

# Generic and disease-specific health-related quality of life in patients with chronic systolic heart failure: impact of depression

Marion Schowalter · Götz Gelbrich · Stefan Störk ·  
Jan-Philip Langguth · Caroline Morbach · Georg Ertl ·  
Hermann Faller · Christiane E. Angermann

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## Abstract

**Aims** Heart failure is known to profoundly affect health-related quality of life (HRQoL). We aimed to describe both generic and disease-specific HRQoL in a large community-based sample of patients with systolic heart failure (SHF) and to identify important somatic and psychosocial correlates.

**Methods and results** Seven hundred and two patients,  $67 \pm 12$  years old, 71 % men, with distributions of New York Heart Association (NYHA) functional classes I/II/III/IV of 2/55/39/4 % were included in this cross-sectional analysis. Generic HRQoL was measured with the SF-36 health survey, disease-specific HRQoL with the Kansas City Cardiomyopathy Questionnaire, and depression with the self-reported Patient Health Questionnaire (PHQ-9). Both generic- and disease-specific HRQoL measurements indicated moderate to poor HRQoL. The KCCQ scores

demonstrated higher sensitivity to the varying levels of heart failure severity as compared to the SF-36 scores. Patients with either a minor (15 %) or a major depression (24 %) reported significantly and substantially lower HRQoL ( $p < .001$ ) than patients without depression did. In multivariable regression analyses, depression accounted for the largest part of the variance of both generic and specific HRQoL (12 and 36 %, respectively), whereas most biomedical variables had no or only a marginal influence. **Conclusion** Patients with SHF suffer from severe limitations of HRQoL. Depression was the most important correlate of both generic and disease-specific HRQoL.

**Keywords** Chronic heart failure · Generic health-related quality of life · Disease-specific health-related quality of life · Depression

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M. Schowalter (✉) · H. Faller  
Department of Medical Psychology, Medical Sociology  
and Rehabilitation Sciences, University of Würzburg,  
Klinikstr. 3, D 97070 Würzburg, Germany  
e-mail: schowalter@uni-wuerzburg.de

G. Gelbrich  
Coordination Center for Clinical Trials,  
University of Leipzig, Leipzig, Germany

G. Gelbrich  
Institute of Clinical Epidemiology and Biometry,  
University of Würzburg, Würzburg, Germany

S. Störk · J.-P. Langguth · C. Morbach · G. Ertl ·  
C. E. Angermann  
Department of Internal Medicine I/Center of Cardiovascular  
Medicine, University Hospital Würzburg, Würzburg, Germany

## Introduction

Systolic heart failure (SHF) is recognized as an increasing public health concern among the aging populations of industrialized countries [1]. Patients with heart failure have a high mortality risk [2, 3] and a serious impairment in all generic and disease-specific domains of health-related quality of life (HRQoL) [4–8]. Comorbid depression and panic disorders occur in these patients at a three- to five-times higher rate than in the general population [2, 9–11]. Many studies have shown an additional negative influence of depression on prognosis [11–13].

In our previous research, we discovered that comorbid major depression was closely related to disease severity and clinical features of SHF [11]. Studies analyzing correlates of low HRQoL indicate an association with New

York Heart Association (NYHA) functional class and various socio-demographic variables, including younger age, social support and female sex [2, 14, 15]. In most studies, objective measures of SHF severity, such as indicators of left ventricular function, were not associated with self-reported HRQoL [16, 17]. However, when psychosocial factors were considered, they contributed substantially to the explained variance [18, 19].

To clarify the significance of individual variables associated with HRQoL, detailed analyses of the various facets of the heart failure syndrome are needed, including objective measures of SHF severity, somatic comorbidities, socio-demographic and psychosocial variables, and patient mood parameters. Only a few previous studies investigating the significance of HRQoL in patients with SHF were performed with large samples and systematically explored disease-specific HRQoL in addition to generic HRQoL, which may allow for a more profound understanding of the HRQoL construct [4, 7, 18, 19]. Moreover most studies failed to recruit a community-based sample, which represent the ‘real world’ heart failure population.

