Exploring Quality of Life in Patients with and without Heart Failure

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Abstract (247 words)

Aims: The EuroHeart Failure Survey Questionnaire (EHFSQ-1) has 39 questions on symptoms and quality of life (QoL); many items are related. We sought to identify underlying clusters amongst EHFSQ-1 questions, construct an overall "QoL score" and investigate its relationship to a single question asking patients to self-rate QoL.

Methods and results: Factor analysis based on the principal component technique was used to identify patterns amongst responses to QoL questions from patients referred with symptoms suggesting heart failure (HF). Of 1031 patients, median age 71 (IQR: 63-77) years, 64% were men and 626 had confirmed HF. For patients with HF, seven symptom-clusters were identified: "breathlessness", "psychological distress", "sleep quality", "frailty", "cognitive/psychomotor function", "cough" and "chest pain". These clusters accounted for 65% of the total variance in QoL score. Cluster pattern was similar in patients with and without HF. A summary factor score was tightly correlated with summary QoL score (correlation coefficient: r=0.96; $p<0.0001$). Both summary factors and QoL scores were highly correlated with patient self-rating of overall health ($r_1=0.61$ and $r_2=0.66$ respectively, $p<0.0001$) or overall QoL ($r_1=0.60$ and $r_2=0.66$, $p<0.0001$). The medians (IQR) of the summary QoL score for patients with HFrEF, HFnEF and no-HF were, respectively, 83 (60-106), 82 (59-104) and 71 (51-94).

Conclusions: EHFSQ-1, comprises seven symptom clusters in patients with HF. Either summary factors or QoL scores can be used as a QoL outcome measure. However, if the key question is 'what is this patient's QoL?' rather than the reason why it is impaired, then a single, direct question may suffice.

Key words: Patterns of quality of life; suspected heart failure; left ventricular systolic dysfunction

Introduction

The goals of treating heart failure are to maintain or improve the quality of life by managing symptoms and reducing morbidity and disability and to prolong useful life. Ultimately, improving the 'patient journey' [1] or quality-adjusted life-years is the objective of both patients and their doctors. However, most clinical trials of heart failure focus on morbidity and mortality rather than on quality of life (QoL), which is usually measured infrequently during the course of the trial, if at all. This partly reflects a lack of confidence amongst both trialists and regulators about the validity of tools used to assess QoL and partly the perceived burden on both patients and investigators of completing existing QoL questionnaires repetitively. However, QoL questionnaires are asking two distinct questions; firstly "what is this patient's QoL?" and secondly, "if impaired, 'why'?". However, in a clinical trial the first question may be of greater importance. The second may give insights into how an intervention has changed QoL but with few exceptions [2], this is never reported in trials. This issue could be addressed if investigators and regulators were willing to accept that the patient is the best judge of their QoL which could reduce the complexity of assessment of QoL to a single question that could be asked at every visit. This would permit the calculation of average QoL throughout the study as well as an assessment of the impact of morbid events on QoL. Trying to measure QoL using questionnaires is not straightforward. Inevitably, questionnaires concentrate on symptoms thought to be important by clinicians, but not necessarily patients, and include a large number of questions that are often highly related. Factor analysis (FA) [3,4] reduces complex information by identifying latent structures in the data and extracting highly correlated

sets of symptoms as “symptom clusters”. Each symptom cluster can be scored and used for further analysis [5,6].

The aim of the present study was to identify symptom clusters in the EuroHeart Failure Survey Questionnaire used in the first survey (EHFSQ-1), to construct an overall “QoL score” from them and then to relate this score to patient self-reported QoL using single questions [7,8] using data acquired routinely as part of a clinical heart failure service.

Methods

Patients referred to a community heart failure clinic (Kingston-upon-Hull, UK) for the assessment of heart failure symptoms were invited to participate. Patients underwent clinical examination, including demographic measurements, symptoms and signs, electrocardiograms, echocardiography and routine haematology and biochemical investigations. The questionnaire was designed by a group of experts to obtain data on symptom severity and quality of life in the first EuroHeart Failure survey. It has not, as far as we are aware, been subjected to detailed methodological validation.

Patients were sent the EuroHeart Failure Survey Questionnaire (EHFSQ-1), which comprises 39 questions (Table 2.1 and 2.2), in the post prior to attending the clinic. No restriction was placed on seeking the advice and opinion of friends and relatives. The first 37 questions (1-37) ask about specific symptoms. The response to each question could be: no, very little, a little, some, a lot, very much, unknown and was coded from 1 to 6; unknown was coded as 7 and was excluded in this study. The following four questions (18-21) were very often left unanswered: inability to work

due to your health; side effects that you think might be due to your treatment; difficulties with sexual function; and cost of medicines or medical care. They were excluded for the purposes of this analysis. The final two questions (38-39) ask about general health, and overall quality of life. Each could be answered: very good, good, quite good, average, quite poor, poor, very poor and unknown. The responses to both questions were coded from 1 to 7; unknown was coded as 8 and was excluded in the study

All patients provided written informed consent for their data to be used and the study was carried out in accordance with the Helsinki Declaration II and the European Standards for Good Clinical Practice. Ethical approval was granted by the Hull and East Yorkshire Local Research Ethics Committee.

Patients were enrolled at first assessment in an out-patient clinic and all had a history suspicious of heart failure or concerns about important cardiac dysfunction. In the context of the sort of patients referred, heart failure was defined as being present if the left ventricular ejection fraction (LVEF) was less than 40% (heart failure with reduced ejection fraction; HFrEF) or, if LVEF was ≥ 40%, by an NT-proBNP >400ng/L (heart failure with normal ejection fraction; HFnEF). Patients who had both LVEF >40% and NT-proBNP <400ng/L were considered not to have heart failure for the purposes of this analysis, although other thresholds and criteria were considered.

Statistical analysis

Continuous variables are expressed as a median with inter quartile range; and categorical variables are given as percentages. Differences between the groups were

examined using independent t-test or Mann-Whitney U test and chi-square tests for continuous and categorical variables respectively. Pearson's correlation coefficient and Spearman's correlation coefficient with scatter plots were used to assess the correlations or relationships between two variables depending on the distribution of the data.

Exploratory factor analysis (FA) was performed using principal component analysis (PCA). PCA is a data reduction technique which transforms a number of correlated variables into a smaller number of uncorrelated variables termed principal components (that is, linear combinations of the original variables) which explain a large proportion of the original sample variance. The 4 questions 18-21 mentioned above were not included in the analysis due to too many missing values and general overall QoL and overall health were not included. The remaining 33 questions were considered in the analysis.

