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ORIGINAL RESEARCH

GERIATRIC CARDIOLOGY

Geriatric Vulnerabilities Among Adults With Heart Failure With Preserved Ejection Fraction

A Cross-Continent Evaluation

Parag Goyal, MD, MSc,[a] Omar Zainul, MD,[a] Yashika Sharma, PhD, RN,[b] Alexandra Reich, BA,[a] Princess Osma, BA,[a] Jennifer D. Lau, MPH,[a] Efthalia Massou, PhD,[c] Meghan Turchioe, PhD,[b] David Russell, PhD,[d] Ruth Masterson Creber, PhD, RN,[b] Christi Deaton, PhD[c]

ABSTRACT

BACKGROUND Heart failure with preserved ejection fraction (HFpEF) disproportionately affects older adults.

OBJECTIVES This study aimed to elucidate the prevalence and prognostic implications of geriatric vulnerabilities across multiple health domains in HFpEF.

METHODS We examined consecutive patients with HFpEF enrolled from the Weill Cornell Medicine (WCM) and the OPTIMISE HFpEF Programs. The primary exposure was the following: multimorbidity, polypharmacy, cognitive impairment, depressive symptoms, frailty, and limited mobility. The primary outcome was a 1-year composite of all-cause hospitalization and mortality. We conducted Cox proportional hazard models to examine associations of the primary outcome with each geriatric vulnerability and the number of impaired domains, adjusting for race and the Meta-Analysis Global Group in Chronic Heart Failure risk score.

RESULTS The WCM cohort included 188 patients with a median age of 76.3 years, the majority of which were NYHA functional class III HF (52.1%); the OPTIMISE cohort included 93 patients with a median age of 79.6 years, the majority of which were NYHA functional class II HF (62.0%). Nearly half of each cohort (42.6% WCM, 46.2% OPTIMISE) had geriatric vulnerabilities spanning all 3 health domains. In fully adjusted models, frailty (WCM: HR: 2.89, 95% CI: 1.65-5.09; OPTIMISE: HR: 2.89, 95% CI: 1.65-5.09) and an increasing number of impaired domains were associated with the primary outcome: with 3 impaired domains conferring a near 4-fold increase in risk (WCM: HR: 3.97, 95% CI: 1.49-10.5, $P = 0.007$]; OPTIMISE: HR: 3.74, 95% CI: 1.26-11.10, $P = 0.017$]).

CONCLUSIONS Geriatric vulnerabilities across multiple health domains commonly co-occur in adults with HFpEF and are associated with a worse prognosis. (JACC Adv. 2025;4:101602) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Program for the Care and Study of the Aging Heart, Department of Medicine, Weill Cornell Medicine, New York, New York, USA; [b]Columbia University School of Nursing, Columbia University Irving Medical Center, New York, New York, USA; [c]Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; and the [d]Department of Sociology, Appalachian State University, Boone, North Carolina, USA.

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ABBREVIATIONS AND ACRONYMS

CCI = Charlson Comorbidity Index

CFS = Clinical Frailty Scale

HF = heart failure

HFpEF = heart Failure with preserved ejection

KCCQ = Kansas City Cardiomyopathy Questionnaire

MoCA = Montreal Cognitive Assessment

PHQ = patient health questionnaire

WCM = Weill Cornell Medicine

Heart failure with preserved ejection fraction (HFpEF) disproportionately affects older adults. Due to the pathophysiologic link between HFpEF and aging processes, HFpEF is frequently described as a geriatric syndrome,[1-3] thus underscoring the importance of identifying and incorporating geriatric vulnerabilities in the routine care of adults with HFpEF. To guide such care, the American College of Cardiology Geriatric Cardiology Section outlined a domain management approach to caring for older adults with heart failure (HF) whereby enumerating 4 key domains to evaluate and consider among older adults with HF—the medical, mind and emotion, physical function, and social environment domains.[4] Studies to date have described the prevalence and impact of individual domains and subdomains. For example, multimorbidity and polypharmacy are nearly universal in HFpEF and have a strong link to prognosis; cognitive impairment and frailty affect up to 78% and 94% of patients with HFpEF, respectively, and contribute to disability, hospitalization, and death.[1]

Despite the known adverse effect of individual geriatric conditions on outcomes in HFpEF, no studies to our knowledge have concurrently evaluated multiple domains and/or examined their overlap. A comprehensive examination of these geriatric vulnerabilities across multiple domains could be important to advance efforts to recognize and integrate geriatric vulnerabilities into the routine management of patients with HFpEF. To address this gap in knowledge, we conducted a retrospective observational study of prospectively collected data from both the United States and the United Kingdom. From the United States, we examined consecutive patients seen in a dedicated HFpEF Program in New York City that applies the domain management approach to the evaluation and provision of routine clinical care;[5,6] and from the United Kingdom, we examined consecutive patients in the OPTIMISE-HFpEF Program, which enrolled and evaluated patients across multiple health domains as part of a research protocol.[7] By examining 2 unique sources of patient data from 2 different countries, we sought to generate insights about the value of comprehensive geriatric assessments in patients with HFpEF that could be generalizable across multiple settings.

METHODS

STUDY DESIGN. This was a retrospective observational study of prospectively collected data from the Weill Cornell Medicine (WCM) HFpEF Program in the United States and the OPTIMISE HFpEF Program in the United Kingdom.

