

Overview of The Minnesota Living with Heart Failure® Questionnaire

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1/1/05

Conceptualization and Design

The Minnesota Living with Heart Failure questionnaire (MLHF) was designed in 1984 to measure the effects of heart failure and treatments for heart failure on an individual's quality of life (1-3). The content of the questionnaire was selected to be representative of the ways heart failure and treatments can affect the key physical, emotional, social and mental dimensions of quality of life without being too long to administer during clinical trials or practice. Responses of patients with heart failure to the Sickness Impact Profile, a comprehensive assessment of the impact of illness in general, and the thoughts of several physicians and nurses caring for patients at the University of Minnesota helped identify pertinent questions for measuring the effects of heart failure on patient's quality of life. The content of other measures of health status and quality of life was considered as well.

These efforts to identify the most pertinent content led to questions that assess the impact of frequent physical symptoms - shortness of breath, fatigue, peripheral edema, and difficulty sleeping, and psychological symptoms of anxiety and depression. In addition, the effects of heart failure on physical/social functions including walking, climbing stairs, household work, need to rest, working to earn a living, going places away from home, doing things with family or friends, recreational activities, sexual activities, eating and mental and emotional functions of concentration, memory, loss of self control, and being a burden to others were incorporated into the measure. Since treatments might have side effects in addition to ameliorating symptoms and functional limitations produced by heart failure, questions about side effects of medications, hospital stays and costs of care were included to help measure the overall impact of a treatment on quality of life. A more recent version of the questionnaire asks about side effects of 'treatments' rather than 'medications' to reflect the growing use of non-pharmaceutical treatments for heart failure.

To measure the effects of symptoms, functional limitations, psychological distress on an individual's quality of life, the MLHF questionnaire asks each person to indicate using a 6-point, zero to five, Likert scale how much each of 21 facets prevented them from living as they desired. This response format was chosen to be consistent with the concept of quality of life and allows each individual to weigh each item using a common scale. Therefore, one can look at which items had the most effect and the sum of responses reflects the overall effects of heart failure and treatments on the individual's quality of life. Although the MLHFQ incorporates relevant aspects of the key dimensions of quality of life, the questionnaire was not designed to measure any particular dimension separately. Given the conceptual basis for the questionnaire, items on the questionnaire are considered to be 'causal' indicators of quality of life in the sense that they can affect someone's quality of life when they occur, but may not be present when other aspects of heart failure are affecting an individual's quality of life (4). Classical psychometric

methods such as factor analysis and other analytic procedures that assess inter-item correlations may not be appropriate for the MLHFQ (5). The total score should be taken as the best measure of how heart failure and treatments impact an individual's quality of life even if all of a patient's responses are not internally consistent. A factor analysis of responses that has been confirmed by others did find a highly inter-related subgroup of 8 questions related to the physical symptoms and another inter-related subgroup of 5 emotional domain questions related to the psychological distress (6, 7). Summation of the responses to these subgroups of questions may be used to help describe the physical and psychological effects of heart failure on quality of life. However, these two factors or dimensions are not sufficient to measure the total impact of heart failure or a treatment on quality of life.

Reliability

As summarized in the following table, the total MLHF score can be highly reliable as demonstrated by estimates of the correlation (r) between repeated baseline assessments and even measures of internal consistency such as Cronbach's alpha coefficient (α). More recently, the reliability coefficient was estimated to be 0.86 using structural equation models of repeated measurements from the Valsartan Heart Failure Trial (unpublished).

Study	Sample Size	NYHA Class	Reliability
Rector et al. (6)	181	III	$\alpha = 0.94$ $r = 0.93$
Rector et al. (8)	152	I-III	$r = 0.87$
Gorkin et al. (9)	135	I	$\alpha = 0.95$
	123	II-III	$\alpha = 0.94$
Bennett et al. (7)	211	I-IV	$\alpha = 0.95$
Bennett et al. (10)	62	I-IV	$\alpha = 0.92$
Reigel et al. (11)	1,136	inpatients	$\alpha = 0.92$

The MLHFQ scores have also been reliable in studies that collected data by telephone rather than self-administration in clinics (unpublished results from study described in reference 17). The interclass correlation coefficient between face-to-face and telephone data collection done two days apart was 0.87 in another study (12).