To identify QoL symptom clusters, only principal components with initial eigenvalues >1 were extracted and an orthogonal factor rotation with Varimax method [9] applied. The symptom clusters were labelled according to the characteristics of the original variables. Variables with a factor loading >0.4 were considered to be an important component of an underlying symptom cluster (Factor loading is a correlation between a variable and a factor. The higher the load the more relevant in defining the factor.). Symptom cluster scores were calculated based on the Anderson-Rubin method [10] for further analysis. The sampling adequacy was checked by the Kaiser-Meyer-Olkin (KMO) test [11]. The 10-fold cross-validation was used to assess the stability of the

analysis and Cronbach's alpha [12] was used for testing the reliability of questions on each symptom cluster.

Overall QoL scores were derived using either (1) the raw summary scores (ranging potentially from 31 (very good health) to 186 (terrible health)); or (2) the summary factor scores derived by the sum of each symptom cluster score, ranging from -5 to 10 in this dataset (a big number is associated with a bad health).

Statistical analysis was carried out using SPSS 17 software package. The two-tailed level of statistical significance was set at $p<0.05$.

Results

Baseline characteristics

Of 1,031 patients, 657 (64%) were men and the median age was 71 years (IQR: 63-77), 626 had HF (377 with HFrEF and 249 with HFnEF) and 405 did not fulfil the criteria for HF (Table 1). As expected, patients with HF had more severe symptoms, more cardiovascular problems, poorer renal function and substantially higher plasma concentrations of NT-proBNP despite receiving more loop diuretics, ACE inhibitors, beta blockers and spironolactone. Patients with HFnEF were older, more often women and had more atrial fibrillation and diabetes. BMI was greater in patients without heart failure but the rate of reported COPD was similar in each group.

The distributions of the responses of QoL questions for patients with HFrEF, HFnEF or No HF are shown in Table 2. This showed a broadly similar pattern in patients with different heart failure phenotypes. There was also an extensive overlap in

symptomatology between patients who were considered to have or not have heart failure. For instance, 15.7% of patients with HFrEF reported ankle swelling in the worst two ranks, compared to 22.8% of those with HFnEF and 17.5% of those without heart failure. Reports of severe breathlessness at rest were uncommon in this out-patient population and rare in patients without heart failure. For breathlessness during daily activity, 34.7% of patients with HFrEF reported scores in the worst two ranks, compared to 37.0% of those with HFnEF and 21.3% of those without heart failure. Fatigue during daily activity was reported in the worst two ranks in 26.8%, 27.7% and 16.3% of the above groups, respectively. Patients scoring chest pain in the worst two ranks were similar across diagnostic groups but patients without heart failure complained more of troublesome cough. The medians (IQR) of the summary QoL scores with IQRs for patients with HFrEF, HFnEF and no-HF were, respectively, 83 (60-106), 82 (59-104) and 71 (51-94). Of those that did not fulfil the criteria for HF, the scores were 85 (69-111) and 64 (48-85) for those taking or not taking loop diuretics and 72 (56-99) and 68 (47-89) above and below an NT-proBNP of 125ng/L.

Patterns of QoL

In the initial factor analysis 33 questions were considered. However, indigestion and SoA variables were removed from final FA because of small values of the communalities (<0.35) (the communality is the proportion of variation in the variable explained by all the symptom clusters). There were seven underlying QoL symptom clusters extracted from the 31 variables explained 65% of total variance. Factor loadings >0.4 were shown and important factor loadings >=0.7 were bolded (Table 3). The KMO test measuring the sampling adequacy was 0.929; values >0.5 indicate that the sample size is appropriate for FA. Bartlett's test of sphericity showed that the

correlations between items were sufficiently large for PCA (chi-square=10273, df = 465 and $p<0.001$). Cronbach's alpha showed a range of scores from 0.62 to 0.89 and five of seven scores had values >0.7, which indicates that the questionnaire has satisfactory internal reliability [13,14].

The following seven symptom clusters were extracted in patients with HF (Table 3):
1. The first cluster called “Breathlessness” accounted for 15% of the total variance in QoL. The cluster Breathlessness was highly related to: inability to do normal daily activities with the factor loading 0.78, fatigue on daily activities (0.76), breathless limiting normal daily activities (0.75) and reduced ability to pursue hobbies (0.73). That is the cluster was mainly loaded by these questions.

2. The second cluster called “Psychological distress” including stress, depression and anxiety accounted for 13% of the total variance.

3. “Sleep quality” including insomnia, waking and lack of refreshing sleep accounted for 9% of the total variance.

4. “Frailty” included questions relating to making you stay in hospital, eating less food, finding going places away from home difficult and the need for stays in hospital accounted for 8% of the total variance.

5. “Cognitive/Psychomotor impairment” (loss of memory, falls, dizziness, and muscles) accounted for 8% of the total variance.

6. “Respiratory symptoms” (cough, wheeze and breathless at night) accounted for 6% of the total variance.

7. “Chest pain” (chest pain at rest, chest pain at daily activity) were also extracted accounted for 6% of the total variance.

A 10-fold cross-validation for patients with HF was used and revealed the stability of the analysis (result was not shown. It can be found from on-line supplement).

Amongst patients who did not have heart failure, an 8th symptom cluster, “falls”, was identified, with the 8 clusters accounting for 66% of total variance (see Table 3). Muscle aches and indigestion were not included in the final analysis due to small values of the communalities. The KMO test (0.919) for this group shows that the sample size was adequate. The components and the order in which they entered the symptom clusters, was slightly different from the patients with heart failure: patients with HF had clearer and more specific patterns than those without HF.

Relationships between single symptom scores and general overall QoL and overall health

There was a strong positive correlation between the summary QoL and the summary symptom cluster scores for both patients with and without HF (Pearson’s correlation coefficient: $r = 0.964/0.954$ respectively with $p<0.001$, Figure 1 and Table 4.1). There was a strong relationship between two individual questions on ‘overall health’ and ‘overall QoL’ (Spearman’s correlation coefficient: $r' = 0.730/0.759$ for patients with/without HF respectively, $p<0.001$). There were also strong relationships between

overall health/overall QoL with the summary score and the summary symptom cluster score (r´= (0.661, 0.614) / (0.658, 0.602) respectively with p<0.001 for HF patients; and r´= (0.667, 0.678) / (0.642, 0.654) respectively with p<0.001 for no HF patients). Only the first symptom cluster ("Breathlessness") was highly related to the single questions on 'overall QoL' and 'overall health' (r´=0.50 and 0.47 respectively, p<0.001 for all; Table 4.2) in patients with HF.

Relationships between QoL scores with NYHA class and NT-proBNP

On average, patients without heart failure had lower summary scores, and lower scores in response to single questions on overall QoL and overall health scores than patients with heart failure represented as NYHA class II/III/IV. QoL scores increased (worsened) as NYHA class deteriorated (Figure 2.1); and in general QoL scores worsened as NT-proBNP increased, especially in patients with AF (Figure 2.2).

