Johansson Isabelle (Orcid ID: 0000-0002-4577-0530)

Factors associated with health-related quality of life in heart failure in 23,000 patients from 40 countries: Results of the G-CHF Research Program

Short title: Correlates of health-related quality of life in HF

Isabelle Johansson MD, PhD[1,2], Kumar Balasubramanian BSc[1], Shrikant Bangdiwala PhD[1,2], Lisa Mielniczuk MD[3], Camilla Hage RN, PhD[4, 5], Sanjib Kumar Sharma MD[6], Kelly Branch MD, MSc[7], Jun Zhu MD[8], Kristian Kragholm MD, PhD[9], Karen Sliwa MD, PhD[10], Francois Alla[11, 12], Gerald Yonga MD[13], Ambuj Roy, MD[14], Andres Orlandini MD[15], Alex Grinvalds BSc[1], Tara McCready PhD, MBA[1], Nana Pogosova MD[16], Stefan Störk MD, PhD[17], John J.V. McMurray MD[18], David Conen MD, MPH[1, 2], Salim Yusuf DPhil[1, 2]
On behalf of the GCHF investigators

[1] Population Health Research Institute, McMaster University, Hamilton, Canada
[2] Department of Health Research Methods, Evidence, and Impact, McMaster University Faculty of Health Sciences, Hamilton
[3] Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario
[4] Karolinska University Hospital Heart, Vascular and Neuro Theme Heart Failure Section
[5] Karolinska Institutet Department of Medicine Cardiology Unit
[6] B P Koirala Institute of Health Sciences, Dharan, Nepal
[7] Division of Cardiology, University of Washington School of Medicine, Seattle
[8] 3 Fuwai Hospital, CAMS & PUMC, China
[9] The Faculty of Medicine, Aalborg University Hospital
[10] Cape Heart Institute, Department of Medicine and Cardiology, Faculty of Health Sciences, University of Cape Town
[11] Bordeaux Population Health Research Center. Inserm, Université de Bordeaux, Bordeaux, France;
[12] Prevention department, CHU, Bordeaux, France. Bordeaux Population Health Research Center. Inserm, Université de Bordeaux, Bordeaux, France;
[13] Shool of Medicine, University of Nairobi.
[14] Department of Cardiology, All India Institute of Medical Sciences, New Delhi, Delhi, India
[15] ECLA (Estudios Clínicos Latino America)
[16] National Medical Research Center of Cardiology, Moscow, Russia
[17] Comprehensive Heart Failure Center, University and University Hospital Würzburg, Würzburg, Germany
[18] BHF Cardiovascular Research Centre, University of Glasgow, Scotland

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Corresponding author: Pre publication Isabelle Johansson, Post publication: Salim Yusuf
Address: Population Health Research Institute, McMaster University, Hamilton, Canada
David Braley Cardiac, Vascular, and Stroke Research Institute
237 Barton St. E, Hamilton, ON, L8L 2X2, Canada
Tel: 905-521-2100 ext 41085; Email: isabelle.johansson@phri.ca

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Abstract (250)

Aims: To examine clinical and social correlates of health-related quality of life (HRQL), in patients with heart failure (HF) from high- (HIC), upper middle- (UMIC), lower middle-(LMIC) and low-income (LIC) countries.

Methods and Results: Between 2017 and 2020, we enrolled 23,292 patients with HF (32% inpatients, 61% men) from 40 countries in the Global Congestive Heart Failure Study. We recorded HRQL at baseline using Kansas City Cardiomyopathy Questionnaire (KCCQ)-12. In a cross-sectional analysis, we compared age- and sex-adjusted mean KCCQ-12 summary scores (SS: 0-100, higher=better) between patients from different country income levels. We used multivariable linear regression examining correlations (estimated coefficients) of KCCQ-12-SS with sociodemographic-, comorbidity-, treatment- and symptom-covariates. The adjusted model (37 covariates) was informed by univariable findings, clinical importance and backward selection. Mean age was 63 years and 40% were in NYHA class III-IV. Average HRQL was 55±0.5. It was 62.5 (95% CI 62.0-63.1) in HIC, 56.8 (56.1-57.4) in UMIC, 48.6 (48.0-49.3) in LMIC, and 38.5 (37.3-39.7) in LICs ($p<0.0001$). Strong correlates (estimated coefficient [95% CI]) of KCCQ-12-SS were NYHA class III vs class I/II (-12.1 [-12.8 to -11.4] and class IV vs. class I/II (-16.5 [-17.7 to -15.3]), effort dyspnea (-9.5[-10.2 to -8.8]) and living in LIC vs. HIC (-5.8[-7.1 to -4.4]). Symptoms explained most of the KCCQ-12-SS variability (partial $R^2=0.32$ of total adjusted $R^2=0.51$), followed by sociodemographic factors ($R^2=0.12$). Results were consistent in populations across income levels.

Conclusion: The most important correlates of HRQL in HF patients relate to HF symptom severity, irrespective of country-income level.

Funding: Bayer **Key words**: Health status, heart failure, correlates, global, quality of life

Introduction

Poor health-related quality of life (HRQL) is common in heart failure (HF) and strongly predicts death and HF hospitalization in all regions of the world.[1-3] Improving HRQL is therefore of major importance for HF patients. Patient-reported outcomes such as the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) systematically and reproducibly quantify HRQL.[4-6] Previously identified correlates of poorer patient-reported HRQL are symptom severity, depressive symptoms, younger age and female sex,[7-10] but important gaps in knowledge remain. Most importantly, the majority of available data include Western populations from high-income countries. It is therefore unknown whether the factors affecting HRQL can be generalized to non-Western populations residing in countries with different health care systems and income levels. If HRQL characterized with a simple, widely available, inexpensive and standardized tool such as the KCCQ-12 is shown to be associated with the same clinical correlates across countries at different income level or in different geographic regions, it would further the usefulness of this tool in research as well as in clinical practice.

The Global Congestive Heart Failure (G-CHF) study is a large contemporary multinational HF cohort,[11] that offers the opportunity to identify factors associated with self-reported HRQL in a well characterized HF population, and to assess whether these differ across high- (HIC), upper middle- (UMIC), lower middle- (LMIC) and low-income (LIC) countries.

Methods

Study population

The design of the prospective G-CHF study has been described previously.[11] This cross-sectional analysis of baseline G-CHF data comprises over 23,000 patients enrolled between

December 2016 and December 2020, from 40 countries. We assigned the income level to each country according to the 4 categories specified by the World Bank's 2017 listing: (HIC [n=8653], UMIC [n=5785], LMIC [n=6945] and LIC [n=1909]). World Bank criteria and the number of patients from each participating country is described in Table I of the Supplement. Adult patients with established HF seen in outpatient clinics or inpatient hospital wards were eligible and selected through convenience sampling. The diagnosis of HF was established by the patient's local physician. Patients were excluded from the current analysis if HRQL was not assessed at baseline (n=140 [0.5%]).

HRQL assessment

Self-reported HRQL was measured at the baseline visit using the self-administered KCCQ-12.[12] KCCQ and the shortened KCCQ-12 surveys have been validated in diverse HF populations from North and South America, Western Europe, and to a limited extent in parts of Asia, Africa, Eastern Europe and the Middle East.[4, 12-18]

The KCCQ-12 consists of 12 items quantifying 4 domains of patient's HF-related health status (supplemental Figure I); i) physical limitation (question 1a-c), ii) symptom frequency (question 2-5), iii) general quality of life (question 6 and 7) and iv) social limitation (question 8a-c). Answers are recorded on a Likert scale with 5 or 7 points, and converted into scores ranging from 0-100 for each domain (higher scores reflect better HRQL). The average of the 4 domains makes up the KCCQ-12-summary score (SS; range 0-100), which was the primary outcome for HRQL in this analysis.

KCCQ-12 is often summarized in 25-point categories, with the following score representations: 0-24 points, very poor; 25-50 poor to fair; 50-74 fair to good; and 75-100 good

to excellent HRQL.[19] A 5-point difference in KCCQ-12-SS is considered a minimally clinically important difference in scores, while 10 points is considered to be of moderate or major clinical importance.[19] The G-CHF study used culturally and linguistically validated versions of the KCCQ-12 (https://www.cvoutcomes.org/licenses).

Statistical analysis

Distributions of baseline patient characteristics were summarized overall and by KCCQ-12-SS 25-point range categories. Continuous variables are presented as means and standard deviations (SD) and categorical variables as counts and proportions. We used ANOVA to compare between-group differences in means and Chi-squared tests to compare differences in frequency distribution. We used a general linear model to compare age- and sex-adjusted means and 95% confidence intervals (CI) of the KCCQ-12 summary and domain scores across country income level strata. We first examined associations between continuous variables graphically with scatter plots, and calculated Pearson's correlation coefficients. We then applied simple and multiple linear regression models to examine the association between patient level characteristics and KCCQ-12-SS (scale 0-100).

