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ORIGINAL ARTICLE

Psychosocial factors partially explain gender differences in health-related quality of life in heart failure patients

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Abstract

Aims There is little information about the influence of gender on quality of life (QoL) in heart failure. The purpose of this study was to evaluate whether the health-related QoL gap between men and women can be explained by the interaction between psychosocial factors and clinical determinants in a real-word cohort of patients with chronic heart failure.

Methods and results We conducted a single-centre, observational, prospective cohort study of 1236 consecutive patients diagnosed with chronic heart failure recruited between 2004 and 2014. To assess QoL, we used the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Female gender was associated with worse global QoL compared to male gender (MLHFQ overall summary score: 49 ± 23 vs. 43 ± 24; *P* value <0.001, respectively) and similarly had poorer scores in physical and emotional dimensions but scored better on social dimension. In univariate models and in models adjusted for clinical determinants, female gender behaved as a predictor of worse global, physical and emotional QoL, and better social QoL compared with men. In models only including psychosocial determinants and in comprehensive models including all psychosocial and clinical factors, these differences according to gender were no longer significant.

Conclusions In this study, we have shown that the gap in health-related QoL between men and women with chronic heart failure can be partially explained by the interaction between biological and psychosocial factors. Biological factors are the main drivers of QoL in HF patients. However, the contribution of psychosocial factors is essential to definitively understand the role of gender in this field.

Keywords Heart failure; Gender; Health related quality of life; Generic and specific questionnaires of quality of life; Real world evidence

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Introduction

As a complex clinical syndrome, heart failure (HF) represents a growing community health problem in terms of prevalence, mortality, and consumption of healthcare resources. Its prevalence is 1%–2% of the general adult population, although it is probably underestimated and is increasing due to the aging of the population.[1,2] The 5-year survival rates improved to 60% but still remains very high compared to other chronic diseases.[3] HF hospitalizations are responsible for 1% to 2%

of all hospital admissions and HF is the most common diagnosis in hospitalized patients older than 65 years.[4]

The main goals of HF care are to improve the so-called 'hard end-points', such as mortality and hospitalization. However, in recent years, patient-reported outcomes (PROs) are being targeted as an important health outcome. As an indispensable component of PROs, health-related quality of life (QoL) has become an essential part in the evaluation of HF-patients' health status.[5] Health-related QoL captures a relevant information on health status from patient perspective and also is a good predictor of mortality and HF hospitalization.[6,7] Health-related QoL measurements include generic and disease-specific instruments. Generic measures are applicable to multiple diseases and the general population. The disease-specific instruments are more sensitive to clinical changes than the generic questionnaires because they focus on the dimensions and components most affected in these patients.[8] These measurements include physical, emotional, social and global domains. These tools allow individualizing their assessment and improving decision making. Their use is increasingly widespread and endorsed by international institutions.[9–11]

Despite advances in this field, HF continues to have an enormous impact on patients' activities of daily living (ADL) and social activity.[12] For this reason, a deeper and more complete characterization of the health-related QoL is necessary. In this regard, there is controversy in the literature about the differences in QoL between men and women with HF: although most studies have described a trend towards a worse QoL in women compared with men despite controlling for biological determinants such as age, ejection fraction, and New York Heart Association (NYHA) classification,[13–16] others have found no significant differences.[17] On the other hand, psychosocial differences between both genders have also been described in the specific context of HF. Most of these inequalities are oriented towards worse outcomes in women than in men in such relevant aspects as socio-economic status or rates of anxiety and depression.[18] This differential psychosocial profile has been previously postulated as the cause that could justify the gap in QoL between men and women, but this hypothesis is pending confirmation.[19]

Given the gaps of knowledge mentioned above, a study was designed to clarify to what extent psychosocial status determines the QoL of HF patients according to their gender. The interaction of psychosocial determinants with physical determinants was also evaluated. For this purpose, a disease-specific tool, MLHFQ, one of the most widely known and used specific health-related QoL questionnaires was used.[8,20,21]

Methods

Study design and patient population

The Definition of the neuro-hormonal Activation, Myocardial function, genOmic expression and CLinical outcomes in hEart failure patients (DAMOCLES) study was a single-centre, observational, prospective cohort study of 1236 consecutive patients diagnosed with chronic HF recruited between January 2004 and January 2014. The methodology of the DAMOCLES study has been published previously by our group.[22–30] Briefly, for inclusion, patients had to be diagnosed with chronic HF according to the European Society of Cardiology diagnostic criteria, had at least one recent acute decompensation of chronic HF requiring intravenous diuretic therapy (either hospitalized or in the day care hospital), and had to be in stable condition at the time of study entry. Exclusion criteria were: significant primary valvular disease, clinical signs of fluid overload, pericardial disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, haemoglobin (Hb) levels $<$8.5 g/dL, active malignancy, and chronic liver disease. The study was approved by the local committee of ethics for clinical research and was conducted in accordance with the principles of the Declaration of Helsinki. All patients gave written informed consent before study entry.

The purpose of this study was to evaluate whether the health-related QoL gap between men and women can be explained by the interaction between clinical determinants and psychosocial factors in a real-word cohort of patients with chronic HF. Additional aims included to explore the influence of clinical and psychosocial factors and its interaction with gender on specific QoL domains. For the present analysis, all DAMOCLES participants were considered for inclusion. Of them, we excluded patients with missing baseline information on health-related QoL. Thus, for the purposes of the present analysis, the final cohort consisted of 1120 patients (*Figure S1*).

Baseline assessment

A detailed baseline evaluation was performed for all participants at study entry. This included collection of information about demographic characteristics, exhaustive medical history to gather clinical and disease-related factors such as NYHA functional class, comorbidities, laboratory information, medical treatments, and the most recent left ventricular ejection fraction (LVEF). Sources of information were the medical history and standardized questionnaires.