SETTINGS. WCM HFpEF Program (United States). The WCM HFpEF Program was established in 2018 to provide dedicated ambulatory subspecialty care to adults with HFpEF. It is located on the Upper East Side of Manhattan in New York City, New York. Its mission is to provide subspecialty care by integrating cardiovascular and geriatric principles and using a domain management approach for the evaluation and management of patients (Supplemental Figure 1). As part of routine care in the HFpEF Program, patients get an evaluation for each of these domains during their first visit.

For the *medical domain*, the team members collect data on HF severity via the NYHA functional class, multimorbidity based on the Charlson comorbidity index (CCI) and record of other conditions, and polypharmacy based on a count of prescription medications abstracted from clinician notes. For the *mind and emotion domain*, they collect data on cognitive impairment via the Mini-Cog[8,9] and depressive symptoms via Patient Health Questionnaire-9 (PHQ-9).[10] For the *physical function domain*, they collect data on frailty via the Clinical Frailty Scale (CFS)[11] and mobility via the 5-m gait speed.[12] They additionally collect data on health-related quality of life based on the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12).[13]

OPTIMISE HFpEF Program (United Kingdom). The OPTIMISE HFpEF research program[7] recruited and followed patients with HFpEF between August 2018 through March 2022 primarily from primary care practices (86%) in the East of England and West Midlands areas of the United Kingdom. The key objective of this program was to characterize multiple domains of health across patients with HFpEF. These domains map to the domain management approach for providing care to patients with HF. Study team members conducted assessments at baseline, 6, and 12 months as part of a research protocol. For the *medical domain*, the study team collected data on HF severity via the NYHA functional class, multimorbidity based on the CCI and record of other conditions, and polypharmacy based on a count of prescription medications abstracted from clinician notes. For the *mind and emotion domain*, the study team collected data on cognitive impairment via the Montreal Cognitive Assessment (MoCA),[14] and depressive symptoms via the Hospital Anxiety and Depression Scale (HADS).[15] For the *physical function domain*, the study team collected data on frailty via

the CFS[16] and mobility via the 6-minute walk test.[17] In addition, the study team collected health-related quality of life data based on a 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ-23).[18]

STUDY POPULATION. We analyzed data from 188 consecutive patients with HFpEF seen between April 2018 and March 2022 at the WCM HFpEF Program and 93 patients with HFpEF from the OPTIMISE HFpEF Program recruited between August 2018 and November 2019. In the WCM HFpEF Program, HFpEF was defined according to the presence of clinical characteristics of HF based on physician assessment with a documented left ventricular ejection fraction of at least 50% on the most recent echocardiogram within 6 months of the encounter. In the OPTIMISE HFpEF Program, HFpEF was defined as signs and symptoms of HF with an ejection fraction 50% or greater on study echocardiogram and relevant structural heart disease and/or diastolic dysfunction consistent with HFpEF. For both cohorts, patients with hypertrophic cardiomyopathy and other causes of HF such as cardiac amyloidosis were excluded since these represent distinct phenotypes with different clinical and treatment implications. Of note, those from the WCM HFpEF Program appeared to have more advanced HF compared to those from the OPTIMISE HFpEF Program (**Table 1**).

This study was approved by the WCM Institutional Review Board, which waived informed consent since the data were part of a registry; and approved by a local ethics committee. The OPTIMISE HFpEF cohort study was approved by the London-Surrey Research Ethics Committee and is registered on ClinicalTrials.gov (NCT03617848).

TABLE 1 Baseline Characteristics Stratified by Cohorts

	Weill Cornell Medicine HFpEF Program N = 188	OPTIMISE HFpEF Program N = 93
Age, y	76.3 (70.1-83.1)	79.6 (74.6-84.1)
Female	126 (67.0%)	43 (46.2%)
White race	124 (66.0%)	90 (96.8%)
Systolic blood pressure, mm Hg	131 (120.0-147.2)	138.5 (123.7-157.6)
Creatinine, mg/dL	1.1 (0.8-1.4)	0.93 (0.76-1.25)
BMI, kg/m^2	30.8 (26.4-37.5)	31.1 (26.6-34.3)
NYHA functional class		
I	11 (5.9%)	16 (17.0%)
II	74 (39.4%)	58 (62.0%)
III	98 (52.1%)	19 (20.0%)
IV	5 (2.7%)	0 (0.0%)
Hypertension	149 (79.3%)	75 (81.5%)
Diabetes mellitus	76 (40.4%)	29 (31.5%)
Atrial fibrillation	85 (45.2%)	29 (32.0%)
Coronary artery disease	60 (31.9%)	23 (25.0%)
Cerebrovascular disease	24 (12.8%)	13 (14.0%)
COPD	40 (21.3%)	29 (31.5%)
Cancer	50 (26.6%)	13 (14.0%)
ACEI/ARB use	81 (43.1%)	57 (63.0%)
ARNI		
Anticoagulation use	83 (44.1%)	46 (51.0%)
Beta-blocker use	113 (60.1%)	44 (48.0%)
Loop diuretics use	136 (72.3%)	52 (57.0%)
Statins use	140 (74.5%)	53 (58.0%)
MAGGIC score	24 (19-29)	12 (8-21)
KCCQ		
Good to excellent	50 (26.6%)	47 (55.0%)
Fair to good	46 (24.5%)	24 (28.0%)
Poor to fair	64 (34.0%)	9 (10.5%)
Very poor to poor	28 (14.9%)	7 (7.0%)
1-y all-cause hospitalization	57 (30.3%)	24 (25.8%)
1-y all-cause mortality	15 (8.0%)	4 (4.3%)

Values are median (IQR) or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BMI = body mass index; COPD = chronic obstructive pulmonary disease; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; MAGGIC = Meta-Analysis Global Group in Chronic.