We examined the normality assumption for the dependent variable using summary and variability estimates, residuals and q-q-plots. We evaluated the effect of one unit change in the independent variables on KCCQ-12-SS, based on the point estimates (estimated coefficients) and their 95% CIs. We used multiple covariate adjustment in the linear regression models to account for confounding bias that was expected in our cross-sectional observational study of a highly diverse HF population. Among 120 potential variables, we selected covariates for the multivariable models based on their impact on KCCQ-12-SS univariably (estimated coefficient

≥5 [chosen because a difference in 5 points is considered a minimally clinically important difference[19]] and $p<0.05$), or based on their clinical interest (Table II in the Supplement). We examined best model fit by adjusted R^2-values, and assessed multicollinearity using variance inflation factor and Eigenvalues. We also used the backward selection procedure in exploratory models set to eliminate variables that did not reach a significance level of 0.1. We used partial R^2-estimates to understand the contribution to the variability in KCCQ-12-SS of 4 different groups of covariates (sociodemographic, comorbidities, treatments and signs and symptoms of congestion; Supplement Table II).

As a sensitivity analysis, we implemented a principal component technique on categorical variables, as explained in detail in the Supplement. The principal component analyses were performed by 4 categories of variables: 1) sociodemographic covariates 2) comorbidities, 3) treatment and 4) signs and symptoms of congestion (Figure II in Supplement).

We constructed a final multivariable model (n=37 variables) and two sensitivity analyses models; 1) a 'Principal component model' (n=14 variables), where individual covariates were replaced by principal component variables to the extent possible and 2) an 'Expanded model' including all the individual covariates that made up the the principal components (n=36 variables); (Tables II-III of the Supplement). The final multivariable models were run overall and stratified by country income level; and in sensitivity analyses by geographical region and by inpatient or outpatient status. In an additional sensitivity analysis we constructed the same simple and multivariable models but replacing income level by geographic region, to explore the predictors of KCCQ-12-SS by geographical region. Lastly, left ventricular ejection fraction (LVEF) was not significantly correlated with KCCQ-12-SS univariably but because of clinical

interest, it was included in the model in a sensitivity analysis. Two tailed p-values of <0.05 were considered to be nominally significant. All analyses were performed with SAS 9.4.

Ethical considerations

The study protocol was approved by each site's local Ethics committee and the study was conducted according to the Declaration of Helsinki.

Results

Patient characteristics

Baseline characteristics overall and by KCCQ-12-SS 25-point categories are presented in Table 1. The study population consisted of 23,292 patients with a mean (SD) age of 63.1 (14.9) years. Overall, 60.9% were men, 39.8% were in NYHA symptoms class III or IV and 31.6% were hospitalized at enrollment. The average KCCQ-12-SS was 55.0 (27). Compared to higher score-categories, patients with KCCQ-12-SS in the lowest category (poorest HRQL) were more often recruited from an inpatient setting, had HF symptoms in NYHA class III or IV and had signs and symptoms of congestion. Patients with KCCQ-12-SS in the lowest category were more frequently women, came from lower income countries, and rural locations, and were less educated and less often had health insurance. Patients with KCCQ-12-SS in the lowest score-category were less likely to receive beta blockers or a renin angiotensin system blocker (RAS [angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor]) but more likely to be taking loop diuretics or digoxin.

Patient characteristics and HRQL by country income level

Patients from lower income country-groups were more often younger, females, recruited from an inpatient setting, more often presented with NYHA functional class III or IV and more frequently showed signs and symptoms of congestion (Table 2). Patients from LICs and LMICs were less likely to receive beta blockers, RAS blockers (only in LMICs) and mineralocorticoid receptor blockers (MRA, compared with UMICs but not HICs), but more likely to be taking loop diuretics or digoxin.

Age- and sex-adjusted mean scores (95% CI) were 38.5 (37.3 to 39.7) in LIC, 48.6 (48.0 to 49.3) in LMIC, 56.8 (56.1 to 57.4) in UMIC, and 62.5 (62.0 to 63.1) in HIC, p for trend <0.0001 (Table 2). The proportion of very poor HRQL (<25 points) was 41% in LICs, 21% in LMICs, 14% in UMICs, and 10% in HICs, respectively (p for trend <0.0001; Figure 1a). Conversely, the proportion with good or very good HRQL (≥50 points) was 34% in LICs, 50% in LMICs, 60% in UMICs and 69% in HICs, respectively (p for trend <0.0001). Differences in scores between the country income level sub-groups were consistent across the various KCCQ-12 domains (Figure 1b-e).

Correlates of HRQL in the G-CHF population

Correlates of KCCQ-12-SS in the overall population identified in the multivariable model are described in Table 3. The total adjusted R^2 in this model was 0.51. Most of the significant correlates of the KCCQ-12-SS were related to congestive signs and symptoms (partial R^2 0.32) followed by sociodemographic factors (0.12), treatments (0.04) and comorbidities (0.03). The strongest correlates of poorer KCCQ-12-SS were higher NYHA class, inpatient status, dyspnea on normal exertion, paroxysmal nocturnal dyspnea, presence of a third heart sound, bilateral ankle edema and hepatomegaly, all of which had estimated coefficients ≥5, which means at least

5 points lower KCCQ-12-SS when a specific symptom was present (Table 3). In this model (after adjusting for all the above variables), participants from a LIC had on average a 5.8 points lower KCCQ-12-SS compared with those from a HIC, while those from a UMIC had a 1.5 points higher score than those from HICs on average. Significant correlates of better KCCQ-12-SS were male sex, urban residence, higher education, and treatment with a RAS blocker, which were associated with 1.9 to 3.2 points higher average KCCQ-12-SS compared with their respective counterparts. The presence or absence of comorbidities had a small but statistically significant association with the KCCQ-12-SS.

Sensitivity analyses using the principal components and expanded models provided similar results (Table IV in the Supplement). Including geographic region instead of country income level as an independent covariate, showed nearly identical results with unchanged effect sizes for the model covariates (Table V in the Supplement). LVEF remained non-significantly correlated with KCCQ-12-SS. The multivariable model run in inpatients and outpatients showed results that were largely consistent with the overall analysis (Table IX in the Supplement).

Correlates of KCCQ-12-SS by country income level

Correlates of KCCQ-12-SS stratified by country income level for the final adjusted model are described in Table 4. Patient characteristics that remained clinically meaningful correlates of KCCQ-12-SS (i.e., absolute value of effect estimates $\geq$5) across all country income levels were all related to congestive HF signs and symptoms (worse NYHA functional class, inpatient status at enrollment, paroxysmal nocturnal dyspnea, dyspnea on normal exertion). Male sex and urban living location remained independent sociodemographic correlates associated with better KCCQ-12-SS, but with a weaker effect than symptoms. While diuretics (a marker of

congestion) were strongly and inversely associated with KCCQ-12-SS, other HF treatments and comorbidities had a weaker association with KCCQ-12-SS across most country income levels.

Independent correlates of the KCCQ-12-SS across country income levels were mostly consistent, with some exceptions. COPD predicted 3.5 points worse KCCQ-12-SS in HICs but had less to non-significant effect on scores in the other country income groups. Ischemic etiology was associated with a worse score (3.9 points) in LMICs but did not meaningfully impact KCCQ-12-SS in the other income strata. Treatment with digoxin predicted a 3.0 points lower KCCQ-12-SS in LICs but was not significantly associated with KCCQ-12-SS in the other country income groups. Having a previous diagnosis of HF predicted worse scores in HICs and UMICs but better scores in LMICs and LICs.

A larger proportion of the variance in average KCCQ-12-SS was explained in poorer vs. richer countries (adjusted R^2: 0.65 in LICs, 0.51 in UMICs, 0.44 in LMICs and 0.44 in HICs; Table 4 bottom panel). The partial R^2-analysis was consistent with observations in the overall population indicating that variables related to signs and symptoms of congestion accounted for the majority of the KCCQ-12-SS variability, followed by sociodemographic characteristics. Signs and symptoms accounted for a larger proportion of the variability in LICs, but less in the populations enrolled from richer countries, suggesting that patients in LIC may not have their symptoms of congestion as well controlled compared to those in richer countries. By contrast, sociodemographic covariates as well as treatments for HF accounted for a relatively larger proportion of the variability in HICs and less in lower income level groups. These results were consistent in various sensitivity analyses (Tables VI and VII in the Supplement).

