# Patient reported outcome in HFpEF: Sex-specific differences in quality of life and association with outcome ☆

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## ARTICLE INFO

## ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is associated with poor quality of life (QoL), or patient reported outcome (PRO). Despite female predominance in HFpEF, sex-specific differences in PROs remain poorly studied. We assessed PRO measures and their association with HF-severity and outcome in HFpEF by sex.
Methods and results: In 378 patients with HFpEF from the KaRen study, EQ-5D-3L® and Minnesota Living with Heart Failure Questionnaire® (MLHFQ) were assessed. Characteristics and comorbidities were largely similar in women (n = 212, 57%) and men. Women expressed worse QoL in EQ-5D-3L®(EQ-VAS), independent of age and HF-severity, mean (SD), 57 (20) vs. 61 (19), p = 0.010. There was no difference in MLHFQ, 31 (21) vs. 29 (21), p = 0.269.
Spearman's correlations with HF-severity (NYHA-class) were for MLHFQ in women $r_s$ 0.37 vs. men 0.41, p for both <0.001, and for EQ-VAS $r_s$ −0.28, p = 0.001 vs. −0.45, p < 0.001. Correlations with natriuretic peptides were for MLHFQ $r_s$ 0.21, p = 0.003 in women vs. men 0.27, p < 0.001, and for EQ-VAS $r_s$ −0.17 vs. −0.27, p both < 0.001.
Associations between PRO and the composite of HF hospitalisation or all-cause death were present in men only, adjusted HR per 5 units increase in MLHFQ 1.06, 95% confidence interval (CI) 1.01–1.11, p = 0.02 and EQ-VAS, HR 0.93, 95% CI 0.88–0.98, p = 0.010.
Conclusion: In HFpEF, women had worse general but similar disease specific QoL compared to men. QoL was more strongly associated with HF-severity in men, and associated with outcomes only in men. In women with HFpEF, QoL appears less determined by HF itself and potentially more by other unknown factors.

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## 1. Introduction

Heart failure with preserved ejection fraction (HFpEF) constitutes half of the world's HF population, is a major health problem and remains without evidence based treatment [1]. As patient centred care is becoming more emphasized, interest in patient reported outcome (PRO) and health related quality of life (HRQoL) is increasing both in clinical decision making and intervention evaluation [2]. Notably, the Food and Drug Administration (FDA) emphasizes the use of PROs as endpoints in clinical trials through the FDA Patient Focused Drug Development Initiative [3].

Patients with HF with reduced ejection fraction (HFrEF) experience impaired QoL, and women with HFrEF rate lower QoL than men independent of left ventricular (LV) function [4]. As in HFrEF, QoL is impaired in HFpEF [5,6]. In contrast to in HFrEF, the female predominance in HFpEF is striking, and sex-specific traits in cardiovascular structure and susceptibility to comorbidity-driven structural and functional changes seem to contribute to an increased risk of HFpEF in women [7,8]. Sex-specific differences in QoL in HFpEF have, to our knowledge, not been studied.

Therefor we assessed HRQoL by sex in an unselective cohort of patients with HFpEF through two widely used and validated PRO measures. The generic, EQ-5D-3L®, and the disease specific, Minnesota Living with Heart Failure Questionnaire® (MLHFQ) were used and the associations of generic and disease specific PRO with HF severity and outcome in women and men were investigated.

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## 2. Methods

### 2.1. Study population

The Karolinska Rennes (KaRen) was a prospective, bi-national, observational study in patients with HFpEF, which has been previously described [9,10]. Patients were included during an acute HF presentation (n = 539). Inclusion criteria were signs and symptoms of HF according to Framingham criteria, B-type natriuretic peptide (BNP) >100 ng/L or N-terminal pro BNP (NT-proBNP) >300 ng/L, and left ventricular ejection fraction (LVEF) ≥45% by echocardiography within the first 72 h of the acute presentation. The aim was to enrol patients similar to those observed in community-based or epidemiological studies, wherefore exclusion criteria were mainly related to states impeding patients from completing the study [9]. In total 387 patients completed QOL questionnaires but considering that KaRen was designed before the new definition of HFpEF [11], 9 patients with LVEF 45–49% were excluded. In the present study the 378 patients with LVEF ≥50% completing the 4–8 weeks follow up visit and QoL questionnaires, were included.