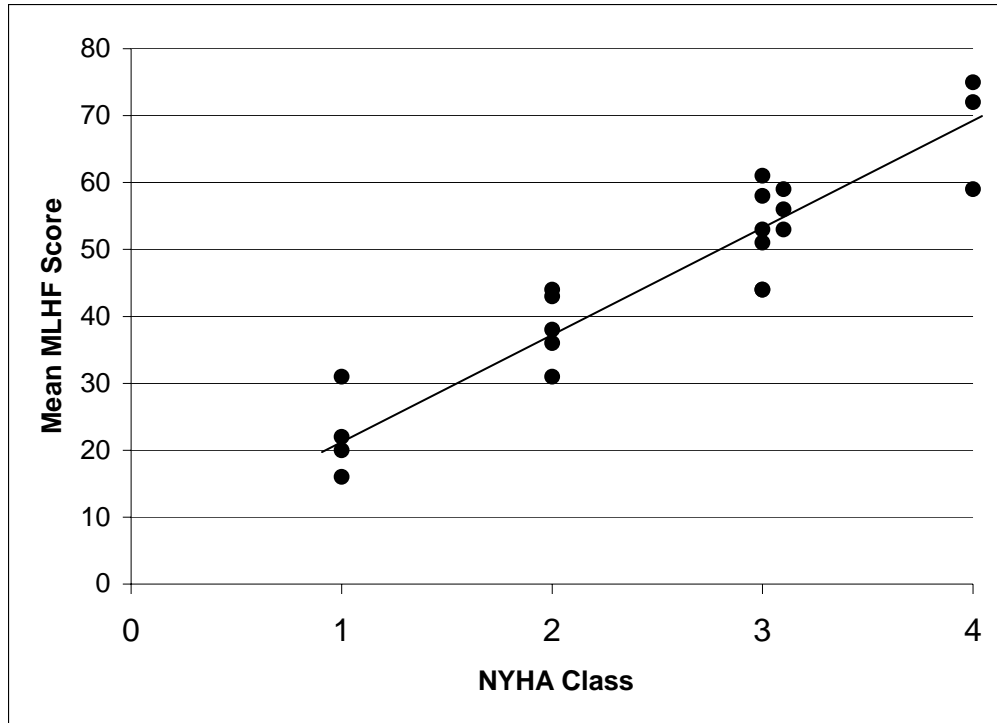
Validity

High internal consistency suggests that the total MLHF score measures a single construct – presumably interrelated effects of heart failure on an individual's quality of life. However, estimates of internal consistency can be increased by increasing the number of interrelated items on a questionnaire. The magnitude of correlations with measures of other constructs shown in the following table vary with the degree of

conceptual overlap with the MLHF providing strong support that the MLHF measures what it purports to measure.

Measure	Correlation with MLHF score
Chronic Heart Failure score	0.81 (7)
Dyspnea subscore	0.63
Fatigue subscore	0.78
Emotional subscore	0.74
Functional Status Scale – physical limitations	0.75 (9)
Emotional Distress	0.64(9)
SF-12 overall score	0.61(13)
SF-12 physical subscore	0.57(7)
SF-12 mental subscore	0.68(7)
Time tradeoff utility (willingness to trade current health for less time in perfect health)	0.56(14)
Dyspnea scale	0.52(9)
Clinician perceptions of patient’s health	0.44(9)
Duration of submaximal bicycle exercise	0.43(15)
Six-minute walk test	0.39(7), 0.26(16)
Anerobic threshold	0.37 (17)
Peak oxygen consumption	0.30(3), <0.10(17)
Ejection Fraction	0.03(9), 0.03(2), <0.10(6)

The following figure shows the relationship between mean MLHF scores and New York Heart Association (NYHA) classifications abstracted from 11 reports where the patients studied were predominantly one NYHA class or MLHF scores were summarized by NYHA class (2,6,7,9,11,18-23). Mean MLHF scores varied significantly ($p < 0.0001$) with NYHA class indicating overlap in what these measures measure. Estimated mean MLHF scores were 21, 37, 53 and 69 in Class I, II, III and IV patients, respectively. A study that used a new standardized questionnaire to classify patients into NYHA classes reported Class III and IV patients had mean MLHFQ scores of 57 and 69, respectively (24).



Responsiveness

Responsiveness of the MLHF refers to its ability to detect changes *in quality of life* that clinicians and patients discern and believe to be important (25). An instrument's ability to detect change depends, in part, on the amount of noise or measurement error inherent in repeated assessments. Changes in an individual's score need to be greater than 2.77 times the standard error of the measurement to be 95% confident that the observed change was not due to measurement error. Variance in measurements that's attributed to measurement error can be estimated as the variance (the standard deviation of the scores squared) times one minus the reliability coefficient of the measure. The square root of this error variance is the standard error of a measurement ($SEM = SD\sqrt{(1-reliability)}$). Estimates of the SEM for MLHF scores are summarized in the following table.

Mean Score	Standard Deviation	Estimate of Reliability	Estimated SEM
31(9)*	25	0.94	6.1
31(8)	24	0.87	8.6
37(10)	25	0.92	7.1
44(9)	26	0.95	5.8
44(6)	22	0.93	5.8
45(7)	27	0.95	6.0
52(11)	25	0.92	7.1

* numbers in parenthesis are references to the data.