Discussion

We previously demonstrated that HRQL quantified by KCCQ-12 in people with HF varied considerably by geographic region but that KCCQ-12 predicted mortality and morbidity everywhere.[3] In the current analysis, we explored the correlates of HRQL in a large cohort of HF patients from 40 countries across 4 different income levels, taking into account a wide range of clinical and sociodemographic variables. We found that signs and symptoms of congestion were the strongest independent correlates of HRQL, and these explained most of the variability in HRQL. This finding was consistent across country income groups, although LIC remained a significant predictor of lower HRQL scores after multivariable adjustment. Thus, it appears that severity of HF is the most important correlate of HRQL in HF, globally.

KCCQ-12 is designed to capture the impact of HF on HRQL, and takes account of the impact of symptoms on usual activities, social interactions, and satisfaction with life.[12] It is therefore not surprising that NYHA class (a physician assessment of functional limitation due to symptoms), inpatient status and congestive signs and symptoms are the variables most strongly associated with patient-reported HRQL.[7, 20, 21, 22, 23] Importantly, our study also shows that these correlates of poorer HRQL are very similar across different countries and income levels. Previous observational studies examining the factors associated with HRQL were mostly conducted in HICs and UMICs.[7, 24, 25] Few multinational studies have reported on the correlates of HRQL measured using the KCCQ across geographic regions and income settings.[20, 21] These reports are in line with our observations, in that they found different markers of disease severity to be among the strongest correlates with HRQL, and these also explained most of the regional variation in HRQL in HF patients. This was consistent in those with preserved as well as reduced ejection fraction.[20, 21]

In our analysis, patients from LICs and LMICs experienced more congestive signs and symptoms than those from richer countries, and these factors explained a larger proportion of the overall HRQL variability in these settings than in UMICs and HICs. Greater congestion and worse HRQL were observed despite more frequent use of loop diuretics and digoxin (probably markers of disease severity) in LICs and LMICs, in addition to similar rates of use of other key HF drugs (beta blockers, RAS blockers and MRAs) across countries at different income levels. Treatments as a group explained only a minor proportion of the variability of HRQL. Use of most HF treatments was weakly correlated with self-reported HRQL in all groups, which is in line with findings from previous cross-sectional analyses.[7, 20] The exception was loop diuretic use (and digoxin use in LICs), which was associated with a greater negative impact on HRQL in LICs compared with wealthier countries, in keeping with same finding for signs and symptoms of congestion. This suggets that the dominant feature influencing HRQL in lower income settings are markers of congestion (and treatment targeted at congestion). Whether the greater burden of congestive symptoms and lower HRQL seen in LMICs and LICs reflects more severe underlying cardiomyopathy, inadequate treatment (despite more diuretic therapy), poorer treatment adherence, lower access to care or other factors discussed below is uncertain. However, our observations should not discount the important findings from major clinical trials where some new drugs improved HRQL over time in HFrEF and HFpEF.[26-32] Achieving better symptom control in patients with HF, and identifying patients earlier in the course of disease, especially those from LICs and LMICs may improve their HRQL. There was a surprising discrepancy in the correlation between HRQL and having a previous diagnosis of HF, which was associated with better HRQL in LICs and LMICs but worse HRQL in HICs and UMICs. The reason behind this observation is not clear. It is possible that it is related to differences in access

to care. In HICs and UMICs where treatment is usually more readily available, a previous diagnosis of HF may reflect disease progression and possibly poorer health status. In LMICs and LICs, it may instead be that having a previous diagnosis of HF means that the patient will have ongoing HF treatment and therefore hopefully a better symptom control and hence better health status than somebody who is newly diagnosed. This however requires further exploration.

Sociodemographic characteristics were the second most important group of variables explaining the variance of the KCCQ-12-SS, with female sex, residing in a rural community and coming from a LIC as the most important correlates. In contrast to signs and symptoms, sociodemographic characteristics explained more of the variability in HRQL in HICs than in LMICs and LICs. This suggests that in HIC, where symptom control is better, other features influence HRQL to a greater extent. Female sex has repeatedly proven to be inversely correlated with self-reported HRQL in the general community as well as in HF populations.[7, 20, 21, 33] Our observations extends this pattern to a global HF population and although underlying reasons were not further explored, it is interesting to note that the impact of female sex on HRQL was stronger in HICs and UMICs than in LMICs and LICs. This may again be a reflection of the greater overall symptom burden in LMICs and LICs and the comparatively lesser importance of other variables in poorer countries.

Markers of lower socioeconomic level such as lower income, lower education level or residence in rural areas, have yielded inconsistent results regarding their association with poorer disease-specific HRQL.[34, 35, 36, 37, 38, 7, 25, 39] Our study provides important insights. First, the small but significantly better HRQL in urban areas across all settings suggests rural residence may be a marker of restricted access to health care, which is more accentuated in poorer countries. This information is important for health care providers, policy makers and health

system organizers. Second, there was a strong univariable association between decreasing country income level and poorer HRQL, but after taking all other patient characteristics into consideration, only patients from LICs had a significantly lower HRQL than HIC-patients. Hence disease severity at presentation, much more than sociodemographic or cultural diversities between the groups of patients from different country income levels, seem to explain most of the observed differences in self-reported HRQL.

Comorbidity related characteristics explained only a minor proportion of the variability of HRQL overall as well as within each country income sub-group. Well established prognostic risk factors in HF such as diabetes, atrial fibrillation or COPD had little impact on HRQL. This is somewhat surprising and partly contrasts previous findings.[7, 20, 21] Notably, the effect of comorbidities on HRQL was somewhat larger in wealthier countries, which is in line with previous data mainly obtained in HICs and UMICs.[7, 20, 40] Some of this variation may be explained by differences in diagnosis and disease severity across different settings.

There are some potential limitations of our study ; First, given the cross-sectional design, we are not able to determine a cause and effect relationship or directionality between the examined correlates with HRQL. Second, we did not assess the association of mental illness with HRQL, which has previously shown to be of importance.[7] Third, we did not examine the impact of HF treatment dose, treatment adherence or biochemical markers such as natriuretic peptides on KCCQ-12-SS. Hence, despite extensive adjustment for known variables, residual confounding can still occur in the highly diverse G-CHF population. Fourth, we do not have information on longitudinal changes in KCCQ-12-SS at the present time. Fifth, although an R^2 of 0.51 suggests that a fair amount of inter-individual variability in KCCQ-12 SS is explained by the variables included in the analyses, there is a substantial degee of variability that remains

unexplained. Future analyses from a G-CHF sub-study of 4000 people, which will have serial measures of HRQL over several years and additionally measures of six-minute walk test, lung function, frailty, depression and various biomarkers could provide further insights. Sixth, the fully adjusted multiple linear regression models had ≈ 23% missing data. However, given the overwhelming consistency of our results, the large remaining sample size and that the observed characteristics were largely similar between the population we used in the final model versus those who had missing data (Table X in the supplements), this should not affect the interpretation of our results.

Versions of the KCCQ-12 in different languages were used. The general consistency of our results shows that the same measurable characteristics explain better or worse HRQL across widely different groups and in different country income levels and geographic regions. This indicates that the KCCQ-12 provides a standardized and reproducible summary of the patients own experience and that the HRQL construct captured by the KCCQ-12 is valid in most regions of the world.

Conclusions

The most important correlates of HRQL in patients with HF are signs and symptoms of congestion, a finding which was consistent across different country income groups. This supports the use of the KCCQ-12 as a useful tool for assessing health status in HF in most parts of the world. Improving symptom control is likely to have a big impact on HRQL, especially in LICs.

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Conflicts of interest

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References

1. Luo N, Teng TK, Tay WT, Anand IS, Kraus WE, Liew HB, Ling LH, O'Connor CM, Pina IL, Richards AM, Shimizu W, Whellan DJ, Yap J, Lam CSP, Mentz RJ, Asian HF, investigators H-A. Multinational and multiethnic variations in health-related quality of life in patients with chronic heart failure. Am Heart J 2017;**191**:75-81.

2. Kristensen SL, Martinez F, Jhund PS, Arango JL, Bělohlávek J, Boytsov S, Cabrera W, Gomez E, Hagège AA, Huang J, Kiatchoosakun S, Kim KS, Mendoza I, Senni M, Squire IB, Vinereanu D, Wong RC, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJ. Geographic variations in the PARADIGM-HF heart failure trial. Eur Heart J 2016;**37**(41):3167-3174.

3. Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA, Kamath D, Alhabib K, Bayes-Genis A, Budaj A, Dans ALL, Dzudie A, Probstfield JL, Fox KAA, Karaye KM, Makubi A, Fukakusa B, Teo K, Temizhan A, Wittlinger T, Maggioni AP, Lanas F, Lopez-Jaramillo P, Silva-Cardoso J, Sliwa K, Dokainish H, Grinvalds A, McCready T, Yusuf S, Investigators GC. Health-Related Quality of Life and Mortality in Heart Failure: The Global Congestive Heart Failure Study of 23 000 Patients From 40 Countries. Circulation 2021;**143**(22):2129-2142.