MULTIDOMAIN ASSESSMENTS

Supplemental Tables 1 and 2 summarizes the tools used for the assessment of each geriatric vulnerability from each cohort.

For the *medical domain*, we assessed multimorbidity in both cohorts using the age-adjusted CCI which has been validated in HF populations as an independent predictor of mortality and HF readmissions.[19,20] The CCI incorporates 19 chronic medical conditions and computes an age-adjusted weighted score from 1 to 6, with higher scores indicating a higher comorbidity disease burden. Multimorbidity was defined as CCI scores >4, according to the scoring system developed in the original CCI validation study.[21] Polypharmacy was defined in both cohorts as taking ≥10 medications which has been validated in multiple HF cohorts for prognostic value.[22,23]

For the *mind and emotions domain*, we assessed cognitive impairment using the Mini-Cog in the WCM HFpEF Program and the MoCA in the OPTIMISE HFpEF Program. The Mini-Cog is a screening tool for cognitive impairment that has demonstrated predictive value for HF readmissions and mortality in multiple HF cohorts.[24,25] The Mini-Cog is a 3-item composite measure including recall and clock drawing, scored on a 5-point scale (1 point for each correct word recalled and 2 points for correct clock drawing), and a score of ≤2 was used to define patients with cognitive impairment.[8] The MoCA is another validated cognitive impairment screening tool.[26,27] MoCA scores <26 were used to identify patients with a cognitive impairment.

We assessed depressive symptoms using the PHQ-9 in the WCM HFpEF Program, and the HADS in the OPTIMISE HFpEF Program. The PHQ-9 is a validated tool for depressive symptoms, with known associations with adverse outcomes in HFpEF.[28] The presence of depressive symptoms was defined by PHQ-9 scores ≥5 (mild to severe depressive symptoms). The HADS is another depression screening tool that has been validated among patients with HF.[29] HADS scores ≥8 were used to identify patients with depressive symptoms.

For the *physical function domain*, we assessed frailty in both cohorts using the CFS. The CFS is scored 1 to 9 based on a semiquantitative evaluation of the patient's symptoms, mobility, inactivity, exhaustion, and disability for basic activities of daily living and instrumental activities of daily living.[11] Frailty was classified as CFS scores ≥4. This cutoff has been validated with reported association with mortality and entrance into an institutional facility among older adults.[30] In addition, this cutoff has a prognostic impact specifically among adults with HFpEF.[16] We assessed limited mobility using the validated 5-m gait speed test[14,31] in the WCM HFpEF Program, and the validated 6-minute walking test[17] in the OPTIMISE Program. For the 5-m gait speed, gait speed ≥6 seconds was used to identify patients with limited mobility. This cutoff was selected based on its demonstrated predictive value for in-hospital mortality and morbidity among cardiac patients.[12] The 6-minute walking test has been widely used among patients with HF and multiple studies showing a prognostic role that a 6-minute walk distance <300 m is indicative of poor prognosis.[32] Therefore, patients who walked <300 m in 6 minutes were classified as having limited mobility.

PRIMARY OUTCOME. The primary outcome was a composite of all-cause hospitalization and all-cause mortality over a 1-year follow-up period after baseline administration of the comprehensive geriatric assessments. For the WCM HFpEF Program, the primary outcome was abstracted from the electronic health record. Of note, the electronic health record incorporates nearly all encounters within the health system and provides extensive access to health care encounters that occur outside of the institution.[5] For the OPTIMISE HFpEF Program, outcomes were collected during routine study visits at 6 months and 12 months, coupled with anonymized linkage through National Health Service Digital databases.

STATISTICAL ANALYSIS. We conducted parallel analyses for data obtained from the WCM HFpEF and OPTIMISE HFpEF cohorts. First, we calculated baseline characteristics using median (IQR) for continuous variables and count and proportions for categorical variables. Then, we created radar plots to examine the relationship between geriatric vulnerability profiles and select health measures. These health measures included quality of life via KCCQ Overall Summary Score (where higher scores indicate better quality of life), and HFpEF illness severity via NYHA functional class and the validated Meta-Analysis Global Group in Chronic (MAGGIC) HF prognostic score (where higher scores indicate worse prognosis). The MAGGIC prognostic risk score has been validated in HFpEF as a predictor of morbidity and mortality[33] and includes the following variables: age, gender, diabetes mellitus, chronic obstructive pulmonary disease, smoking status, body mass index, systolic blood pressure, creatinine, left ventricular ejection fraction, first HF diagnosis within the prior 18 months of baseline visit, NYHA functional class, and current beta-blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker usage. We obtained data for the MAGGIC score from chart review conducted at the time of the baseline assessment. We also created Venn-diagrams for each cohort to display the overlapping prevalence of impaired health domains (impairment of a health domain was defined as having at least one vulnerability present).

We estimated Kaplan-Meier curves with a log-rank test to examine crude differences in outcomes among those with and without each geriatric vulnerability after testing each vulnerability-outcome pair for proportional hazards assumption using Schoenfeld residuals. For the geriatric vulnerabilities that met the proportional hazards assumption, we conducted Cox proportional hazard models to examine the association between each vulnerability and the primary outcome (1-year composite of all-cause mortality or hospitalization) adjusting for the MAGGIC score and race. For the OPTIMISE HFpEF cohort, we adjusted the Cox proportional hazard models with only MAGGIC score because the cohort was predominately White adults (96.8%). Of note, there were no missing covariates. Since 5 different exposures were tested for each cohort, we used a Bonferroni adjustment, whereby we considered a $P < 0.01$ statistically significant.