The ability of a quality of life measure to detect differences when used in controlled clinical trials depends on the reliability of the measure in the population being studied, the completeness of the measurements made by investigators, the number of patients studied, the participants' baseline quality of life, the study duration, the number and effects of deaths and withdrawals from the study, the effects observed in the control group and finally the magnitude and consistency of the intervention's true effect on patients' quality of life. Despite all of these contingencies, the MLHF has detected statistically significant effects in randomized, controlled studies of several interventions including,

- Oral inotropes, pimobendan and vesnarinone, and flosequinan, a direct-acting vasodilator with inotropic properties (6, 18, 26). The maximal dose-dependent average improvement in the MLHF score ranged from 3 to 7 points above small, non-significant placebo effects observed in these studies.
- Enalapril improved the MLHF score by 5 points more than placebo. Placebo had no aggregate effect on MLHF scores (27). The angiotension II receptor blocker valsartan added to an angiotensin converting enzyme inhibitor produced a small, but significant average incremental effect of approximately 2 MLHF points (28). Studies comparing losartan to captopril and enalapril to hydralazine plus isosorbide dinitrate observed significant changes from baseline in the MLHF score that averaged 2 to 3 points in both treatment groups (29, 30). Another study that did not report the MLHF scores did not detect differences between candesartan and enalapril (31).
- Randomized controlled studies of heart failure disease management programs have demonstrated substantially greater improvements of 12 to 13 points, on average, in the total MLHF score (32, 33). A similar study of a disease management program in Australia noted a difference of 8 points that did not quite reach statistical significance (34). A comparison of two education programs provided as patients were being discharged from a hospital admission for heart failure found similar improvements in MLHFQ scores averaging 15 and 18 points after 30 days and 18 versus 13 after 6 months (35). A randomized study of heart failure specialist care provided to patients after they were discharged observed similar improvements in MLHFQ scores of 23 points versus 28 points when the AlereNet monitoring system was added for 6 months (36).
- The MLHF score detected a mean improvement of 14 MLHF points during exercise training in a randomized controlled trial wherein the control group did not change significantly (37).
- The significant beneficial effect of cardiac resynchronization on MLHF scores was 9, on average, compared to a concurrent control group; 14 in a randomized crossover study; and the median effect was 6 in a parallel study of cardiac resynchronization with a defibrillator (20-22).
- Observed differences in the overall MLHF score averaged a significant 23 points in a randomized controlled comparison of atrioventricular junction

ablation plus DDDR pacing to pharmacologic treatment of atrial fibrillation in patients with heart failure (38). Differences of 4 MLHF points were not statistically significant in a similar study by the same investigators using VVIR pacing (39). Pharmacologic therapy improved average MLHF scores by 7 points in both of these studies.

- A placebo-controlled, double blind crossover trial of sildenafil in 35 patients also found a significant difference of less than 5 points (40). Placebo had no effect on MLHFQ scores in this study.

There was a large difference in MLHF scores equal to 17 points among survivors in a randomized controlled study of a left ventricular assist device (23). This difference was not statistically significant due to the small number of 1-year survivors (n=6) in the control group.

A controlled clinical trial of digoxin did not find significantly greater improvements in the MLHF score compared to placebo (19). There was substantial unexplained improvement averaging 5 to 6 points in the placebo group in this study. A controlled study of randomly withdrawing digoxin did observe a significantly greater percentage of people whose MLHF scores worsened when digoxin was withdrawn compared to a group where digoxin was continued (41).

The MLHF did not show significant effects in most randomized, controlled studies of beta-adrenergic receptor blockers. Reported MLHF scores improved as much in the placebo group, 7 points, as the groups assigned to different doses of carvedilol (42). In a small study of patients with severe heart failure that was terminated early, the carvedilol group improved by nearly 12 points on average compared to 9 points in the placebo group even though the investigators demonstrated the MLHF scores were reproducible at baseline (43). In a study of patients with mild heart failure, an average MLHF improvement of 5 points in the carvedilol group was not statistically greater than the improvement of 2 points noted in the placebo group (44). Investigators in a single center in Italy did show a significant effect of 4 MLHF points after 4 weeks of treatment with carvedilol compared to an average effect of zero in the placebo group (15). The same investigators observed average improvements of 7 to 8 MLHF points in two groups randomly assigned to either carvedilol or metoprolol (45). A mean non-significant difference in MLHF scores of approximately 1 was found in a study of extended-release metoprolol compared to placebo (46). Scores on the MLHF changed by less than 1, on average, in both treatment groups in the later study. Scores on the MLHF improved by 5 points on average among patients treated with varying doses of bucindolol compared to a similar mean improvement in the comparison group given placebo (47).

