Health-Related Quality of Life Predicts Long-Term Survival in Patients with Peripheral Artery Disease

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ABSTRACT

Objectives: Patient-rated health-related quality of life (HRQoL) has been shown to predict mortality in cardiac patients, therefore we examined whether HRQoL predicts long-term survival in patients with peripheral artery disease (PAD) independent of established prognostic risk factors.

Methods: In 2004, data on 711 consecutive patients with PAD undergoing vascular surgery were collected from 11 hospitals in the Netherlands. After one year, patients were contacted to complete the EuroQol Questionnaire (EQ-5D), of which 503 (79%) complied. HRQoL assessed by the EQ-5D was divided into tertiles, i.e. poor, intermediate and good HRQoL. Mortality was subsequently assessed three years after surgery.

Results: Of the 503 patients, 55 (11%) patients died during follow-up. Mortality was 21% in patients with poor HRQoL, 8% in patients with intermediate HRQoL, and 5% in patients with good HRQoL. Patients with poor HRQoL (HR=5.4; 95%CI 2.3–12.5) had a worse survival compared to patients with a good HRQoL, after adjusting for established prognostic factors.

Conclusions: Impaired HRQoL predicts long-term survival in patients with PAD, and provides prognostic value above established risk factors. HRQoL measurements could be used in clinical practice to identify patients at high risk for adverse health outcomes, who may benefit from more intensive treatment.

Key words: Health-related quality of life; peripheral artery disease; disease management; prognosis
INTRODUCTION

Peripheral artery disease (PAD) is a marker of generalized atherosclerosis affecting multiple vascular beds simultaneously\(^1\). This polyvascular disease phenomenon frequently leads to conditions such as intermittent claudication, myocardial infarction (MI), dementia, and stroke\(^1,2\).

PAD is associated with increased cardiovascular morbidity, poor physical functioning, and adverse health outcomes\(^3,4\). Long-term survival after vascular surgery in patients with PAD is predominantly determined by the associated risk of coronary artery disease (CAD)\(^5\). Despite the known risk patients with PAD do not achieve comparable risk control as patients with other cardiovascular diseases\(^6,7\). Patients with PAD have poor long-term survival even more so than patients with CAD only\(^8\). Taken together, patients with PAD constitute a high-risk group that needs stringent risk management and monitoring\(^2\).

Health related quality of life (HRQoL) reflects patient physical, mental and social beliefs and perceptions in relation to health. HRQoL has been shown to have prognostic value in predicting adverse clinical events independent of conventional risk factors in CAD\(^9-12\). Prognostic information is pertinent for providing tailored patient management. Importantly, information about HRQoL and health status, as perceived by the patient, can help optimize patient-centred care in clinical practice\(^13\). Moreover large general population survey (N=12.375) has shown that self-rated health is a strong predictor of mortality\(^14\). Although HRQoL and the risk of mortality in patients with PAD are generally comparable to that of patients with CAD\(^15\), the impact of HRQoL on mortality in PAD has not yet been investigated. HRQoL might help to identify patients with PAD at high risk for adverse health outcomes in addition to established biomedical risk factors.

Hence, the objective of the present study was to examine if HRQoL predicts long-term survival in patients with PAD beyond established biomedical risk factors.

METHODS

Study population

The study population was derived from the Netherlands Heart Foundation Health Care Programme, entitled Peripheral Arterial Disease Survey. Details are only reported here as relevant
to the current analyses. More details on the study population and methods of data collection can be found in an earlier publication on this survey\textsuperscript{16}. Between May and December 2004, data on 711 patients with PAD undergoing non-cardiac vascular surgery were collected from 11 hospitals in the Netherlands. The consecutively enrolled patients were seen at the participating vascular surgery departments when undergoing endovascular or open procedures. Endovascular surgery procedures included aortic endografts or peripheral angioplasties with and without stenting. The open procedures comprised abdominal aortic surgery, carotid endarterectomy, or infrainguinal arterial reconstruction. All patients were asked for informed consent before participation. The 11 participating hospitals met the requirements for ethical approval based on local standards.