Discussion

This analysis suggests that when the main question of interest is simply "what is the patient's quality of life", then asking the patients to rate it directly using a single question may be sufficient or perhaps superior to asking a series of related questions that skirt the issue, as is the case with QoL questionnaires. Use of a single question to assess QoL could greatly increase the acquisition of QoL data in clinical trials. Rather than being measured at infrequent intervals or not at all, it could become a standard part of every assessment. QoL is unlikely to be stable over long-periods of time in patients with heart failure. It will decline with progression of heart failure or due to intercurrent illness and, hopefully, improve with treatment. Acquiring more frequent information allows the relationship between events and interventions to be explored

more effectively. However, a single question may not be the optimal method of assessing QoL in a clinical trial when used alone. A mixed approach, with frequent use of a single-question supported periodically by more detailed QoL questionnaires would provide a high density of information about QoL combined with insights about why it might be imperfect. Further research is required to identify whether the single question approach we used is the optimal method of patient self-rating or whether other approaches such as visual analogue scales might be better.

The EHFSQ-1 was designed as a tool to capture data on symptoms of heart failure and common associated co-morbidities as well as more general aspects of living that affect QoL. EHFSQ-1 has not yet been validated as a QoL tool, either in terms of reproducibility or in comparison to other QoL instruments such as MLWHFQ (MLHFQ [15]) or KCCQ [16]. However, the questions in quality of life questionnaires are broadly similar and it is likely that their results are highly correlated. Whether KCCQ or MLHFQ is more sensitive to change is a matter of debate. EHFSQ-1, with its more extensive set of questions is likely to capture more aspects of QoL if the patient completes all the questions. Despite this, the factor analysis could explain only about two thirds of the variability in response to a single question about QoL. The responses to the two single questions about QoL were highly correlated suggesting that the problem may lie with the failure of more complex questionnaires to capture information that impinge substantially on and/or deal with the heterogeneous factors that affect an individual patient's QoL. Interestingly, when asked in the context of an out-patient visit, patients did not seem to differentiate between general and health-related QoL suggesting that health was the dominant issue affecting their QoL. Whether differences would be observed if the questions were

asked outside of a healthcare context is unclear and uncertain. Nonetheless, the breathlessness symptom cluster score was strongly related to the single questions on overall health and overall QoL. Indeed, if these questions were added to the factor analysis, they were both incorporated into the breathlessness symptom cluster.

Comparison of patients with and without heart failure shows substantial differences in clinical characteristics including age, and co-morbidities as well as cardiac dysfunction. There are also differences in symptomatology but these are relatively subtle, supporting the notion that diagnosis of heart failure by symptoms alone is unreliable. About 80% of patients with heart failure reported that they developed some degree of breathlessness during normal daily activity, although this was marked in only one third of patients. However, two-thirds of patients without heart failure reported some breathlessness during daily activity and this was marked in more than 20%. Many of these patients had other problems such as obesity, angina, COPD or musculo-skeletal problems that could provoke breathlessness and impair QoL. It was also possible that some patients were misclassified; the cut-off for NT-proBNP may have been too high or diuretics could have concealed features of heart failure. Indeed, patients who were not taking diuretics or who had an NT-proBNP <125ng/L had better QoL scores. Interestingly, patients taking diuretics that had no other criteria for heart failure had similar QoL scores to patients with mild to moderate heart failure, suggesting that the diagnostic criteria for heart failure may have been too strict. Patients taking loop diuretics are known to have a worse prognosis [17] even if they have not been recognized to have heart failure.

Amongst patients with heart failure, EHFSQ-1 suggests that functional limitation due to breathlessness is a key determinant of QoL. This is not surprising. However, it accounted for only 15% of variability of the overall QoL score, which was only slightly more than psychological health. Sleep quality, general frailty, cognitive function, cough and chest pain made smaller contributions on average but clearly, some will have made a substantial contribution in some patients and none at all in others. Questionnaires such as EQ5D [18, 19], MLWHFQ, KCCQ and EHFSQ-1 may be valuable in determining what has led to an impaired QoL on average or in an individual patient. This analysis suggests that EHFSQ-1 might be reduced to seven key questions. However, it depends on why the questionnaire is being applied. For instance, knowledge about the severity of ankle swelling may be considered important for many reasons even if it is not an important determinant of QoL. Thus the complete EHFSQ-1 might be used for patient profiling, the seven question version for assessing why QoL is impaired and the single question for rating patient-perceived QoL.

There are very few reports on the distribution of symptom scores in questionnaires in consecutive patients with heart failure referred for diagnosis and care to a heart failure clinic and none on patients with suspected heart failure where the diagnosis was refuted. The EHFSQ-1 score was much higher (worse) in patients where the diagnosis of heart failure was confirmed and in patients who were in a more severe NYHA class. QoL score appeared to be related to NT-proBNP, a marker of the severity of cardiac dysfunction and prognosis. Our NT-proBNP threshold for the diagnosis of heart failure was based on an interpretation of the 2008 guidelines on heart failure of the European Society of Cardiology [20]. Guidelines have since revised the threshold downward and it is likely that some patients with HFnEF but well-controlled

congestion will have 'contaminated' the no heart failure group. This sort of problem cannot be resolved until a clear and robust definition of HFnEF is agreed. However, patients with HFnEF and an NT-proBNP <400ng/L have a much better prognosis than those with higher levels. Moreover, there is, as yet, no specific disease-modifying therapy for HFnEF and therefore subtle differences in the definition will not alter management decisions.

We used principal component analysis (PCA) to extract factors. There is a basic difference between factor analysis and PCA. Factor analysis is based on a statistical model. It seeks the smallest number of unobserved latent variables (or potential factors) that explain the original data. On the other hand, PCA is a transformation, which reduces a relatively large number of variables into a small number of 'principal' components that explain a large proportion of the total sample variance of the original variables[5]. However, Rietveld and Van Hout pointed out that "the difference between factor analysis and PCA decreased when the number of variables and the magnitudes of the factor loadings increased [21]" and the results of PCA are little different from those derived from factor analysis [22]. Exploratory factor analysis has the advantages of analysing the structure of data especially when correlations between variables are reasonably high and there are a large number of variables. Although the method overcomes many of the problems related to analysis of a high number of variables many of which are related.

There are some limitations. In EHFSQ-1, four questions related to work, drug side effects, costs of care and sexual activities were excluded due to a large number of missing values, perhaps reflecting the age of this population and free access to health

care provided by the NHS in the UK. Clearly, the EHSQ-1 should be tested for reproducibility, sensitivity to change, assessed in additional datasets and healthcare settings and compared to other QoL tools. Several such projects are underway. However, 10-fold cross-validation has been used to assess the stability of the analysis and Cronbach's alpha method has been used for testing the internal consistency of questions scores.