Evaluation of health-related quality of life

Details on evaluation of HRQoL in the DAMOCLES study have been published previously.[29] Briefly, to assess HRQoL, we used the Minnesota Living with Heart Failure Questionnaire (MLHFQ) instrument developed specifically to assess QoL in patients with chronic HF. This questionnaire is composed of 21 items from which a total score and three dimensions are obtained: physical (8 items), emotional (5 items), and social

(4 items). The response options range from 0 points, which indicates unaffected health-related QoL, to 5 points, which indicates the maximum impact on health-related QoL. The questionnaire score, both general (0–105) and by dimensions (physical, 0–40; emotional, 0–25; social, 0–20), is obtained by adding the responses to each of the items. *Table S1* lists the individual items for each dimension and the meaning of the scores obtained. This questionnaire has been validated in the Spanish population.[31,32]

For the purpose of this study, we defined impaired global health-related QoL when individual scores were in the upper quartile of the MLHFQ overall summary score (>63 points). Similarly, impaired health-related QoL in each dimension was defined when individual scores were in the upper quartile of the MLHFQ summary score of the physical dimension (>39 points), emotional dimension (>8 points), and social dimension (>9 points).

Psychosocial evaluation

Details on psychosocial evaluation in the DAMOCLES study have been previously reported.[22,28,30] To fully characterize patients in their psychosocial dimension, prospective information was collected on education and literacy, marital status, cohabitation with a partner and the presence and need of a caregiver. Likewise, several validated instruments were administered in order to define important psychosocial aspects such as cognitive function and dependency on basic and instrumental ADL, social support, family function, and affective status.

Cognitive function was evaluated by means of the administration of the Short Portable Mental State Questionnaire (SPMSQ)[33] and the Mini-Mental State Examination questionnaire (MMSE).[34] Cognitive impairment was defined as abnormal scoring in any of the two questionnaires (MMSE $<$ 24 or 3 or more mistakes in the SPMSQ).

Dependency to perform basic ADL was evaluated by calculating the Barthel Index.[35] The scores of this index range from 0 (total dependence) to 100 (independence). Dependency to perform instrumental ADL was evaluated using the Lawton and Brody scale.[36] We used the 8–30 points version, where higher scores define a greater level of dependency for instrumental ADL. Dependency for instrumental ADL is defined when scores in the Lawton and Brody scale are greater than 8 points.

To assess the self-perceived social support, we administered the 11-item Duke-UNC Functional Social Support Questionnaire.[37] Scores in this questionnaire range from 11 and 55, higher scores meaning better functional social support. For the purpose of this study, impaired social support was defined when scores in the Duke-UNC questionnaire below or equal the 25th percentile (47 points).

Family function was evaluated using the Family APGAR test.[38] This questionnaire captures important functional components of family function such as adaptability, partnership, growth, affection, and commitment to devote time to family members. Scores range from 0 (*severe family dysfunction*) to 10 (*normal family functioning*). For the purpose of this study, we defined impaired family function when scores were below 10 points.

Finally, affective status was evaluated using the 15-item geriatric depression scale (GDS-15). In this scale, scores range from 0–15. Abnormal affective status, defined by the presence of depressive symptoms, was determined using a cut-off point $\geq$4 points in the GDS-15 score.

Statistical analyses

Demographic, clinical, and psychosocial data were summarized with basic descriptive statistics in collected data from the DAMOCLES cohort. Continuous data are presented as mean ± standard deviation and were compared between men and women using the Student's *t* test. Categorical variables are expressed as a percentage and were compared using χ^2. Continuous variables were compared using Student's *t* test or Mann–Whitney *U* test, as applicable.

The analyses were stratified according the two groups of interest (male and female). The dependent variables of the analyses were the summary scores of the instrument used to assess health-related QoL (MLHFQ). Univariate and multivariate linear regression models were applied for the scores of the various continuous variables obtained.

Univariate linear regression models and univariate logistic regression models were conducted to assess demographic, clinical, and psychosocial factors associated with health-related QoL including age and gender. Based on these univariate analyses, several multivariate models were performed using the stepwise backward elimination method to determine which factors maintained an independent association with health-related QoL both in the global QoL score and in each of the three dimensions considered (physical, emotional, and social).

To explore the association of gender with QoL, we designed three different models for each one of the QoL outcomes: global QoL, physical QoL, emotional QoL and social QoL. The first model evaluated the influence of gender on QoL in the context of clinical or disease-related determinants (clinical model). The second model evaluated the influence of gender on QoL in the context of important psychosocial factors (psychosocial model). The final model evaluated the effect of gender on QoL including both clinical and psychosocial determinants (comprehensive model). All models were also adjusted for age.

All statistical tests and confidence intervals (CI) were constructed with a type I error alpha level of 5%, with no ad-

Table 1 Baseline demographic, disease-related, and psychosocial characteristics of patients included in the study, both overall and according to gender

