

Health-related Quality of Life After Cardiac Transplantation: Results of a UK National Survey With Norm-based Comparisons

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- Background:** Health-related quality of life (HRQOL) is an important measure of outcome that is known to improve after cardiac transplantation, and some studies have suggested that the HRQOL approaches levels found in normal populations. This study presents descriptive analyses of HRQOL and norm-based comparisons after cardiac transplantation in the UK.
- Methods:** A cross-sectional postal survey of cardiac transplant recipients at their first-, third- or fifth-year anniversary after transplantation was undertaken using the Short Form-36 (SF-36), EuroQol (EQ-5D) and Hospital Anxiety and Depression Scale (HADS) questionnaires. Data from the SF-36 and EQ-5D were then compared with normative data from the UK.
- Results:** Of 429 questionnaires issued, 323 were completed and returned, a response rate of 75%. One year after surgery, 66% and 28% of respondents reported much better and somewhat better health, respectively. No deterioration in general health was reported at 3 and 5 years after transplantation. Norm-based comparisons suggested significantly poorer ($p < 0.05$) HRQOL for the EQ-5D and all dimensions of the SF-36 except mental health. Data from the HADS showed that 89% of respondents had symptoms compatible with normality or mild depression. There was no statistically significant difference in HRQOL between respondents at 1, 3 or 5 years after transplantation for any of the dimensions tested.
- Conclusions:** Cardiac transplant recipients in the UK indicated an improvement in general health after transplantation. Respondents at 3 and 5 years after transplantation reported stability, or improvement, but no deterioration in their general health. Norm-based comparisons suggested lower HRQOL for all dimensions except mental health. Some dimensions of health identified in this study may be areas for further investigation that may ultimately be amenable to focused medical management. *J Heart Lung Transplant* 2008;27:675–81. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Clinicians involved in human cardiac transplantation have, from the outset, been confident that transplantation improves both the length and quality of life of their patients. The high financial cost of this technology has meant scrutiny from healthcare purchasers, with both survival and health-related quality of life (HRQOL) being evaluated soon after the introduction of cardiac transplantation into clinical practice in both the USA and the UK.¹

Doubts have been raised about the survival advantage of cardiac transplantation.² However, in the absence of randomized, controlled trials, there remain methodologic difficulties in evaluating this advantage, particularly with regard to selection of an appropriate control group.^{2,3}

The conviction that HRQOL is improved after transplantation remains, and has objective support. Historic studies examining HRQOL have generally reported significant improvements after transplantation.^{1,4} These and other studies have also suggested that HRQOL may

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be similar to that of normal populations and that HRQOL is sustained over time.⁵ More contemporary norm-based studies have supported these data but suggested poorer physical functioning and better psychologic well-being.⁶

The UK Cardiothoracic Transplant Audit currently audits outcomes of cardiac transplantation in this country. The Audit has reported 1- and 3-year survival rates of 80% and 74%, respectively.⁷ The present study adds to these data by presenting cross-sectional HRQOL findings from this contemporary national cohort of patients and compares this with normative data from the UK.

METHODS

Study Context

The UK Cardiothoracic Transplant Audit is an ongoing, multi-center, prospective cohort study involving all transplant centers that undertake cardiopulmonary transplantation in the UK. The Audit describes the practice of cardiopulmonary transplantation in the UK, provides clinical audit, and examines outcomes and process in an effort to improve the provision for cardiopulmonary transplantation in this country.⁷ All patients placed on the waiting list for transplantation and all patients transplanted since April 1995 have been recruited into the study after being tracked through the national waiting list and national transplant database at UK Transplant. This study adds HRQOL data to previously published survival data. Eventually, we will aim to collect HRQOL data longitudinally. It is the descriptive analyses from an initial survey that are presented herein.

Study Population

All cardiac transplant recipients ≥ 18 years of age at the time of transplant, and who were transplanted in the UK after April 1995, were eligible to be recruited into the study.

Patients at their first, third and fifth transplant anniversaries were flagged for recruitment at monthly intervals during the study period (May 2001 to May 2002). These are significant short- to mid-term anniversaries commonly reported in the literature for survival after cardiothoracic transplantation.