4. Kelkar AA, Spertus J, Pang P, Pierson RF, Cody RJ, Pina IL, Hernandez A, Butler J. Utility of Patient-Reported Outcome Instruments in Heart Failure. JACC Heart Fail 2016;**4**(3):165-75.

5. Masterson Creber R, Polomano R, Farrar J, Riegel B. Psychometric properties of the Kansas City Cardiomyopathy Questionnaire (KCCQ). Eur J Cardiovasc Nurs 2012;**11**(2):197-206.

6. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS, Cardiovascular Outcomes Research C. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J 2005;**150**(4):707-15.

7. Baert A, De Smedt D, De Sutter J, De Bacquer D, Puddu PE, Clays E, Pardaens S. Factors associated with health-related quality of life in stable ambulatory congestive heart failure patients: Systematic review. Eur J Prev Cardiol 2018;**25**(5):472-481.

8. Hwang SL, Liao WC, Huang TY. Predictors of quality of life in patients with heart failure. Jpn J Nurs Sci 2014;**11**(4):290-8.

9. Riedinger MS, Dracup KA, Brecht ML. Predictors of quality of life in women with heart failure. SOLVD Investigators. Studies of Left Ventricular Dysfunction. J Heart Lung Transplant 2000;**19**(6):598-608.

10. Son YJ, Song Y, Nam S, Shin WY, Lee SJ, Jin DK. Factors associated with health-related quality of life in elderly Korean patients with heart failure. J Cardiovasc Nurs 2012;**27**(6):528-38.

11. Joseph P, Dokainish H, McCready T, Budaj A, Roy A, Ertl G, Gomez-Mesa JE, Leong D, Ezekowitz J, Hage C, Lanas F, Maggioni AP, Sliwa K, Zhu J, Rouleau J, Balasubramanian K, Yusuf S, Investigators G-C. A multinational registry to study the characteristics and outcomes of heart failure patients: The global congestive heart failure (G-CHF) registry. Am Heart J 2020;**227**:56-63.

12. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes 2015;**8**(5):469-76.

13. Okello S, Abeya FC, Lumori BAE, Akello SJ, Moore CC, Annex BH, Buda AJ. Validation of heart failure quality of life tool and usage to predict all-cause mortality in acute heart failure in Uganda: the Mbarara heart failure registry (MAHFER). BMC Cardiovasc Disord 2018;**18**(1):232.

14. Nave-Leal E, Pais-Ribeiro J, Oliveira MM, Da Silva N, Soares R, Fragata J, Ferreira R. Psychometric properties of the portuguese version of the Kansas City cardiomyopathy questionnaire in dilated cardiomyopathy with congestive heart failure. Rev Port Cardiol 2010;**29**(3):353-72.

15. Comin-Colet J, Garin O, Lupon J, Manito N, Crespo-Leiro MG, Gomez-Bueno M, Ferrer M, Artigas R, Zapata A, Elosua R, group V-Ks. Validation of the Spanish version of the Kansas city cardiomyopathy questionnaire. Rev Esp Cardiol 2011;**64**(1):51-8.

16. Miani D, Rozbowsky P, Gregori D, Pilotto L, Albanese MC, Fresco C, Fioretti PM. The Kansas City Cardiomyopathy Questionnaire: Italian translation and validation. Ital Heart J 2003;**4**(9):620-6.

17. Patel H, Ekman I, Spertus JA, Wasserman SM, Persson LO. Psychometric properties of a Swedish version of the Kansas City Cardiomyopathy Questionnaire in a Chronic Heart Failure population. Eur J Cardiovasc Nurs 2008;**7**(3):214-21.

18. Huang W, Teng T-HK, Tay WT, Richards AM, Kadam U, Lawson CA, Shimizu W, Loh SY, Anand I, Lam CSP. Patient-reported outcomes in heart failure with preserved vs. reduced ejection fraction: focus on physical independence. ESC heart failure 2020;**7**(5):2051-2062.

19. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;**76**(20):2379-2390.

20. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W, Lefkowitz MP, Shi VC, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, McMurray JJV, Solomon SD, Investigators P-H. Health-Related Quality of Life in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial. JACC Heart Fail 2019;**7**(10):862-874.

21. Hamo CE, Heitner JF, Pfeffer MA, Kim HY, Kenwood CT, Assmann SF, Solomon SD, Boineau R, Fleg JL, Spertus JA, Lewis EF. Baseline distribution of participants with depression and impaired quality of life in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial. Circ Heart Fail 2015;**8**(2):268-77.

22. Cully JA, Phillips LL, Kunik ME, Stanley MA, Deswal A. Predicting quality of life in veterans with heart failure: the role of disease severity, depression, and comorbid anxiety. Behav Med 2010;**36**(2):70-6.

23. Greene SJ, Butler J, Spertus JA, Hellkamp AS, Vaduganathan M, DeVore AD, Albert NM, Duffy CI, Patterson JH, Thomas L, Williams FB, Hernandez AF, Fonarow GC. Comparison of New York Heart Association Class and Patient-Reported Outcomes for Heart Failure With Reduced Ejection Fraction. JAMA Cardiol 2021.

24. Naveiro-Rilo JC, Diez-Juarez MD, Flores-Zurutuza L, Rodriguez-Garcia MA, Rebollo-Gutierrez F, Romero Blanco A. [Quality of life in patients with heart failure: the perspective of primary health care]. Gac Sanit 2012;**26**(5):436-43.

25. Verma AK, Schulte PJ, Bittner V, Keteyian SJ, Fleg JL, Pina IL, Swank AM, Fitz-Gerald M, Ellis SJ, Kraus WE, Whellan DJ, O'Connor CM, Mentz RJ. Socioeconomic and partner status in chronic heart failure: Relationship to exercise capacity, quality of life, and clinical outcomes. Am Heart J 2017;**183**:54-61.

26. Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-Related Quality of Life Outcomes in PARADIGM-HF. Circ Heart Fail 2017;**10**(8).

27. Lewis EF, Kim HY, Claggett B, Spertus J, Heitner JF, Assmann SF, Kenwood CT, Solomon SD, Desai AS, Fang JC, McKinlay SA, Pitt BA, Pfeffer MA, Investigators T. Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial. Circ Heart Fail 2016;**9**(3):e001937.

28. Ekman I, Chassany O, Komajda M, Bohm M, Borer JS, Ford I, Tavazzi L, Swedberg K. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J 2011;**32**(19):2395-404.

29. Kosiborod MN, Jhund P, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL, Inzucchi SE, Koeber L, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, Bengtsson O, Lindholm D, Niklasson A, Sjostrand M, Langkilde AM, McMurray JJV. Effects of Dapagliflozin on Symptoms, Function and Quality of Life in Patients with Heart Failure and Reduced Ejection Fraction: Results from the DAPA-HF Trial. Circulation 2019.

30. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, Giannetti N, Januzzi JL, Pina IL, Lam CSP, Ponikowski P, Sattar N, Verma S, Brueckmann M, Jamal W, Vedin O, Peil B, Zeller C, Zannad F, Packer M, Committees EM-RT, Investigators. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. European heart journal 2021;**42**(13):1203-1212.

31. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, Lamba S, Sharma K, Khan SS, Chandra L, Gordon RA, Ryan JJ, Chaudhry SP, Joseph SM, Chow CH, Kanwar MK, Pursley M, Siraj ES, Lewis GD, Clemson BS, Fong M, Kosiborod MN. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med 2021;**27**(11):1954-1960.

32. Butler J, Filippatos G, Jamal Siddiqi T, Brueckmann M, Bohm M, Chopra VK, Pedro Ferreira J, Januzzi JL, Kaul S, Pina IL, Ponikowski P, Shah SJ, Senni M, Vedin O, Verma S, Peil B, Pocock SJ, Zannad F, Packer M, Anker SD. Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. Circulation 2022;**145**(3):184-193.

33. Dewan P, Rorth R, Jhund PS, Shen L, Raparelli V, Petrie MC, Abraham WT, Desai AS, Dickstein K, Kober L, Mogensen UM, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJV. Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women. J Am Coll Cardiol 2019;**73**(1):29-40.

34. Nesbitt T, Doctorvaladan S, Southard JA, Singh S, Fekete A, Marie K, Moser DK, Pelter MM, Robinson S, Wilson MD, Cooper L, Dracup K. Correlates of quality of life in rural patients with heart failure. Circ Heart Fail 2014;**7**(6):882-7.

35. Seid MA. Health-related quality of life and extent of self-care practice among heart failure patients in Ethiopia. Health Qual Life Outcomes 2020;**18**(1):27.

36. Zhang J, Gilmour S, Liu Y, Ota E. Effect of health literacy on quality of life among patients with chronic heart failure in China. Qual Life Res 2020;**29**(2):453-461.