In this paper, we extend our previous research, in which we explored and focussed on the somatic correlates of depression, including blood parameters, such as leucocyte count and hemoglobin level, and certain diseases, such as chronic obstructive pulmonary disease (COPD), diabetes, and hyperuricemia [11]. In contrast, the present study analyses the correlates of HRQoL by including depression as a potential predictor. Furthermore, we provide a detailed description of the generic and disease-specific HRQoL in a large community-based sample of patients suffering from SHF. Further, we aim to clarify important correlates of HRQoL, especially depression.

## Methods

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the institutional Ethics Committees. Written informed consent was obtained from all patients.

### Subjects

The interdisciplinary network for heart failure (INH) at the University of Würzburg Cardiovascular Centre promotes patient-oriented research in community-based heart failure populations. Within this frame, adult patients hospitalized for SHF [echocardiographic left ventricular ejection fraction (LVEF) <40 %] were recruited consecutively in nine hospitals of the Würzburg area to take part in the randomized control INH study [11]. The aim was to obtain a

large representative sample of the ‘real world’ heart failure population. Therefore, exclusion criteria were kept to a minimum and comprised only acutely decompensated SHF following new-onset structural heart disease (e.g., acute coronary syndrome), linguistic problems likely to preclude patient evaluation, and patient refusal to complete the psychometric questionnaires. All patients had been hospitalized for aggravated heart failure conditions. However, NYHA functional class as reported in the current manuscript was assessed at randomization, which occurred after best possible recompensation. As such, the symptoms experienced by many patients had improved considerably while in the hospital. LVEF was measured shortly before or after randomization.

Complete reversal of (pulmonary and/or peripheral) edema, i.e., complete recompensation, could not be achieved in all patients. When sufficient dosages of diuretic and concomitant cardiac treatment were documented, but complete stabilization had not yet been achieved, a status of “best possible cardiac recompensation” was accepted.

### Procedure

All study participants underwent psychometric evaluation prior to discharge and after best possible cardiac recompensation. The Short Form (SF)-36 Health Survey was used to assess generic HRQoL [20]. The SF-36 is a common international standardized tool with proven reliability and validity [21]. It contains eight subscales, physical function, role-physical, bodily pain, general health, vitality, role-emotional, social function, and mental health, and two summary scales: the physical health (subscales 1–4) and mental health (subscales 5–8) component scores. The mental health component score includes items related to depression so that a high correlation with depression scales (e.g., Patient Health Questionnaire depression module PHQ-9) may be found. The scores range from 0 to 100, with higher scores indicating a better HRQoL.

The patients’ disease-specific HRQoL was measured using the self-reported Kansas City Cardiomyopathy Questionnaire (KCCQ). This recently developed tool was specifically designed for SHF patients, and both the original US [22] and German [23] versions have demonstrated very good reliability and validity. The following areas are covered by the KCCQ: physical function, symptoms (frequency, severity), self-efficacy, quality of life (psychological well-being), and social limitations. The scores range from 0 to 100, with higher scores again indicating a better health status. The functional status summary scale, which indicates the patient’s physical state, is composed of the physical function and symptoms subscales. A clinical summary scale that incorporates all subscales except for self-efficacy is also available.

Depression was assessed using the German version of the Patient Health Questionnaire depression module PHQ-9 [24–26], a self-report screening tool consisting of nine items. It may be used to identify a probable current major or minor depressive episode (no depression: PHQ-Score <9, minor depression: PHQ-Score 9–11, major depression: PHQ-score >11). Compared to other screening tools, the PHQ-9 compared well when evaluated against the structured clinical interview for DSM-IV as a reference standard [26].

A thorough standardized check-up including physical examination, laboratory assessment, 12-lead-electrocardiogram, pulmonary function testing and two-dimensional echocardiography was performed for every patient, as detailed elsewhere [27]. Physicians performing the clinical tests were blinded to the psychometric results.

### Data analysis

All statistical analyses were performed using SPSS 14.0 for Windows (SPSS Inc. Chicago, Ill., USA). For the test of group differences, analyses of variance were used. Inter-collinearity was checked. Block-wise linear regression analyses were applied to identify independent predictors of quality of life outcomes (SF-36 physical and mental health summary scales and the KCCQ clinical summary and functional status scales). Four different blocks of variables, basic socio-demographic variables, medications and indicators of SHF severity, comorbidities and risk factors, and depression, were used. Rationale behind this strategy was to identify the contribution of each block for the prediction of outcomes in a step-by-step manner.

