

University of Groningen

Health related quality of life and lung transplantation

Vermeulen, Karin Marianne

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2004

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Vermeulen, K. M. (2004). Health related quality of life and lung transplantation. Groningen: s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Introduction

Lung transplantation (LgTX) is a treatment option for patients with end stage lung disease. Apart from clinical outcome measures to assess the effectiveness of a medical intervention, such as survival, Health Related Quality of Life (HRQL) has become an important measure of effect. The measurement of HRQL is of particular importance when comparing two or more study treatments, developing or implementing therapeutic programs, and justifying or refuting different types of medical treatment. Another important reason for assessing HRQL is to establish information about the range of problems that affect patients. Patients themselves often express the wish for more emphasis upon research into quality of life issues. In this thesis the effects of LgTX on HRQL were studied in different subgroups of patients, and during both the waiting period and post transplant follow up, applying cross sectional and longitudinal analysis.

Summary and conclusions

Chapter 2

With rapid developments in healthcare, Medical Technology Assessments (MTA), also referred to Health Technology Assessments (HTA) have become an important part of research. MTA's aim at providing information on among others, costs, clinical effectiveness, and quality of life. MTA's are a particularly useful tool for decision-makers. Chapter 2 gives an introduction in economic evaluation and HRQL in general, and shows results of studies on cost-effectiveness analysis of LgTX programs, and of studies assessing HRQL. Different types of economic evaluations are distinguished and described. Studies on the costs and effects in terms of life years provided to the recipient are summarized in this chapter. However, survival is not the only yardstick by which to measure treatment effectiveness. HRQL data are increasingly important for evaluating the consequences of an intervention such as LgTX. After introducing and defining HRQL, an overview of the literature on the effects of LgTX on HRQL is given. Results of most studies described in this chapter showed that patients surviving LgTX could expect a considerable improvement in most domains of HRQL. Finally in this chapter it is concluded that LgTX is an expensive but effective intervention compared to conventional medical treatment. LgTX provides many life-years to the recipient, and contributes positively to HRQL of surviving patients over time.

Chapter 3

Most studies on the effects of LgTX on HRQL were based on small groups of patients, and had a relatively short period of follow-up. Furthermore, few studies assessed changes over time after LgTX. Therefore, the aim of the study described in chapter 3 was to assess the effects of LgTX on HRQL over time in a group of patients that survived at least 55 months after LgTX. As comorbid conditions after transplantation influence HRQL, their presence and effects were taken into account. We followed a group of 28 patients before and until 55 months after transplantation. HRQL was measured at various points in time by using self-assessment questionnaires that were mailed to the patients by post. Before transplantation patients reported limited HRQL in almost all domains. Until approximately 43 months after transplantation there were remarkable improvements with regard to energy, mobility, sleep,

social isolation and emotional reaction and more patients could walk without dyspnea. In addition, important improvements occurred with regard to the levels of anxiety, depression, and well being. Activities of daily life could be performed without help by most patients. After approximately 43 months patients experienced more dyspnea, anxiety, depression, and a lower level of well being. The number of patients suffering from a decrease of kidney function, drug treated hyperlipidemia, insulin dependent diabetes mellitus, and bronchiolitis obliterans syndrome (BOS) increased. This study concludes that patients experienced a stable and better overall quality of life after transplantation compared to the situation before. Long-term after lung transplantation patients experienced a decline on several dimensions of quality of life, which may be explained by an increase of comorbid conditions and BOS.

Chapter 4

Previous studies assessing the effects of LgTX on HRQL generally studied mixed groups of patients with various diagnoses. Therefore, until recently, it was not clear if LgTX has the same effects on HRQL in patients with different pre-transplant diagnosis. The most common diagnosis for LgTX is emphysema, and the survival benefit in this group is not as favorable as in groups of patients with other diagnoses. Apart from survival, changes in HRQL must be taken into account when assessing the overall benefits of LgTX. Therefore, in this chapter the HRQL before and after LgTX was studied in a group of 23 patients with emphysema, and compared to a group of 19 patients with other indications. Assessments took place before and during a period up to 25 months after LgTX. Before transplantation patients reported limited HRQL on many domains, especially with regard to experienced energy, mobility, well being, depression and dyspnea. These limitations were comparable in both groups of patients. About 4 months after transplantation most HRQL measures improved significantly in both groups of patients. These improvements were maintained until the end of the follow-up period, at 25 months after transplantation. This study concludes that both patients with emphysema and patients with other indications can expect a substantial benefit from LgTX in terms of HRQL. Effects in both groups are comparable.