In conclusion, for patients with suspected HF, if the aim is to measure QoL it may be best just ask the patient a simple question such as ‘how do you rate your overall health?’ or ‘how do you rate your overall QoL? Only if it is important to know why a patient’s QoL is less than ideal is it necessary to ask further questions. When QoL is being used as an outcome measure then it is usual only to report a summary score or a summary symptom cluster score and all the underlying detailed information usually goes unreported. Thus, a single question about QoL or patient well-being may suffice for most purposes. The greater number and frequency of questions asked the less likely they are to be completed. Less is more.

Supplementary material

Supplementary material is available at International journal of cardiology online.

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Figure legend

Figure 1: The correlation between the sum of the seven (or eight for patients without heart failure) cluster scores and the sum of scores from the 33 valid individual QoL questions

Figure 2.1: The means and the standard deviations: average of raw total score from 33 questions and patient-rating of overall QoL and overall health using single questions for each of NYHA class. Higher values indicate worse QoL

Figure 2.2: Relationship between quintiles of NT-proBNP and different QoL scores in patients who were atrial fibrillation (AF) or sinus rhythm (mean with SD within each quintile) (The quintiles of NT-proBNP was calculated based on all patients regardless of diagnosis or heart rhythm)

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Figure 1

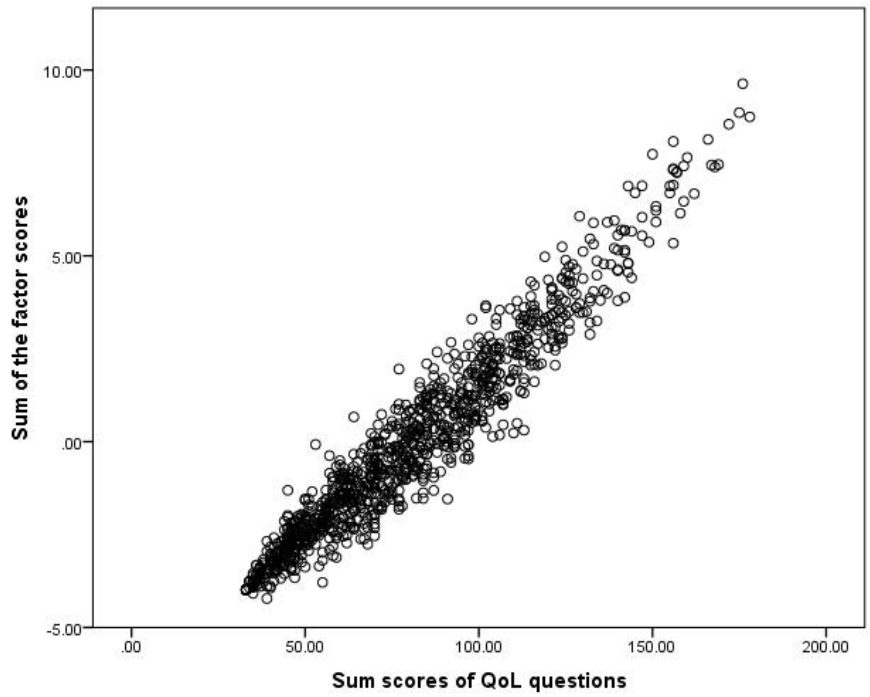

Figure 1: The correlation between the summary symptom cluster scores and the summary scores of QoL questions for all patients (r=0.96, p-value<0.0001)

Figure 2

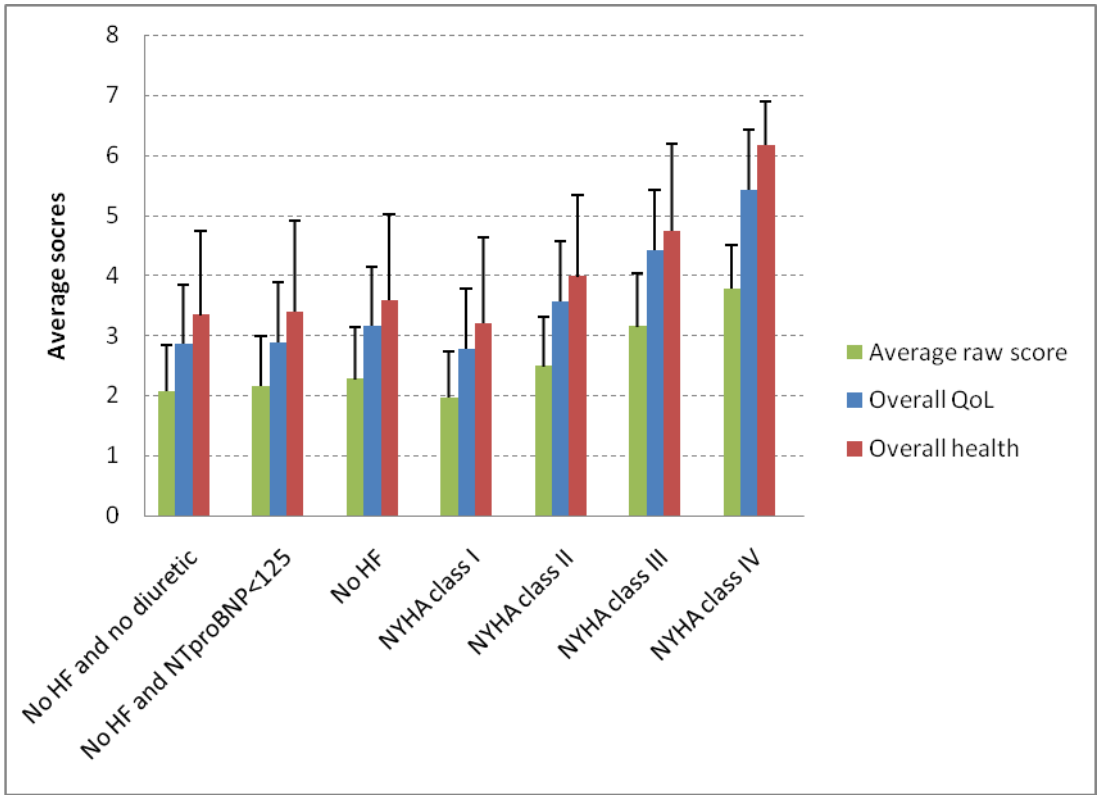

Figure 2.1: The means and the standard deviations of the average raw total QoL score from 33 questions and patient-rating using single questions of a) overall QoL and b) overall health for each NYHA class. Higher values indicate worse QoL. Best possible score for average QoL raw score is 6 and for single questions is 7; worst possible score is 1 for the both.