No patients were formally excluded from the study although it was recognized that some patients, such as critically ill patients ventilated on intensive care units (ITUs), would be inappropriate candidates to enter the study.

Study Instruments and Data Collection

Questionnaires were selected based on the expectation that they would be appropriate measures of HRQOL in

our study population, and also to address the needs and some of the limitations of the study design. These characteristics are similar to those described by O'Brien et al in their original study of cardiac transplantation in the UK.¹ Included were the following: the need to adopt a method of measuring HRQOL with the minimum of developmental work; the use of instruments sensitive to a wide range of health states within the study population; the use of reasonably well established and widely used instruments—to allow comparisons with other populations—in particular normative data from the UK; and to allow efficient administration of questionnaires and data handling within resource constraints.

Three generic questionnaires and one disease-specific questionnaire were used for the study. The generic questionnaires used were the UK version of the standard Short Form-36 (SF-36),⁸ the EuroQol (EQ-5D, tariff and visual analog scale [VAS])⁹ and the Hospital Anxiety and Depression Scale (HADS).¹⁰ Although it is appropriate in studies such as this to include a disease-specific questionnaire there is none that has been validated for this population of patients.

After multicenter research ethics committee (MREC) approval, a booklet containing the questionnaires was issued to patients along with a standard explanatory letter from each director of transplantation, on headed paper from each unit, and a freepost envelope for patients to return questionnaires.

Liaison between the audit team and potential recruits to the study was done through locally designated staff that already worked in the respective transplant units. There were two reasons for this: (1) because the audit only has access to unique transplant registration numbers and not patient names or addresses; and (2) to facilitate better communication with potential recruits who generally have established relationships and trust with their respective transplant units.

Transplant centers were encouraged to issue questionnaires to as many patients as possible unless there were compelling reasons not to, such as if the patient was critically ill and ventilated on ITU. Reasons for not issuing questionnaires to patients were documented pro forma and returned to the Audit monthly.

The locally designated staff issued telephone or written reminders if forms had not been returned at 2 months after issuance. A further pro forma was provided for staff to document reasons for non-response from patients who did not return the questionnaire following the reminder. Data on infection and rejection episodes in the year preceding the survey (and that might influence response) were obtained from our existing database.

Table 1. Characteristics of Respondents and Non-responders

Characteristic	Responders (n = 323)	Non-responders (n = 106)	p-value
Male	63.8%	58.5%	0.33
Female	36.2%	41.5%	
Median age (IQR)	55.1 years (48.1–60.0)	50.9 years (41.5–57.6)	0.0002
Total rejection episodes	89	16	0.68
Total infection episodes	77	32	0.27

Similar data noted at 1, 3 and 5 years after transplantation, although only pooled data are shown. IQR, interquartile range.

Data Analysis

Comparisons between responders and non-responders were performed using the rank-sum test and chi-square test for proportions.

Missing data were treated in accordance with guidelines issued by authors of the respective HRQOL instruments in their manuals. If such guidelines could not be found data were not analyzed, which explains the slightly different numbers on individual analyses. Norm-based comparisons were undertaken for the SF-36 and EQ-5D questionnaire using the studies by Jenkinson et al (for patients up to the age of 65 years)¹¹ and Kind et al¹² as reference points for the general UK population. The population scores were directly standardized for age and gender to reflect the age and gender distribution of respondents as described by Ratcliffe et al.¹³

To make the interpretation of differences across SF-36 scales easier, all SF-36 scales were standardized.¹⁴ Linear transformations were undertaken to transform scores to a mean of 50 and standard deviation of 10. This transformation achieves the same mean and standard deviation for all eight scales of the SF-36. Without referring to norms, any time a scale score was <50 health status was considered below average, with each point being one-tenth of a standard deviation.

Comparisons of HRQOL at 1, 3 and 5 years after transplantation were undertaken using the Kruskal-Wallis test, and comparisons with population data undertaken using the unpaired *t*-test with Bonferroni's correction for multiple statistical comparisons. Analyses were 2-tailed and statistical significance was assumed at $p < 0.05$.