	n	Whole cohort (*n* = 1120)	Men (*n* = 636)	Women (*n* = 484)	*P* value
Demographic and clinical factors					
Age, years	1120	72 ± 11	71 ± 12	75 ± 10	<0.001
Systolic blood pressure, mmHg	1118	124 ± 22	124 ± 22	124 ± 21	0.689
Heart rate, bpm	1117	74 ± 14	73 ± 14	75 ± 15	0.036
NYHA functional class, *n* (%)	1114				<0.001
I		145 (13)	113 (18)	32 (7)	
II		514 (46)	307 (49)	207 (43)	
III		371 (33)	176 (28)	195 (41)	
IV		84 (8)	36 (6)	48 (10)	
HF hospitalization previous year, *n* (%)	1118	928 (83)	513 (81)	415 (86)	0.033
HF diagnosis < 3 months (recent), *n* (%)	1118	551 (49)	290 (46)	261 (54)	0.007
LVEF, %	1117	45 ± 17	40 ± 15	50 ± 17	<0.001
HFpEF, *n* (%)	1117	454 (41)	186 (29)	268 (56)	<0.001
Ischaemic aetiology of HF, *n* (%)	1120	427 (38)	304 (48)	123 (25)	<0.001
Comorbidities					
Hypertension, *n* (%)	1120	900 (80)	490 (77)	410 (85)	0.001
Diabetes mellitus, *n* (%)	1119	516 (46)	288 (45)	228 (47)	0.56
Previous MI, (%)	1120	286 (26)	219 (34)	67 (14)	<0.001
CKD, *n* (%)	1115	618 (55)	291 (46)	327 (29)	<0.001
Anaemia, *n* (%)	1120	544 (49)	298 (47)	246 (51)	0.188
Iron deficiency, *n* (%)	1098	643 (59)	346 (55)	297 (63)	0.016
Treatments (%)					
ACEI or ARBs	1116	821 (74)	462 (73)	359 (75)	0.546
Beta-blockers	1119	981 (88)	565 (89)	416 (86)	0.127
MRA	1117	420 (38)	274 (43)	146 (30)	<0.001
Diuretics	1119	1,018 (91)	565 (89)	453 (94)	0.008
Antiplatelet or anticoagulant therapy	1119	920 (82)	538 (85)	382 (79)	0.012
Laboratory					
Haemoglobin, g/dL	1120	12.6 ± 2.3	13.1 ± 2.6	12.1 ± 1.7	<0.001
Creatinine	1118	1.3 ± 0.59	1.4 ± 0.6	1.2 ± 0.5	<0.001
NT-proBNP, pg/mL	1107	1,585 [686–3,715]	1,516 [642–3,714]	1,658 [742–3,862]	0.635
Serum albumin, g/dL	1108	3.8 ± 0.49	3.9 ± 0.49	3.8 ± 0.49	0.002
Psychosocial factors					
Barthel Index, points	971	92 ± 16	94 ± 14	88 ± 18	<0.001
Dependency for ADL, n (%)	971	387 (40)	159 (29)	228 (54)	<0.001
Lawton test, points	1031	13 ± 5	12 ± 5	14 ± 6	<0.001
Dependency instrumental activities, *n* (%)	1031	770 (75)	398 (68)	372 (83)	<0.001
Literacy	1016				<0.001
Illiterate		84 (8)	18 (3)	66 (15)	
Primary school		610 (60)	316 (55)	294 (67)	
Secondary school		240 (24)	166 (29)	74 (17)	
University school		28 (3)	26 (5)	2 (1)	
Advanced university degree		54 (5)	52 (9)	2 (0.2)	
Significant cognitive impairment, yes vs. no	906	76 (8)	26 (5)	50 (13)	<0.001
APGAR family function, points	989	8.7 ± 3	8.5 ± 3	8.9 ± 2	0.006
Poor family function, *n* (%)	989	142 (14)	89 (16)	53 (12)	0.051
Self-perceived social support (Duke Scale), points	971	49 ± 9	48 ± 10	50 ± 9	0.019
Poor social support, n (%)	993	66 (7)	42 (8)	24 (6)	0.219
Score in the Geriatric Depression Scale (GDS), points	970	4 ± 3	3 ± 3	4 ± 3	<0.001
Depressive symptoms, *n* (%)	970	312 (32)	141 (26)	171 (41)	<0.001
Living with a partner, yes vs. no	1078	580 (54)	398 (65)	182 (39)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease, defined as date <60 mL/min/1.73 m^2; eGFR, estimated glomerular filtration; HF, heart failure; HFpEF, heart failure with preserved ejection fraction ≥50; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal fraction of natriuretic propeptide type B; NYHA, New York Heart Association functional class; QoL, quality of life.

Note: Anaemia was defined according to the WHO Criteria. Dependency for ADL, defined as Barthel Index ≤99 points. Dependency instrumental activities, defined as Lawton test <8 points. Significant cognitive impairment was defined as abnormal Mini Mental State Examination or Pfeiffer Tests adjusted for age and literacy. Poor Family Function was defined as Apgar Test <10 points. Poor social support was defined as Duke Scale 47 points (corresponding to scores below to Q1). Depressive symptoms were defined as Geriatric Depression Scale (GDS) ≥ 5 points.

justments for multiplicity. *P* values below 0.05 were considered statistically significant. All analyses were performed using SPSS software (version 25.0; IBM, Armonk, NY) and R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

From the total 1236 HF patients included in the DAMOCLES study, only those with information on health-related QoL measured with the instrument MLHFQ were selected (*N* = 1120, men = 636, women = 484) for the present analysis (*Figure S1*). MLHFQ overall summary score of the whole cohort was 46 ± 24 indicating a marked limitation in self-perceived health status. Mean scores in the specific dimensions were 27 ± 14 for the MLHFQ physical dimension score, 5 ± 5 for the MLHFQ emotional dimension score and 5 ± 5 for the MLHFQ social dimension score.

The demographic and disease-related characteristics as well as psychosocial factors of the patients, general and according to gender (female or male), are shown in *Table 1*. Considering the clinical profile, and in line with that described in previous studies, women were older and more frequently hypertensive than men. They also had lower haemoglobin levels and had iron deficiency more frequently. Although they had preserved LVEF much more frequently, their functional class was markedly worse than that of men. In contrast, the prevalence of ischaemic heart disease as well as chronic kidney disease was more frequent in men.

A higher frequency of dependence for basic and instrumental activities, a lower educational level, and a more frequent cognitive impairment as well as a higher frequency of depressive symptoms drew a significantly worse psychosocial profile of women in our cohort than those of the men. In addition, men lived with a partner more often than women.

Female gender was associated with worse global and dimension-specific QoL compared with male gender. Crude (unadjusted) scores of the MLHFQ were higher in women than in men (MLHFQ overall summary score: 49 ± 23 vs. 43 ± 24; *P* value $<$ 0.001, respectively), indicating worse QoL in female gender. Similarly, women compared with men had worse scores in physical QoL (MLHFQ physical dimension score: 30 ± 13 vs. 25 ± 15; *P* value $<$ 0.001, respectively) and emotional QoL (MLHFQ emotional dimension score: 6 ± 5 vs. 4 ± 5; *P* value $<$ 0.001, respectively).