The first block of independent variables consisted of the following socio-demographic variables: age, sex, family status (living alone, living together with a partner) and educational level. A low educational level was assigned to patients who had undergone basic education (8 years) or less, with and without occupational training. The second block added medications, such as diuretics and statins (3-hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitors), and indicators of SHF severity, such as leukocyte count >8,000 mm<sup>-3</sup>, NYHA functional class, and LVEF, to the model. The third block additionally included comorbidities and risk factors: hypercholesterolemia (total cholesterol >200 mg/dl or on lipid-lowering drugs), hyperuricemia (uric acid >6.5 mg/dl), diabetes, hypertension (blood pressure >140/90 mmHg or on antihypertensive drugs), renal dysfunction (GFR <60 mL/min/1.73 m<sup>2</sup>), anemia [hemoglobin (g/dl) <13 (male), <12 (female)], COPD, cerebrovascular disease (transient ischemic attack, apoplexy), coronary heart disease (CHD), obesity (body mass index >30 kg/m<sup>2</sup>) and current smoking habit. The PHQ-9 summary score was used as a continuous variable in

the fourth block. The amount of variance ( $R^2$ ) explained by the four blocks of variables was determined.

Values are given as means (SD) or percentages, statin; hypercholesterolemia: total cholesterol >200 mg/dl or on lipid-lowering drugs; hyperuricemia: uric acid >6.5 mg/dl; hypertension: blood pressure >140/90 mmHg or on anti-hypertensive drugs; renal dysfunction: GFR <60 mL/min/1.73 m<sup>2</sup>; anemia: hemoglobin (g/dl) <13 (male), <12 (female); COPD: chronic obstructive pulmonary disease; obesity: body mass index >30 kg/m<sup>2</sup>; dpw: drinks per week, 1 drink: 0.25 l of beer or 0.1 l of wine or 0.02 l of hard liquor; major/minor depression: suspected according to PHQ sum: greater than 11 (major depression), between 9 and 11 (minor depression).

## Results

### Descriptive statistics

Out of 834 eligible patients, 702 patients provided informed consent (rejection rate: 15.8 %) and had complete psychometric, clinical and laboratory data available. Demographic and clinical characteristics, important laboratory parameters, comorbidities, risk factors and information on depression are given in Table 1. The main causes of SHF were CHD in 58 %, cardiomyopathy in 27 %, hypertension in 7 % and other diseases in 9 %.

The mean scores of HRQoL according to severity of depression subgroups are summarized in Table 2. As shown, all scales of the SF-36 and the KCCQ indicate moderate to poor HRQoL and correspond to the sum scores of other patients with chronic diseases. Patients with either minor or major depression reported significantly and substantially worse HRQoL than patients without depression did. Figure 1 displays the summary scores of both the SF-36 (physical and mental health component scores) and the KCCQ (functional status, clinical summary scale) by NYHA class. A decrease in HRQoL concurs with increasing severity of SHF according to the NYHA classification. The figure shows that the KCCQ summary scores seems to discriminate patients at different NYHA classes better than the SF-36 summary scores do, particularly in advanced SHF stages. For example, in comparing NYHA classes 1 and 4, the effect sizes of the KCCQ summary scores are much larger than the respective effect sizes of the SF-36 summary scores are, with the KCCQ effects not being included in the 95 % confidence intervals of the SF-36 effects.

### Predictors of health-related quality of life

Tables 3 and 4 detail the results of the block-wise regression analyses of the SF-36 physical and mental health

**Table 1** Descriptive statistics of study participants ( $n = 702$ )

Age (years), mean (SD)	67.3 (12.2)
Female sex (%)	28.6
Family status: living alone (%)	32.8
Low education (%)	63.1
NYHA class (%)	
I/II (%)	2.4/55.1
III/IV (%)	38.5/4.0
Ejection fraction (%), mean (SD)	30.2 (8.3)
Ischemic etiology of heart failure (%)	57.5
Leukocytes $>8,000 \text{ mm}^{-3}$ (%)	45
Diuretic (%)	87
Statin (%)	41
Comorbidities/risk factors	
Hypercholesterolemia (%)	55.8
Hyperuricemia (%)	51.0
Diabetes (%)	34.8
Hypertension (%)	74.2
Renal dysfunction (%)	41.3
Anemia (%)	32.8
COPD (%)	18.9
Cerebrovascular disease (%)	13.8
Obesity (%)	24.6
Smoker (current) (%)	11.5
Alcohol consumption (dpw), mean (SD)	5.1 (10.5)
No alcohol consumption (%)	39.3
Major depression (%)	24
Minor depression (%)	15