RESULTS

During the study period, 468 cardiac transplant recipients were eligible to be recruited into the study, and 124 had reached their first, 171 their third and 173 their fifth post-transplant anniversary. Of the 429 questionnaires issued (115, 158 and 156 for recipients at their first, third and fifth anniversaries, respectively), 323 were returned (80 [70%], 127 [80%] and 116 [74%] for recipients at their first, third and fifth anniversaries, respectively), giving an overall response rate of 75%. The major reasons for not issuing questionnaires to the additional 39 candidates included deaths that the Audit was unaware of until after forms had been sent (31%), and patients for whom a current address could not be found (39%). Only 4 (10%) questionnaires were not issued because candidates were considered too unwell to respond.

Of the questionnaires issued but not returned, the reasons for non-return could not firmly be ascertained in 83 cases (78%). However, there were only 3 (2.8%) non-responders who were known to be too unwell to respond at the time of survey. Other documented reasons for non-return of forms included refusal to participate in the study (9 cases, 8.5%), loss to follow-up (3 cases, 2.8%) and English not being the candidates first language (2 cases, 1.9%). Non-responders were significantly younger than responders but there was no gender difference between the two groups (Table 1). Similarly, there was no statistically significant difference between the total number of rejection and infection episodes between the two groups in the year preceding the survey (see Table 1). Respondent characteristics at Years 1, 3 and 5 are summarized in Table 2.

Table 2. Characteristics of the 323 Respondents by Follow-up Period Post-transplantation

Characteristic	Year 1 (n = 80)	Year 3 (n = 127)	Year 5 (n = 116)
Male (n)	54 (67.5%)	87 (68.5%)	65 (56.0%)
Female (n)	26 (32.5%)	40 (31.5%)	51 (44.0%)
Median age for males ^a	53.4 (47.5–59.0)	54.6 (47.7–59.6)	57.9 (48.8–62.8)
Median age for females ^a	53.3 (49.4–56.7)	53.6 (46.3–58.6)	57.4 (50.6–60.6)

^aInterquartile range in parentheses.

Table 3. SF-36, EQ-5D Tariff and EQ-5D VAS Scores for Heart Transplant Recipients After Transplantation^a

Dimension	1-year (n = 80)	Population norm	3-years (n = 127)
Physical functioning	65.0 ¹ (58.5–71.5)	84.88 (80.7–89.1)	63.5 ² (58.6–68.5)
Role–Physical	44.6 ¹ (34.5–54.8)	83.77 (76.9–90.7)	51.2 ⁴ (43.3–59.1)
Bodily pain	42.3 ² (40.2–44.4)	80.43 (75.5–85.4)	40.4 ⁵ (38.2–42.5)
General health	57.9 ² (53.9–62.0)	71.06 (66.5–75.6)	56.2 ⁴ (52.6–59.8)
Vitality	54.3 ² (48.8–59.8)	62.08 (57.7–66.4)	53.4 ⁴ (49.0–57.8)
Social functioning	71.0 ² (64.9–77.0)	88.19 (83.7–92.7)	69.3 ⁸ (64.2–74.4)
Role–emotional	65.4 ³ (55.7–75.0)	84.76 (78.2–91.3)	68.3 ⁶ (60.9–75.8)
Mental health	72.10 ⁴ (67.7–76.5)	75.85 (72.1–79.6)	74.9 ⁴ (71.1–78.7)
EQ-5D tariff	0.70 (0.64–0.75)	0.83 (0.82–0.84)	0.71 ³ (0.66–0.76)
EQ-5D VAS	69.9 ² (65.6–74.3)	81.6 (77.8–85.4)	68.9 ⁴ (65.4–72.5)

^aData are compared with UK population means (standardized for age and gender based on the age and gender distribution of respondents in this study). Results are presented as means with 95% confidence intervals (superscript numerals indicate number of missing values).

The distribution of most dimensions of the SF-36 demonstrated positive skewness, as did data for the EQ-5D tariff and visual analog scores. The role–physical and role–emotional dimensions of the SF-36 demonstrated a bimodal distribution.