Determinants of quality of life in unadjusted analyses

We used univariate linear regression models to assess the influence of gender and other clinical and psychosocial characteristics on determinants of global health-related QoL and of each of its dimensions (physical, emotional, and social). As shown in *Table 2*, in these unadjusted analyses, female gender was associated with higher MLHFQ scores indicating poorer global, physical, and emotional QoL (QoL overall summary score: standardized coefficient β = 0.123; *P* value $<$ 0.001; QoL physical dimension: standardized coefficient β = 0.153; *P* value $<$ 0.001; QoL emotional dimension: standardized coefficient β = 0.162; *P* value $<$ 0.001). Univariate binary logistic regression models confirmed these findings: female gender was associated with worse global QoL (impaired global QoL: odds ratio [OR] 1.4, 95% CI [1.1, 1.8]; *P* value 0.007), worse physical QoL (impaired physical QoL: OR 1.6, 95% CI [1.2, 2.1]; *P* value $<$0.001), and worse emotional QoL (impaired emotional QoL: OR 1.9, 95% CI [1.4, 2.4]; *P* value $<$0.001). Interestingly, in linear regression models, female gender was associated with lower scores indicating better social QoL (QoL social dimension: standardized coefficient β = $-$0.081; *P* value = 0.007). This finding was confirmed in univariate logistic regression models where female gender was significantly associated with better social QoL (impaired social QoL: OR 0.6, 95% CI [0.4, 0.8]; *P* value 0.002) compared with men.

As shown in *Table 2*, several clinical factors were associated with MLHFQ scores in unadjusted analysis. Among these, heart rate, NYHA functional class, recent diagnosis, use of diuretics, N-terminal fraction of natriuretic propeptide type B levels and serum albumin showed the strongest association with global QoL. Moreover, important psychosocial determinants such as dependency for ADL and dependency for instrumental activities were also associated with global, physical and emotional QoL, but not with social QoL. Only depressive symptoms were associated with global score and the three individual dimension scores.

The role of gender in models adjusted for clinical determinants of QoL

In the clinical multivariable linear regression models adjusted for HF-related determinants of QoL (*Table S2* and *Figure 1*), female gender remained as an independent predictor of higher MLHFQ scores indicating worse global, physical and emotional QoL compared with men (QoL overall summary score: standardized coefficient β = 0.068; *P* value = 0.012; QoL physical dimension: standardized coefficient β = 0.068; *P* value = 0.012; QoL emotional dimension: standardized coefficient β = 0.127; *P* value $<$ 0.001). As observed in univariate analysis, female gender was an independent predictor of better social QoL (lower adjusted scores) than men in multivariable models adjusted for clinical factors (QoL social dimension: standardized coefficient β = $-$0.072; *P* value = 0.013).

Table 2 Univariate linear regression models exploring interaction between gender (female and male) and other demographic, clinical and psychosocial determinants and QoL overall summary score and its physical, emotional and social dimension