There was no significant improvement in quality of life as measured by the MLHF in several studies of calcium channel blockers added to converting enzyme inhibitor therapy (48-49). In contrast to the negative studies of beta-blockers and digoxin cited previously, there was no placebo effect in these studies. Like digoxin and the beta-blockers, there's no other evidence that calcium channel blockers do indeed substantially improve the quality of life of people with heart failure. Thus, one should not surmise that the MLHF is unresponsive based on lack of significant effects in studies with unexplained changes in MLHF scores in the control group and lack of evidence that the

treatment being studied does indeed improve the quality of life of a substantial proportion of patients.

Interpretation

‘Clinically meaningful’ refers to an effect that would prompt patients and physicians to consider using a treatment if the risk and costs are acceptable. An improvement of 5 points in the MLHF score was considered to be sufficient for a majority of patients in one study to take a medication that had no side effects or costs (51). Approximately 40% of these patients were willing to take a 5% chance of drug-induced death for this degree of improvement in their MLHF score. Others have suggested that a change of 5 points is a minimal clinically significant change based on the mean change in the MLHFQ score observed in a group of patients who rated their change in overall condition as ± 2 or ± 3 on a -7 to $+7$ scale (12).

Some investigators have suggested that a change of one SEM may be clinically meaningful (52, 53). Estimates of the SEM for the MLHF score are approximately 6-7. However, one’s statistical confidence that an individual change of this magnitude in either direction would not be due to measurement error would be only about 50%. There are no gold standards to determine when an individual’s quality of life has truly changed to help define cutoff values for improvement and deterioration. Patient reports of whether or not they ‘felt better’ after 3-months of being referred to a heart failure clinic have been used to calculate the sensitivity, specificity and area under the receiver-operating-characteristic (ROC) curve by varying MLHF score cut-points (13). The estimated area under the ROC was 0.70 indicating that the MLHF score did discriminate patients who said they did or did not feel better. A single best cutoff value for MLHF scores to identify those who definitely felt better or worse was not determined. Average improvements in the MLHF score were 21, 14 and 12 among small groups of patients who said they felt markedly, moderately or mildly improved. Average scores worsened by 3 in the group that said they felt slightly worse.

Examination of the relationships between the MLHF and other outcome measures that are more familiar to clinicians can help provide some perspective on interpreting scores. Although the average effects reported in clinical trials are mixtures of individuals who did and did not improve (or deteriorate), the average effects summarized in the section on responsiveness provide some perspective for interpreting scores. As shown in the previous figure, differences between NYHA classes equate to a mean difference of 16 on the MLHF scale. A 10-point decrement in the MLHF score assessed in 101 patients 1-month after a hospital admission for heart failure was associated with an unadjusted 23% increase in the risk of death and a 31% increase in the risk of re-hospitalization or death during an average follow-up of 18 months (54).

Basing judgments about meaningful improvement or deterioration in quality of life scores on measurements of other phenomena is somewhat ambiguous and contrary to the rationale for measuring quality of life – because other clinical assessments do not. Clinicians often prescribe treatments that have some likelihood of helping patients live longer and stay out of the hospital even when the results of controlled clinical trials indicate that the majority of patients most likely will not experience these benefits. Since maintaining and improving patients’ health-related quality of life is a primary objective

of health care, treatments that have a proven benefit using a valid measure of quality of life in a randomized, blinded controlled trial should be given due consideration by clinicians and patients regardless of the magnitude of the average effect since some patients are likely to benefit in terms of improved quality of life.

Translations

Translating a questionnaire including instructions into another language requires a rigorous process. Numerous linguistic translations of the Minnesota of Living with Heart Failure have been developed by the Mapi Research Institute using state of the art methodology (55). Existing translations include English for Australia, Canada, Ireland and United Kingdom; Spanish for Spain, Argentina and the United States; French for France, Belgium, Switzerland and Canada; German; Polish; Italian; Dutch and Dutch for Belgium; Portuguese; Swedish; Finnish; Danish; Norwegian; Latvian; Lithuanian; Estonian; Russian; Romanian; Slovakian; Croatian; Czech; Hungarian; Greek; Hebrew; and Portuguese for Brazil. Be aware that the instructions for administering the questionnaire and the wording of the questionnaire about side effects have been modified somewhat after most of these translations were done.

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55. If you need any translations, please contact: MAPI Research Trust, 27 rue de la Villette, 69003, Lyon, France (www.mapi-research-trust.org; see licensing arrangements for questionnaire), Tel: +33 (0) 4 72 13 65-75; Fax +33 (0) 4 72 13 66 68).