### 2.2. Baseline clinical data

At the 4–8 week visit in stable state, patients underwent clinical examination, blood sampling, electrocardiogram (ECG), echocardiography, and QoL assessment. Blood samples were collected in the fasting state and analysed by local hospital laboratory. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [12].

Echocardiography and ECG data were assessed by core-labs. The 12 lead ECGs were analysed at Karolinska University Hospital and the echocardiograms were recorded using Vivid7 or ViVide9 ultrasound systems (GE Healthcare, Horten, Norway) and analysed using Echopac PC BT 12 instrumentation and software (GE Healthcare, Horten, Norway) at the Rennes University Centre for Clinical Research; methods have been described previously [13].

### 2.3. Quality of life questionnaires

Patients completed two validated HRQoL forms during the visit, the generic EQ-5D-3L® [14,15] and the disease specific; MLHFQ [16]. Instruments in French and Swedish were used according to study site and all 378 patients completed both questionnaires.

The EQ-5D-3L® contains a descriptive part with five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with three response options (no problems, some problems, and extreme problems). The second part, the EQ Visual Analogue Scale (EQ-VAS) records the patient's self-rated global health on a VAS-scale where the endpoints are labelled "Best Imaginable Health State" (100) and "Worst imaginable health state" (0), and hence higher values of EQ-VAS denotes better QoL [14,15,17].

The MLHFQ is a HF specific instrument with 21 items covering the effects on QoL of symptoms, functional limitations, and psychological reactions associated with HF or HF treatment. Response options range from no limitation (0) to very much limited (5). A total score of 0–105 is given and a higher score indicates worse QoL [16,18].

### 2.4. Outcomes

The patients were followed until September 2012 when patient's status was assessed by review of charts, telephone contact or by national population registries, and adjudicated by local investigators. The primary endpoint was the composite of all-cause death or hospitalisation for HF. No patient was lost to follow up.

### 2.5. Ethics

The study conformed to the Declaration of Helsinki, had ethics approval by the local ethics committees in Sweden and in France and all participants provided written informed consent [19].

### 2.6. Statistics

Baseline clinical data are presented by sex as mean and standard deviation (SD), and analysed with two sample *t*-test. Biochemistry data are presented as median and interquartile range (IQR) and analysed with Wilcoxon rank sum test due to absence of normal distribution (assessed graphically). Categorical baseline data are presented as numbers and percentages and analysed with Pearson's chi-squared test, except for NYHA-class where Fisher's exact test was used due to low number of expected cases.

Measurements of natriuretic peptides were missing in 31 (8%) of patients, measured as NT-proBNP in 312 (83%) patients, and as BNP in 35 (9%) patients. To include both NT-proBNP and BNP, natriuretic peptides were analysed as quartiles based on the entire population in subsequent analyses, taking the risk of bias due to small number of patients with BNP-measurements into consideration.

Data of QoL from part 1 of the EQ-5D-3L® are presented graphically for the three levels in each of the five dimensions. The three response levels were dichotomized into having or not having any problems and analysed with Chi Square Test. Part two of EQ-5D-3L® (EQ-VAS) and MLHFQ data are presented as mean and standard deviation (SD) and were analysed by sex by ANCOVA, crude and adjusted for age and HF severity as NYHA-class and quartiles of NT-proBNP/BNP respectively in two separate analyses.

Spearman's coefficient was used to assess the correlation of EQ-VAS, as a measure of global QoL and the HF specific MLHFQ, with different markers of HF severity; NYHA-class, quartiles of B-type natriuretic peptides, and mitral inflow to mitral relaxation velocity ratio (E/e') as a measure of degree of diastolic dysfunction in women and men respectively. The correlation between the two PRO instruments (MLHFQ and EQ-VAS) was also assessed.