One year after surgery, 634 of 711 (89\%) patients were still alive. Survivors were sent the EuroQol Questionnaire and questions concerning their cardiovascular events by mail, which they were asked to complete. Of 634 patients, 503 (79\%) completed the questionnaire, comprising the sample available for statistical analyses in this study (Fig. 1). As 21\% of the patients did not complete the EuroQol Questionnaire, the characteristics of these patients were compared with the sample included in the analyses. Comparison of the responders (n=503) versus the non–responders (n=131) showed great similarities, with the exception of non–responders being less likely to be males (73.2\% vs. 57.3\%; P<.001) but more likely to have congestive heart failure (3.4\% vs. 7.6\%; P=.021).

**Data collection**

Baseline measurements, patient characteristics and risk factors, were collected before surgery by trained research assistants. The hospital charts were searched for information on relevant clinical characteristics, such as history of chronic obstructive pulmonary disease (COPD), diabetes mellitus, and renal insufficiency as cardiovascular morbidity. Data with respect to the incidence of angina pectoris (AP), MI, history of revascularization, prior arrhythmias, history of congestive heart failure, and history of cerebrovascular disease were once again updated one year after surgery. All data were entered into the electronic Case Record Form and transferred regularly via
the Internet to the central database at the Erasmus Medical Centre, Rotterdam, the Netherlands. Three years after surgery, survival status was obtained through the civil registries.

**Health-related Quality of Life**

HRQoL was measured one year after surgery with the Dutch version of the EuroQol Questionnaire\(^{17, 18}\). This instrument consists of two facets, the EQ-5D and the EQ visual analogue scale. To intensively investigate the clinical application of HRQoL assessment, the focus of this cohort was on the EQ-5D. The validated EQ-5D is a standardized, generic measure of self-reported HRQoL which has been used in patients with PAD\(^{16}\) and other cardiovascular diseases\(^{9}\).

The EQ-5D descriptive system assesses the following five clinically relevant dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions has three levels of severity, corresponding to “no problems”, “moderate problems” and “severe problems”. Patients were asked which statement best described their health. More details on and instructions for the EQ-5D can be found on [http://www.euroqol.org/](http://www.euroqol.org/).

**Statistical analyses**

Descriptive statistics included count plus percentages for nominal variables, and mean values with corresponding standard deviations for continuous variables. Responders were compared with non-responders by use of Pearson chi-square tests. Differences between survivors and deceased patients on demographic and clinical characteristics in relation to survival were compared by use of univariable Cox regression analysis. The five dimensions of the EQ-5D were computed to form a utility score using a standard set of general population weights. These scores can range from -0.594 to 1, with a score <0 regarded as a HRQoL that is worse than death and 1 representing full health, from the perspective of the general population. The general population weights were obtained on value sets derived from the Dutch population by the time trade-off valuation technique\(^{17}\). To examine the effect of a high score on the EQ-5D versus one that is lower in rank, the utility scores were divided into tertiles for parsimony, i.e. poor HRQoL, intermediate HRQoL, and good HRQoL. The Kaplan-Meier curves were computed for each tertile with all-cause mortality
as the endpoint. To investigate the prognostic ability of the individual dimensions of the EQ-5D, the dimensions were dichotomized into: “no problems” vs. a cluster of “moderate problems” and “severe problems”, prior to statistical analyses. Univariable Cox regression analyses were conducted to determine the prognostic ability of HRQoL utility score, tertiles, and individual dimensions on mortality. Multivariable Cox regression analyses were performed to adjust for potential confounders including age, gender, AP, MI, history of revascularization, prior arrhythmias, history of congestive heart failure, cerebrovascular disease, COPD, renal insufficiency, and diabetes mellitus. Sensitivity analyses were performed to adjust for medication use (statins, aspirins, beta-blockers). Results from the Cox regression analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI). For all tests, a probability value <0.05 (two-sided) was considered significant. All statistical analyses were performed with SPSS statistical software, version 15.0 (SPSS Inc, Chicago, Ill).

RESULTS
The mean age of the 503 included patients was 67±10 years and 73% were male. During the follow-up period, 55 (11%) patients died. Patients who died during follow-up had in general more risk factors compared to survivors. Univariable Cox regression analysis revealed significant increased risk for long-term survival for age ≥70 years (HR=3.6; 95%CI 2.0–6.5), COPD (HR=2.8; 95%CI 1.5–5.1), renal insufficiency (HR=3.2; 95%CI 1.5–6.8), prior arrhythmias (HR=2.3; 95%CI 1.1–4.5), and history of congestive heart failure (HR=2.6; 95%CI 1.1–6.1). Baseline demographic and clinical characteristics of the sample are provided in Table 1.