	QoL overall summary score			QoL physical dimension			QoL emotional dimension			QoL social dimension		
	βSc	R^2	*P* value	βSc	R^2	*P* value	βSc	R^2	*P* value	βSc	R^2	*P* value
Demographic and disease-related determinants												
Gender, women *vs*. men	0.123	0.015	<0.001	0.153	0.023	<0.001	0.162	0.026	<0.001	−0.081	0.007	0.007
Age, 1 year	0.016	0.000	0.599	0.116	0.013	<0.001	−0.004	0.000	0.900	−0.258	0.067	<0.001
Systolic blood pressure, mmHg	−0.099	0.010	0.001	−0.080	0.006	0.008	−0.078	0.006	0.009	−0.081	0.007	0.007
Heart rate, 1 bpm	0.143	0.020	<0.001	0.134	0.018	<0.001	0.116	0.013	<0.001	0.075	0.006	0.012
NYHA functional class, III–IV *vs*. I–II	0.242	0.059	<0.001	0.243	0.059	<0.001	0.207	0.043	<0.001	0.090	0.008	0.003
HF Hospitalization previous year, yes vs. no	0.386	0.149	<0.001	0.408	0.166	<0.001	0.194	0.038	<0.001	0.153	0.023	<0.001
HF diagnosis<3 months (recent), yes vs. no	0.271	0.073	<0.001	0.309	0.095	<0.001	0.086	0.007	0.004	0.102	0.011	0.001
Time since HF diagnosis, 1 day	−0.123	0.015	<0.001	−0.153	0.023	<0.001	−0.001	0.000	0.964	−0.048	0.002	0.112
LVEF, 1%	0.061	0.004	0.040	0.119	0.014	<0.001	0.026	0.001	0.380	−0.102	0.010	0.001
HFpEF, yes vs. no	0.075	0.006	0.012	0.125	0.016	<0.001	0.034	0.001	0.263	−0.079	0.006	0.008
Ischaemic aetiology, yes vs. no	−0.058	0.003	0.051	−0.088	0.008	0.003	−0.027	0.001	0.371	−0.015	0.000	0.610
Comorbidities												
Hypertension, yes vs. no	0.087	0.008	0.004	0.127	0.016	<0.001	0.040	0.002	0.179	−0.042	0.002	0.157
Diabetes mellitus, yes vs. no	0.105	0.011	<0.001	0.096	0.009	0.001	0.070	0.005	0.020	0.040	0.002	0.186
Previous MI, yes vs. no	0.013	0.000	0.665	−0.026	0.001	0.386	0.010	0.000	0.727	0.041	0.002	0.167
CKD, yes vs. no	0.096	0.009	0.001	0.114	0.013	<0.001	0.075	0.006	0.013	−0.021	0.000	0.476
Anaemia, yes vs. no	0.053	0.003	0.074	0.056	0.003	0.061	0.031	0.001	0.302	−0.027	0.001	0.362
Iron deficiency, yes vs. no	0.084	0.007	0.005	0.103	0.011	0.001	0.016	0.000	0.593	−0.012	0.000	0.686
Treatments												
ACEI or ARBs, yes vs. no	−0.094	0.009	0.002	−0.116	0.013	<0.001	−0.039	0.002	0.189	0.026	0.001	0.388
Beta-blockers, yes vs. no	−0.093	0.009	0.002	−0.115	0.013	<0.001	−0.037	0.001	0.216	0.007	0.000	0.804
MRA, yes vs. no	−0.069	0.005	0.022	−0.113	0.013	<0.001	−0.042	0.002	0.157	0.123	0.015	<0.001
Diuretics, yes vs. no	0.165	0.027	<0.001	0.194	0.038	<0.001	0.061	0.004	0.041	0.064	0.004	0.032
Antiplatelet or anticoagulant therapy, yes vs. no	0.025	0.001	0.408	0.022	0.000	0.462	0.037	0.001	0.211	−0.038	0.001	0.208
Laboratory												
Haemoglobin, g/dL	−0.043	0.002	0.153	−0.059	0.004	0.047	−0.052	0.003	0.085	0.072	0.005	0.016
Creatinine, mg/dL	0.081	0.007	0.007	0.085	0.007	0.005	0.043	0.002	0.147	0.028	0.001	0.354
NT-proBNP, pg/mL	0.125	0.016	<0.001	0.141	0.020	<0.001	0.054	0.003	0.071	0.029	0.001	0.338
Serum albumin, g/dL	−0.213	0.045	<0.001	−0.224	0.050	<0.001	−0.130	0.017	<0.001	−0.89	0.008	0.003
Psychosocial determinants												
Barthel Index, 1 point	−0.173	0.030	<0.001	−0.187	0.035	<0.001	−0.186	0.035	<0.001	−0.008	0.000	0.795
Dependency for ADL, yes vs. no	0.198	0.039	<0.001	0.242	0.059	<0.001	0.192	0.037	<0.001	−0.037	0.001	0.250
Lawton test, 1 point	0.216	0.047	<0.001	0.240	0.058	<0.001	0.225	0.051	<0.001	−0.021	0.000	0.500
Dependency instrumental activities, yes vs. no	0.107	0.011	0.001	0.164	0.027	<0.001	0.098	0.010	0.002	−0.108	0.012	<0.001
Literacy												
Illiterate	0.062	0.004	0.048	0.072	0.005	0.021	0.089	0.008	0.005	−0.046	0.002	0.146
Primary school	0.058	0.003	0.064	0.076	0.006	0.016	0.032	0.001	0.313	−0.021	0.000	0.502
Secondary school	−0.048	0.002	0.128	−0.048	0.002	0.125	−0.064	0.004	0.040	0.030	0.001	0.344
University school	−0.061	0.004	0.052	−0.093	0.009	0.003	−0.015	0.000	0.639	0.020	0.000	0.524
Advanced university degree	−0.068	0.005	0.030	−0.095	0.009	0.002	−0.045	0.002	0.049	0.031	0.001	0.321
Significant cognitive impairment, yes vs. no	0.008	0.000	0.816	0.018	0.000	0.580	0.071	0.005	0.033	−0.088	0.008	0.008
Poor family function, yes vs. no	0.064	0.004	0.044	0.026	0.001	0.420	0.097	0.009	0.002	0.068	0.005	0.031
Self-perceived social support (Duke Scale), 1 point	−0.082	0.007	0.011	−0.001	0.000	0.978	−0.161	0.026	<0.001	−0.163	0.027	<0.001
Poor social support, yes vs. no	0.032	0.001	0.313	−0.011	0.000	0.728	0.085	0.007	0.008	0.094	0.009	0.003

(*Continues*)

Table 2 (continued)

	QoL overall summary score			QoL physical dimension			QoL emotional dimension			QoL social dimension		
	*β*Sc	R^2	*P* value	*β*Sc	R^2	*P* value	*β*Sc	R^2	*P* value	*β*Sc	R^2	*P* value
Score in the Geriatric Depression Scale (GDS), 1 point	0.237	0.056	<0.001	0.135	0.018	<0.001	0.428	0.183	<0.001	0.149	0.022	<0.001
Depressive symptoms, yes vs. no	0.193	0.037	<0.001	0.115	0.013	<0.001	0.350	0.123	<0.001	0.114	0.013	<0.001
Living with a partner, yes vs. no	−0.067	0.005	0.028	−0.091	0.008	0.003	−0.070	0.005	0.021	0.052	0.003	0.087

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease, defined as date <60 mL/min/1.73 m^2; eGFR, estimated glomerular filtration; HF, heart failure; HFpEF, heart failure with preserved ejection fraction ≥50; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal fraction of natriuretic propeptide type B; NYHA, New York Heart Association functional class; QoL, quality of life.

Note: Anaemia was defined according to the WHO Criteria. Dependency for ADL, defined as Barthel Index ≤99 points. Dependency instrumental activities, defined as Lawton test <8 points. Significant cognitive impairment was defined as abnormal Mini Mental State Examination or Pfeiffer Tests adjusted for age and literacy. Poor Family Function was defined as Apgar Test <10 points. Poor social support was defined as Duke Scale 47 points (corresponding to scores below to Q1). Depressive symptoms were defined as Geriatric Depression Scale (GDS) ≥ 5 points.

Multivariate logistic regression analyses adjusted for HF-related determinants of QoL (clinical model) confirmed the independent association of female gender with impaired global (OR 1.6, 95% CI [1.1, 2.3]; *P* value 0.005), physical (OR 1.5, 95% CI [1.0, 2.1]; *P* value 0.018) and emotional QoL (OR 2.1, 95% CI [1.5, 2.9]; *P* value < 0.001). As observed in univariate logistic regression models, female gender was an independent predictor of better social QoL in multivariable models adjusted for clinical determinants (OR 0.6, 95% CI [0.4, 0.9]; *P* value 0.039) compared with men.

Other factors that remained significantly associated with overall MLHFQ summary scores in multivariable models only including clinical determinants of QoL were age (standardized coefficient β = −0.148; *P* value < 0.001), NYHA functional Class III or IV (standardized coefficient β = 0.163; *P* value < 0.001) and hospitalization previous year (standardized coefficient β = 0.269; *P* value < 0.001). These factors were also associated with the three individual domains of QoL.

