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Variable Contribution of Heart Failure to Quality of Life in Ambulatory Heart Failure With Reduced, Better, or Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES The relative contribution of heart failure (HF) compared with other medical and nonmedical factors on diminished quality of life (QOL) across subtypes with reduced, better, and preserved left ventricular ejection fraction (LVEF) in a large ambulatory HF population was evaluated.

BACKGROUND Dominant factors influencing limited QOL in patients with HF have not been investigated.

METHODS Before routine HF clinic visits, 726 patients with ambulatory HF (mean age 56 ± 15 years, 37% women) completed a 1-page questionnaire that assessed QOL and relative contributions of HF compared with other medical and nonmedical factors to their QOL limitations. Visual analogue scales were used to assess overall QOL, breathing, and energy level. Results were compared across reduced (57%), preserved (16%) and better (improvement in LVEF ≥50%) (19%) subtypes.

RESULTS Just under one-half of patients (48%) rated QOL as limited dominantly by HF, 19% rated HF and medical problems as equally limiting, 18% cited medical problems as dominant, and 15% cited nonmedical factors. Patients with HF with better LVEF had the highest overall QOL score and less dyspnea burden than those with HF with preserved EF. Independent correlates of HF-dominated diminished QOL were prior cardiac surgery, worse New York Heart Association functional class, renin-angiotensin-aldosterone antagonism, use of diuretic agents, lower body mass index, lower LVEF, and lack of arthritis or history of cancer.

CONCLUSIONS Fewer than one-half of patients with ambulatory HF rated HF as the greatest limitation to their QOL, suggesting that this important outcome will be difficult to affect by HF-targeted therapies alone, particularly in those with higher LVEFs and comorbidities. Patients with HF with better LVEF represent a distinct subtype with better overall QOL. (J Am Coll Cardiol HF 2016;4:184–93) © 2016 by the American College of Cardiology Foundation.

The increasing prevalence and evolving profile of chronic heart failure (HF) have increased awareness of the importance of incorporating patient-centered outcomes, including quality of life (QOL), in routine ambulatory care (1). Patients with HF and related conditions predisposing to HF, including myocardial infarction, diabetes, and obesity, are living longer in the setting of more advanced therapies and interventions and frequently rate improved QOL as more important than longer survival (2). HF has a significant negative impact on all aspects of health-related QOL, particularly those related to physical functioning, mental health, and social domains (3–5). Even compared with other serious cardiac or noncardiac chronic conditions, impairment in QOL is greatest in patients with HF,

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determined largely by New York Heart Association (NYHA) functional class (5,6). Reduced QOL has been consistently associated with worse prognosis in patients with HF, predictive of both rehospitalization and mortality (7–10).

Although many current HF therapies have had a positive impact on QOL, major limitations in QOL often persist in patients with HF (11). The degree of QOL limitation has been shown to be similar across HF populations with preserved or reduced left ventricular ejection fraction (LVEF) (4,12). However, in the contemporary complex and aging HF population, with patients often carrying significant burdens of associated cardiac and noncardiac comorbid conditions (13,14), multiple factors beyond HF may influence patients' perceptions of their QOL. Despite this, little is known about the relative contributions of other medical comorbidities and even nonmedical factors on QOL impairment in patients with HF. Meanwhile, the success of current medical and device therapies has created a new HF population distinct from those with HF with reduced LVEF (HFrEF) and HF with preserved LVEF (HFpEF), composed of patients with previously reduced but now improved LVEFs to ≥50%, or HF with better LVEF (HFbetterEF) (15,16). Although frequently misclassified as having HFpEF, these patients are both clinically and biochemically distinct, with a lower comorbidity profile, milder HF symptom burden, and lower event rate than patients with either HFpEF or HFrEF (15,16).

We hypothesized that given the heterogeneity in functional status across HF subtypes, heterogeneity may also arise in patients' perceived dominant limitations to their QOL; patients with HF may be equally or predominantly limited in their QOL by superimposed disease or even independent factors. Accordingly, the principal aim of the present study was to determine the contribution of HF compared with medical and nonmedical factors to patients' perceived dominant limitations to their overall health-related QOL and its clinical correlates in a large, ambulatory HF population including patients with HFrEF, those with HFpEF, and those with HFbetterEF. Second, patient-perceived severity of dyspnea and fatigue and overall QOL rating were investigated within these HF-dominant or not QOL subgroups and additionally according to distinct LVEF HF subtype.

METHODS

PATIENT POPULATION AND PROTOCOL. All patients seen in the ambulatory HF clinic at Brigham and Women's Hospital were encouraged to complete a questionnaire assessing their QOL as part of a quality improvement intervention. Participants were given a self-administered 1-page questionnaire (Online Appendix) prior to the visit that assessed their overall QOL, functional status, and degree to which their HF, as well as other conditions, affected their QOL. Data provided by the questionnaire were then used by clinicians to facilitate the clinic encounter. Patients younger than 18 years of age, recipients of ventricular assist devices, those with non-HF-related terminal conditions such as stage IV cancer, and those returning incomplete questionnaires were excluded from the present analysis.