Impact of Health Related Quality of Life
There was a clear relationship between HRQoL and mortality. Mean utility scores were 0.79±0.22 in survivors versus 0.64±0.27 in those who died (p<.001). The mean utility score and range of the individual tertiles were 0.48±0.24 (-0.26-0.77) for poor HRQoL, 0.80±0.03 (0.78-0.86) for intermediate HRQoL, and 0.97±0.05 (0.90-1.00) indicating good HRQoL. Mortality was 21% in patients with poor HRQoL, 8% in patients with intermediate HRQoL, and 5% in patients with good
HRQoL. Kaplan-Meier curves revealed similar results, i.e. patients with poor HRQoL had the poorest prognosis, followed by intermediate HRQoL (Fig. 2). To examine if HRQoL predicts mortality beyond conventional clinical risk factors, analyses were adjusted for potential confounders including age, gender, AP, MI, history of revascularization, prior arrhythmias, history of congestive heart failure, cerebrovascular disease, COPD, renal insufficiency, and diabetes mellitus. The adjusted analyses showed impaired HRQoL as a predictor of mortality, i.e. poor vs. good HRQoL (HR=5.4; 95%CI 2.3–12.5) and intermediate vs. good HRQoL (HR=2.0; 95%CI 0.8–4.8). Sensitivity analysis adjusting also for medication use (statins, aspirins, beta-blockers) revealed comparable results, poor vs. good HRQoL (HR=5.4; 95%CI 2.3–12.7) and intermediate vs. good HRQoL (HR=2.0; 95%CI 0.8–5.0).

There was also a clear relationship between the severity of impairment on the individual dimensions of the EQ-5D and long-term mortality. The more severely impaired the HRQoL dimension, the more severe the impact on survival (Fig. 3). Multivariable analyses revealed significant associations between reporting problems and long-term mortality for the dichotomized dimensions of the EQ-5D. Patient-rated problems reached statistical significance for mortality in all of the dimensions of the EQ-5D. The results of the adjusted analyses were significant for mobility (HR=2.7; 95%CI 1.3-5.6), self-care (HR=4.5; 95%CI 2.5-8.2), usual activities (HR=2.2 95%CI 1.2-4.0), pain/discomfort (HR=1.8 95%CI 1.0-3.4), and for anxiety/depression (HR=1.9 95%CI 1.0–3.6) (Table 2).

**DISCUSSION**

To our knowledge this is the first study to investigate the relationship between HRQoL and mortality in PAD. This study demonstrates HRQoL, as measured by the EQ-5D, to be strongly associated with long-term survival in patients with PAD. After adjusting for other established risk factors, poor HRQoL remained an independent predictor of mortality, with the risk being 5-fold compared to patients with a good HRQoL. The risk factors that were adjusted for in multivariable analyses are known for being the most important predictors of mortality in patients with PAD. In
addition, impaired health status assessed by the EQ-5D has previously been shown to independently predict mortality in CAD patients as well\textsuperscript{9}.

HRQoL assessments provide unique information about the impact of the disease as perceived by the patient, which was confirmed in the current study, as poor HRQoL had predictive value in addition to established biomedical risk factors. Quality of life assessed by questionnaires such as the Short Form Health Survey 36 (SF-36) Physical Component, the 46-item Patient Concerns Checklist, and the quality-of-life Index-Cardiac Version have also shown to be independent predictors of mortality in cardiac patients\textsuperscript{10, 19}.

The primary goal of therapy in patients with PAD is to improve HRQoL. In previous research, surrogates of objective measures of disease, including the ankle-brachial index, has been shown to correlate weakly with HRQoL\textsuperscript{20}. In addition, physician evaluated health status of cardiac patients are known to have limited reproducibility and sensitivity with regard to clinical changes\textsuperscript{13, 21}. Routine clinical practice often does not assess directly unobservable components such as self-care, social functioning, general health perception and coping with illness that are imbedded in self-rated health. Therefore, it is important to assess HRQoL as rated by the patient\textsuperscript{22}.