Values are means (SD) or percentages; statin: (3-hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitor); hypercholesterolemia: total cholesterol  $>200 \text{ mg/dl}$  or on lipid-lowering drugs; hyperuricemia: uric acid  $>6.5 \text{ mg/dl}$ ; hypertension: blood pressure  $>140/90 \text{ mmHg}$  or on antihypertensive drugs; renal dysfunction:  $\text{GFR} <60 \text{ mL/min/1.73 m}^2$ ; anemia: hemoglobin (g/dl)  $<13$  (male),  $<12$  (female); COPD chronic obstructive pulmonary disease, Obesity body mass index  $>30 \text{ kg/m}^2$ , dpw drinks per week, 1 drink 0.25 l of beer or 0.1 l of wine or 0.02 l of hard liquor; major/minor depression: suspected according to PHQ sum  $>11/9-11$

component scores and the KCCQ clinical summary and functional status scales. For each of these variables, the results of the block-wise regression analysis were similar: demographics, as well as clinical predictors and comorbidities, explained only a marginal degree of HRQoL variance (models 1–3), whereas the final model, by adding the PHQ summary score, explained between 31 and 53 % of the variance. The increase of explained variance ( $\Delta R^2$ ) from model 3 (without PHQ) to model 4 (including PHQ) was substantial and ranged from 12 to 37 %, respectively. Besides the PHQ sum score, age, NYHA functional class, hyperuricemia, and COPD were significant predictors for the SF-36 scores in the final model. Regarding the KCCQ scales, demographic variables, i.e., gender, family status

and education, also contributed significantly to the model. In addition, NYHA functional class, diuretics, hyperuricemia, and coronary artery disease had predictive power.

The final model (model 4) demonstrated that the PHQ sum score had the strongest association with HRQoL: higher PHQ sum scores were associated with lower scores on all four HRQoL summary scales. A lower SF-36 physical health component score was seen in patients with increased depressive symptoms, those with NYHA functional classes III/IV, those of increasing age, and those with hyperuricemia, anemia and COPD. The SF-36 mental health component score was not associated with any other variables in addition to the PHQ sum score. Lower scores in KCCQ functional status were found in depressed patients, females, those who lived alone, patients with a lower educational level, those with NYHA functional classes III/IV, those with hyperuricemia, those with coronary artery disease and those who used diuretics. Lower scores in the KCCQ clinical summary scale were linked with depression, female sex, living alone, NYHA functional classes III/IV, use of diuretics, and hyperuricemia.

## Discussion

We have performed a study using a large community-based sample to evaluate the influence of objective measures of SHF severity, somatic comorbidities, socio-demographic variables, and depressive symptoms on both generic and disease-specific HRQoL in patients suffering from SHF.

The findings confirm the large influence of depression on HRQoL summary scores, whereas biomedical predictors showed only marginal effects. This finding holds true for both generic HRQoL as well as disease-specific HRQoL. Most interestingly, factors that were previously identified as correlates of depression, such as increased leukocytes as an indicator of inflammatory activity and somatic comorbidities [11], were not or only marginally predictive for HRQoL. In congruence with previous research, LVEF did not influence HRQoL when depression was included.

The remarkable association between depression and HRQoL in SHF, which corresponds to previous studies [18, 19], cannot be interpreted as a result of confounding of the measurement tools, i.e., similar contents of the questionnaire items [28]. The fact that HRQoL items other than those reflecting psychosocial burden were sensitive to the effect of depression suggests a need for alternative explanations. Although the causal pathways between depression and HRQoL in chronic diseases such as SHF cannot be determined by a cross-sectional study, several possible associations may be considered. A lower HRQoL may reflect more severe physical and mental limitations. Bodily pain and functional impairment, both characteristics of a