37. Erceg P, Despotovic N, Milosevic DP, Soldatovic I, Zdravkovic S, Tomic S, Markovic I, Mihajlovic G, Brajovic MD, Bojovic O, Potic B, Davidovic M. Health-related quality of life in elderly patients hospitalized with chronic heart failure. Clin Interv Aging 2013;**8**:1539-46.

38. Gott M, Barnes S, Parker C, Payne S, Seamark D, Gariballa S, Small N. Predictors of the quality of life of older people with heart failure recruited from primary care. Age Ageing 2006;**35**(2):172-7.

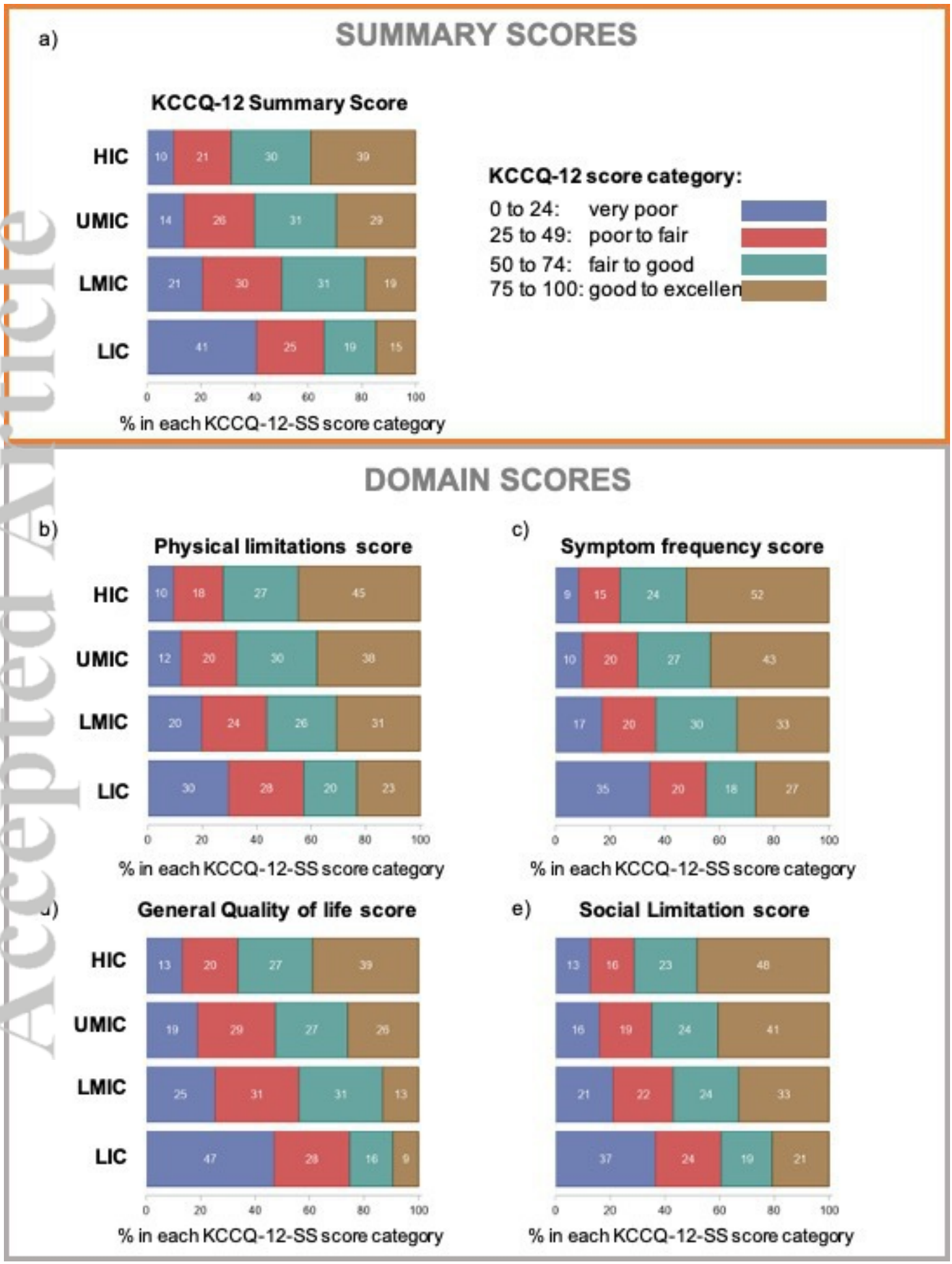
39. Khariton Y, Nassif ME, Thomas L, Fonarow GC, Mi X, DeVore AD, Duffy C, Sharma PP, Albert NM, Patterson JH, Butler J, Hernandez AF, Williams FB, McCague K, Spertus JA. Health Status Disparities by Sex, Race/Ethnicity, and Socioeconomic Status in Outpatients With Heart Failure. JACC Heart Fail 2018;**6**(6):465-473.

40. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002;**39**(7):1151-8.

Legends

Figure 1 Proportion of patients in each KCCQ-12 summary and domain score category, stratified by country income level. Patients from poorer countries exhibit a much worse health related quality of life in all domains covered by the KCCQ-12. Panel a) summary score (orange frame), b) physical limitation domain, c) symptom frequency domain, d) quality of life domain and e) social limitation domain. Numbers in boxes are proportions of the total in each KCCQ-12 score category. Between-country income level comparisons were significant ($p<0.001$) for the summary score and for all domains.

Graphical abstract. Signs and symptoms of congestion were the strongest independent correlates of HRQL and explained most of the variability in the KCCQ-12-SS. This was consistent across country income groups and most pronounced in LICs. Improved symptom control may have a big impact on HRQL, especially in LICs. *Estimates (estimated coefficients) after multivariable adjustment. Estimates indicate the change in mean KCCQ-12-SS by each unit change in the covariate. KCCQ-12-SS range (0 to 100, higher score=better HRQL). Abbreviations: Adj, adjusted; HF, Heart failure; HIC, High income country; KCCQ-12-SS, Kansas City Cardiomyopathy questionnaire-12 summary score; LIC, Low income country; LMIC, Lower-middle income country; NYHA, New York Heart Association; UMIC, Upper-middle income country **Partial R^2-values represents contribution of groups of covariates when added as follows: 1) Sociodemographic characteristics, 2) comorbidities, 3) treatments for HF and 4) signs and symptoms of congestion.



EJHF_2535_Figure 1.jpg

Table 1. Baseline characteristics by KCCQ-12-summary score stratified by 25-point categories

		KCCQ-12 Summary Score category			
	Missing	**Poor**	**Poor-Fair**	**Fair-Good**	**Good-Excellent**
Variable		**0-24**	**25-49**	**50-74**	**75-100**
		n=3870 16.6%	n=5898 25.3%	n=6874 29.5%	n=6650 28.5%
KCCQ-12-SS, mean (SD)	0	13.4 (7.5)	37.6 (7.3)	62.3 (7.4)	87 (7.6)
Demographics					
Age (years), mean (SD)	0	61.8 (17.0)	63.6 (15.2)	64.0 (14.3)	62.6 (13.9)
Male sex, n (%)	0	1977 (51.1)	3407 (57.8)	4194 (61.0)	4609 (69.3)
Recruited as hospital inpatient, n (%)	4	2369 (61.2)	2438 (41.4)	1843 (26.8)	712 (10.7)
Previous HF diagnosis	2	2846 (73.6)	4697 (79.6)	5802 (84.4)	6160 (92.6)
Country income level	0				
HIC		855 (22.1)	1856 (31.5)	2567 (37.3)	3375 (50.8)
UMIC		804 (20.8)	1510 (25.6)	1768 (25.7)	1703 (25.6)
LMIC		1431 (37.0)	2053 (34.8)	2171 (31.6)	1290 (19.4)
LIC		780 (20.2)	479 (8.1)	368 (5.4)	282 (4.2)
Region	0				
North America		258 (9.5)	612 (22.6)	808 (29.8)	1032 (38.1)
Western Europe		350 (9.2)	821 (21.5)	1136 (29.7)	1519 (39.7)
Eastern Europe		258 (14.2)	606 (33.4)	646 (35.6)	305 (16.8)
East Asia		233 (12.3)	583 (30.8)	679 (35.9)	399 (21.1)
South Asia		244 (8.2)	813 (27.3)	1180 (39.7)	737 (24.8)
Africa		1947 (36.4)	1522 (28.4)	1128 (21.1)	755 (14.1)
South America		362 (12.5)	624 (21.5)	803 (27.7)	1108 (38.3)
Middle East		218 (12.0)	317 (17.4)	494 (27.1)	795 (43.6)
Rural living location, n (%)	6	1287 (33.3)	1619 (27.5)	1697 (24.7)	1313 (19.8)
Education level, n (%)	83				
None/primary school		2185 (21.3)	2685 (26.2)	2928 (28.5)	2463 (24.0)
Secondary school		1096 (14.2)	1992 (25.8)	2371 (30.7)	2260 (29.3)
Post-secondary		580 (11.1)	1198 (22.9)	1556 (29.8)	1895 (36.2)
Health insurance, n (%)	12	1857 (48.0)	3546 (60.2)	4262 (62)	4714 (70.9)
Primary HF etiology ischemic, n (%)	1208	1046 (28.5)	2180 (39.0)	2821 (43.3)	2826 (44.8)
NYHA functional class, n (%) III and IV	117	3185 (82.8)	3283 (56.1)	1998 (29.2)	742 (11.2)
LVEF category, n (%)	4090				
<30%		1062 (20.6)	1303 (25.3)	1422 (27.6)	1362 (26.5)
30-39%		913 (17.2)	1420 (26.7)	1529 (28.8)	1449 (27.3)
40-49%		599 (14.8)	1045 (25.7)	1256 (30.9)	1161 (28.6)
≥50%		873 (18.7)	1234 (26.4)	1379 (29.5)	1195 (25.5)
Hemoglobin (g/L)	4157	123.3 (22.6)	127.8 (21.7)	129.6 (20.7)	133.9 (19.0)