	No HF and no diuretic	No HF and NT-proBNP<125	No HF	NYHA class I	NYHA class II	NYHA class III	NYHA class IV
No. of patients	254	202	405	331	509	179	12

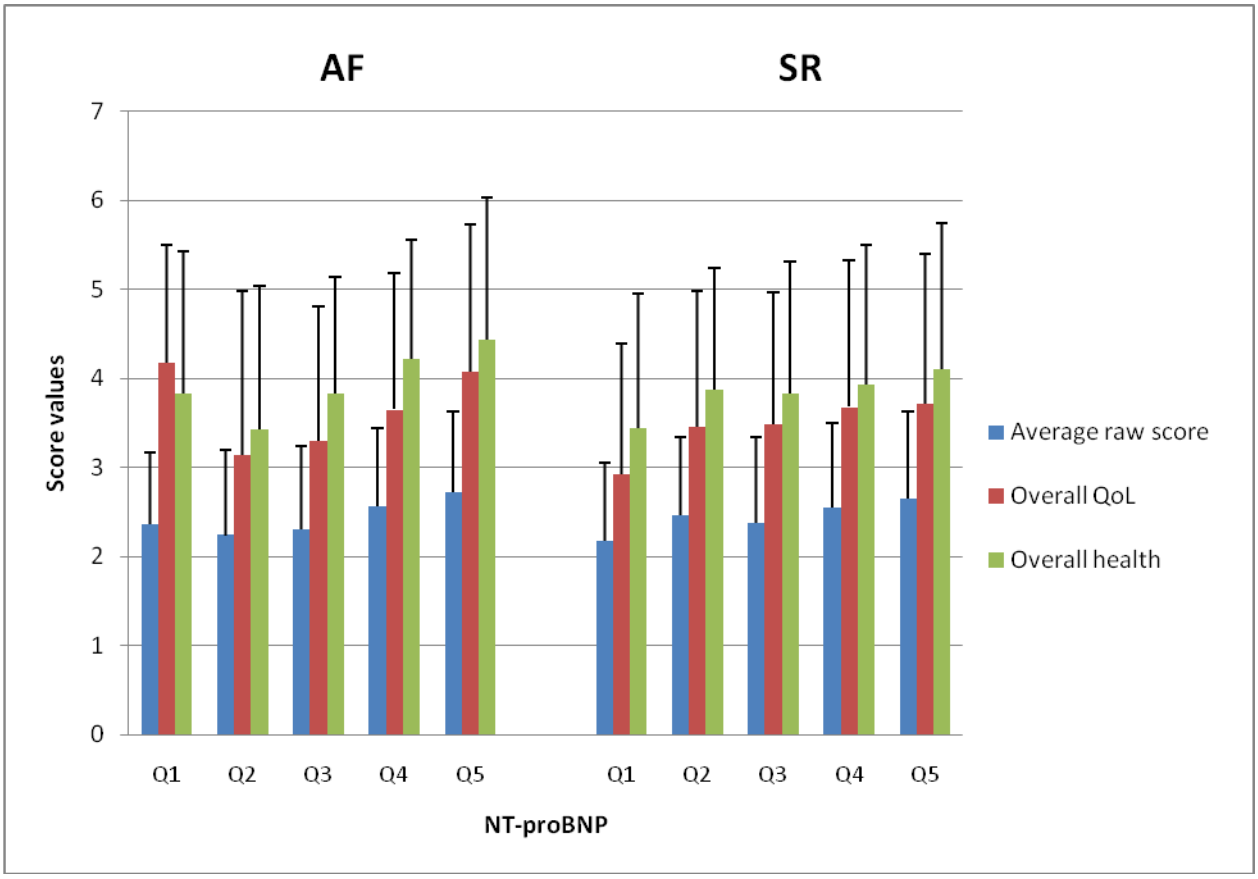

Figure 2.2: Relationship between quintiles of plasma NT-proBNP and QoL scores (mean with SD) in patients who were or were not in sinus rhythm (quintiles of NT-proBNP were calculated based on all patients regardless of heart rhythm). Heart rhythm is known to have a major effect on plasma NT-proBNP concentration that might could have affected relationship with symptoms. The following table provides the number of patients used in each group. Note the small number of patients with AF and NT-proBNP <250ng/L.

NT-proBNP (ng/L)	Quintile 1 68 (38-92)	Quintile 2 189 (148-249)	Quintile 3 548 (415-695)	Quintile 4 1403 (1089-1792)	Quintile 5 4191 (3048-6952)
Not SR	6	14	53	92	100
SR	200	192	153	114	107

Supplements:

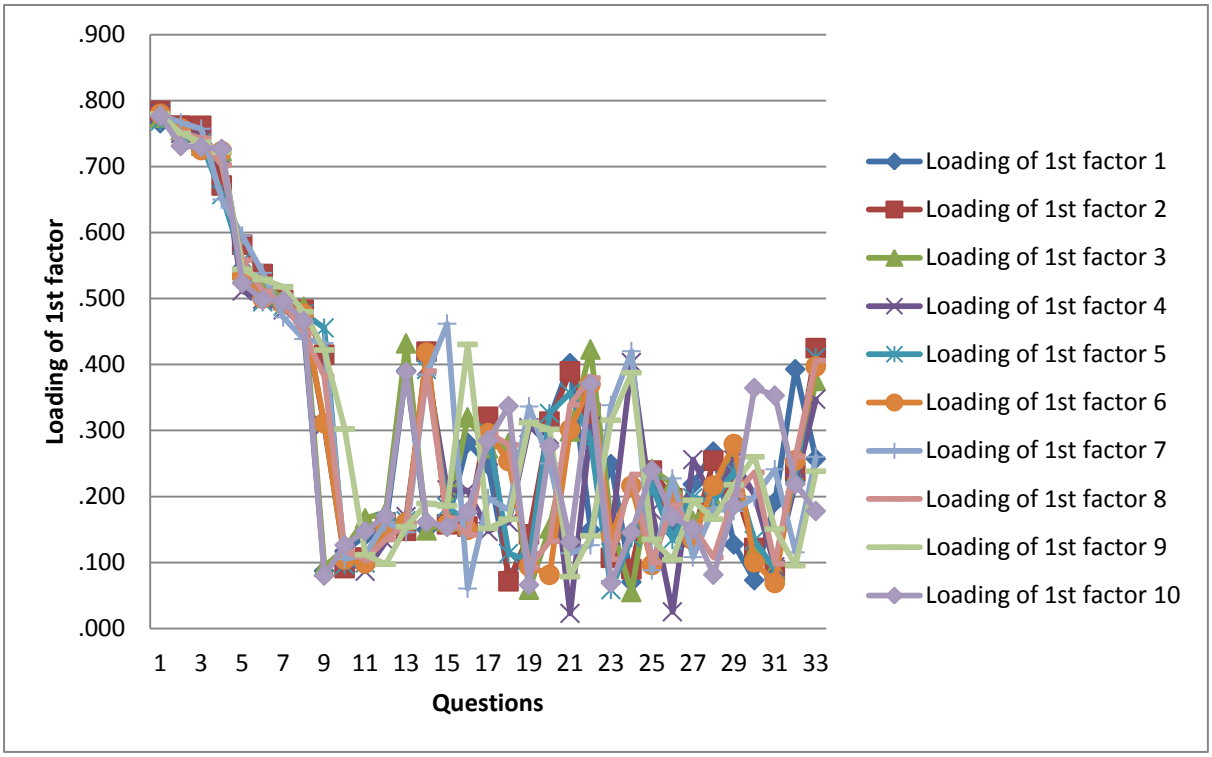

Figure 1: Loading of first factor ("breathlessness") for each dataset in 10-fold cross-validation for patients in heart failure. It shows a consistent pattern over all the 10 datasets. Interpretation of the values (the 33 QoL questions) on the x-axis is provided in Table 2.