One year after transplantation, 66%, 28% and 6% of respondents reported much better general health, somewhat better health and no change, respectively (based on the SF-36 health transition question). Respondents 3 and 5 years after transplantation reported stability, or improvement, but no deterioration in their general health.

Table 3 shows SF-36, and EQ-5D tariff and VAS scores at the different time-points after transplantation and age- and gender-adjusted data for the population mean. Figure 1 shows raw scale scores for the SF-36 against UK population means adjusted for age and gender, whereas Figure 2 shows the same data after undertaking linear transformations to transform raw scale scores to a mean of 50 and standard deviation of 10.

Comparisons with normative data suggest poorer HRQOL for the EQ-5D tariff and VAS scores, and all dimensions of the SF-36, except mental health, at 1, 3 and 5 years after surgery. Significance levels were $p < 0.05$ for all of these data, except mental health, and $p < 0.0005$ for the majority of dimensions. Bodily pain scores appeared especially low, whereas mental health scores were similar to general population data. There was no statistically significant difference in HRQOL at 1, 3 and 5 years for any of the questionnaires or dimensions tested ($p > 0.2$ for all comparisons).

Data for anxiety and depression based on the HADS are shown in Table 4. Pooled data for the HADS questionnaire suggested normality, or mild, moderate or severe depression in 74%, 15%, 8% and 3% of respondents, respectively.

DISCUSSION

Principal Findings

One year after surgery the vast majority of cardiac transplant recipients reported much or somewhat better general health than prior to transplantation. Furthermore, cardiac transplant recipients at 3 and 5 years after

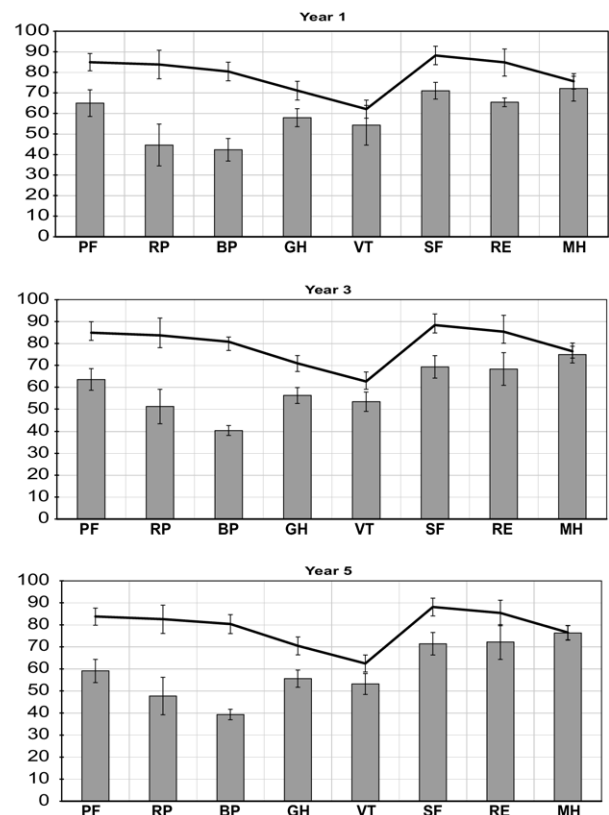


Figure 1. SF-36 raw scores (95% confidence interval) vs UK population means (95% confidence interval) standardized for age and gender based on the age and gender distribution of respondents in this study at 1, 3 and 5 years after transplantation.