**Table 2** Health-related quality of life in the total cohort and in severity of depression subgroups

SF-36	Total sample* (n = 699)			No depression (n = 427)		Minor depression (n = 102)		Major depression (n = 170)		p value
	Mean	SD	Range	Mean	SD	Mean	SD	Mean	SD	
Physical function	45.9	29.5	0–100	56.3	27.1	35.5	25.6	26.1	24.5	<0.001
Role-physical	27.1	39.3	0–100	37.6	42.9	12.5	26.8	9.0	23.3	<0.001
Bodily pain	60.2	33.6	0–100	70.3	29.6	50.6	30.6	40.7	34.8	<0.001
General health	45.9	18.9	0–100	52.0	17.8	40.1	15.2	34.1	16.6	<0.001
Vitality	39.4	23.1	0–100	49.4	21.4	29.0	14.8	20.1	15.6	<0.001
Social function	64.3	30.0	0–100	75.6	24.1	55.6	25.1	40.6	29.1	<0.001
Role-emotional	50.4	47.6	0–100	63.7	45.3	33.7	45.2	25.3	41.5	<0.001
Mental health	61.7	22.2	4–100	72.3	17.0	52.5	17.1	40.6	18.8	<0.001
SF-36 PCS	35.2	10.5	11–59	38.3	10.0	32.1	9.1	29.1	9.1	<0.001
SF-36 MCS	44.3	12.3	10–68	49.5	10.1	39.5	9.9	33.7	10.6	<0.001

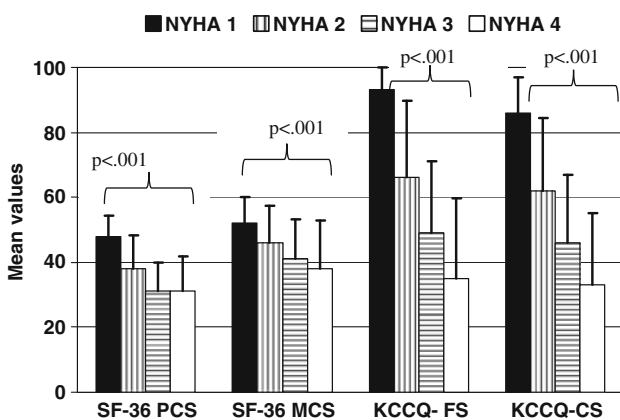
  

KCCQ	Total sample (n = 690) <sup>a</sup>			No depression (n = 424)		Minor depression (n = 98)		Major depression (n = 168)		p value
	Mean	SD	Range	Mean	SD	Mean	SD	Mean	SD	
Physical limitation	58.2	28.3	0–100	67.9	24.2	53.0	24.0	37.0	28.1	<0.001
Symptoms	59.7	27.8	0–100	70.1	23.9	53.9	24.5	36.6	23.5	<0.001
Self-efficacy	63.5	25.7	0–100	67.2	25.3	60.0	22.0	55.9	27.0	0.001
Quality of life	50.6	26.2	0–100	62.0	23.1	41.0	17.7	28.1	20.4	<0.001
Social limitation	52.3	31.7	0–100	63.8	28.8	45.7	24.2	27.6	27.0	<0.001
KCCQ-FS	59.0	25.2	1.6–100	69.1	21.2	53.4	20.2	36.9	21.7	<0.001
KCCQ-CS	55.4	23.8	1.0–100	66.1	19.7	48.6	17.1	32.5	18.2	<0.001

p-values are indicated for comparison of patients with no versus minor versus major depression (ANOVA)

SF-36 Short Form-36 Health Survey, no depression PHQ-Score <9, minor depression PHQ-Score ≥9 and ≤11, major depression: PHQ >11, KCCQ Kansas City Cardiomyopathy Questionnaire, PCS physical health component score, MCS mental health component score, CS clinical summary score, FS functional status score

<sup>a</sup> Reduction of the total sample size due to missing data



**Fig. 1** Quality of life scores (mean values and standard deviations) by New York Heart Association (NYHA) functional classes. All differences between NYHA classes are significant at  $p < .001$  (ANOVA). SF-36 PCS Short Form-36 Physical Health Component Score; SF-36 MCS Short Form-36 Mental Health Component Score; KCCQ-CS Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-FS Kansas City Cardiomyopathy Questionnaire Functional Status Score

chronic disease, may complicate or inhibit positive social activities and relationships, which may lead to the development or aggravation of depression. On the other hand, depression may cause a biased perception and reporting of the actual health status. Depressed patients experience the burden of the disease more profoundly and over-report subjective symptoms, such as fatigue, which may well be a symptom of heart failure, thus yielding worse reports of HRQoL [29]. The enormous influence of the PHQ-depression score on HRQoL may be explained by both of these bidirectional associations, i.e., the loss of reinforcement because of the activity limitations and the negative perception of the quality of life. On a more global methodical level, shared method variance due to common self-report assessment methods of PHQ, KCCQ and SF-36 may contribute to the associations found. Further research is needed to clarify the causal direction of the association between HRQoL and depression as well as the mechanisms by which it is mediated. The reason as to why some patients with SHF develop a depression and others do not