Taken together, due to the unique prognostic value of patient-rated HRQoL, there is an argument for adopting HRQoL assessments into clinical practice in order to guide treatment and enhance secondary prevention in patients with cardiovascular disease\textsuperscript{9, 10, 19, 23}. The prognostic ability of HRQoL may complement traditional clinical practice, by identifying patients at high risk for mortality independent of biomedical factors. Further research is warranted to investigate the mechanisms that may be responsible for the relationship between HRQoL and mortality. Thus far depression and distressed (type-d) personality have shown to predict impaired HRQoL and poor survival independent of disease status \textsuperscript{24, 25}. In addition, depression is associated with poor medication adherence independent of patient experiencing somatic sensations due to disease \textsuperscript{26}. Nevertheless, even if there is still no clear evidence concerning the mechanisms, patients with impaired HRQoL may benefit from more intensive treatment. These high-risk patients should be monitored more carefully and be invited to clinical follow-ups more frequently, and may also
profit from more intensive disease management. Such disease management should probably be multi-factorial, consisting of adjustment in medication, exercise training, behavioural intervention, and the adoption of a confronting coping strategy, which have been shown to improve HRQoL\textsuperscript{27-29}. Smoking cessation and following a careful diet may also be beneficial.

The major advantage of the EQ-5D is its brevity, making the transition to implement, understand, and use HRQoL as an additional tool in clinical practice less taxing both for health-care professionals and patients. The EQ-5D consists of five questions, whereas most other HRQoL measures predicting mortality are much more lengthy (range 19-46)\textsuperscript{10-12}. Although the EQ-5D is brief, our results indicate a clear differentiation between patients with PAD in terms of long-term survival. Multivariable statistical analyses even specify prognostic value for just the individual dimensions of the EQ-5D. Furthermore, the EQ-5D has shown to have a comparable sensitivity and specificity to more lengthy questionnaires, such as the generic questionnaire SF-36 and the disease-specific questionnaire the Vascular Quality of Life in preoperative patients with PAD\textsuperscript{30}.

The results of the current study should be interpreted with some caution. First, the study may be subject to selection bias, which is an inherent limitation of cohort studies due to non-response. Nevertheless, responder versus non-responder baseline characteristics analyses showed almost no differences. Second, we had no information on socio-economic factors that may serve as confounders on the relationship between HRQoL and mortality. Third, the use of tertiles and dichotomizing the reported problems is arbitrary, even though dichotomization enhances the clinical applicability of the results. Fourth, despite the found link between HRQoL and long-term mortality in patients with PAD, we do not know whether HRQoL is a risk marker for a third variable on the causal pathway between HRQoL and mortality, nor which mechanisms, e.g. behavioral or biological, that may explain the link with mortality. Finally, although this cohort demonstrates HRQoL as predictor of long-term survival in patients with PAD, we still need to know the effect of HRQoL on different time points, including assessment prior to surgery.

In conclusion, patients with PAD constitute a high-risk group that needs stringent risk management and monitoring. Patient-rated HRQoL, as measured by the EQ-5D, identifies patients with PAD at high risk for mortality independent of established biomedical risk factors. The EQ-5D
could be used in clinical practice to identify patients at high risk, who may benefit from more intensive treatment and behavioural intervention and support but also as a performance measure to enhance the quality of care in clinical practice.

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**Disclosures**

None.
References


Legend

Table 1. Clinical characteristics of the total sample and stratified by survival status.

Table 2. Comparison of symptom reports on the EuroQol dimensions between survivors and deceased patients three years after surgery.

Fig 1. Flowchart of patient selection.

Fig 2. Survival stratified by differences in HRQoL.

Fig 3. Long-term mortality, according to severity of reported problems on the EuroQol dimensions.

FU, follow-up.

