1.25; 1.58)	1.25 (1.11; 1.41)	1.59 (1.54; 1.63)	1.43 (1.38; 1.47)	1.76 (1.62; 1.92)	1.50 (1.38; 1.64)
HFmrEF		1.31 (1.05; 1.64)	1.20 (0.95; 1.50)	1.58 (1.51; 1.65)	1.44 (1.38; 1.50)	2.02 (1.76; 2.33)	1.78 (1.54; 2.05)
HF-related hospitalization							
HFpEF	Referent	1.10 (0.92; 1.31)	0.98 (0.82; 1.16)	1.66 (1.61; 1.72)	1.50 (1.45; 1.55)	1.82 (1.67; 1.99)	1.57 (1.44; 1.72)
HFrEF		1.20 (1.01; 1.44)	1.05 (0.88; 1.26)	1.61 (1.54; 1.67)	1.41 (1.35; 1.48)	1.59 (1.41; 1.80)	1.33 (1.17; 1.51)
HFmrEF		1.37 (0.97; 1.92)	1.24 (0.88; 1.75)	1.77 (1.66; 1.89)	1.54 (1.44; 1.65)	1.90 (1.54; 2.36)	1.59 (1.28; 1.97)

Notes: Model covariates: age, gender, race, ethnicity, hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, ventricular tachycardia/fibrillation, ACE inhibitors, angiotensin II receptor blockers, ß-blockers, and statin. ACE = angiotensin-converting enzyme; HFpEF = HF with preserved ejection fraction; HFrEF = HF with reduced ejection fraction; HFmrEF = HF with mid-range ejection.

such as individuals with kidney cancer and those with colorectal cancer (23,24). Findings from these studies suggest that this approach to measure mobility limitation may help investigators using administrative claims data to better capture the complexity and improve the care of this vulnerable population of older adults. Although we did not individually adjudicate each patient's records to confirm the presence of clinical HF, prior studies in the Cardiovascular Research Network population have shown a high-positive predictive value for our diagnosis code-based algorithms to reliably identify patients with HF (20,25). We also studied a large population receiving care within healthcare delivery systems, but our findings may not be fully applicable to all adults with HF. However, given the breadth of geographic and sociodemographic diversity in our community-based populations, our findings are likely to be generalizable to the large fraction of patients with HF in the U.S. within "real-world" practice settings. Although we evaluated a wide range of comorbid conditions, detailed information about the duration, severity, or extent of the chronic conditions studied was unavailable. However, our approach to characterizing the burden of noncardiac conditions/mobility limitation in patients with HF may be readily applied as healthcare systems develop and implement novel informatics approaches at the point-of-care to assist in clinical decision-making (26).

Conclusions

Our findings underscore the importance of the association between noncardiac conditions and mobility limitation with adverse outcomes in patients with varying types of HF, middle-aged and older persons, and in men as well as women. The presence of noncardiac conditions and/or mobility limitation in patients with HF substantially increases the complexity of their care, as practitioners face the challenge of managing multiple conditions simultaneously that may increase therapy-associated side effects (1,25,27–29). With the aging of the U.S. population, the number of patients affected by HF will increase dramatically over the coming decades (30,31), especially those with a high burden of noncardiac-related conditions and mobility limitation, which will create greater demands on healthcare providers and the systems in which they work. Clinical trials of treatments for HF have usually excluded older adults with a high burden of noncardiac-related conditions, which has led to evidence gaps in how to optimally treat this complex, vulnerable population (28,29).

In summary, our findings suggest that there is an additive association of mobility limitation, beyond the burden of noncardiac multimorbidity, with survival in patients with HF and less so for any cause and HF-related hospitalization. Younger patients with HF appear to be at highest risk for adverse outcomes with concomitant mobility limitation in the presence or absence of a high burden of noncardiac-related morbidity burden.

Funding

The work was supported by R24 AG045050 and R33AG057806 from the National Institute on Aging, as well as RC1 HL099395 and U19 HL91179 from the National Heart, Lung, and Blood Institute. The National Institute on Aging and the NIH had no role in the preparation, review, or approval of the manuscript, or decision to submit the manuscript for publication.

Conflict of Interest

A.S.G. reports receiving grant funding through his institution (Kaiser Permanente Northern California Division of Research) from Novartis and GlaxoSmithKline, as well as from NHLBI, NIDDK, and NIA. D.H.S. reports

receiving grant funding through his institution (Center for Health Research, Kaiser Permanente Northwest) from Novartis to undertake an FDA mandated drug safety study. K.R. reports receiving grant funding through her institution (Department of Research and Evaluation, Kaiser Permanente Southern California) from Novartis; Amgen Inc., Merck & Co., and Novartis as well as from NHLBI, NIA, PCORI, and AHRQ. The other authors report no conflicts.

Authors' Contribution

Study concept and design: M.T., J.H.G., A.S.G.; Acquisition of data: J.H.G., K.R., D.H.S., A.S.G.; Analysis and interpretation of data: M.T., J.H.G., H.F., D.F., K.R., D.H.S., S.H.S., R.G., A.S.G.; Preparation of manuscript: M.T., J.H.G., A.S.G.; Critical revision of the manuscript: J.H.G., K.R., D.H.S., R.G., R.J.G.

Sponsor's Role:

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