Chapter 5

Cystic fibrosis (CF) is the most common inherited disease among the Caucasian population, and is usually diagnosed in early infancy with both respiratory and gastrointestinal symptoms. With advancing age, patients become chronically ill, experience an impaired HRQL and generally die at young age predominantly due to respiratory failure. Nowadays isolated lung transplantation is an accepted treatment modality for these patients. When the effect of LgTX is measured by means of survival, the absolute survival rates in this group compare favorably to those in patients with other diagnoses. However, no information was available on the effect of LgTX on HRQL in CF patients compared to patients with other diagnoses. Therefore, the aim of the study described in Chapter 5 was to assess the effects of LgTX on HRQL in a group of CF patients surviving at least 31 months after LgTX compared to a group of patients with other diagnoses. Results showed that CF patients were younger, had spent more days on the waiting list, and were more likely to be working or going to school compared to patients with other indications. As expected, before transplantation patients in both groups experienced restrictions on almost all HRQL dimensions, compared to the general population. Analysis of differences between the two groups showed that CF patients were less restricted

Chapter 9

with regard to energy and mobility compared to other patients. After transplantation patients in both groups experienced dramatic improvements on most HRQL dimensions. At some points in time after transplantation, CF patients had fewer restrictions regarding mobility and sleep compared to patients with other indications. Until the end of the study period (31 months after transplantation) scores remained more or less stable over time in both groups.

Chapter 6

Although studies focussing on the effects of LgTX on survival and HRQL generally report positive findings, long-term results in LgTX are not as good as in most other solid organ transplant recipients. The most important factor limiting long term survival is bronchiolitis obliterans syndrome (BOS). BOS is a relatively common complication after LgTX, with a cumulative incidence of at least 50% of the patients who survive at least 3 months after transplantation. BOS clinically presents with progressive dyspnea, and a decline in exercise tolerance associated with persistent or recurrent cough. It has been described before that patients who develop BOS after LgTX experience an impaired HRQL compared to recipients without this condition. However, small numbers of patients and short periods of follow-up hindered these few previous studies. Therefore, in the study described in this chapter, the effects of BOS on HRQL in 29 LgTX patients that survived at least 18 months after developing BOS were studied longitudinally. To assess the effect of BOS on HRQL, measurements took place in the same group of patients at 4 different points in time. The pre-BOS assessment was the last HRQL questionnaire filled in before the occurrence of BOS. This was at a median of 3 months before the diagnosis. For post-BOS assessments, the HRQL measurements closest to the dates 6, 12, and 18 months after BOS were diagnosed were used. Only those patients were included who had at least 18 months of follow-up after the occurrence of BOS.

The study described in this chapter confirmed previous findings that BOS has a negative influence on HRQL. Furthermore, it can be concluded that HRQL decreases over time especially regarding experienced energy and mobility. In addition, it gradually takes more effort to perform ADL activities, and patients experienced more dyspnea over time after the onset of BOS. In addition, a significant increase in feelings of depression was found. Although this study concludes that HRQL is negatively influenced by the onset of BOS, even patients who develop BOS may at least temporarily benefit from LgTX. As no effective treatment is currently available for BOS, future studies should focus on prevention, and treatment. Furthermore, attempts should be made to develop specific interventions that are aimed at improving HRQL after the onset of BOS; specifically regarding the level of experienced energy and mobility.

Chapter 7

Due to a shortage of suitable donor lungs, waiting lists for LgTX are long. In the Dutch lung transplant program, the mean waiting time amounts to almost one and a half years. Most workers in the field of solid organ transplantation have observed that the waiting period is extremely stressful for patients, and the experienced stress may affect patients' behavior and compliance and may afflict, especially if not recognized, doctors decisions and patients health and survival. Therefore, it is important for nurses and doctors working with pre transplant

patients to understand their fears and concerns. Most studies on the subject of stress, anxiety and depression focussed on patients waiting for heart transplantation and only few studies have examined the experiences of patients waiting for LgTX. Therefore, in the study described in this chapter, potential stressful events that patients experience during the waiting period for LgTX were explored, and the level of anxiety, depression and well being were assessed. In addition, the use of coping strategies was explored. Assessments took place at pre-set time points between placement on the waiting list and 15 months thereafter. Convenience samples of all available completed questionnaires were used, and thus, the numbers of included patients at the different time points varied. Feeling tension caused by 'having to wear a beeper', and 'being afraid that the transplantation will come too late' were identified as important stressors. At all points in time patients on the waiting list experienced more anxiety and depression, and a lower level of well being compared to the general population. The longer patients had been on the waiting list, the more anxiety and depression they seemed to experience and the lower their levels of well being appeared to be. The most frequently used were positive coping strategies like 'trying to relax' and 'thinking it could be worse'. Negative strategies like 'taking sedatives' and 'taking it out on others' were less popular. No associations could be found between the use of coping strategies and the experienced levels of anxiety and depression. This chapter concludes that stress, anxiety, and depression occurs frequently in patients waiting for LgTX, and may play an important role in the patient-doctor interaction. Therefore, it is important to recognize and handle these problems, for example by stimulating the use of positive coping strategies.