The association of MLHFQ and EQ-VAS, with the composite endpoint in women and men respectively, was analysed with Cox proportional hazards model, crude ("Model 1") and in two multivariable models. In "Model 2", adjusted for age, kidney function (eGFR), and the following comorbidities: diabetes (DM), anaemia, chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD), and in "Model 3" adjusted for the covariates in "Model 2" and also quartiles of B-type natriuretic peptides. Comorbidities were chosen as clinically relevant and possibly influencing QoL and 5 units change in score in the PROs was chosen as a clinically relevant change.

All p-values were 2-sided and statistical significance was set at 0.05. Statistical analyses were performed in Stata, StataCorp 2015, *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.

## 3. Results

### 3.1. Baseline characteristics, comorbidities and treatment

A total of 378 patients were studied in stable state 4–8 weeks after acute HF. Of these, 212 were women (57%). Baseline characteristics are shown in Table 1. Women were older, mean (SD), 77 (9) vs. 75 (9) years, p = 0.014, had higher LVEF, 64 (7) vs. 62 (6) %, p = 0.005. Women also had signs of higher filling pressures measured as E/e' 14 (7) vs. 11 (5), p = 0.001, and heart rate, 72 (17) vs. 68 (13) beats/min p = 0.022. NT-proBNP levels were similar, median (IQR), 1408 (507–2369) vs. 1480 (611–2840) ng/L, p = 0.17 while the patients where BNP was analysed (n = 35), women had higher levels than men, 301 (229–476) vs. 108 (98–570) ng/L, p = 0.041. Kidney function measured as eGFR CKD-EPI was similar in both sexes.

Comorbidities did not differ between sexes except for CAD which was less common in women, 27 vs. 38% (p = 0.016) and anaemia, defined as haemoglobin <120 g/L for women and <130 g/L in men, 35 vs. 51% (p = 0.004). There was no difference in therapy.

### 3.2. Quality of life

In EQ-5D-3L® part one, women expressed considerably more difficulties related to mobility 53 vs. 41%, (p = 0.019), usual activities 46 vs. 33% (p = 0.013), and anxiety and depression 51 vs. 39% (p = 0.013). There were only nominal differences related to self-care 22 vs. 17%, p = 0.230, and pain/discomfort 60 vs. 53%, p = 0.179, Fig. 1. Regarding perceived global health, women rated worse QoL than men in EQ-VAS, mean (SD), 57 (20) vs. 61 (19), p = 0.027. The difference persisted after adjustment for age and HF severity through B-type natriuretic peptides, p = 0.010 and was borderline significant after adjustment for age and NYHA-class, p = 0.056. There was no difference between men and women in MLHFQ, mean (SD), 31 (21) vs. 29 (21), univariable p = 0.329, Fig. 2.

### 3.3. Associations between quality of life and markers of heart failure severity

Both MLHFQ and EQ-VAS correlated with HF severity measured as either NYHA-class or as quartiles of natriuretic peptides in both sexes; but with numerically weaker associations in women. Spearman's correlations between MLHFQ and NYHA-class were in women; $r_s$ 0.37 vs. in men 0.41, p for both <0.001 and with quartiles natriuretic peptides in women; $r_s$ 0.21, p = 0.003 vs. in men 0.27, p < 0.001. The correlation of EQ-VAS with NYHA-class were in women $r_s$ −0.28, p < 0.001 and in men $r_s$ −0.45, p < 0.001. Similarly, EQ-VAS and natriuretic peptides correlated in women, $r_s$ −0.17, p = 0.018 and in men, $r_s$ = −0.27, p < 0.001. There was no significant correlation between MLHFQ and E/e' in neither women, nor men; $r_s$ 0.13 p = 0.088 vs. 0.09 p = 0.320 while the EQ-VAS correlated weakly with E/e' in men only, $r_s$ = −0.21, p = 0.018 vs. in women $r_s$ −0.13, p = 0.085. The two different