Table 3. Continued

Population norm	5-years (<i>n</i> = 116)	Population norm
84.85 (81.4–88.3)	59.1 ⁴ (53.8–64.3)	83.75 (79.9–87.6)
83.73 (78.1–89.4)	47.7 ⁷ (39.2–56.2)	82.56 (76.1–89.0)
80.82 (76.8–84.8)	39.3 ³ (36.9–41.7)	80.38 (76.0–84.7)
70.89 (67.2–74.6)	55.6 ⁵ (51.7–59.5)	70.48 (66.4–74.5)
62.61 (59.1–66.1)	53.2 ⁴ (48.4–57.9)	62.47 (58.6–66.3)
88.43 (84.8–92.1)	71.4 ⁶ (66.3–76.5)	88.07 (84.0–92.1)
85.40 (80.1–90.7)	72.2 ⁷ (64.3–80.1)	85.4 (79.6–91.2)
76.37 (73.4–79.4)	76.3 ⁴ (73.0–79.7)	76.46 (73.2–79.7)
0.83 (0.82–0.84)	0.70 ⁴ (0.65–0.75)	0.82 (0.81–0.83)
81.5 (78.4–84.6)	67.7 ³ (63.8–71.6)	80.9 (77.5–84.3)

transplantation reported no deterioration in their general health from the preceding year.

Norm-based comparisons, however, suggest poorer HRQOL than age- and gender-adjusted data from the UK for the EQ-5D tariff and VAS, and all dimensions of the SF-36 except mental health. Problems with work or daily activities as a result of physical health or emotional problems had a bimodal distribution, with respondents

generally reporting low or high scores. Bodily pain experienced by transplant recipients appears to have been especially prominent compared with normative data, whereas mental health scores were similar to general population data. Moderate or severe depression as defined by HADS was apparent in only 11% of respondents with 89% reporting symptoms compatible with normality or mild depression. There was no statistically significant difference in HRQOL between respondents at 1, 3 or 5 years after transplantation in any of the dimensions tested.

Strengths and Weaknesses of the Study, and Comparisons With Other Studies

The main strength of this study is that it has reported results from a contemporary national cohort of patients using two generic questionnaires and one dimension-specific questionnaire. The absolute number of respondents was also relatively large in comparison to previous studies. Although the response rate of 75% was relatively good, as with any other cross-sectional survey there is the possibility of information bias leading to inaccurate estimates of the HRQOL. This study is unlikely to have grossly overestimated HRQOL as transplant patients form relatively stable populations and significant health problems become well known to local transplant centers in most instances. Although non-responders in the study were younger, there were no differences between them and responders with regard to rejection and infection episodes in the year preceding the survey, and only 3 patients (2.8%) were definitely known to be too unwell to respond to the survey. So, if anything, there is the possibility that HRQOL was underestimated.

Pre-transplant HRQOL data for each patient and each dimension of the questionnaires were not available. Therefore, unlike other studies,^{1,6,15} we cannot quantify which dimensions improved after transplantation,

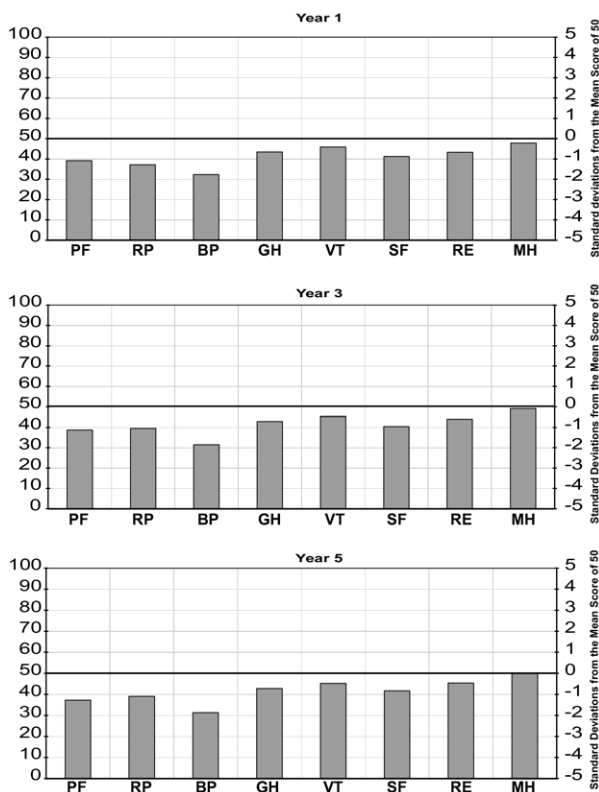


Figure 2. SF-36 raw scale scores against UK population means (standardized for age and gender based on the age and gender distribution of respondents in this study), at 1, 3 and 5 years after transplantation after implementing linear transformations to transform raw scale scores to a mean of 50 and standard deviations of 10.