We also estimated Kaplan-Meier curves with a log-rank test alongside Cox proportional hazard models to examine the association between the count (0-3) of impaired domains (medical, mind and emotions, physical function) as a continuous variable and the primary outcome, whereby a count of 0 to 1 impaired domains was the referent.

All analyses were conducted using R, version 4.3.1 (R Foundation for statistical Computing).

RESULTS

CLINICAL CHARACTERISTICS. WCM HFpEF Program. Of the 188 patients in the WCM HFpEF Program, the median age was 76.3 years, 67% were women, and 66.0% were White (Table 1). Most patients had NYHA functional class III HF (52.1%). The most common comorbid conditions were hypertension (79.3%), atrial fibrillation (45.2%), and diabetes mellitus (40.4%). The median MAGGIC score was 24 (IQR: 19-29), and the median KCCQ-12 overall summary score was 50 (IQR: 30.1-75). For self-reported health according to the KCCQ-12, 26.6% of patients scores were categorized as described their health as "good" to "excellent"; 24.5% were "fair" to "good"; 34.0% were "poor" to "fair"; and 14.9% were "very poor" to "poor." During the 1-year follow-up, 38.3% (95% CI: 31.3% to 45.7%) experienced the composite outcome; 30.3% of patients experienced an all-cause hospitalization, and 8.0% of patients died.

OPTIMISE HFpEF Program. Of the 93 patients in the OPTIMISE cohort, the median age was 79.6 years, 46.2% were women, and 96.8% were White (Table 1). Most patients had NYHA functional class II HF (62.0%). The most common comorbid conditions were hypertension (81.5%) and atrial fibrillation (32.0%). The median MAGGIC score was 12 (IQR: 8-21), and the median KCCQ-23 overall summary score was 77.5 (IQR: 58-91). For self-reported health according to the KCCQ-23, 55.0% of participant scores were categorized as "good" to "excellent"; 28.0% were "fair" to "good"; 10.5% were "poor" to "fair"; and 7.0% were "very poor" to "poor." During the 1-year follow-up, 26.9% (95% CI: 18.2%-37.1%) experienced the composite outcome—25.8% experienced an all-cause hospitalization and 4.3% of patients died.

PREVALENCE OF GERIATRIC VULNERABILITIES. Table 2 presents the prevalence of geriatric vulnerabilities stratified by the WCM HFpEF and OPTIMISE HFpEF cohorts. Within the *medical domain*, 84.6% of patients had multimorbidity burden according to the CCI and 51.6% of patients had polypharmacy in the WCM HFpEF cohort; 44.6% of participants had multimorbidity and 36.6% of patients had polypharmacy in the OPTIMISE HFpEF cohort. Among the *mind and emotion domain*, 45.7% of patients had mild to severe depression based on the PHQ-9 in the WCM HFpEF cohort, and 46.7% of participants had mild to moderate depressive symptoms based on the HADS in the OPTIMISE HFpEF cohort. Additionally, 18.1% of patients had cognitive impairment according to the Mini-Cog in the WCM HFpEF cohort, and 46.1% of participants had mild cognitive impairment according to the MoCA. Within the *physical function domain*, 57.4% of patients in the WCM HFpEF cohort had frailty and 51.1% of participants in the OPTIMISE HFpEF cohort had frailty according to the CFS; 67.6% of patients in the WCM HFpEF cohort had limited mobility based on the 5-m gait speed and 53.5% of participants in the OPTIMISE HFpEF cohort had limited mobility as detected by the 6-minute walking test.

TABLE 2 The Prevalence of Geriatric Condition Stratified by Cohorts

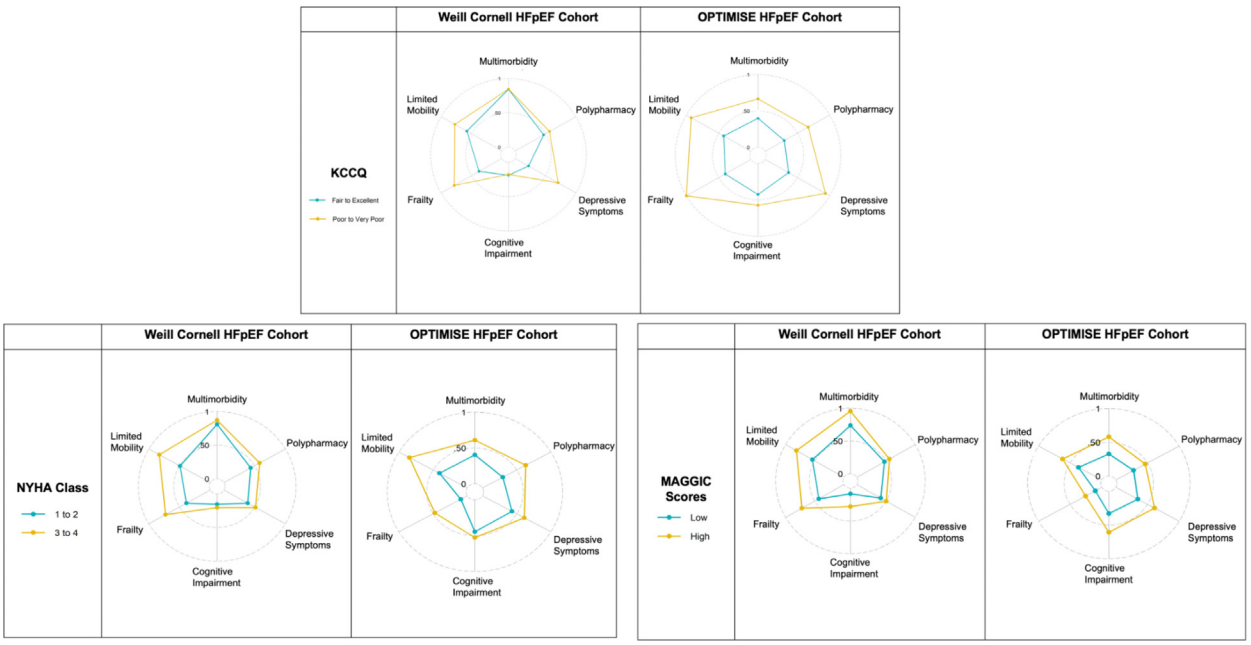
	Weill Cornell Medicine HFpEF Program (n = 188)	OPTIMISE HFpEF Program (n = 93)
Medical domain		
Multimorbidity (CCI >4)	159 (84.6%)	41 (44.6%)
Polypharmacy (≥10 medications)	97 (51.6%)	34 (36.6%)
Mind and emotion domain		
Mild to severe depressive symptoms	86 (45.7%)	42 (46.7%)
Cognitive impairment	34 (18.1%)	41 (46.1%)
Physical function domain		
Frailty	108 (57.4%)	47 (51.1%)
Limited mobility	117 (67.6%)	38 (53.5%)