Chapter 8

Analyses of HRQL in LgTX patients are often hampered by relatively large numbers of patients who have one or more missing questionnaires, for example due to their poor health status, or because they die. Missingness of questionnaires is an important problem, and deserves careful attention. Missing data can cause bias reduced sample sizes. Depending on the research question, the magnitude of the missing data problem and the reason for missing different methods of analysis can be performed to deal with this problem. Besides addressing the problem of missing data in the field of lung transplantation, the aim of the study described in chapter 8 was to compare three methods of analysis: cross-sectional, complete case and multi-level analysis. Scores on the dimension 'energy' of the Nottingham Health Profile (NHP) after transplantation were used to illustrate the differences in results between the various methods. Results showed that patterns over time estimated with the three methods were comparable. Results from the complete case analysis showed the most, and from the multi level analysis the least favorable energy scores. Compared to the complete case analysis, the cross-sectional and multi level analysis included more patients per time point, and allowed for a longer period of follow-up. In the multi level analysis possible confounding variables were included, which was impossible in the complete case analysis due to the small number of patients. The model which included age, BOS, and gender showed the best fit to the data. This chapter concludes that differences between the various methods of analysis do exist, and that depending on the research question and the type of missing each of the three methods has its merits. Finally, multi level analysis proved to be very useful to analyze longitudinal changes.

General considerations and future perspectives

Knowledge on the effects of a therapy is important in many respects. One of its merits is that it can help clinicians to explain to patients what they can expect from a specific therapy. In addition, when more than one therapeutic option is available, this knowledge can help patients and clinicians in making rational choices concerning the most appropriate therapy. An important outcome measure to assess the effectiveness of a therapy is HRQL. In this thesis, the effects of lung transplantation on HRQL were the central theme.

The way information is collected is of vital importance to the outcome of the study, especially when assessing the long-term effects of an intervention. The strength of the studies described in this thesis lies for an important part in the continuous data collection.

Until 2001, the Groningen University Hospital was the only center in the Netherlands that performed lung transplantations. In general, patients return to this center on a regular basis during the waiting period, and after transplantation, and tend to feel very committed to this center. This may explain the relatively high response with regard to the HRQL questionnaires. In addition, the Netherlands is a small country where it is easy to follow-up patients.

Therefore, in the Dutch situation we were able to set-up and maintain a successful ongoing data collection system in which all patients aged 18 years or older are invited to participate from the moment they are placed on the waiting list for lung transplantation. The amount of data collected this way enabled us to perform long term-analysis, and subgroup analysis, and to apply modeling techniques. This way of continuous data collection, and especially the focus on long term after lung transplantation is needed to render information on the long term effects of the intervention, and on the need for interventions to enhance adjustment post transplant. Unfortunately not many transplant programs have been able to perform similar ongoing studies.

With regard to the instruments used to measure HRQL the following remarks can be made: HRQL has become, and will continue to be an important aspect of medical interventions. The measurement and valuation of HRQL have evolved over the past decade. In the Dutch lung transplant program, HRQL was measured without interruptions, almost since the start of the program. This implies that at the start, HRQL instruments were chosen that were considered the most appropriate to measure the desired dimensions of HRQL in patients before and after LgTX. In addition, when possible, the same instruments were chosen as the ones used in Dutch transplant programs for other solid organ transplantations [Bonsel, Bot, Boterblom, 1988; Bonsel, Essink-Bot, Klompmaker et al., 1992]. To ensure continuity, these instruments are still used today. Two advantages are associated with this: First of all, this represents the rare opportunity to study the long-term effects of LgTX on HRQL. Secondly, it enables comparison of short term and long term effects to the results from studies regarding other solid organ transplantations. However, because solid organ transplantations have become accepted treatment options, and little knowledge is available on the long term effects of these interventions, there may be a need for (lung) transplantation specific instruments, to identify problems and design interventions aimed at these specific problems such as psychological effects of post transplant comorbidity, and possible rejection of the transplanted organ. To our knowledge, no such instrument is available yet.