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Retrospective chart review was performed to collect patient demographics and clinical characteristics, including HF etiology and medical comorbidities. HFpEF was defined as LVEF ≥50% in the absence of a history of left ventricular (LV) systolic dysfunction or dilated cardiomyopathy. HFrEF was defined as persistent LVEF <50% in association with an ischemic or nonischemic cardiomyopathy. HFbetterEF defined those patients who had prior echocardiographic evidence of HFrEF but whose LVEFs subsequently improved to ≥50% by the time of the study clinic visit (15). In addition, symptom profile, including NYHA functional class, current medications, and the presence or absence of HF signs on clinical examination on the day of the clinic visit, were noted. Body mass index (BMI) was calculated on the basis of height and weight measurements recorded on the day of the outpatient visit. The results of transthoracic echocardiography within 18 months of the index appointment were also reviewed. LVEF and other standard echocardiographic measurements were performed according to current guidelines applied uniformly by the noninvasive echocardiography laboratory at Brigham and Women's Hospital (17–19).

The Institutional Review Board of Brigham and Women's Hospital approved this retrospective, cross-sectional observational study.

QUESTIONNAIRE DESIGN AND QOL ASSESSMENT. Questionnaires were designed to focus on 3 key areas: 1) overall QOL; 2) symptom burden due to shortness of breath and fatigue; and 3) patients' perceived dominant overall limitations to their QOL status. Separate vertical visual analogue scales (VAS) were used to assess overall QOL, ease of breathing, and

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CI = confidence interval

HF = heart failure

HFbetterEF = heart failure with better left ventricular ejection fraction

HF=Med = patients' perceived quality of life limited equally by heart failure and medical conditions

HFMost = patients' perceived quality of life limited predominantly by their heart failure

HFpEF = heart failure with preserved left ventricular ejection fraction

HFrEF = heart failure with reduced left ventricular ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

MedMost = patients' perceived quality of life limited predominantly by their medical conditions

Non-Med = patients' perceived quality of life limited predominantly by nonmedical factors

NYHA = New York Heart Association

OR = odds ratio

QOL = quality of life

VAS = visual analogue scale

energy versus fatigue (20–23). VAS scores as a generic instrument for overall QOL assessment are a key component of the well-validated European Quality of Life-5 Dimension tool (23). Patients were asked to mark a score ranging from 0 to 100 for each VAS, with 0 representing the worst possible health and 100 the best possible health. Patients were then specifically asked if their overall QOL was affected more, equally, or less by their HF compared with other medical conditions and/or nonmedical factors (Online Appendix). The total population was subsequently divided into 4 groups according to whether patients perceived themselves to be limited most by their HF (HFMost), equally limited by HF and medical conditions (HF=Med), limited most by non-HF medical conditions (MedMost), or limited most by nonmedical factors (Non-Med).

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD if normally distributed or as medians and interquartile ranges if not normally distributed. Categorical variables are presented as frequencies and percentages. Multiple-group comparisons were performed using analysis of variance, Kruskal-Wallis, or chi-square tests as appropriate. Post-hoc correction for multiple comparisons between groups was performed using the Bonferroni method.

Univariate and multivariate logistic regression analyses were performed to determine the clinical determinants of HFMost as the dominant perceived limitation to QOL compared with the other QOL limitation groups. All univariate variables with p values < 0.05 were considered for the multivariate analysis. Collinearity (defined as R $\geq$0.50) was checked between relevant variables, and only 1 of the 2 variables was entered into the final model if demonstrated. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Model fit was assessed using the Hosmer-Lemeshow test.

All statistical tests were 2 sided, and p values <0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

PATIENTS. A total of 726 patients with ambulatory HF completed QOL questionnaires prior to the start of their routine clinic evaluations. The mean age of the total population was 56 ± 15 years, and the majority (63%) were men. Patients predominantly were white (83%), were married (63%), and had college-level educations or higher (51%). According to LVEF classification, 57% (n = 412) had HFrEF, 19% (n = 138) had HFbetterEF, and 16% (n = 115) had HFpEF. A minority of patients (n = 61 [8%]) attended the ambulatory HF clinic for cardiomyopathy risk assessment. The mean LVEF in the total population was 41 ± 16%.

PATIENT CHARACTERISTICS STRATIFIED BY THE PERCEIVED DOMINANT LIMITATION TO QOL. Approximately one-half of patients (48%) believed that HF affected their QOL the most (HFMost), while 19% believed that HF and other medical conditions affected their overall QOL equally (HF=Med). Medical conditions other than HF dominated QOL in 18% (MedMost), and 15% cited nonmedical problems as the most important factor limiting their QOL (Non-Med). Patient demographics and clinical characteristics according to perceived most important factor limiting QOL are shown in **Table 1**.