Values are n (%). Missing values: Weill Cornell Medicine: Limited mobility: 15; OPTIMISE: Multimorbidity: 1, Depression: 3, Cognitive impairment: 4, Frailty: 1, Limited mobility: 25.
CCI = Charlson comorbidity index; other abbreviation as in Table 1.

As shown in Figure 1, patients in the WCM HFpEF cohort with poor to very poor self-reported health on the KCCQ had more severe polypharmacy, depressive symptoms, frailty, and limited mobility compared to those with fair to excellent self-reported health. This pattern was also observed for those with more severe HF compared to those with less severe HF based on the NYHA functional class and MAGGIC score. Participants in the OPTIMISE HFpEF cohort with poor to very poor self-reported health had more severe multimorbidity, polypharmacy, depressive symptoms, cognitive impairment, frailty, and limited mobility compared to those with fair to excellent self-reported health (Figure 1). This pattern was also observed for those with more severe HF compared to those with less severe HF based on NYHA functional class and MAGGIC score.

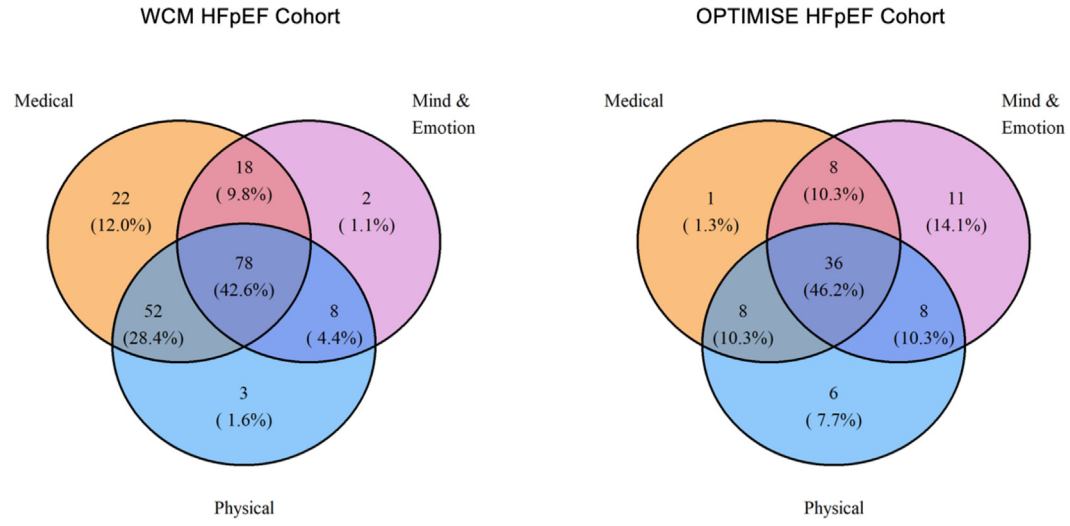
Figure 2 displays the degree of overlapping impairments across health domains for both cohorts. In the WCM HFpEF cohort, 42.6% of patients had geriatric vulnerabilities spanning all 3 health domains, 42.6% had vulnerabilities spanning 2 health domains, 14.7% had vulnerabilities spanning one health domain, and 2.7% had none. In the OPTIMISE HFpEF cohort, 46.2% of participants had geriatric

FIGURE 1 Radar Plots of Geriatric Conditions According to KCCQ-12 Quality of Life Scores, NYHA Functional Class, and MAGGIC Scores for WCM and OPTIMISE



HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; MAGGIC = Meta-Analysis Global Group in Chronic; WCM = Weill Cornell Medicine.

FIGURE 2 Overlapping Prevalence of Impairments in Health Domains Including Medical, Mind and Emotion, and Physical Function for WCM HFpEF and OPTIMISE HFpEF Cohorts



Abbreviations as in Figure 1.