Table 4. Percentage of All Respondents Reporting Anxiety and Depression at Different Times After Transplantation (*n* = 310)

HADS score by category	Anxiety			Depression		
	Year 1 (<i>n</i> = 75)	Year 3 (<i>n</i> = 123)	Year 5 (<i>n</i> = 112)	Year 1 (<i>n</i> = 75)	Year 3 (<i>n</i> = 123)	Year 5 (<i>n</i> = 112)
0–7 (normal)	77.3	70.7	80.4	80.0	70.7	74.1
8–10 (mild)	13.3	12.2	12.5	13.3	15.5	15.2
11–14 (moderate)	2.7	7.3	4.4	4.0	11.4	8.0
15–21 (severe)	6.7	9.8	2.7	2.7	2.4	2.7

or by how much (although this was not one of the primary objectives of the study). Longer-term follow-up beyond 5 years is needed to assess the impact of more chronic immunosuppression on HRQOL, and this is awaited with interest.

As with previous studies this study has suggested that HRQOL improves after transplantation, as patients at 3 and 5 years after transplantation reported stability or improvement (but no deterioration) in their symptoms when compared with the year preceding the study. The cross-sectional design of this study means that we cannot strictly infer that HRQOL was sustained at 5 years after transplantation; however, such an improvement has been demonstrated in longitudinal studies.⁵

These data suggest that psychologic or mental health levels approached that of the general population. This is in contrast to the original study of HRQOL undertaken in the UK using the Nottingham Health Profile.¹ However, in that study, a relatively small number of patients were assessed in the comparisons with normative data and these data were not subjected to formal statistical tests. Our findings are more in keeping with results from a recent cohort of patients from New Zealand.⁶ That study also used the SF-36, and demonstrated significantly better mental health and vitality scores in comparison to normative data from New Zealand, but also indicated significantly poorer scores for other dimensions.

The rates of depression seen in patients 5 years after transplantation were not dissimilar to those seen in more long-term studies,¹⁶ although emotional role and social functioning appeared to have been better in our population at this earlier time-point. Some studies have suggested that depression may be one of the most important variables affecting overall HRQOL⁵ and, although our study has suggested similar mental health scores among the general population in the UK, this may also be an area where focused medical management may improve the HRQOL in this patient cohort.

Meaning of the Study: Specific Implications of Study for Clinicians or Policymakers

Patients seem to adapt and respond well to their newly acquired and improved health states. Although they do

not achieve “normality” or regain full physical health, they appear to come to terms with any residual health deficit. As others have pointed out, this may simply be that they are happy to be alive and better off than they were before surgery.¹⁷

Unanswered Questions and Future Research

Although it is relatively easy to understand why a number of factors, including the burden of immunosuppression, may not allow cardiac transplant recipients to achieve full physical health, it is more difficult to comment about the degree of bodily pain experienced by respondents in this study. Developers of the SF-36 advised caution in interpreting bodily pain scores between standard and developmental versions of the questionnaire because of increased skewness of the score distribution in the developmental scoring method.⁸ They did, however, point out that the difference in pain scores may vary with the prevalence of pain. The nature of the questionnaires used does not allow a more detailed analysis of the nature and causes of such pain. A high prevalence of pain has been reported in the lung transplant population and has been analyzed in more detail.¹⁸ Therefore, this may be an area for further investigation, as reduction of pain may be relatively amenable to medical management.

With the relative scarcity of donor organs and the possible need to define which patients may benefit the most from transplantation, it may be useful to examine pre-operative predictors of HRQOL as well as predictors of survival.³ Longer term and longitudinal follow-up of this and similar populations will further identify patterns of HRQOL and changes with time, and perhaps identify areas amenable to medical or other supportive management modalities. In addition to survival data, HRQOL may be an important area for the auditing of results of transplantation in the future.

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