HFMost patients had significantly lower LVEFs and higher LV end-diastolic dimensions compared with the other 3 groups ($p \leq 0.001$ for all comparisons). They were less likely to be categorized as having HFpEF compared with the HF=Med or MedMost groups and less likely to be categorized as having HFbetterEF compared with the MedMost or Non-Med groups. HFMost patients were also significantly more likely to have implantable cardioverter-defibrillators and less likely to have arthritis than patients in all other groups. Compared with MedMost and Non-Med patients, HFMost patients had significantly lower systolic blood pressure, had more functional limitations, and were more likely to be treated with renin-angiotensin-aldosterone-system antagonists, beta-blockers, diuretic agents, antithrombotic and antiarrhythmic therapy, and cardiac resynchronization therapy. Compared with HF=Med patients, they had significantly less medical comorbidity burden (diabetes, depression, and cancer) and significantly lower BMIs. In contrast, Non-Med patients were younger, more likely to be in NYHA class I, and less likely to have diabetes, chronic kidney disease, hypertension, depression, and arthritis as well as less likely to be taking diuretic agents or nitrates compared with all other groups. Furthermore, they were less likely to be female than HF=Med or MedMost patients and compared with HFMost or HF=Med groups were more likely to have higher LVEFs and/or to have HFbetterEF and less likely to have had prior cardiac surgery, intervention, or device implantation. There were no significant differences in overall rates of implantable cardioverter-defibrillator shocks among the HFMost, HF=Med, MedMost, and Non-Med groups (4.0%, 3.6%, 2.3%, and 2.8%, respectively; p = 0.79).

VAS SCORES ACCORDING TO THE PERCEIVED DOMINANT LIMITATION TO QOL. Mean scores for the QOL VAS, breathing VAS, and fatigue VAS for the

TABLE 1 Patient Demographics and Clinical Characteristics According to Perceived Dominant Limitation to Quality of Life

	HFMost (n = 347)	HF=Med (n = 139)	MedMost (n = 132)	Non-Med (n = 108)	p Value*
Demographic					
Age, yrs	57 ± 14§	58 ± 17§	59 ± 16§	50 ± 16	<0.001
Female, %	32†‡	45§	45§	31	0.004
HFrEF, %	67‡§	58‡§	36	45	<0.001
HFbetterEF, %	16‡§	14‡§	25	30	0.001
HFpEF, %	11†‡	21	26§	13	<0.001
Prior MI, %	21‡§	17	9.8	9.3	0.004
PCI, %	16§	12§	11	4.6	0.02
Prior cardiac surgery, %	23‡§	19§	12	7.4	0.001
ICD, %	50‖	40‡§	18	20	<0.001
CRT, %	16‡§	14‡§	3.8	1.9	<0.001
Diabetes mellitus, %	21†§	31§	25§	4.6	<0.001
Obstructive lung disease, %	17	19	20	9.3	0.13
Chronic kidney disease, %	14§	15§	18§	4.6	0.02
Hypertension, %	43§	50§	52§	28	0.001
History of atrial fibrillation/flutter, %	32§	32§	24	19	0.03
Prior CVA/TIA, %	7.5	4.3	6.8	6.5	0.65
History of cancer, %	10†‡	20	27§	15	<0.001
Depression, %	20†§	29§	26§	11	0.005
Arthritis, %	24‖	37§	43§	12	<0.001
Clinical					
NYHA functional class, %					<0.001
I	27‡§	30‡§	48§	81	
II	43	41	33	15	
III	28	29	19	3.7	
IV	2	0	0.8	0	
BMI, kg/m^2	29 ± 7†	31 ± 8§	31 ± 7	28 ± 5	0.003
Systolic blood pressure, mm Hg	118 ± 19‡§	123 ± 18	126 ± 18	123 ± 17	<0.001
Heart rate, beats/min	74 ± 14	73 ± 15	74 ± 14	72 ± 16	0.69
Echocardiographic					
LVEDD, cm	5.8 ± 1.2‖	5.3 ± 1.1	5.0 ± 0.93	5.3 ± 0.95	<0.001
LVESD, cm	4.8 ± 1.4‖	4.2 ± 1.3	3.8 ± 1.1	4.0 ± 1.1	<0.001
LVEF, %	36 ± 16‖	42 ± 16‡§	49 ± 13	47 ± 13	<0.001
LVH, %	20†‡	29	30	21	0.008
MR grade ≥2, %	63‡§	61§	49	43	0.001
TR grade ≥2, %	61‡§	56§	50§	29	<0.001
PASP, mm Hg	32 ± 13§	31 ± 14§	31 ± 14§	25 ± 9	<0.001
Medications, %					
ACE inhibitors/ARBs	76‡	78‡	60	69	0.001
Beta-blockers	85‡§	83‡	71	75	0.001
MRAs	31‡§	24§	16	13	<0.001
Hydralazine	3.5	2.2	6.1	0.9	0.13
Nitrates	17§	14§	16§	1.9	0.001
Diuretic agents	71‡§	65‡§	40§	28	<0.001
Digoxin	35‖	21§	14	11	<0.001
Warfarin	44‡§	35‡§	24	20	<0.001
Antiarrhythmic agents	23‡§	18‡§	9.1	8.3	<0.001