TABLE 3 Associations of Geriatric Conditions With the Composite of All-Cause Mortality and Hospitalization

	Weill Cornell Medicine HFpEF Program						OPTIMISE HFpEF Program					
	Crude HR	95% CI	*P* Value	Adj. HR	95% CI	*P* Value	Crude HR	95% CI	*P* Value	Adj. HR	95% CI	*P* Value
Multimorbidity	3.66	1.34-10.0	0.012	3.43	1.18-9.91	0.023	1.45	0.66-3.19	0.351	1.49	0.65-3.44	0.345
Polypharmacy	2.15	1.32-3.52	0.002	2.08	1.27-3.41	0.004	0.92	0.42-2.08	0.84	0.9	0.39-2.10	0.805
Depressive symptoms	1.56	0.98-2.48	0.06	1.61	1.01-2.56	0.045	1.31	0.59-2.91	0.51	1.32	0.57	0.516
Frailty	3.00	1.74-5.17	<0.001	2.89	1.65-5.09	<0.001	4.63	1.73-12.36	0.002	5.31	1.92-14.71	0.001
Limited mobility	2.51	1.34-4.70	0.004	2.41	1.24-4.67	0.009	3.68	1.17-11.50	0.025	4.03	1.23-13.21	0.022

For Weill Cornell Medicine HFpEF Program, models are adjusted for MAGGIC heart failure score and race. For OPTIMISE HFpEF Program, models are adjusted only for MAGGIC heart failure score because the cohort was predominately White adults (96.8%).

Abbreviation as in Table 1.

vulnerabilities spanning all 3 health domains, 30.9% had vulnerabilities spanning 2 health domains, 23.1% had vulnerabilities spanning one health domain, and 16.1% of patients had none.

ASSOCIATION OF VULNERABILITIES WITH OUTCOMES. Table 3 presents the results of Cox proportional hazard models examining the association between each vulnerability and the primary outcome for each cohort. For those in the WCM HFpEF cohort, polypharmacy (HR: 2.08, 95% CI: 1.27-3.41, $P = 0.004$), frailty (HR: 2.89, 95% CI: 1.65-5.09, $P < 0.001$), and limited mobility (HR: 2.41, 95% CI: 1.24-4.67, $P = 0.009$) were each associated with the primary composite outcome of all-cause hospitalization or mortality in a fully adjusted model. For those in the OPTIMISE HFpEF cohort, only frailty (HR: 5.31, 95% CI: 1.92-14.71, $P = 0.001$) was associated with the primary outcome in a fully adjusted model. Of note, we did not conduct a Cox proportional hazards model for cognition for either cohort because the hazards were not constant over time and intersected in the middle of the study period, violating the proportional hazards assumption. Supplemental Figures 2 to 7 show Kaplan-Meier curves for the primary outcome for each geriatric vulnerability within each cohort.

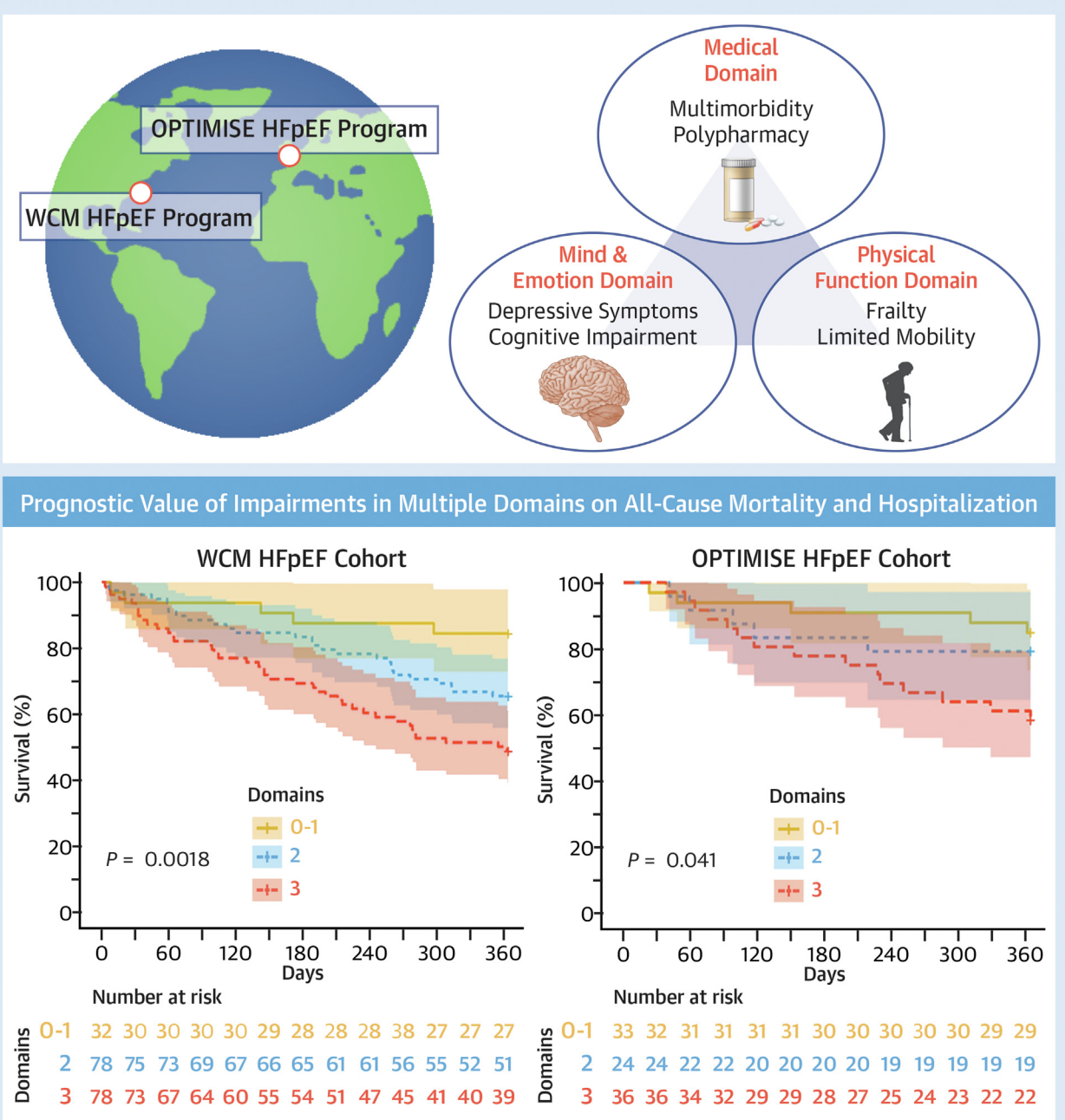
The **Central Illustration** presents Kaplan-Meier curves for the primary outcome based on the number of impaired health domains. With a higher number of impaired domains, patients experienced the primary outcome increasingly frequently. **Figure 3** shows a forest plot indicating the associations between the number of impaired health domains and the primary outcome for each cohort. In a fully adjusted Cox proportional hazard model, impairments in 3 health domains were strongly associated with the primary outcome, conferring a nearly 4-fold increase in risk of all-cause hospitalization or mortality compared to 0 to 1 impaired domains in both cohorts. (WCM HFPEF: HR: 3.97, 95% CI: 1.49-10.5, $P = 0.006$]; OPTIMISE HFpEF: HR: 3.74, 95% CI: 1.26-11.10, $P = 0.017$]).