Systolic BP (mmHg)	64	122 (24.7)	123.6 (22.1)	123.7 (20.5)	124.1 (19.5)
Disease History, n (%)					
Hypertension	2	2453 (63.4)	3991 (67.7)	4617 (67.2)	4223 (63.5)
Valvular heart disease	1	1038 (26.8)	1600 (27.1)	1469 (21.4)	1157 (17.4)
Coronary artery disease	1	1031 (26.6)	2311 (39.2)	2810 (40.9)	2605 (39.2)
Atrial fibrillation	2	1028 (26.6)	1796 (30.5)	1950 (28.4)	1614 (24.3)
COPD	1	427 (11.0)	775 (13.1)	730 (10.6)	506 (7.6)
Diabetes mellitus	2	1127 (29.1)	1912 (32.4)	2183 (31.8)	1967 (29.6)
Stroke	1	326 (8.4)	489 (8.3)	523 (7.6)	394 (5.9)
Hyperlipiaemia	2	986 (25.5)	1992 (33.8)	2473 (36)	2698 (40.6)
Sleep apnea	1	387 (10)	564 (9.6)	561 (8.2)	496 (7.5)
HF related signs and symptoms, n (%)					
Paroxysmal nocturnal dyspnea	8	2788 (72.1)	2642 (44.8)	1693 (24.6)	561 (8.4)
Neck vein distention	9	2049 (53.0)	1580 (26.8)	1112 (16.2)	555 (8.4)
Rales	9	2049 (53.0)	1740 (29.5)	1078 (15.7)	354 (5.3)
Third heart sound	8	1177 (30.4)	798 (13.5)	424 (6.2)	158 (2.4)
Bilateral ankle edema	10	2793 (72.2)	3122 (53.0)	2604 (37.9)	1192 (17.9)
Dyspnea on normal exertion	10	3558 (92.0)	4882 (82.8)	4579 (66.6)	2584 (38.9)
Hepatomegaly	9	1336 (34.5)	859 (14.6)	449 (6.5)	176 (2.7)
Treatment and devices, n (%)					
Beta blocker	8	2758 (71.3)	4649 (78.9)	5485 (79.8)	5778 (86.9)
RAS blocker	7	2664 (68.9)	4317 (73.2)	5378 (78.2)	5563 (83.7)
Mineralocorticoid receptor antagonist	10	2170 (56.1)	3369 (57.2)	3838 (55.8)	3532 (53.1)
Loop diuretic	8	3574 (92.4)	5102 (86.6)	5366 (78.1)	4383 (65.9)
Digoxin or digitoxin	7	1004 (26.0)	1068 (18.1)	979 (14.2)	685 (10.3)
Implanted cardiac device	2	78 (2.0)	174 (3.0)	272 (4.0)	345 (5.2)

Abbreviations: BP, Blood pressure; COPD, Chronic obstructive pulmonary disease; HF, Heart failure; HIC, High income country; KCCQ, Kansas City Cardiomyopathy questionnaire; LIC, Low income country; LMIC, Lower-middle income country; LVEF, Left ventricular ejection fraction; NYHA, New Your Heart Association; RAS, Renin angiotensin system (includes angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor); SD, Standard deviation; UMIC, Upper-middle income country.

Table 2. Baseline characteristics stratified by country income level.

		Country income level			
	Missing	**HIC**	**UMIC**	**LMIC**	**LIC**
Variable		n=8653 (37%)	n=5785 (25%)	n=6945 (30%)	n=1909 (8%)
Demographics					
Age (Years), mean ± SD	0	67.2 (12.9)	65.3 (13.8)	57.8 (15.4)	57.1 (17.1)
Male sex, n (%)	0	5896 (68.1)	3555 (61.5)	3853 (55.5)	883 (46.3)
Recruited as hospital inpatient, n (%)	4	2116 (24.5)	1731 (29.9)	2916 (42)	599 (31.4)
Previous diagnosis of HF, n (%)	2	7969 (92.1)	5232 (90.5)	5001 (72)	1303 (68.3)
Rural living location, n (%)	6	1535 (17.8)	1070 (18.5)	2497 (36)	814 (42.6)
Education level, n (%)	83				
None/primary school		2824 (32.6)	2766 (47.8)	3414 (49.1)	1257 (65.8)
Secondary School		3237 (37.7)	1929 (33.4)	2183 (31.4)	370 (19.4)
Post-Secondary		2520 (29.4)	1079 (18.7)	1348 (19.4)	282 (14.8)
Health insurance, n (%)	12	7709 (89.2)	5081 (87.9)	1197 (17.2)	392 (20.5)
NYHA class, n (%) III and IV	117	2726 (31.9)	2218 (38.4)	3123 (45.0)	1141 (59.8)
LVEF categories, n (%)	4090				
<30%		1943 (29.3)	1092 (22.7)	1542 (26.2)	572 (30.9)
30-39%		1811 (27.3)	1250 (26.0)	1762 (29.9)	488 (26.3)
40-49%		1442 (21.7)	1177 (24.5)	1089 (18.5)	353 (19.1)
≥50%		1445 (21.8)	1295 (26.9)	1501 (25.5)	440 (23.8)
Hemoglobin (g/L)	4157	130.3 (20.3)	132.7 (21.9)	126.1 (20.5)	124.1 (23.1)
eGFR* (mL/min/1.73m^2)	3788	61.1 (25.1)	67.7 (27.4)	68.2 (33.1)	72.8 (34.4)
Systolic BP (mmHg)	64	122.9 (19.9)	123.5 (19.7)	123.6 (22.6)	125.6 (27.7)
Pulse rate (bpm)	133	72.8 (14.6)	76.1 (16.0)	85 (18.1)	86 (19.1)
Disease History, n (%)					
Hypertension	2	6171 (71.3)	3999 (69.2)	3999 (57.6)	1115 (58.4)
Valvular heart disease	1	2090 (24.2)	1261 (21.8)	1529 (22)	384 (20.1)
Coronary artery disease	1	3774 (43.6)	2787 (48.2)	2034 (29.3)	162 (8.5)
Atrial fibrillation or flutter	2	3571 (41.3)	1510 (26.1)	1068 (15.4)	239 (12.5)
COPD	1	1212 (14)	733 (12.7)	420 (6.1)	73 (3.8)
Diabetes Mellitus	2	3407 (39.4)	1697 (29.3)	1831 (26.4)	254 (13.3)
Stroke	1	70 (3.7)	378 (5.4)	579 (10)	705 (8.2)
Hyperlipidemia	2	118 (6.2)	868 (12.5)	2498 (43.2)	4665 (53.9)