**Table 3** Regression analyses for the SF-36 physical health and mental health component scores

	SF-36 physical health component score				SF-36 mental health component score			
	Beta weights				Beta weights			
	Model 1 $R^2 = 0.07$	Model 2 $R^2 = 0.15$	Model 3 $R^2 = 0.19$	Model 4 $R^2 = 0.31$	Model 1 $R^2 = 0.01$	Model 2 $R^2 = 0.05$	Model 3 $R^2 = 0.04$	Model 4 $R^2 = 0.41$
Age	−0.21***	−0.14**	−0.10*	−0.12**	−0.02	03	0.05	0.01
Female sex	−0.09*	−0.06	−0.08	−0.06	−0.05	−0.02	−0.01	0.02
Living alone	−0.06	−0.05	−0.05	−0.04	−0.03	−0.01	−0.02	0.00
Low education	−0.07	−0.06	−0.04	−0.01	−0.11*	−0.11*	−0.10*	−0.05
NYHA		−0.27***	−0.24***	−0.16***		−0.18***	−0.17***	−0.03
LVEF		−0.01	−0.02	−0.05		0.09*	0.09*	0.04
Leukocytes >8,000 mm <sup>−3</sup>		−0.05	−0.05	−0.02		−0.02	−0.02	0.04
Diuretic		−0.10*	−0.09*	−0.07		−0.03	−0.03	0.01
Statin		0.01	0.04	0.02		0.04	0.01	−0.02
Hypercholesterolemia			−0.02	−0.03			0.04	0.04
Hyperuricemia			−0.12**	−0.10**			0.02	−0.07
Diabetes			0.01	−0.01			−0.02	−0.01
Hypertension			0.04	0.02			−0.01	−0.05
Renal dysfunction			−0.01	0			0	−0.02
Anemia			−0.09*	−0.07*			−0.02	0.01
COPD			−0.15***	−0.11**			−0.06	0.02
Cerebrovascular disease			−0.08*	0.03			−0.03	0.02
Coronary heart disease			−0.06	−0.04			0.02	0.05
Obesity			−0.03	−0.01			0	0.03
Smoker (current)			0.03	0.03			0.05	0.05
PHQ Sum Score				−0.36***				−0.64***

\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , SF-36 short form-36 health survey, NYHA New York Heart Association functional class, LVEF left ventricular ejection fraction, statin (3-hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitor), hypercholesterolemia total cholesterol >200 mg/dl or on lipid-lowering drugs, hyperuricemia uric acid >6.5 mg/dl, hypertension blood pressure >140/90 mmHg or on antihypertensive drugs, renal dysfunction GFR <60 mL/min/1.73 m<sup>2</sup>, anemia hemoglobin (g/dl) <13 (male), <12 (female), COPD chronic obstructive pulmonary disease, Obesity body mass index >30 kg/m<sup>2</sup>, PHQ depression score of the Patients Health Questionnaire.  $R^2$  proportion of variance explained by the model

also remains unclear. Presumably positive resources, such as social networks, supportive family relationships, religious involvement and positive activities, e.g., hobbies, may be protective factors enhancing the potential for effective coping with the psychosocial burdens of chronic diseases [30, 31]. In contrast to other studies, our results showed a lower number of patients with symptoms of minor depression compared to major depression. We do not have any explanation for this result. It may limit the generalizability of the results.

Apart from depression, socio-demographic variables, such as age, sex, family status, and educational level, somatic risk factors or comorbidities, such as hyperuricemia, CHD and COPD, as well as use of diuretics and NYHA classification accounted for only marginal amounts of HRQoL variance.