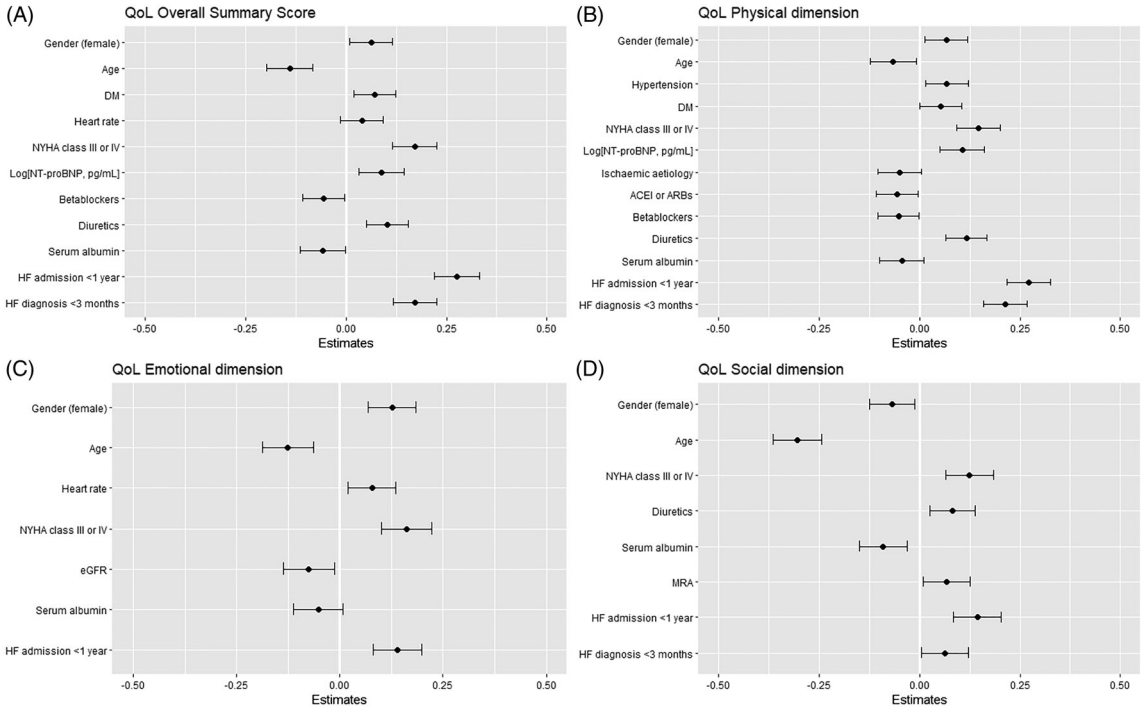
The role of gender in models adjusted for psychosocial determinants of QoL

As shown in *Table S3* and *Figure 2*, models only including psychosocial determinants of QoL showed that differences according to gender in overall (global QoL), physical, emotional and MLHFQ summary scores were no longer significant. In these models, several psychosocial factors were associated with QoL. Dependency on instrumental activities was the stronger independent determinant of global QoL and was the only psychosocial factor associated with higher scores (indicating worse QoL) for global and the three specific dimension scores. Lower literacy was associated with impaired global and physical QoL, depressive symptoms with impairment in global and emotional QoL, and social support was associated with social QoL.

The role of gender in comprehensive adjusted models including clinical and psychosocial determinants of QoL

We finally wanted to assess the role of gender on QoL in the context of both clinical and psychosocial determinants of self-perceived health status. We accordingly designed several multivariable linear regression models including gender, age, and all determinants explored in the clinical and psychosocial models to generate new comprehensive models including all these factors. As shown in *Table S4* and *Figure 3*, in comprehensive models taking into account clinical and psychosocial determinants, female gender was no longer an independent predictor of impaired QoL compared with male gender.

Figure 1 Standardized β coefficients and standard errors obtained using multivariate linear regression analysis evaluating the association between clinical determinants and quality of life (QoL) overall summary score (*A*), QoL physical dimension score (*B*), QoL emotional dimension score (*C*) and QoL social dimension score (*D*). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DM, diabetes mellitus; eGFR, estimated glomerular filtration; HF, heart failure; NTproBNP, N-terminal fraction of natriuretic propeptide type B; NYHA, New York Heart Association.



This was particularly true for the association between female gender and overall MLHFQ summary scores (standardized coefficient β = 0.018; *P* value 0.642) and physical MLHFQ dimension scores (standardized coefficient β = 0.034; *P* value 0.353). Interestingly, female gender was significantly associated with higher emotional MLHFQ dimension scores (standardized coefficient β = 0.071; *P* value 0.042) indicating worse emotional QoL and this association was independent from important clinical and psychosocial determinants included in this model. In contrast, as shown in unadjusted linear regression models, female gender was significantly associated with lower social MLHFQ dimension scores (standardized coefficient β = −0.079; *P* value 0.035) indicating better social QoL despite adjusting for self-perceived social support, family function, and dependency, along with other important prognostic clinical factors.