Table 1

Table 1: Baseline characteristics by patient groups: patients with HFrEF (LVEF <40% or LVI>Mild), patients with HFnEF (LVEF >=40% or LVI<=Mild but NT-proBNP>400ng/L) and patients with no HF (LVI<=Mild and NT-proBNP<=400ng/L)

	Missing values	HF (n = 626)			HF (n = 626)	No HF (n = 405)	P-value
		HFrEF (n = 377)	HFnEF (n = 249)	p-value			
Age (years)	0	69 (11)	74 (9)	<0.001	71 (10)	67 (10)	<0.001
Men (%)	0	77%	54%	<0.001	65%	233 (58%)	0.001
IHD (%)	0	64%	39%	<0.001	54%	159 (39%)	<0.001
Diabetes (%)	131	19%	21%	0.461	20%	50 (14%)	0.037
BMI (kg/m^2)	0	27.1 (24.4-30.3)	27.4 (24.3-31.3)	0.336	27.2 (24.3-30.8)	29.0 (26.1-32.7)	<0.001
COPD (%)	0	7%	10%	0.170	8%	6%	0.395
AF (%)	0	17%	43%	<0.001	27.3%	1%	<0.001
QRS width (msec)	41	112 (98-142)	96 (86-110)	<0.001	104 (92-126)	92 (82-101)	<0.001
LVI > Mild (%)	0	100%	0	<0.001	60%	0	<0.001
Left atrial dimension (cm)	0	4.4(4.0-4.9)	4.2 (3.9-4.9)	0.637	4.3 (3.9-4.9)	3.8 (3.4-4.1)	<0.001
MR> mild (%)	106	125(35%)	58(25%)	0.013	31%	2%	<0.001
NT-proBNP (ng/L)	0	1592 (652-3718)	1194 (728-2338)	0.079	1389 (678-3049)	127 (68-212)	<0.001
NT-proBNP(ng/L) in sinus rhythm	0	1135(493-2925)	1044(639-1880)	0.931	1104(566-2558)	120(68-211)	<0.001
Sodium (mmol/L)	0	140 (137-141)	140 (137-141)	0.663	140 (137-141)	140 (138-141)	<0.001
Potassium (mmol/L)	7	4.4 (4.1-4.7)	4.4 (4.0-4.8)	0.466	4.4 (4.1-4.7)	4.3 (4.0-4.6)	0.001
Urea (mmol/L)	0	6.7 (5.3-9.6)	6.8 (5.2-9.4)	0.607	6.8 (5.3-9.5)	5.3(4.3-6.5)	<0.001
Creatinine (umol/L)	0	107 (89-135)	103 (87-129)	0.126	106 (87-132)	88(77-101)	<0.001
eGFR($ml/min/1.73m^2$)	8	61 (45-73)	57 (45-72)	0.166	59 (45-72)	72 (61-83)	<0.001
Hb (g/dL)	0	13.7 (12.4-14.7)	13.2 (11.8-14.3)	0.002	13.5 (12.3-14.5)	14.1 (13.2-15.0)	<0.001
Loop diuretics (%)	19	74%	67%	0.045	71%	32%	<0.001
ACEi (%)	19	73%	54%	<0.001	66%	40%	<0.001
ARB (%)	19	7%	7%	0.999	7%	6%	0.630
BB (%)	19	56%	48%	0.035	53%	39%	<0.001
Digoxin (%)	19	16%	29%	<0.001	21%	2%	<0.001
Spironolactone (%)	19	23%	10%	<0.001	18%	2%	<0.001

*LVI: left ventricular impairment; IHD: ischemic heart disease; BMI: body mass index; Hb: haemoglobin; BB: beta blocker

Table 2

Table 2.1*: The distributions of the responses to QoL questions for different patient groups (Each cell represents the percentage of all patients for that group. The explanation of the abbreviated terms in the left column is described in the footnote to the table).

	Group	No	Very little	Little	Some	A lot	Very much	N
SoA	HFrEF	47.5	10.3	10.3	16.2	11.7	4.0	377
	HFnEF	38.6	6.8	12.9	18.9	12.4	10.4	249
	No HF	48.9	10.9	6.2	16.5	12.8	4.7	405
SoB at rest	HFrEF	44.3	14.1	10.9	18.6	9.0	3.2	377
	HFnEF	48.2	16.1	9.6	16.9	7.2	2.0	249
	No HF	55.6	11.1	13.8	14.8	4.4	0.2	405
SoB at night	HFrEF	52.3	13.0	9.5	14.3	5.6	5.3	377
	HFnEF	56.6	14.5	6.8	14.1	4.4	3.6	249
	No HF	71.1	9.1	7.7	8.6	3.2	0.2	405
SoB during normal activity	HFrEF	20.2	7.7	13.0	24.4	21.2	13.5	377
	HFnEF	27.7	8.8	9.2	17.3	22.1	14.9	249
	No HF	35.1	11.1	9.1	23.5	13.6	7.7	405
Fatigue at rest	HFrEF	39.0	13.3	15.6	16.7	9.5	5.8	377
	HFnEF	40.2	14.1	14.9	19.7	8.0	3.2	249
	No HF	51.1	12.3	11.1	17.0	6.7	1.7	405
Fatigue during daily activity	HFrEF	22.5	13.5	15.4	21.8	18.0	8.8	377
	HFnEF	28.5	12.9	7.2	23.7	18.5	9.2	249
	No HF	35.1	14.8	13.1	20.7	10.1	6.2	405
Loss of appetite	HFrEF	54.6	11.1	10.1	12.5	7.2	4.5	377
	HFnEF	54.6	8.8	12.0	12.9	7.2	4.4	249
	No HF	75.3	6.7	7.2	8.4	2.0	0.5	405
Anxiety	HFrEF	41.1	12.7	13.0	16.2	11.4	5.6	377
	HFnEF	41.8	11.6	14.1	19.7	8.0	4.8	249
	No HF	42.0	14.6	14.6	16.3	9.6	3.0	405
Depression	HFrEF	54.4	9.8	14.3	14.1	5.8	1.6	377
	HFnEF	61.8	14.5	7.6	9.6	4.8	1.6	249
	No HF	63.7	9.9	10.4	10.6	3.0	2.5	405
Decreased concentration	HFrEF	47.2	11.9	16.2	14.6	6.4	3.7	377
	HFnEF	50.6	13.7	16.1	13.7	5.6	0.4	249
	No HF	52.6	12.3	14.1	13.8	6.4	0.7	405
Stress	HFrEF	45.6	14.9	14.6	14.6	6.6	3.7	377
	HFnEF	48.2	14.5	13.3	17.3	5.2	1.6	249
	No HF	45.9	12.8	12.3	19.5	6.9	2.5	405
Insomnia	HFrEF	43.2	10.3	10.1	16.4	10.1	9.8	377
	HFnEF	46.6	10.4	9.2	16.1	10.0	7.6	249
	No HF	47.9	9.1	11.9	14.8	10.6	5.7	405
Waking early	HFrEF	29.4	11.4	13.8	19.1	16.7	9.5	377
	HFnEF	28.9	15.7	14.1	14.9	16.5	10.0	249
	No HF	31.4	13.6	15.1	17.8	15.6	6.7	405
Lack of refreshing sleep	HFrEF	36.9	8.8	12.7	18.6	14.1	9.0	377
	HFnEF	36.1	10.8	11.2	21.7	11.6	8.4	249
	No HF	36.8	9.4	12.3	22.2	12.8	6.4	405
Reduction in daily activity	HFrEF	25.7	10.1	10.3	22.3	15.1	16.4	377
	HFnEF	27.7	8.8	11.2	19.3	20.5	12.4	249
	No HF	41.5	11.4	10.4	16.8	11.1	8.9	405
Reduced enthusiasm for hobbies	HFrEF	22.3	10.3	8.0	16.4	19.1	23.9	377
	HFnEF	31.7	7.6	7.2	10.4	22.9	20.1	249
	No HF	37.0	7.9	10.4	16.3	15.6	12.8	405