Values are mean ± SD or %. All post-hoc p values are Bonferroni adjusted. See text for definitions of QOL limitation groups. *Represent differences across 4 groups. †$p < 0.05$ for comparison with HF=Med. ‡$p < 0.05$ for comparison with MedMost. §$p < 0.05$ for comparison with Non-Med. ‖$p < 0.05$ for comparison with all other groups.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CRT = cardiac resynchronization therapy; CVA = cerebrovascular accident; HFbetterEF = heart failure with better left ventricular ejection fraction; HF=Med = patients' perceived quality of life limited equally by heart failure and medical conditions; HFMost = patients' perceived quality of life limited predominantly by their heart failure; HFpEF = heart failure with preserved left ventricular ejection fraction; HFrEF = heart failure with reduced left ventricular ejection fraction; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVH = left ventricular hypertrophy; MedMost = patients' perceived quality of life limited predominantly by their medical conditions; MI = myocardial infarction; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; Non-Med = patients' perceived quality of life limited predominantly by nonmedical factors; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; QOL = quality of life; TIA = transient ischemic attack; TR = tricuspid regurgitation.

TABLE 2 Visual Analogue Scale Scores According to Perceived Dominant Limitation to Quality of Life

VAS	HFMost (n = 347)	HF=Med (n = 139)	MedMost (n = 132)	Non-Med (n = 108)	p Value*
QOL	59 ± 26‡	61 ± 27‡	65 ± 26‡	80 ± 22§	<0.001
Breathing	65 ± 28†‡	70 ± 25‡	74 ± 29‡	88 ± 20§	<0.001
Fatigue	57 ± 25‡	60 ± 24‡	62 ± 25‡	83 ± 16§	<0.001

Values are mean ± SD. All post-hoc p values are Bonferroni adjusted. See text for definition of QOL limitation groups. *Represent differences across 4 groups. †p < 0.05 for comparison with MedMost. ‡p < 0.05 for comparison with Non-Med. §p < 0.05 for comparison with all other groups.

VAS = visual analogue scale. Other abbreviations as in Table 1.

total population were 64 ± 26, 71 ± 28, and 63 ± 25, respectively. Overall, scores for all 3 VAS parameters differed significantly across the 4 groups (p < 0.001) (Table 2). Non-Med patients had significantly better VAS scores for QOL and both symptom scales compared with the other 3 groups (p < 0.001 for each comparison). HFMost patients had significantly lower scores for ease of breathing compared with MedMost patients.

VAS SCORES ACCORDING TO LVEF SUBTYPE. VAS scores according to LVEF subtype are shown in Table 3. Patients with HFbetterEF had the highest overall QOL scores and significantly better breathing VAS scores compared with those with HFpEF. Mean QOL VAS scores in each of the 4 groups of dominant limitation to QOL further stratified by LVEF subtype are shown in Figure 1. QOL was similar regardless of perceived dominant limitation in patients with HFpEF (p = NS). For both patients with HFrEF and those with HFbetterEF, QOL scores was worst in the HFMost group and best in the Non-Med group (p < 0.001 for both subtypes across QOL groups).

CLINICAL DETERMINANTS OF HF AS THE PERCEIVED DOMINANT LIMITATION TO QOL. Univariate and multivariate logistic regression analyses investigating the significant determinants of HF being perceived as the dominant limitations to QOL are shown in Table 4.

TABLE 3 Visual Analogue Scale Scores According to Left Ventricular Ejection Fraction Subtype

VAS	HFrEF (n = 412)	HFbetterEF (n = 138)	HFpEF (n = 115)	p Value*
QOL	63 ± 26	69 ± 27†	58 ± 29	0.004
Breathing	71 ± 26†	73 ± 29†	64 ± 30‡	0.02
Fatigue	63 ± 25	65 ± 26	58 ± 24	0.11

Values are mean ± SD. All post-hoc p values are Bonferroni adjusted. Sixty-one patients (8%) without heart failure diagnoses, seen at the clinic for cardiomyopathy risk assessment, were not included in this analysis. *Represent differences across 3 groups. †p < 0.05 for comparison with HFpEF. ‡p < 0.05 for comparison with the other 2 groups.

Abbreviations as in Tables 1 and 2.

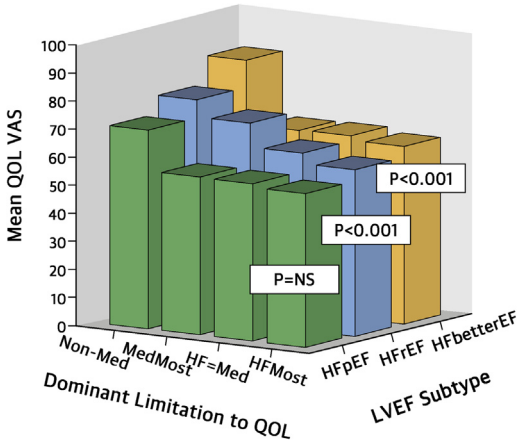
Independent determinants of HFMost were prior cardiac surgery (OR: 2.0; 95% CI: 1.0 to 3.8; p = 0.03), lack of history of cancer (OR: 0.41; 95% CI: 0.21 to 0.77; p = 0.006) or of arthritis (OR: 0.43; 95% CI: 0.26 to 0.72; p = 0.001), higher NYHA class (for III vs. I: OR: 3.3; 95% CI: 1.7 to 6.5; p = 0.001), taking a renin-angiotensin-aldosterone-system antagonist (OR: 1.8; 95% CI: 1.0 to 3.1; p = 0.048), current diuretic therapy (OR: 1.8; 95% CI: 1.1 to 3.1; p = 0.03), lower BMI (OR: 0.96; 95% CI: 0.92 to 0.99; p = 0.01), and lower LVEF (OR: 0.97; 95% CI: 0.95 to 0.99; p = 0.001). Figure 2 summarizes clinical parameters independently associated with patients with ambulatory HF being more likely to perceive themselves as limited predominantly by their HF or equally or greater by medical or nonmedical factors.