Sleep Apnea	1	46 (2.4)	385 (5.5)	317 (5.5)	1260 (14.6)
Signs and symptoms of congestion, n (%)					
Paroxysmal nocturnal dyspnea	8	1452 (16.8)	2084 (36.0)	2940 (42.3)	1208 (63.3)
Neck vein distention	9	1178 (13.6)	1368 (23.7)	1908 (27.5)	842 (44.1)
Rales	9	955 (11.0)	1455 (25.2)	2042 (29.4)	769 (40.3)
Third heart sound	8	286 (3.3)	358 (6.2)	1403 (20.2)	510 (26.7)
Bilateral ankle edema	10	2692 (31.1)	2576 (44.6)	3382 (48.7)	1061 (55.6)
Dyspnea on normal exertion	10	4419 (51.1)	4365 (75.5)	5303 (76.4)	1516 (79.4)
Hepatomegaly	9	238 (2.8)	787 (13.6)	1263 (18.2)	532 (27.9)
Treatment and devices, n (%)					
Beta blocker	8	7728 (89.3)	4809 (83.2)	4778 (68.8)	1355 (71.0)
RAS blocker	7	7110 (82.2)	4633 (80.2)	4610 (66.4)	1569 (82.2)
Mineralocorticoid receptor antagonist	10	4074 (47.1)	3693 (63.9)	4073 (58.7)	1069 (56.0)
Loop diuretic	8	6563 (75.9)	4095 (70.9)	6024 (86.8)	1745 (91.4)
Digoxin or digitoxin	7	745 (8.6)	943 (16.3)	1409 (20.3)	519 (27.2)
KCCQ-12 scores*, 95% CI					
KCCQ-12 summary score	-	62.5 (62.0 to 63.1)	56.8 (56.1 to 57.4)	48.6 (48.0 to 49.3)	38.5 (37.3 to 39.7)
KCCQ-12 physical limitation score	545	62.9 (62.3 to 63.6)	58.9 (58.1 to 59.7)	49.1 (48.4 to 49.8)	41.5 (40.1 to 42.8)
KCCQ-12 symptom frequency score	2	68.6 (68 to 69.2)	64.0 (63.3 to 64.7)	56.7 (56 to 57.4)	46.2 (44.9 to 47.5)
KCCQ-12 general quality of life score	13	55.7 (55.1 to 56.3)	46.6 (45.8 to 47.3)	38.7 (38.1 to 39.4)	27.7 (26.4 to 28.9)
KCCQ-12 social limitation score	988	62.9 (62.2 to 63.6)	57.2 (56.4 to 58)	49.7 (48.9 to 50.5)	38.2 (36.7 to 39.6)

*Average scores are adjusted for age and sex, possible scores range from 0 to 100 where higer means better health related quality of life.

Abbreviations: BP, Blood pressure; CI, Confidence interval, eGFR, Estimated glomerular filtration rate according to the MDRD (Modification of diet in renal disease) formula; HIC, High-income country; KCCQ, Kansas City Cardiomyopathy questionnaire; LVEF, Left ventricular ejection fraction; LIC, Low-income country; LMIC, Lower-middle income country; RAS, Renin angiotensin system (includes angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor); NYHA, New York Heart Association; SD, standard deviation; UMIC, Upper-middle income country.

Table 3. Correlates of KCCQ-12-SS in the G-CHF population in the multivariable model. Estimates (estimated coefficients) indicate the change in mean KCCQ-12-SS by each unit change in the covariate. Significant correlates are presented in bold, KCCQ-12-SS range (0 to 100, higher score=better HRQL).

	Multiple Linear Regression Model 1*		
Number of observations	23292		
Number used in model	17934		
Variables	**Estimate (95%CI)**	**P-value**	**Partial R^2 (% of total R^2) per covariate group****
Sociodemographic			0.12 (24%)
Living location, urban vs. rural	**2.14 (1.46 to 2.82)**	<.0001	
Age by 10-year increments	**-0.49 (-0.71 to -0.28)**	<.0001	
Male vs. female	**3.16 (2.54 to 3.78)**	<.0001	
Education level, referent: None/primary school			
Secondary school	0.09 (-0.59 to 0.76)	0.81	
Post-secondary school	**2.19 (1.41 to 2.96)**	<.0001	
Previous Diagnosis of HF	-0.13 (-0.97 to 0.7)	0.76	
Health insurance	-0.37 (-1.20 to 0.46)	0.38	
Country income level, referent: HIC			
UMIC	**1.48 (0.68 to 2.27)**	0.0003	
LMIC	-0.56 (-1.56 to 0.45)	0.28	
LIC	**-5.75 (-7.07 to -4.43)**	<.0001	
Comorbidities			0.03 (6.3%)
HF ischemic vs. non-ischemic etiology	**1.86 (1.24 to 2.48)**	<.0001	
Systolic BP (10 mmHg increments)	**0.31 (0.17 to 0.45)**	<.0001	
Hemoglobin level (10 g/L increments)	**0.23 (0.09 to 0.37)**	0.002	
Diabetes mellitus	**-1.04 (-1.67 to -0.4)**	0.001	
Atrial fibrillation	**-1.37 (-2.06 to -0.68)**	0.0001	
COPD	**-1.45 (-2.37 to -0.53)**	0.002	
Treatment			0.04 (8.3%)
Betablocker	0.35 (-0.41 to 1.10)	0.37	
RAS blocker	**1.88 (1.18 to 2.58)**	<.0001	
Digoxin/Digitoxin	-0.32 (-1.13 to 0.50)	0.45	
Loop diuretic	**-3.94 (-4.70 to -3.17)**	<.0001	
Mineralocorticoid receptor antagonist	0.28 (-0.32 to 0.89)	0.36	
Implanted cardiac device	1.57 (0.12 to 3.01)	0.03	
Signs and symptoms of congestion			0.32 (63.4%)
Inpatient vs. outpatient	**-7.01 (-7.72 to -6.3)**	<.0001	
NYHA functional class, referent: I or II			

class III	**-12.08 (-12.8 to -11.36)**	<.0001	
class IV	**-16.52 (-17.74 to -15.31)**	<.0001	
Paroxysmal nocturnal dyspnea	**-7.86 (-8.64 to -7.08)**	<.0001	
Neck vein distention	**-0.99 (-1.85 to -0.14)**	0.02	
Rales	**-1.61 (-2.44 to -0.78)**	0.0001	
Radiographic cardiomegaly	**-1.18 (-1.84 to -0.53)**	0.0004	
Acute pulmonary edema	**-2.21 (-3.33 to -1.10)**	0.0001	
Third heart sound	**-6.62 (-7.65 to -5.6)**	<.0001	
Increased JVP (>6 cm H_2O at right atrium)	1.15 (-0.08 to 2.38)	0.07	
Hepatojugular reflux	**1.85 (0.80 to 2.91)**	0.001	
Weight loss >4.5 kg the last 5 days in response to treatment	**-3.64 (-4.71 to -2.58)**	<.0001	
Bilateral ankle edema	**-5.00 (-5.67 to -4.32)**	<.0001	
Nocturnal cough	**-1.82 (-2.56 to -1.08)**	<.0001	
Dyspnea on normal exertion	**-9.51 (-10.22 to -8.8)**	<.0001	
Hepatomegaly	**-6.25 (-7.24 to -5.25)**	<.0001	
Pleural effusion	**-1.22 (-2.16 to -0.28)**	0.01	
Decrease in VC by 1/3 from maximum rec.	-0.90 (-1.81 to 0.01)	0.05	
Tachycardia (heart rate >120 beats/min)	0.36 (-0.66 to 1.38)	0.49	
Adjusted R^2			**0.51 (100%)**

Abbreviations: BP, Blood pressure; COPD, chronic obstructive pulmonary disease; HF, Heart failure; HIC, High income country; JVP, jugular vein pressure; KCCQ, Kansas City Cardiomyopathy questionnaire; LIC, Low income country; LMIC, Lower-middle income country; NYHA, New York Heart Association; RAS, Renin angiotensin system; UMIC, Upper-middle income country; VC, Vital capacity.

* Left ventricular ejection fraction was not significantly associated with KCCQ-12-SS in sensitivity analyses and was not included in the final model.

**Partial R^2-values represents contribution of groups of covariates when added in descending order.

Table 4. Multivariable model showing correlates of the KCCQ-12-SS stratified by country income level. Estimates (estimated coefficients) indicate the change in mean KCCQ-12-SS by each unit change in the covariate. Significant correlates in bold, covariate names in bold if significant across all income levels. KCCQ-12-SS range (0 to 100, higher score=better HRQL).