Although some studies identified age as a significant predictor of HRQoL [15, 19], the direction of the association

between age and HRQoL was inconsistent. In this study, higher age was shown to be associated with lower HRQoL, which can be explained by a higher rate of comorbidities accompanied by impaired physical functioning among older individuals. Gender differences have also been studied previously. In correspondence with other studies, our study showed poorer HRQoL for female than for male patients [32]. Reasons for this gender difference are still unclear, but higher depression rates among women and different symptom perceptions are being discussed as possible explanations [33]. However, in this study, female sex was still associated with lower HRQoL even after adjustment for depression had been made. Moreover, stress and depression are more prevalent in patients with lower socio-economical status [34]. Among demographics, partnership status also emerged as a correlate of HRQoL. The previously reported positive impact of social support on HRQoL [18] may explain the lower HRQoL in patients living without a partner.

**Table 4** Regression analyses of the KCCQ functional status and clinical summary scales

	KCCQ functional status				KCCQ clinical summary			
	Beta weights				Beta weights			
	Model 1 <i>R</i> <sup>2</sup> = 0.12	Model 2 <i>R</i> <sup>2</sup> = 0.25	Model 3 <i>R</i> <sup>2</sup> = 0.28	Model 4 <i>R</i> <sup>2</sup> = 0.49	Model 1 <i>R</i> <sup>2</sup> = 0.08	Model 2 <i>R</i> <sup>2</sup> = 0.21	Model 3 <i>R</i> <sup>2</sup> = 0.23	Model 4 <i>R</i> <sup>2</sup> = 0.53
Age	−0.18***	−0.9*	−0.04	−0.06	−0.14***	−0.06	−0.00	−0.02
Female sex	−0.16***	−0.12*	−0.13**	−0.10**	−0.15***	−0.11**	−0.13**	−0.09**
Living alone	−0.12**	−0.10**	−0.10**	−0.09**	−0.11**	−0.09*	−0.08*	−0.07*
Low education	−0.15***	−0.15***	−0.13***	−0.09**	−0.13**	−0.13**	−0.10**	−0.05
NYHA		−0.30***	−0.27***	−0.15***		−0.33***	−0.27***	−0.14***
LVEF		0.04	0.04	0.01		0.08*	0.06	0.03
Leukocytes >8, 000 mm <sup>−3</sup>		−0.05	−0.04	−0.01			−0.02	0.01
Diuretic		−0.15***	−0.12	−0.10**			−0.10**	−0.08**
Statin		0.07	0.08	0.06			0.06	0.01
Hypercholesterolemia			0.04	0.02			0.06	0.03
Hyperuricemia			−0.10**	−0.07*			0.10*	0.06*
Diabetes			−0.03	−0.02			−0.01	0
Hypertension			−0.02	−0.03			−0.01	−0.03
Renal dysfunction			0	−0.01			0.02	0
Anemia			−0.05	−0.04			−0.06	−0.04
COPD			−0.11**	−0.05			−0.12*	−0.05
Cerebrovascular disease			−0.05	−0.02			−0.06	−0.02
Coronary heart disease			−0.08	−0.07*			−0.08	−0.06
Obesity			−0.05	−0.04			−0.02	0.01
Smoker (current)			0.03	0.03			0.03	0.04
PHQ Sum Score				−0.49***				−0.59***

\* *p* < 0.05, \*\* *p* < 0.01, \*\*\* *p* < 0.001, KCCQ Kansas City Cardiomyopathy Questionnaire, NYHA New York Heart Association functional class, LVEF left ventricular ejection fraction, statin (3-hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitor), hypercholesterolemia total cholesterol >200 mg/dl or on lipid-lowering drugs, hyperuricemia uric acid >6.5 mg/dl, hypertension blood pressure >140/90 mmHg or on antihypertensive drugs, renal dysfunction GFR <60 mL/min/1.73 m<sup>2</sup>, anemia hemoglobin (g/dl) <13 (male), <12 (female), COPD chronic obstructive pulmonary disease, Obesity body mass index >30 kg/m<sup>2</sup>, PHQ depression score of the Patients Health Questionnaire. *R*<sup>2</sup> proportion of variance explained by the model

Somatic comorbidities are frequent in patients with SHF and create further burdens associated with the disease. This raises the question whether patients with SHF who suffer from additional comorbidities have a low HRQoL because of the associated restrictions (e.g., pain, limited physical functioning) or because of the development of depressive symptoms that decrease HRQoL, or both. Those results that were not controlled for depression (see Tables 3, 4, Model 3) show that patients with additional comorbidities do indeed have a lower HRQoL—especially patients who have comorbidities with clearly noticeable restrictive symptoms (e.g., COPD). From a psychological perspective, limited physical functioning may result in a decrease of positive activities and therefore an increase in depression. This corresponds to the behavioral model of depression postulated by Lewinsohn et al. [35], which states that depression can result from a stressor that disrupts normal behavior patterns, thus causing a loss of positive reinforcement.