DISCUSSION

In the present study, more than one-half of a large cohort of patients with ambulatory HF were found to rate other medical and/or nonmedical factors as equally or more important limitations to their QOL as their HF. Patients perceiving HF as the dominant limitation to QOL were more affected by dyspnea than those patients in whom diminished QOL was dominated by medical conditions. Patients with HFbetterEF had the highest overall QOL scores and less dyspnea burden compared with those with HFpEF, highlighting the importance of considering this contemporary group as a distinct subtype for patient-centered outcomes. Patients with HF with prior cardiac surgery, those with higher NYHA class, and those taking renin-angiotensin-aldosterone-system agents and diuretic agents were more likely to perceive their HF itself as the dominant limitation to their QOL, whereas those with higher BMIs, higher LVEFs, histories of arthritis, or prior cancer were more likely to be primarily limited by noncardiac medical or nonmedical factors.

DIFFERENTIAL CONTRIBUTIONS TO QOL IMPAIRMENT IN AMBULATORY HF. Health-related QOL is significantly reduced in the majority of patients with HF, regardless of etiology or LVEF (3-5,12). Increasingly, impaired QOL is being recognized not only as an adverse prognostic marker in HF (7-10) but also as an important modifiable patient-centered outcome (1). However, the evolving complexity and aging profile of patients with HF coupled with the emerging availability of more sensitive diagnostic techniques and successful therapies has contributed to an increasingly heterogeneous HF population. Hitherto, the majority of previous studies of QOL assessment in patients with HF have focused primarily on overall

FIGURE 1 Mean Quality of Life Visual Analogue Scale Scores Stratified by Both Groups of Perceived Dominant Limitation to Quality of Life and Left Ventricular Ejection Fraction Subtype



P values represent the overall differences in mean quality of life (QOL) scores across all 4 dominant QOL limitation groups for each left ventricular ejection fraction (LVEF) subtype. See text for definitions. HFbetterEF = heart failure with better LVEF; HF=Med = patients' perceived quality of life limited equally by heart failure and medical conditions; HFMost = patients' perceived quality of life limited predominantly by their heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MedMost = patients' perceived quality of life limited predominantly by their medical conditions; Non-Med = patients' perceived quality of life limited predominantly by nonmedical factors; VAS = visual analogue scale score.

QOL, whether measured by disease-specific (4,10,12) or global (5,12) questionnaires, rather than analyzing its components and contributors. In particular, the relative contributions of HF itself to QOL versus comorbid non-HF medical conditions remain unexplored. Both impaired QOL and depressive symptoms have been shown to be more prevalent in older patients with HF with chronic comorbidities, particularly diabetes and obstructive lung disease (3). More recently, in a subanalysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial), better QOL was demonstrated in patients with HF without angina, diabetes, or asthma (24). Meanwhile, in younger patients with HF, psychosocial factors independent of disease status have been shown to significantly affect overall QOL perception (25).

In the present analysis, the prevalence of HF-dominated diminished QOL, compared with non-HF comorbid conditions and nonmedical factors, was determined in a large ambulatory chronic HF population, of variable etiologies and mixed LVEF subtypes. More than one-half of the patient population did not rate HF as the primary limitation to their QOL. Specifically, those with higher BMIs, higher LVEFs, and histories of arthritis or prior cancer were more likely to perceive their QOL as limited by noncardiac medical or nonmedical factors. Conversely, patients with more extensive LV systolic dysfunction and remodeling, prior cardiac surgery, greater functional limitations, and prescription of disease-specific pharmacological and device therapies were more likely to perceive that HF was the dominant factor in their reduced QOL. This finding—that patients may be more limited in their QOL by superimposed medical disease or even nonmedical factors—highlights the futility of focusing on HF-specific therapies alone in modifying QOL in all patients with HF. It may also explain why evidence-based therapies, largely proved to have clinical utility in reduced LVEF populations (1), are less likely to have a sustained, meaningful impact on QOL in higher LVEF populations (11), in which QOL may be influenced more by additional or independent factors.