	Multiple Linear Regression Full model*			
	HIC	**UMIC**	**LMIC**	**LIC**
Number of observations	8653	5785	6945	1909
Number used in model	6759	4359	5205	1611
Variables	**Estimate (95%CI)**	**Estimate (95%CI)**	**Estimate (95%CI)**	**Estimate (95%CI)**
Sociodemographic				
Living location, urban vs. rural	**1.63 (0.36 to 2.89)**	**2.38 (0.76 to 4.01)**	**2.26 (1.20 to 3.31)**	**2.45 (0.55 to 4.36)**
Age by 10-year increments	**-0.48 (-0.88 to -0.07)**	-0.25 (-0.73 to 0.23)	**-0.39 (-0.75 to -0.04)**	-0.22 (-0.76 to 0.31)
Male vs. female	**3.88 (2.81 to 4.95)**	**3.40 (2.11 to 4.69)**	**2.58 (1.50 to 3.65)**	**1.75 (0.01 to 3.49)**
Education level, referent: None/primary school				
Secondary school	0.96 (-0.18 to 2.09)	-0.93 (-2.34 to 0.47)	0.44 (-0.74 to 1.61)	-0.69 (-2.98 to 1.61)
Post-secondary school	**3.01 (1.76 to 4.27)**	1.31 (-0.37 to 3.00)	**2.10 (0.70 to 3.50)**	-1.17 (-3.83 to 1.49)
Previous diagnosis of HF	**-2.23 (-4.11 to -0.36)**	**-5.73 (-7.78 to -3.68)**	**1.30 (0.09 to 2.51)**	**2.15 (0.26 to 4.03)**
Health insurance	1.42 (-0.16 to 3.00)	-0.18 (-2.15 to 1.79)	**-1.36 (-2.68 to -0.04)**	**-2.48 (-4.76 to -0.20)**
Comorbidities				
HF ischemic vs. non-ischemic etiology	**1.31 (0.32 to 2.30)**	1.02 (-0.25 to 2.30)	**3.85 (2.71 to 5.00)**	-0.07 (-2.34 to 2.19)
Systolic BP (10 mmHg increments)	**0.49 (0.24 to 0.74)**	**1.22 (0.90 to 1.54)**	-0.09 (-0.32 to 0.14)	-0.10 (-0.42 to 0.23)
Hemoglobin level (10 g/L increments)	**0.60 (0.34 to 0.86)**	**0.35 (0.05 to 0.64)**	**-0.30 (-0.55 to -0.05)**	-0.03 (-0.41 to 0.34)
Diabetes mellitus	**-1.23 (-2.23 to -0.23)**	**-2.76 (-4.08 to -1.45)**	-0.06 (-1.25 to 1.12)	0.91 (-1.63 to 3.44)
Atrial fibrillation	**-1.95 (-3.01 to -0.90)**	-0.59 (-2.01 to 0.83)	**-1.82 (-3.20 to -0.44)**	1.55 (-1.13 to 4.23)
COPD	**-3.51 (-4.88 to -2.14)**	1.19 (-0.57 to 2.96)	-1.50 (-3.51 to 0.52)	1.61 (-2.78 to 6.01)
Treatment				
Beta blocker	**1.83 (0.19 to 3.47)**	**1.71 (0.08 to 3.33)**	-1.10 (-2.21 to 0.02)	1.07 (-0.86 to 3.01)
RAS blocker	**2.59 (1.33 to 3.86)**	0.38 (-1.14 to 1.89)	**2.26 (1.16 to 3.35)**	2.27 (-0.09 to 4.63)
Digoxin/Digitoxin	0.61 (-1.05 to 2.28)	0.97 (-0.68 to 2.62)	-0.98 (-2.33 to 0.37)	**-3.03 (-5.07 to -0.98)**
Loop diuretic	**-4.73 (-5.93 to -3.54)**	**-3.12 (-4.57 to -1.68)**	**-2.28 (-3.82 to -0.74)**	**-5.27 (-8.52 to -2.02)**
Mineralocorticoid receptor antagonist	-0.77 (-1.76 to 0.22)	0.63 (-0.69 to 1.95)	1.00 (-0.11 to 2.11)	-0.34 (-2.16 to 1.47)
Implanted cardiac device	**1.96 (0.26 to 3.65)**	-2.76 (-6.45 to 0.93)	4.96 (-1.01 to 10.94)	11.28 (-21.57 to 44.13)

Signs and symptoms of congestion				
Hospital Inpatient vs. Outpatient	**-9.91 (-11.27 to -8.56)**	**-7.65 (-9.08 to -6.22)**	**-4.67 (-5.92 to -3.42)**	**-7.87 (-9.96 to -5.79)**
NYHA functional class, referent: I or II				
class III	**-12.55 (-13.79 to -11.32)**	**-10.89 (-12.4 to -9.37)**	**-12.58 (-13.81 to -11.36)**	**-12.75 (-15.13 to -10.36)**
class IV	**-17.94 (-20.82 to -15.05)**	**-14.02 (-16.46 to -11.58)**	**-16.2 (-18.21 to -14.2)**	**-17.56 (-20.54 to -14.59)**
Paroxysmal nocturnal dyspnea	**-6.94 (-8.49 to -5.40)**	**-8.72 (-10.21 to -7.24)**	**-6.62 (-7.87 to -5.36)**	**-9.35 (-11.83 to -6.88)**
Neck vein distention	-0.53 (-2.20 to 1.13)	-0.15 (-1.90 to 1.61)	-0.91 (-2.32 to 0.50)	**-5.62 (-7.81 to -3.44)**
Rales	**-2.83 (-4.58 to -1.08)**	**-2.43 (-4.09 to -0.76)**	0.06 (-1.22 to 1.35)	**-3.73 (-6.04 to -1.41)**
Radiographic cardiomegaly	**-2.73 (-3.89 to -1.57)**	1.24 (-0.10 to 2.58)	**-2.76 (-3.93 to -1.59)**	0.10 (-1.87 to 2.06)
Acute pulmonary edema	-0.58 (-2.98 to 1.81)	-2.14 (-5.02 to 0.73)	**-3.64 (-5.19 to -2.08)**	0.24 (-2.56 to 3.05)
Third heart sound	**-5.35 (-8.22 to -2.47)**	**-8.86 (-11.42 to -6.31)**	**-3.99 (-5.46 to -2.52)**	**-5.58 (-7.94 to -3.21)**
Increased JVP (>6 cm H_2O at right atrium)	1.06 (-1.14 to 3.26)	1.01 (-1.71 to 3.74)	0.34 (-1.78 to 2.46)	1.23 (-1.98 to 4.45)
Hepatojugular reflux	**4.43 (2.31 to 6.56)**	-0.30 (-2.52 to 1.92)	**1.69 (-0.03 to 3.42)**	**2.62 (0 to 5.25)**
Weight loss >4.5 kg last 5 days in response to treatment	**-3.72 (-5.95 to -1.48)**	**-7.07 (-9.07 to -5.07)**	**-2.43 (-4.10 to -0.77)**	**-1.09 (-4.22 to 2.04)**
Bilateral ankle edema	**-2.61 (-3.79 to -1.43)**	**-7.13 (-8.52 to -5.73)**	**-5.76 (-6.94 to -4.59)**	**-7.32 (-9.27 to -5.36)**
Nocturnal cough	-0.75 (-2.27 to 0.77)	**-2.75 (-4.14 to -1.35)**	**-1.53 (-2.74 to -0.32)**	**-3.87 (-6.1 to -1.64)**
Dyspnea on normal exertion	**-8.17 (-9.3 to -7.04)**	**-8.49 (-10.05 to -6.94)**	**-11.85 (-13.16 to -10.53)**	**-9.59 (-12.18 to -6.99)**
Hepatomegaly	**-4.77 (-7.75 to -1.78)**	**-2.73 (-4.63 to -0.83)**	**-8.21 (-9.74 to -6.68)**	**-5.56 (-8.01 to -3.10)**
Pleural effusion	**-3.62 (-5.36 to -1.88)**	1.43 (-0.55 to 3.42)	-0.98 (-2.56 to 0.60)	1.20 (-1.25 to 3.65)
Decrease in VC by 1/3 from maximum rec.	**-2.12 (-3.59 to -0.66)**	-1.22 (-3.15 to 0.70)	**2.81 (1.18 to 4.45)**	**9.36 (3.9 to 14.82)**
Tachycardia (heart rate >120 beats/min)	-0.24 (-2.47 to 2.00)	1.05 (-0.96 to 3.05)	-0.87 (-2.47 to 0.72)	**2.50 (-0.04 to 5.04)**
Partial R^2 (% of total R2) per covariate group*				
Sociodemographic	0.05 (11%)	0.04 (8.6%)	0.02 (4.1%)	0.04 (6.2%)
Comorbidities	0.07 (15.5%)	0.05 (12.1%)	0.05 (10.4%)	0.06 (9.8%)
Treatment	0.04 (11.4%)	0.05 (11.3%)	0.04 (7.5%)	0.05 (7.3%)
Signs and symptoms	0.28 (64.9%)	0.30 (68.3%)	0.40 (78.6%)	0.50 (76.7%)
Adjusted R^2	**0.44 (100%)**	**0.44 (100%)**	**0.51 (100%)**	**0.65 (100%)**

Abbreviations: BP, Blood pressure; COPD, chronic obstructive pulmonary disease; HF, Heart failure; HIC, High income country; JVP, jugular vein pressure; KCCQ, Kansas City Cardiomyopathy questionnaire; LIC, Low income country; LMIC, Lower-middle income country; NYHA, New York Heart Association; RAS, Renin angiotensin system blocker; UMIC, Upper-middle income country; VC, Vital capacity.

* Left ventricular ejection fraction was not significantly associated with KCCQ-12-SS in sensitivity analyses and was not included in the final model.

**Partial R^2-values represents contribution of groups of covariates when added in descending order.