After controlling for depression (see Tables 3, 4, Model 4), the effect of additional comorbidities remained virtually unchanged, but depression still played the most important role. This suggests that HRQoL is influenced by both additional comorbidities as well as depression.

The use of diuretics can be regarded as a marker for heart failure severity, which influences the disease-specific aspect of HRQoL (KCCQ scales). Other measures of heart failure severity, such as NYHA and LVEF, only have a marginal or no influence on the predictive ability of HRQoL. Although LVEF is an important factor in determining heart failure severity, it does not seem to play a role in the patients' subjective evaluation of restrictions due to their disease. While a decrease in HRQoL was seen with increasing severity of SHF, as indicated by NYHA classification, NYHA class independently explained only a small proportion of variance of HRQoL. This finding is in accordance with previous research [19]. The association between depression and physician-reported NYHA functional class

may also be considered to be bidirectional. A higher functional class may reflect more severe disease limitations, which may in turn account for the development of depression. Conversely, physicians may classify their depressed patients to be in higher NYHA functional classes because the patients are likely to report more pronounced functional impairments.

Our data also support the finding that SHF is associated both with a severe reduction of generic and disease-specific HRQoL [7], as well as with an increased prevalence of minor or major depression [2].

In contrast to the generic SF-36 component scores, the disease-specific KCCQ summary scores were more widely distributed across the possible ranges of the scales, so that in patients with varying levels of heart failure severity, as measured by NYHA classification, clearly different KCCQ scores were observed. Thus, as compared to the generic SF-36 component scores, the disease-specific KCCQ summary scores were more sensitive for heart failure severity because they showed better differentiation between subgroups according to NYHA classification. Moreover, the KCCQ scales showed effects of socio-demographic variables, such as sex, family status, and educational level, which were not significant within the SF-36 component scores. Consequently, whereas the KCCQ appears to be more sensitive for the impact of the disorder in question, i.e., heart failure, demographic variables may also be risk factors for impaired HRQoL. Taken together, both assessment tools may provide the most complete picture of HRQoL in chronic heart failure patients.

The following limitations should be considered in the interpretation of this study. One limitation is the use of self-reports of depression with resulting diagnoses that were not confirmed by a structured interview. To confirm a diagnosis of depression, a structured interview performed by a professional would be necessary. The employed PHQ-9 has an excellent sensitivity and specificity, particularly regarding major depression, for general medical patients [26]. However, the sensitivity of the PHQ-9 is lower among cardiac patients [36]. In spite of this, it has been recommended by the American Heart Association for the screening of depression and was therefore used in this study [37].

Another limitation is that we examined a sample of hospitalized patients. Some studies have indicated that hospitalization may decrease quality of life. Furthermore, the direction of causality could not be examined due to the cross-sectional study design. To confirm possible causal directions, experimental studies are necessary. Our sample of patients with SHF was also heterogeneous according to NYHA classes. However, our sample represents a typical ‘real world’ sample of patients with SHF.

To conclude, our results indicate that both generic and disease-specific HRQoL are considerably impaired in SHF. Moreover, our results show that depression plays a major role in explaining variance of both types of HRQoL, whereas other variables only have a marginal or no impact. This finding strongly indicates that comorbid depression is relevant for the HRQoL of patients with SHF. From a clinical perspective, we recommend to include the assessment of depression in the routine medical evaluation of patients with SHF to optimize the treatment of patients with comorbid depressive disorders. Our findings indicate that the non-cardiac factor depression is more important than cardiac functioning itself in determining the HRQoL of patients suffering from SHF. Therefore, HRQoL should only be used as a valid measure of health status in patients with SHF if depression is considered as well. Our study outcomes indicate that depression is more important than cardiac functioning in determining the HRQoL of patients suffering from SHF. Furthermore, taking into consideration that depression is not only frequent among patients with SHF but also increases their mortality risk [38] and has a negative impact on compliance with treatment [39], improved diagnosis and treatment of this comorbidity are warranted.

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