DIFFERENTIAL RELATIONSHIPS BETWEEN QOL AND SYMPTOM BURDEN IN AMBULATORY HF. Greater symptom burden and worse functional status, as manifested by higher NYHA class, are consistent determinants of worse QOL in patients with HF (4,5). Independent of the strong prognostic role of NYHA class in chronic HF, self-reported dyspnea and fatigue have also been associated with worse survival and morbidity outcomes, as demonstrated in a subanalysis of the COMET (Carvedilol or Metoprolol European Trial) (26). The relationship between patients' reported burden of these specific symptoms according to the perceived dominant factor limiting their QOL was thereby explored in our ambulatory HF cohort, to facilitate further insight into the potential clinical impact of more refined QOL assessment in this population. In addition to higher NYHA class being an independent associate of HF-dominated diminished QOL, patients perceiving HF as their principal limitation were more likely to report worse scores on the breathing VAS. This new finding, that greater burden of dyspnea is most linked with HF-dominated QOL, rather than QOL in all patients with HF, suggests that treatment directed at dyspnea alone will not significantly affect overall QOL in more than 50% of the chronic HF population. Reassuringly, patients with HF who reported themselves to be most limited by nonmedical factors were almost universally in NYHA class I and reported significantly lower

TABLE 4 Clinical Determinants of Heart Failure as Perceived Dominant Limitation to Quality of Life

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yrs	1.00 (0.99–1.00)	0.52		
Female	0.68 (0.50–0.92)	0.01	1.10 (0.66–1.80)	0.73
HFrEF	2.30 (1.70–3.20)	<0.001	–	–
HFbetterEF	0.65 (0.44–0.95)	0.02	–	–
HFpEF	0.48 (0.32–0.73)	0.001	–	–
Prior MI	1.90 (1.30–2.90)	0.001	0.79 (0.39–1.60)	0.51
Prior cardiac surgery	1.90 (1.30–2.80)	0.001	2.00 (1.10–3.80)	0.03
ICD	2.70 (2.00–3.70)	<0.001	0.88 (0.52–1.50)	0.63
CRT	2.50 (1.50–4.10)	<0.001	–	–
Diabetes mellitus	0.95 (0.66–1.40)	0.76		
Obstructive lung disease	1.00 (0.71–1.50)	0.82		
Chronic kidney disease	1.10 (0.69–1.60)	0.80		
Hypertension	0.94 (0.70–1.30)	0.65		
History of atrial fibrillation/flutter	1.40 (0.99–1.90)	0.06		
Prior CVA/TIA	1.30 (0.73–2.40)	0.36		
History of cancer	0.44 (0.29–0.67)	<0.001	0.41 (0.21–0.77)	0.006
Depression	0.86 (0.60–1.20)	0.41		
Arthritis	0.67 (0.48–0.93)	0.02	0.43 (0.29–0.72)	0.001
ACE inhibitors/ARBs	1.50 (1.10–2.00)	0.02	1.80 (1.00–3.10)	0.048
Beta-blockers	1.80 (1.20–2.60)	0.003	0.90 (0.46–1.80)	0.76
MRAs	2.00 (1.40–2.80)	<0.001	1.10 (0.64–1.90)	0.74
Diuretic agents	2.90 (2.10–3.90)	<0.001	1.80 (1.10–3.10)	0.03
Digoxin	2.80 (2.00–4.10)	<0.001	0.98 (0.57–1.70)	0.93
Warfarin	2.10 (1.60–2.90)	<0.001	1.30 (0.76–2.10)	0.37
Antiplatelet agents	1.60 (1.20–2.20)	0.001	1.50 (0.90–2.40)	0.12
Antiarrhythmic agents	2.10 (1.40–3.10)	<0.001	1.60 (0.84–2.90)	0.16
NYHA class (vs. I)				
II	2.70 (1.90–3.80)	<0.001	2.10 (1.20–3.60)	0.006
III	2.90 (2.00–4.40)	<0.001	3.30 (1.70–6.50)	0.001
IV	15.00 (1.80–120.00)	0.01	12.00 (0.86–168)	0.07
BMI, kg/m^2	0.97 (0.95–0.998)	0.03	0.96 (0.92–0.99)	0.01
Systolic blood pressure, mm Hg	0.98 (0.97–0.99)	<0.001	0.998 (0.99–1.00)	0.77
LVEDD, cm*	1.70 (1.40–1.90)	<0.001	–	–
LVEF, %	0.96 (0.95–0.97)	<0.001	0.97 (0.95–0.99)	0.001
LVH	0.61 (0.43–0.86)	0.006	0.62 (0.36–1.10)	0.08
MR grade ≥2	1.60 (1.20–2.20)	0.002	0.88 (0.53–1.50)	0.63
TR grade ≥2†	1.90 (1.40–2.60)	<0.001	–	–
PASP, mm Hg	1.00 (1.00–1.00)	0.007	1.00 (0.99–1.00)	0.67

Hosmer-Lemeshow test: chi-square = 6.8, p = 0.56. HFpEF, HFrEF, and HFbetterEF were not placed into the final model given the presence of LVEF as a continuous variable; CRT was not placed into the model in addition to ICD given patient overlap. *For LVEDD and LVEF, R > 0.5. †For TR and MR grade ≥2, R > 0.5.