Ns, not significant
Table 1. Clinical characteristics of the total sample and stratified by survival status.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>N(%)</th>
<th>Alive</th>
<th>N(%)</th>
<th>Dead</th>
<th>N(%)</th>
<th>HR (95% CI) for mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>503</td>
<td>(100%)</td>
<td>440</td>
<td>(88%)</td>
<td>55</td>
<td>(11%)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>67 ±10</td>
<td></td>
<td>66 ±10</td>
<td></td>
<td>74 ±10</td>
<td></td>
<td>1.1 (1.0 - 1.1)</td>
</tr>
<tr>
<td>≥ 70 years</td>
<td>208</td>
<td>(41%)</td>
<td>167</td>
<td>(38%)</td>
<td>39</td>
<td>(71%)</td>
<td>3.6 (2.0 - 6.5)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>368</td>
<td>(73%)</td>
<td>320</td>
<td>(73%)</td>
<td>43</td>
<td>(78%)</td>
<td>1.2 (0.7 - 2.4)</td>
</tr>
<tr>
<td>COPD</td>
<td>65</td>
<td>(13%)</td>
<td>49</td>
<td>(11%)</td>
<td>15</td>
<td>(27%)</td>
<td>2.8 (1.5 - 5.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>93</td>
<td>(19%)</td>
<td>79</td>
<td>(18%)</td>
<td>13</td>
<td>(24%)</td>
<td>1.4 (0.8 - 2.7)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>28</td>
<td>(6%)</td>
<td>20</td>
<td>(5%)</td>
<td>8</td>
<td>(15%)</td>
<td>3.2 (1.5 - 6.8)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>83</td>
<td>(17%)</td>
<td>72</td>
<td>(16%)</td>
<td>9</td>
<td>(16%)</td>
<td>1.0 (0.5 - 2.1)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>51</td>
<td>(10%)</td>
<td>39</td>
<td>(9%)</td>
<td>11</td>
<td>(20%)</td>
<td>2.3 (1.1 - 4.5)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>26</td>
<td>(5%)</td>
<td>19</td>
<td>(4%)</td>
<td>7</td>
<td>(13%)</td>
<td>2.6 (1.1 - 6.1)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>75</td>
<td>(15%)</td>
<td>68</td>
<td>(16%)</td>
<td>7</td>
<td>(13%)</td>
<td>0.7 (0.3 - 1.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>80</td>
<td>(16%)</td>
<td>69</td>
<td>(16%)</td>
<td>11</td>
<td>(20%)</td>
<td>1.2 (0.6 - 2.4)</td>
</tr>
<tr>
<td>Previous coronary revascularization</td>
<td>90</td>
<td>(18%)</td>
<td>76</td>
<td>(17%)</td>
<td>13</td>
<td>(24%)</td>
<td>1.5 (0.8 - 2.8)</td>
</tr>
</tbody>
</table>

N, number; SD, standard deviation; HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.
Table 2. Comparison of symptom reports on the EuroQol Questionnaire and stratified by survival status.