DISCUSSION

There are several key insights from this study of ambulatory patients with HFpEF recruited from 2 different settings (primary care and cardiology) on 2 continents (the United States and the United Kingdom). First, the prevalence of geriatric vulnerabilities across both cohorts is high and impairments in multiple health domains often co-occur. Second, among individual vulnerabilities, only frailty was independently associated with 1-year adverse outcomes across both cohorts. Third, an increasing number of impaired health domains was incrementally associated with worse outcomes. Taken together, our findings highlight the importance of comprehensive geriatric assessments in the evaluation and management of patients with HFpEF.

Geriatric vulnerabilities are common in HFpEF, because HFpEF is a multi-organ syndrome whose pathophysiology is closely intertwined with aging.[1,34] Many physiologic changes that occur with aging are implicated in the pathogenesis of HFpEF, as well as in the pathogenesis of geriatric vulnerabilities like multimorbidity, frailty, and cognitive impairment.[1,35] Of note, our study examined geriatric vulnerabilities in 2 distinct settings on 2 different continents—the WCM HFpEF Program is a subspecialty HFpEF clinical program in the United States; and the OPTIMISE HFpEF Program is a research program that enrolled participants from primary care practices in the United Kingdom. Relatedly, those from the WCM HFpEF cohort had a higher prevalence of multimorbidity and polypharmacy, more severe HF (based on NYHA functional class and KCCQ score), and overall worse prognosis (based on MAGGIC score) compared to those from the OPTIMISE HFpEF cohort. Yet, the prevalence of geriatric vulnerabilities including

CENTRAL ILLUSTRATION **A Multicontinental Evaluation of Geriatric Vulnerabilities in HFpEF**



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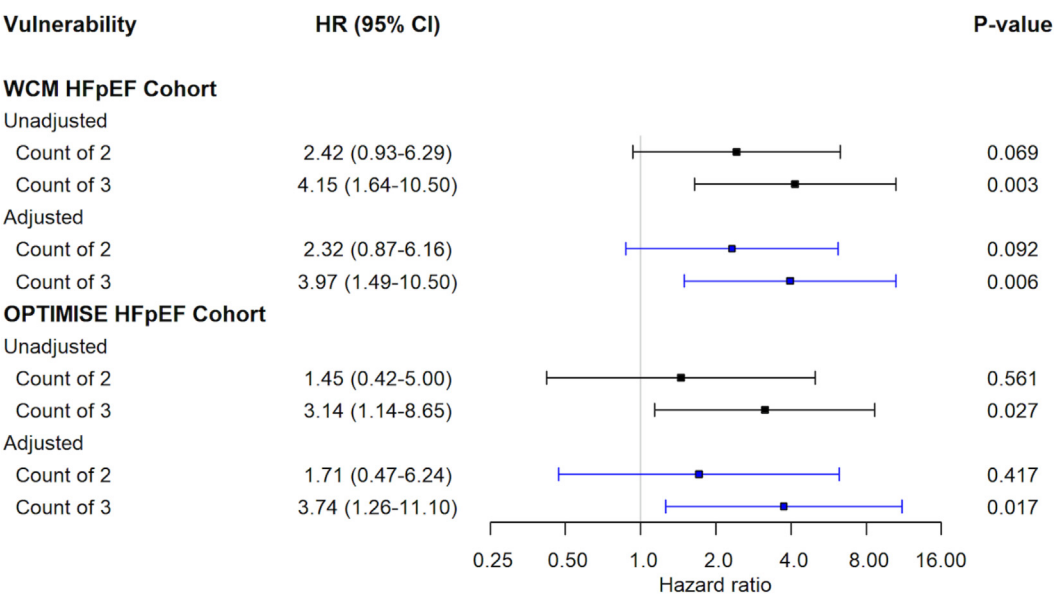
Abbreviations as in **Figure 1**.