Abbreviations as in Tables 1 and 2.

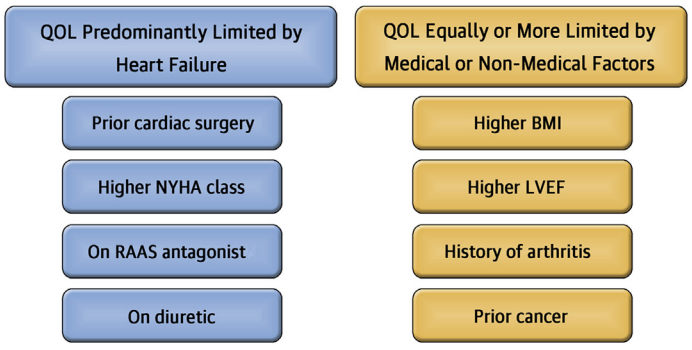
symptom burden and significantly better overall QOL using VAS scores compared with the other groups. Identifying these patients up front in the clinic setting may facilitate better medical resource utilization by indicating less frequent need for tertiary-level hospital follow-up and/or indicating potential benefit of multidisciplinary assessment and ancillary service input (including but not limited to psychological, pharmacological, educational, rehabilitation-based, and socioeconomically driven care) to improve residual impaired QOL.

QOL ASSESSMENT ACROSS HFrEF, HFpEF, AND HFbetterEF SUBTYPES. Previous comparisons of overall QOL in patients with HF according to the presence or absence of preserved LV systolic function have demonstrated similar impairments across both groups (4,12). Specifically, the health-related QOL substudy of the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trials found no significant differences in Minnesota Living with Heart Failure Questionnaire summary scores across patients stratified by a baseline LVEF <40% versus ≥40% at the time of enrollment into the component trials (4). The present study provides several updated insights into QOL in patients with HF according to LVEF subtype. First, the population was stratified into 3 LVEF subtypes, with comprehensive retrospective chart review (including serial echocardiogram review) facilitating delineation of the distinct subgroup of patients with HF with improved or "recovered" LVEF, termed HFbetterEF. Almost one-fifth of our large contemporaneous HF population fell into this category, a recently emerging phenotype paralleling the success of currently available antiremodeling therapies (27). Punnoose et al. (16) found in a retrospective study of 121 subjects with HF with LVEF recovered to ≥40%, among a total cohort of 358 patients with HF, that these patients were clinically distinct from those with HFpEF or HFrEF on the basis of their younger age and mildest HF symptoms, as well as having less coronary artery disease compared with patients with HFrEF and fewer comorbidities compared with patients with HFpEF. Basuray et al. (15), in a prospective cohort of 1,821 patients with chronic HF recruited as part of the PHFS (Penn Heart Failure Study), subsequently demonstrated persistently abnormal myocardial biomarkers (including troponin I and brain natriuretic factor) in patients with HF with "recovered" LVEF (defined similarly to the present study as LVEF ≥50%, having previously been <50%), although their overall biomarker profile was more favorable than the other 2 already established LVEF subtypes. Furthermore, although these patients showed better event-free survival compared with those with HFpEF or HFrEF, they remained at risk for HF hospitalizations. Patients with HFbetterEF therefore appear to be a clinically distinct HF subgroup, as defined by ameliorated, but not abolished, risk compared with the traditionally accepted phenotypes of HFpEF and HFrEF. Definitive pathophysiological and pathobiological models for these patients remain to be defined; however, it

seems these patients are characterized by the presence of factors influencing favorable reverse remodeling in parallel with factors inducing persistent adverse neurohormonal activation and thereby risk for ongoing cardiomyocyte injury.

The present study expands on the developing evidence base for this contemporary subtype by demonstrating for the first time significant differences in their patient-reported outcomes. Overall QOL was significantly higher in these patients, and dyspnea burden was significantly lower in the HFbetterEF group compared with the HFpEF group, highlighting the importance of not misclassifying these patients as having HFpEF for QOL-driven, as well as clinical, endpoints. Second, our analysis also considered relative contributions of differential disease- or non-disease-specific factors to diminished QOL across each of the 3 LVEF subtypes, rather than simply noting the degree of impaired QOL within each subtype. Although patients with HFrEF were more likely to cite HF-dominated reduction in QOL, those with HFbetterEF were more likely to rate medical or nonmedical factors as dominant contributors to their QOL. Additionally, QOL in patients with HFpEF was perceived as equally or predominantly affected by medical comorbidities. Finally, self-reported QOL score was compared across LVEF subtypes according to patients' perceived dominant limitations to their QOL. Although a progressive gradient in QOL was seen in patients with HFrEF and those with HFbetterEF (worst in HF-dominated QOL, better in other groups), patients with HFpEF showed similarly impaired QOL scores regardless of whether they perceived their QOL to be dominated by HF or equally or greater by medical comorbidities. This additional layered analysis underscores the relevance of not only assessing overall QOL according to LVEF subtype, which may appear similar if looked across HFrEF and HFpEF groups, but also assessing its perceived components, which may affect uniform response of traditional HF therapies directed at patient-reported outcomes in HFpEF populations.