<table>
<thead>
<tr>
<th>EQ-5D</th>
<th>Total N(%)</th>
<th>Alive N(%)</th>
<th>Dead N(%)</th>
<th>Univariate HR (95% CI) for mortality</th>
<th>Multivariate HR (95% CI) for mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>503 (100%)</td>
<td>440 (88%)</td>
<td>55 (11%)</td>
<td>1.2 (1.1 - 1.3)</td>
<td>1.2 (1.1 - 1.4)</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>.77±.23</td>
<td>.79±.22</td>
<td>.64±.27</td>
<td>2.3 (1.0 - 5.6)</td>
<td>2.0 (0.8 – 4.8)</td>
</tr>
<tr>
<td>Tertiles:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>178 (35%)</td>
<td>166 (38%)</td>
<td>9 (16%)</td>
<td>5.8 (2.5 -13.2)</td>
<td>5.4 (2.3 – 12.5)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>187 (37%)</td>
<td>168 (38%)</td>
<td>17 (31%)</td>
<td>3.3 (1.6 - 6.8)</td>
<td>2.7 (1.3 – 5.6)</td>
</tr>
<tr>
<td>Poor</td>
<td>138 (27%)</td>
<td>106 (24%)</td>
<td>29 (53%)</td>
<td>2.5 (1.4 - 4.5)</td>
<td>2.2 (1.2 – 4.0)</td>
</tr>
<tr>
<td>Dimensions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no problems</td>
<td>196 (39%)</td>
<td>185 (42%)</td>
<td>10 (18%)</td>
<td>2.2 (1.2 – 4.0)</td>
<td></td>
</tr>
<tr>
<td>moderate problems</td>
<td>303 (60%)</td>
<td>254 (58%)</td>
<td>42 (76%)</td>
<td>2.5 (1.4 - 4.5)</td>
<td>2.2 (1.2 – 4.0)</td>
</tr>
<tr>
<td>severe problems</td>
<td>4 (1%)</td>
<td>1 (0%)</td>
<td>3 (6%)</td>
<td>2.5 (1.4 - 4.5)</td>
<td>2.2 (1.2 – 4.0)</td>
</tr>
<tr>
<td>Self-care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no problems</td>
<td>439 (87%)</td>
<td>399 (91%)</td>
<td>33 (60%)</td>
<td>2.0 (1.1 - 3.7)</td>
<td>1.8 (1.0 – 3.4)</td>
</tr>
<tr>
<td>moderate problems</td>
<td>55 (11%)</td>
<td>37 (8%)</td>
<td>17 (31%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>severe problems</td>
<td>9 (2%)</td>
<td>4 (1%)</td>
<td>5 (9%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>Usual activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no problems</td>
<td>272 (54%)</td>
<td>247 (56%)</td>
<td>19 (35%)</td>
<td>2.0 (1.1 - 3.7)</td>
<td>1.8 (1.0 – 3.4)</td>
</tr>
<tr>
<td>moderate problems</td>
<td>205 (41%)</td>
<td>177 (40%)</td>
<td>27 (49%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>severe problems</td>
<td>26 (5%)</td>
<td>16 (4%)</td>
<td>9 (16%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>Pain/ discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no problems</td>
<td>219 (44%)</td>
<td>199 (45%)</td>
<td>17 (31%)</td>
<td>2.0 (1.1 - 3.7)</td>
<td>1.8 (1.0 – 3.4)</td>
</tr>
<tr>
<td>moderate problems</td>
<td>249 (50%)</td>
<td>214 (49%)</td>
<td>32 (58%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>severe problems</td>
<td>35 (7%)</td>
<td>27 (6%)</td>
<td>6 (11%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no problems</td>
<td>405 (81%)</td>
<td>359 (82%)</td>
<td>40 (73%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>moderate problems</td>
<td>86 (17%)</td>
<td>70 (16%)</td>
<td>14 (26%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
<tr>
<td>severe problems</td>
<td>12 (2%)</td>
<td>11 (3%)</td>
<td>1 (2%)</td>
<td>1.7 (0.9 - 3.0)</td>
<td>1.9 (1.0 – 3.6)</td>
</tr>
</tbody>
</table>

N, number; SD, standard deviation; HR, hazard ratio; CI, confidence interval.

a Hazard per 0.1 decline in EQ-5D utility score.

b References group for analyses is the tertile that represents a good HRQoL.

c To examine the relationship between reporting problems on the EQ-5D dimensions and survival by use of Cox regression, the three levels of severity were dichotomised in: “no problems” vs. reporting problems (a cluster of “moderate problems” and “severe problems”).
Fig 1. Flowchart of patient selection.

- Patient met inclusion criteria: 711
  - Alive at one year FU: 634
  - Dead at/ after one year FU: 77
  - Responders on EuroQol questionnaire: 503
    - Alive after three years FU: 440
    - Dead at/ after three years FU: 55
    - Lost due to FU: 8
  - Non-responders on EuroQol questionnaire: 131
**Fig 2.** Survival stratified by differences in HRQoL.

![Graph showing survival stratified by HRQoL](image)

- **Log rank p < .001**

**Number at risk**

<table>
<thead>
<tr>
<th>HRQoL Level</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
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</thead>
<tbody>
<tr>
<td>Good HRQoL</td>
<td>172</td>
<td>172</td>
<td>170</td>
<td>168</td>
<td>113</td>
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<tr>
<td>Intermediate HRQoL</td>
<td>184</td>
<td>180</td>
<td>177</td>
<td>172</td>
<td>120</td>
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<tr>
<td>Poor HRQoL</td>
<td>135</td>
<td>125</td>
<td>120</td>
<td>118</td>
<td>75</td>
</tr>
</tbody>
</table>
**Fig 3.** Long-term mortality, according to severity of reported problems on the EuroQol dimensions.