FIGURE 3 Association of Number of Impaired Health Domains With the Composite Outcome of All-Cause Mortality or Hospitalization in WCM HFpEF and OPTIMISE HFpEF Cohorts (Reference Category = 0-1 Vulnerabilities)



Abbreviations as in Figure 1.

depressive symptoms, frailty, and limited mobility each affected nearly half of the patients in both cohorts. We also found that nearly half of each cohort had concurrent impairments in the medical, mind and emotion, and physical function domains.

To our knowledge, this is the first study to examine the degree of overlap of impairments across multiple domains of health mapping back to the American College of Cardiology's domain management approach to caring for older adults with HF.[4] This finding is important because it means that when one vulnerability is present, other vulnerabilities may also be present. Shared biological pathways such as inflammation and senescence, among other key hallmarks of aging, may explain this finding at least in part.[1,35] This lends further support to leveraging geroscience to concurrently target multiple impairments for improving outcomes in HFpEF. Exercise has emerged as a gerotherapeutic strategy that can address multiple hallmarks of aging, and relatedly could improve multiple geriatric vulnerabilities.[35] However, further data are needed to identify the best modes of safe and effective exercise-based interventions; and whether outcomes would be improved with multidimensional interventions such as those that also incorporate health coaching, which is an emerging approach to improving chronic disease management.[36]

Among individual geriatric vulnerabilities, only frailty was associated with 1-year outcomes in both cohorts (driven by all-cause hospitalizations). This was observed even after accounting for comorbidity burden and HF severity, suggesting that frailty provides important prognostic information beyond illness severity. We found this association in 2 different cohorts recruited from very different patient populations across 2 different continents. Of note, OPTIMISE HFpEF included a substantial proportion of patients with NYHA functional class II and a relatively low comorbidity burden who were primarily referred from primary care practices. While frailty is well-known to geriatricians and is becoming increasingly familiar to cardiologists and HF specialists,[37] other disciplines that routinely care for patients with HFpEF (such as general internists, which take care of a significant number of patients with HFpEF in the United States and the United Kingdom among other countries) should similarly become familiar with how to measure and incorporate frailty into the management of patients with HFpEF.

In addition to examining individual geriatric vulnerabilities, we also examined the prognostic impact of the accumulation of geriatric vulnerabilities across multiple health domains and found that prognosis was incrementally worse with an increasing number of affected health domains. While this finding is relatively intuitive and aligned with calls by expert groups such the American College of Cardiology to conduct comprehensive geriatric assessments on adults with HFpEF,[4] it is still not part of the standard of care. Impairments in multiple health domains are necessary to understand prognosis, which should be communicated to patients and incorporated into clinical decision-making. Identifying impairments in multiple health domains is also important because they should prompt clinical strategies to mitigate the negative effects of these impairments. Indeed, conditions like depression and frailty may be modifiable. When not modifiable, they at least merit accommodative strategies—for example, as recently outlined in a scientific statement put forth by the Heart Failure Society of America, some important accommodations to consider when cognitive impairment is present include activation of the social circle, tailoring education, and use of alternative care delivery models such as telehealth or home visits.[38] Taken together, our findings support the clinical relevance of multidomain health assessments (previously described as the Domain Management Approach) for older adults with HFpEF. Future research should focus on examining whether routine implementation of multidomain health assessments can improve clinical outcomes in patients with HFpEF.

There are several strengths to this study, most notably including the comprehensive health assessments collected in 2 distinct settings on 2 different continents. Although this study only represented 2 specific geographic locations, findings were largely concordant suggesting that these findings may be generalizable across countries. There are also several study limitations worth noting. The sample size limited conducting additional analyses such as those related to select subgroups. In addition, health domain assessment tools used were not the same for both cohorts, impacting the ability to combine data. Of note, both cohorts used validated assessment tools, and there were comparable prevalence for several domains between the cohorts, with the exception of cognitive impairment where prevalence differed due to differences in the sensitivity and specificity of the MoCA and Mini-Cog.[38] In addition, our results are vulnerable to limitations inherent to chart review. This includes the possibility of inaccurate or missing documentation related to clinical characteristics and/or outcomes. Of note, both institutions studied here have robust electronic medical record systems that link to multiple other hospitals within the local region and across the country, which mitigates this concern.

CONCLUSIONS

Our study across 2 continents found that nearly half of real-world older adults with HFpEF experience impairments in 3 different health domains. Moreover, we found that an increasing number of impaired health domains was incrementally associated with worse outcomes—impairment of 3 domains was associated with a 4-fold increase in risk for all-cause hospitalization and all-cause mortality. These results support the value of comprehensive geriatric multidomain assessments, though additional studies are needed to better understand whether such assessments can ultimately lead to improved outcomes.

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ADDRESS FOR CORRESPONDENCE: Dr Parag Goyal, Department of Medicine, Weill Cornell Medicine, 420 East 70th Street, New York, New York 10021, USA. E-mail: pag9051@med.cornell.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Geriatric conditions are common and frequently co-occur in adults with HFpEF. The prognostic risk increases incrementally as patients aggregate geriatric vulnerabilities.

TRANSLATIONAL OUTLOOK: Large-scale studies are needed to identify if other geriatric conditions (eg, delirium, falls, social isolation) affect the prognosis of patients with HFpEF. There is a pressing need for future research to determine if geriatric conditions are modifiable that can improve outcomes in adults with HFpEF.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.