Discussion

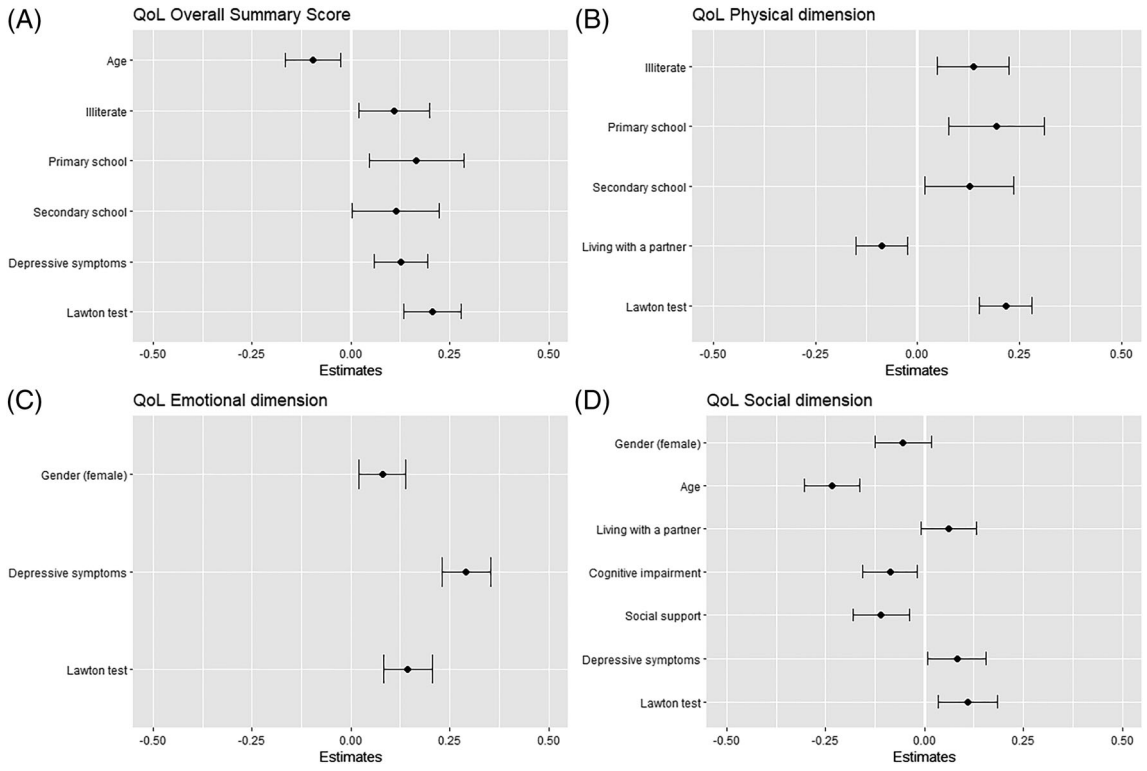
In this study, we have found that the gap in health-related QoL between men and women with HF can be, at least, partially explained by the interaction between biological and psychosocial factors. Clinical factors are the main drivers of QoL. However, the contribution of psychosocial factors is essential to definitively understand the role of gender in patient-reported outcomes.

We have found that female gender is an independent predictor of poorer overall, physical and emotional QoL in models adjusted only for biological factors. The trend is reversed in the social dimension: female gender predicts better social QoL compared with male gender. Interestingly, this influence is cancelled out in comprehensive models that include both biological and psychosocial factors.

There are few studies that have analysed the influence of gender on QoL in HF. Most of these focused on determining the existence of the gap between both genders based on small samples and obtaining disparate results on many occasions.[15,16,19,39–42] On the contrary, our study has been specifically designed to explain this phenomenon. In consequence, we report for the first time how the interaction of physical and psychosocial factors contributes to explain the differences in QoL between men and women with HF.

In our analysis, we have found a clinical (biological) and psychosocial profile consistent with previous studies.[15,16,43] Specifically, that women develop HF in older age, that they have preserved LVEF more frequently and less ischaemic heart disease than men. They also report a poorer QoL and a worse functional class. The psychosocial profile in terms of years of literacy, cognitive function, dependency on basic and instrumental ADL or depressive symptoms, among

Figure 2 Standardized β coefficients and standard errors obtained using multivariate linear regression analysis evaluating the association between psychosocial determinants and quality of life (QoL) overall summary score (*A*), QoL physical dimension score (*B*), QoL emotional dimension score (*C*), and QoL social dimension score (*D*).



others, is also markedly worse in the female gender. The scope of our analysis exceeds the previous ones because those were basically limited to describing these differences in several clinical contexts, for example, according to LVEF or in different populations. The sense of the results was maintained in all these contexts. Unlike these studies, our analysis seeks to respond to the causes that justify this fact, proposing integrative models of the physical and psychosocial reality of the HF patient.

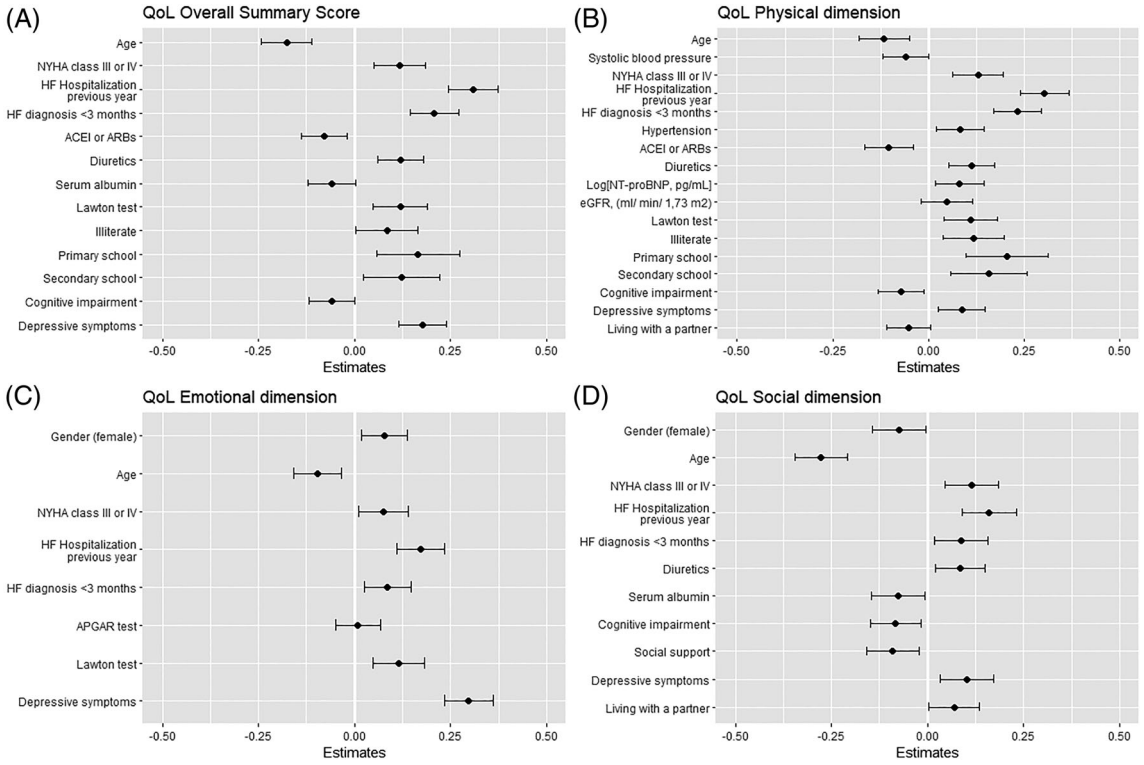
In this study, we used the MLHFQ to assess health-related QoL. In recent years, the HF-specific questionnaires have become one of the most important tools to predict adverse events. Given their ability to predict mortality and hospitalization, they allow improving the precision of decision making and the choice of services offered to these patients. A systematic, standardized comparison of available measures by Garin *et al*. identified the MLHFQ as one of the instruments with the best properties with an EMPRO overall score of 60.7 (55.2–65.9) only preceded by the KCCQ with an overall score of 64.4 (60.2–81.9).[20] The MLHFQ is especially useful when self-administration of the questionnaire is of interest. Moreover, the recent definition of the social domain allows a refined evaluation of the social dimension of health-related QoL. Its use is supported by extensive international experience, has been translated into more than 30 languages, and has demonstrated its psychometric validity in many studies.[44] In addition, this instrument has been translated into Spanish and evaluated in the Spanish population[31] and in primary care.[32]