Friends down	HFrEF	56.5	10.1	8.8	15.9	4.5	4.2	377
	HFnEF	52.6	12.0	15.3	11.2	4.8	4.0	249
	No HF	70.1	8.6	7.9	7.9	3.5	2.0	405
Loss of control	HFrEF	44.3	10.3	13.3	15.1	8.5	8.5	377
	HFnEF	49.4	9.2	14.5	12.9	8.4	5.6	249
	No HF	58.3	7.4	13.1	11.4	5.4	4.4	405
Lonely	HFrEF	60.2	10.3	9.8	9.5	4.5	5.6	377
	HFnEF	60.6	8.8	12.4	11.2	4.0	2.8	249
	No HF	74.8	4.0	8.6	6.7	2.7	3.2	405
Burden	HFrEF	50.9	10.3	11.9	14.3	6.9	5.6	377
	HFnEF	55.0	9.2	10.8	13.7	6.0	5.2	249
	No HF	69.4	6.7	7.9	10.6	3.2	2.2	405
Loss of Memory	HFrEF	40.8	14.9	15.6	15.6	7.7	5.3	377
	HFnEF	43.0	13.3	20.9	14.9	5.6	2.4	249
	No HF	40.5	16.3	19.3	17.8	3.5	2.7	405
Chest pain at rest	HFrEF	63.4	12.2	8.0	11.7	3.4	1.3	377
	HFnEF	69.5	8.8	8.8	10.4	2.4	0	249
	No HF	61.2	13.8	9.9	11.4	3.2	0.5	405
Chest pain at Daily activity	HFrEF	54.6	10.1	12.5	13.0	5.3	4.5	377
	HFnEF	58.6	9.2	10.4	15.7	4.8	1.2	249
	No HF	50.9	16.5	12.1	13.6	5.4	1.5	405
Dizziness	HFrEF	47.7	14.1	12.7	14.1	8.5	2.9	377
	HFnEF	50.2	11.2	14.5	18.5	4.4	1.2	249
	No HF	56.3	10.1	15.1	13.3	3.5	1.7	405
Falls	HFrEF	81.2	6.1	5.3	5.6	1.9	0	377
	HFnEF	83.1	8.0	4.0	3.2	1.6	0	249
	No HF	88.4	3.7	2.5	4.0	1.0	0.5	405
Cough	HFrEF	39.3	13.0	14.1	19.9	9.3	4.5	377
	HFnEF	43.0	12.9	13.7	20.1	6.0	4.4	249
	No HF	44.9	12.1	12.3	14.8	11.6	4.2	405
Wheeze	HFrEF	43.5	11.4	15.6	15.4	9.8	4.2	377
	HFnEF	47.4	11.6	14.5	18.5	6.0	2.0	249
	No HF	50.1	10.1	12.8	17.5	7.4	2.0	405
Muscles & Joints	HFrEF	27.1	10.9	15.4	22.5	12.7	11.4	377
	HFnEF	23.3	9.6	10.4	25.7	18.5	12.4	249
	No HF	21.0	9.9	10.4	28.1	19.8	10.9	405
Indigestion	HFrEF	56.5	11.9	8.5	14.3	6.6	2.1	377
	HFnEF	55.0	10.0	10.0	15.7	6.8	2.4	249
	No HF	50.6	11.9	10.4	16.3	6.4	4.4	405
Have to rest During the day	HFrEF	17.8	10.1	17.5	24.4	12.6	5.0	377
	HFnEF	18.5	10.4	16.5	24.1	12.1	6.4	249
	No HF	26.4	10.9	19.0	23.2	8.9	2.7	405
Make you eat less of food you like	HFrEF	46.4	8.8	9.3	17.2	6.5	5.3	377
	HFnEF	46.6	6.0	11.6	16.9	5.8	7.2	249
	No HF	63.0	7.9	5.9	14.1	3.2	2.7	405
Going places away from home difficult	HFrEF	48.0	6.4	9.5	9.8	9.7	6.9	377
	HFnEF	42.2	5.6	8.8	10.8	11.3	10.0	249
	No HF	65.4	4.4	7.2	8.4	5.7	3.2	405
Making you stay in Hospital	HFrEF	60.5	6.4	6.9	8.8	2.7	12.2	377
	HFnEF	59.8	6.0	4.4	7.6	4.2	13.7	249
	No HF	80.2	2.0	3.2	3.0	1.1	9.4	405

The full descriptive terms of the abbreviation of the questions are as follows (the questions are: how much did any the following (1-33) affect you in the last month?):