The long waiting period due to the shortage of donor lungs, causes the need to measure

HRQL, and aspects such as stress and coping, recognize the problems, and look for ways to handle these problems.

The same need may exist with regard to long term effects of lung transplantation. Although we concluded that patients experienced a stable and better HRQL compared to the situation before, long-term after LgTX, patients experienced a decline on several dimensions of HRQL, which may be explained by an increase of comorbid conditions such as hyperlipidemia, diabetes mellitus and bronchiolitis obliterans syndrome. More research is necessary to determine the influence of comorbid conditions on HRQL. In order to study this, a valid measurement instrument suitable for the lung transplant population is necessary. In addition, a model, can be used to estimate the effect of developing one or more specific comorbid conditions on HRQL.

Research into the side effects of immunosuppressive agents, and reduction of these side effects is a major task in transplantation medicine. Side effects of immunosuppressive therapy, potential stress, and fear of rejections may decrease HRQL, and therefore limit the benefits of LgTX in the medium and short term after LgTX [Reimer, Franke, Philipp, Heemann, 2002]. In addition, adherence to strict medical and lifestyle regimens post transplantation is of huge importance to continued survival and prevention of post transplant complications. From a study conducted among heart, liver and lung transplant patients, it became clear that over 80% of heart patients, more than half of the liver patients, and about one third of lung patients reported some difficulty in following lifestyle regimens [Littlefield, Abbey, Fiducia et al, 1996]. Although in this respect lung transplant patients compare favorably to other solid organ patients, the fact that one third of the patients report these problems expresses the need to monitor and promote healthy lifestyle regimens.

Research into the effectiveness of LgTX, as well as other solid organ transplantation, differs from evaluations of other therapies in the way that it is uncertain at which moment a suitable organ becomes available, and therapy can be started. When the effects of a therapy like LgTX are studied, a pre-transplant assessment is needed to compare the post-transplant results to. Regarding solid organ transplantations, it is difficult to determine when to measure pre transplant HRQL. In our studies in which pre- and post transplant assessments took place, we choose to use the first assessment after placement on the waiting list as a pre transplant value. With long waiting periods of variable duration the health status of the patient may have deteriorated depending on the duration of the waiting period. However, the amount of time patients had waited before being transplanted appeared not to be of influence on the NHP dimension energy after transplantation. Further research is needed to determine the influence of the pre-transplant waiting period on the outcome of other HRQL dimensions after transplantation. In addition, the waiting period was identified as a stressful period in which anxiety and depression appeared to be higher than in the general population. Although stress, anxiety and depression seemed to be higher when patients had been on the waiting list for a longer period of time, from chapter 7 it could not be concluded that the negative feelings increase over time. Due to the cross-sectional study design, we were not able to assess changes over time. Moreover, it can be argued if a longitudinal design during the waiting period would be feasible. Because waiting list patients leave the waiting list at variable points in time due to transplantation or death, longitudinal analysis would be based on a very specific subgroup of waiting list patients. The selected subgroup would consist of those patients that are well enough to survive on the waiting list for a longer period, and for whom a

Chapter 9

suitable organ has not yet been found. Therefore, a cross-sectional design was considered more suitable for the explorative study.

In conclusion, the studies described in this thesis assessed the effects of LgTX on HRQL in various groups of patients, and at different points in time before, and after transplantation. Overall, after transplantation, an improvement in HRQL was found compared to the situation on the waiting list. In addition, several subjects and opportunities for further research were identified. Thus, studies into the assessment of different aspects of HRQL related to lung transplantation will still be of importance in future.

References

- Bonsel GJ, Bot ML, Boterblom A. The costs and effects of heart transplantation: quality of life before and after heart transplantation: report 2a, 2b, and 2c (in Dutch). Rotterdam, the Netherlands: Institute of Medical Technology Assessment, Erasmus University 1988.
- Bonsel GJ, Essink-Bot ML, Klompmaker IJ, et al. Assessment of the quality of life before and following liver transplantation. *Transplantation* 1992; 53: 796-800.
- Reimer J, Franke GH, Phillip T, Heemann U. Quality of life in kidney recipients; comparison of tacrolimus and cyclosporine-micro-emulsion. *Clin Transplant* 2002; 16 : 48-54.
- Littlefield C, Abbey S, Fiducia D et al. Quality of life following transplantation of the heart, liver, and lungs. *Gen Hosp Psychiatry* 1996; 18: 36S-47S.