As a novelty, in this work we have used the social dimension suggested and validated by Garin *et al*.[8] Interestingly, we have found that the scores in this domain were better in women compared with men, just the opposite findings observed in the other three dimension evaluated. These data are opposite to those found in other studies where the social dimension was better in the male gender.[19] The causes of these discrepancies are not clear, although factors related to the measurement instrument itself (few items included) as well as the sociocultural influence could explain it.

Several previous studies had described a markedly worse psychosocial profile in women than in men in the setting of HF based on factors similar to ours.[19,39,45] Some authors have hypothesized that this would explain the differences in health-related QoL. We demonstrate this hypothesis using integrative models that capture the influence of biological and psychosocial factors at the same time. Indeed, this approach provides a more realistic insight of the factors that determine patient-reported measures of QoL in real-world patients.

Biological factors, such as NYHA class or HF hospitalizations in the past year, provide most of the predictive power of

Figure 3 Standardized β coefficients and standard errors obtained using multivariate linear regression analysis evaluating the association between all clinical and psychosocial determinants and quality of life (QoL) overall summary score (*A*), QoL physical dimension score (*B*), QoL emotional dimension score (*C*), and QoL social dimension score (*D*). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DM, diabetes mellitus; eGFR, estimated glomerular filtration; HF, heart failure; NTproBNP, N-terminal fraction of natriuretic propeptide type B; NYHA, New York Heart Association.



these models (adjusted R^2). This finding is consistent with previous studies that have revealed that the physical component has, by far, a greater weight in determining QoL of HF patients.[46–48] The weight of psychosocial variables in the predictive capacity of the models is much less, but we believe that they are essential to definitively understand the role of gender on QoL. Future research is needed to confirm this effect of psychosocial determinants and expand the knowledge about their interaction with clinical factors to determine the HF-patients QoL.

Limitations

This analysis has the intrinsic limitations of cross-sectional studies. The simultaneous measurement of the QoL and the biological and psychosocial factors does not allow evaluating QoL changes with a temporal perspective or to establish causal relationships. The analysis was carried out on a sample of patients representative of a subgroup of specific HF patients in the hospital setting. It is not possible to determine whether the results would hold in other subgroups of HF patients such as HF patients living in the community. The single-centre design is an additional limitation so that results may not be transferable to other healthcare settings.

The specific instrument used to measure QoL, MLHFQ, is one of the most widespread and with the most experience in use, but it has its own limitations. First, the selection of the items considered to compute subscales may vary between studies; second, the instrument has a limited power to assess QoL in patients with mild HF due to floor effect[21]; third, a multidimensional assessment of QoL may be limited using the overall summary score of the instrument[49]; and fourth, construct validity is not homogeneous across all items.[50] In addition, personality, a psychosocial factor that has been related to outcomes in patients with chronic HF, has not been directly assessed in this study.[51]

Finally, the patients in this study were recruited between January 2004 and January 2014. In these years, the paradigm of HF treatment, especially in HFrEF, has undergone changes that could modulate the role of gender in health related QoL. Future studies in this field are warranted.

Conclusions

In this single-centre, observational, prospective analysis conducted with a large sample of chronic HF patients, we have found that the gap in health-related QoL between men and women may be partially explained by the interaction between biological and psychosocial factors. Clinical factors are the main drivers of QoL in HF patients. However, the contribution of psychosocial factors is essential to definitively understand the role of gender in this field.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Patient flow diagram of the enrolment in the DAMOCLES study for present analysis.
Table S1. Minnesota Living with Heart Failure Questionnaire (MLHFQ) and its individual item scores.
Table S2. Multivariate linear regression analyses evaluating the association of demographic and disease-related (clinical) factors with QoL overall summary score, QoL physical dimension, QoL emotional dimension and QoL social dimension of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) using backward stepwise methods.
Table S3. Multivariate linear regression analyses evaluating the association of psychosocial factors with QoL overall summary score, QoL physical dimension, QoL emotional dimension and QoL social dimension of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) using backward stepwise methods.
Table S4. Multivariate linear regression analyses evaluating the association of all demographic, disease-related (clinical) and psychosocial factors with QoL overall summary score, QoL physical dimension, QoL emotional dimension and QoL social dimension of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) using backward stepwise methods.

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