1.SoA: Swelling of ankles or legs;
2. SoB at rest: Breathlessness while sitting at rest;
3. SoB at night: Breathlessness waking you from sleep;
4. SoB normal activity: Breathless that limits your ability to do normal daily activities;
5. Fatigue at rest
6. Fatigue daily activity: Fatigue that limits your ability to do normal daily activities
7. Loss of appetite
8. Anxiety:Anxiety or worry
9. Depression
10. Concentration:Loss of concentration
11. Stress
12. Insomnia:Inability to get to sleep
13. Waking:Waking up in the night and having difficulty getting back to sleep
14. Lack of refreshing sleep
15. Daily activity down:Inability to do normal daily activities due to your health
16. Hobbies down:Inability to do hobbies or sports due to your health
17. Friends down:Inability to enjoy the company of friends & family due to your health
18*. Work down: Inability to work due to your health
19*. Side effects: Side-effects that you think might be due to your treatment
20*. Sex: Difficulties with sexual function
21*. Drug cost: Costs of medicines or medical care
22. Loss of control:Feelings of loss of control over your life
23. Lonely:Feelings of loneliness
24. Burden:Feelings that you are a burden to others
25. Loss of memory:Loss of memory for names or recent events
26. Chest pain at rest: Chest pains (inc. Angina) occurring while sitting at rest
27. Chest pain daily activity:Chest pains (inc. Angina) occurring while doing normal daily activates
28. Dizziness
29. Falls:Falls or Blackouts
30. Cough
31. Wheeze
32. Muscles:Aching muscles or joints
33. Indigestion:Indigestion or dyspepsia
34. Have to rest during the day
35. Make you eat less of food you like
36. Going places away from home difficult
37. Making you stay in hospital more often

Note that the above 4 questions (*) were not included in the analysis due to too many missing values. A copy of the survey is available in Appendix.

Table 2.2: The distributions of the responses of overall QoL questions for different patient groups (Each cell represents the percentage of total patients of each group.

		Very good	Good	Quite good	average	Quite poor	Poor	Very poor	N
Overall health	HFrEF	3.4	10.9	16.4	34.2	14.1	13.5	7.4	377
	HFnEF	3.2	15.7	18.9	30.1	10.0	16.9	5.2	249
	No HF	7.9	17.5	19.8	30.9	12.3	10.4	1.2	405
Overall QoL	HFrEF	7.2	17.8	19.6	29.7	11.1	9.0	5.6	377
	HFnEF	8.0	19.7	18.1	27.3	8.8	13.3	4.8	249
	No HF	14.6	24.4	20.0	24.9	6.2	8.1	1.7	405

Table 3

Table 3: Factor loadings after rotation for each symptom cluster in patients with HF (626 patients) and without HF (405 patients)

	HF							No HF							
	Breathlessness	**Psychological distress**	**Sleep quality**	**Frailty**	**Cognitive / Psychomotor function**	**Cough**	**Chest pain**	**Breathlessness**	**Chest pain/ Breathlessness**	**Psychological distress**	**Sleep quality**	**Frailty**	**Cognitive / Psychomotor function**	**Respiratory symptoms**	**Falls**
SoA	--	--	--	--	--	--	--								0.43
SoB at rest	0.49								0.64						
SoB at night						0.45			0.60						
SoB normal activity	**0.75**							**0.70**	0.42						
Fatigue at rest	0.52							0.47	0.52						
Fatigue on daily activity	**0.76**							**0.72**							
Loss of appetite			0.42									0.44			
Anxiety		**0.77**								**0.84**					
Depression		**0.81**								**0.79**					
Concentration		0.51			0.55								0.62		
Stress		**0.81**								**0.80**					
Insomnia			**0.82**								**0.82**				
Waking			**0.83**								**0.88**				
Lack of refreshing sleep			**0.75**								**0.78**				
Daily activity down	**0.78**							**0.79**							
Hobbies down	**0.73**							**0.72**							
Friends down	0.48														0.42
Loss of control	0.52	0.45						0.44							
Lonely		0.64								0.60					
Burden	0.41	0.53								0.41					0.41
Loss of memory					**0.71**								**0.74**		

Chest pain at rest							**0.84**		**0.79**						
Chest pain at daily activity							**0.83**		**0.75**						
Dizziness					0.60				0.40				0.42		0.40
Falls					0.62										**0.74**
Cough						**0.84**								**0.81**	
Wheeze						**0.76**								**0.79**	
Muscles					0.43			--	--	--	--	--	--	--	--
Indigestion	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Have to rest during the day	0.41			0.58				0.52				0.45			
Make you eat less of food you like				**0.74**								**0.77**			
Going places away from home difficult				**0.70**				0.40				0.64			
Making you stay in hospital				**0.78**								**0.72**			
Variance explained (%)	14.51	12.60	9.20	8.35	7.52	6.25	6.14	13.02	10.52	10.00	8.33	7.04	6.09	5.57	5.53
Cumulative variance explained (%)	14.51	27.11	36.31	44.66	52.18	58.43	64.57	13.02	23.54	33.55	41.88	48.91	55.01	60.58	66.11
Cronbach's alpha	0.89	0.83	0.83	0.79	0.62	0.68	0.84	0.88	0.83	0.84	0.89	0.67	0.73	0.75	0.64

Table 4

Table 4.1: The relationships between overall health, overall QoL, a summary QoL score, a summary symptom cluster scores and NYHA class for patients with HF (626 patients) / without HF (405 patients) respectively

	Overall health	Overall QoL	Sum score QoL	Sum symptom cluster score	NYHA class
Overall health	1.00				
Overall QoL	0.730/0.759 (p<0.001)	1.00			
Sum score of QoL	0.661/0.667 (p<0.001)	0.658/0.642 (p<0.001)	1.00		
Sum symptom cluster score	0.614/0.678 (p<0.001)	0.602/0.654 (p<0.001)	0.964/0.954 (p<0.001)	1.00	
NYHA class	0.312/0.393 (p<0.001)	0.322/0.404 (p<0.001)	0.435/0.463 (p<0.001)	0.410/0.389 (p<0.001)	1.00

*Correlation is significant at the 0.01 level (2-tailed) use the Spearman's rank correlation test.

Table 4.2: The relationships between each individual symptom cluster scores and overall health and overall QoL scores and NYHA class in patients with HF (626 patients)

	Breathlessness	Psychological distress	Sleep quality	Frailty	Cognitive / psychomotor function	Chest pain	Respiratory symptoms
Overall health	0.50 (p<0.001)	0.28 (p<0.001)	0.17 (p<0.001)	0.24 (p<0.001)	0.17 (p<0.001)	0.19 (p<0.001)	0.05 (p=0.22)
Overall QoL	0.47 (p<0.001)	0.32 (p<0.001)	0.15 (p<0.001)	0.26 (p<0.001)	0.20 (p<0.001)	0.12 (p=0.004)	0.03 (p=0.40)
NYHA class	0.32 (p<0.001)	0.12 (p=0.002)	0.21 (p<0.001)	0.17 (p<0.001)	0.02 (p=0.612)	0.22 (p<0.001)	0.01 (p=0.728)