FIGURE 2 Clinical Determinants of Dominant Contributors to Diminished Quality of Life in Ambulatory Heart Failure



Clinical parameters that may act as markers of heart failure–dominated diminished quality of life (QOL) **(left)** or non-heart failure–dominated QOL **(right)** in an ambulatory heart failure population. BMI = body mass index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone-system.

DISEASE-SPECIFIC VERSUS GENERIC: METHODS OF QOL ASSESSMENT. Disease-specific instruments for assessing QOL in patients with HF facilitate greater precision as well as being more likely to reflect changes in clinical status, even if small (22). However, disease-specific instruments may not enable patients with HF to consider their overall health-related QOL, which as demonstrated may be impaired not only by their HF but also reflect impairments due to other medical comorbidities, which are increasingly encountered in this population, as well as nonmedical issues independent of their disease but still affecting their QOL. Generic instruments, capable of detecting "all-comer" QOL impairments, have also been validated as measures of QOL in patients with HF. One of these is the European Quality of Life-5 Dimension instrument, which includes a vertical VAS as one of its key components, and which has already been widely used in HF clinical trials (23,24,28). The TOPCAT subanalysis trial previously mentioned incorporated both the European Quality of Life-5 Dimension VAS and the disease-specific Kansas City Cardiomyopathy Questionnaire measures to determine baseline distribution of QOL in enrolled participants and found a significant correlation between both measures in this HFpEF population (24). VAS scores for QOL assessment have also been recently associated with increased risk for 30-day all-cause mortality or readmission for HF in hospitalized patients with HF (28). In addition to its well-validated background, correlation with disease-specific instruments, and demonstrated prognostic role, the VAS instrument for overall QOL assessment was selected as the instrument of choice in the present study given its ease of administration, which resulted in a high feasibility of routine QOL data collection in the real-world clinic setting.

STUDY LIMITATIONS. Several limitations are acknowledged. This was a retrospective analysis of prospectively acquired patient-reported QOL data; however, comprehensive review of the electronic health record at our institution allowed detailed phenotyping of all enrolled patients. Our single-center study population

(mean age 56 ± 15 years, predominantly male, more than 50% college educated) may not be generalizable to all HF populations, although notably, no demographic variables were independent determinants of HF as the perceived dominant limitation to QOL in the final model. The study population was restricted to an ambulatory HF cohort and thus cannot be generalized to hospitalized patients with HF, likely to demonstrate greater dyspnea and other symptom burden (29). However, clear differences across both QOL groups and LVEF subtypes in overall and symptom VAS scores were still evident in this chronic ambulatory population. Furthermore, although we included an overall well-phenotyped patient population, several disease severity parameters (including B-type natriuretic peptide, glomerular filtration rate, and nutritional parameters) were not systematically available for all patients. However, considerable variation in QOL may exist even across similar disease severity (4), and the determination of clinical parameters associated with HF, rather than other factors, as the dominant limitation to QOL may better inform therapy decisions aimed at improving this important outcome compared with specific disease severity assessment alone. Finally, prospective assessment of our findings, including the identification of QOL limitation groups up front in therapy-driven trials and the clear distinction between contemporary LVEF subtypes when evaluating QOL and other patient-centered outcomes, is recommended.

CONCLUSIONS

Heterogeneity in patients' perceptions of their dominant limitations to QOL exists in a large ambulatory contemporary HF population, with at least one-half of these patients rating other medical and/or nonmedical factors as equally or more important limitations to their QOL. Patients with HFbetterEF appear to represent a distinct subgroup with better overall QOL. These findings have important implications for therapies and interventions targeted at improving health-related QOL in ambulatory HF populations, particularly in those with higher or improved LVEFs, higher BMIs, and noncardiac comorbidities.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: QOL assessment can be easily performed in a routine ambulatory visit using a self-administered 1-page questionnaire including VAS assessments for overall QOL, shortness of breath, and fatigue. Importantly, not all diminished QOL in HF is due to HF itself: the heterogeneity of patient and comorbidity profiles across this disease means that other medical comorbidities and nonmedical factors should be considered as equally or more dominant limitations to QOL, particularly in patients with higher LVEFs, higher BMIs, and histories of arthritis or prior cancer. These findings highlight the futility of focusing on the efficacy of HF-specific therapies alone on positive QOL modification in all patients with HF and may partially explain why evidence-based therapies, largely proved to have clinical utility in reduced LVEF populations, are less likely to have a sustained, meaningful impact on QOL in higher LVEF populations.

TRANSLATIONAL OUTLOOK: To achieve meaningful further impact on QOL in contemporary HF populations, a shift away from the traditional disease-centric model to a more individualized approach may be warranted. Future therapy-driven studies should consider the identification of patients' perceptions of the dominant contributors to their diminished QOL up front in addition to their specific LVEF subtypes and base assessments of downstream efficacy accordingly.

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KEY WORDS better left, heart failure, left ventricular ejection fraction, quality of life

APPENDIX For a copy of the quality-of-life questionnaire for a routine clinic visit, please see the online version of the article.