

# Symptom experience, nonadherence and quality of life in adult liver transplant recipients

G. Drent<sup>1\*</sup>, S. De Geest<sup>2,3</sup>, F. Dobbels<sup>3</sup>, J.H. Kleibeuker<sup>1</sup>, E.B. Haagsma<sup>1</sup>

<sup>1</sup>Departments of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, <sup>2</sup>Institute of Nursing Science, University of Basel, Basel, Switzerland, <sup>3</sup>Centre for Health Services and Nursing Research, University of Leuven, Leuven, Belgium,

\*corresponding author: tel: +31 (0)50-361 61 61, fax: +31 (0)50-361 31 51, e-mail: g.drent@int.umcg.nl

## ABSTRACT

Survival outcomes after liver transplantation in adult patients have gradually improved with a five-year survival of about 70% and a ten-year survival of about 60%. The present review focuses on relevant patient-reported outcomes such as self-perceived side effects of immunosuppressive drugs, medication nonadherence and long-term health-related quality of life after liver transplantation. These entities are interrelated but have often been studied separately.

Self-perceived symptom experience in liver transplant recipients has not been studied extensively. Symptoms that cause distress differ between men and women, e.g. symptoms related to cosmetic side effects of drugs.

Medication nonadherence seems to be infrequent, but if present may have serious consequences. Important risk factors were found to be the costs of drugs, age <40 years, psychiatric disorders, side effects of drugs, beliefs that drugs were harmful, and large influence of the liver transplant on the patient's life.

Health-related quality of life is satisfactory, but below the level of the general population. Results, however, must be interpreted with caution as quality-of-life improvements may have been overstated due to variables such as selection bias (e.g. exclusion of severely ill and deceased patients), too many short-term studies, and suboptimal methodology. Presently we lack data on the influence of recurrence of disease, 'de novo' diseases and gender differences on health-related quality of life in liver transplanted patients.

## KEYWORDS

Adherence, compliance, concordance, quality of life, side effects, solid organ transplantation

## INTRODUCTION

For several decades liver transplantation (LT) has been the accepted treatment for a gradually expanding variety of indications.<sup>1,2</sup> Life expectancy improved over time, due to better surgical techniques and preoperative and postoperative care,<sup>1,3</sup> with a five-year survival of about 70%, and a ten-year survival of about 60%.<sup>2,4</sup> An update on liver transplantation by Verdonk *et al.* was recently published in this journal.<sup>1</sup>

Formerly, the results of solid organ transplantation were mostly evaluated from the perspective of clinicians in terms of objective clinical outcomes, such as postoperative complications, renal impairment, hypertension, malignancies, osteoporosis, diabetes, and patient and graft survival. Nowadays, it is increasingly recognised that an evaluation of outcomes should incorporate the subjective experiences of the patients.<sup>5</sup>

The Food and Drug Administration in the USA strongly recommends that patient-reported outcomes (PRO) should be incorporated to evaluate the impact of treatment on patients' daily life and well-being. A patient-reported outcome can be defined as '*any outcome based on data provided by patients or by patient proxy as opposed to data provided from other sources*'.<sup>5</sup> Patient-reported outcomes may help to improve the quality of health care, and need to be taken into account when developing new drugs. PROs that are of importance to liver transplant patients are symptom experience, medication adherence and health-related quality of life.

The effectiveness of the treatment after solid organ transplantation depends both on the skills of the healthcare team and on the life-long, active cooperation of the patient.<sup>6,7</sup> Side effects as a consequence of taking of immunosuppressive medications may occur. Assessment of side effects as perceived by the patients provides the

transplant field with valuable information regarding the benefit and burden of immunosuppressive regimens.<sup>8</sup> A relationship has been found between symptom experience and nonadherence and health-related quality of life in heart, renal and lung transplant recipients.<sup>9-23</sup> The current review explores whether evidence supports these relationships in liver transplant patients.

Adherence (also called compliance or concordance) is defined as: 'the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with the *agreed* recommendations from a healthcare provider'.<sup>24</sup>

Nonadherence with the immunosuppressive regimen in solid organ transplant recipients is recognised as a major long-term problem with a negative impact on clinical outcome<sup>25-30</sup> and worse economic outcome.<sup>31-34</sup> The majority of research on adherence in transplantation, however, has been done in renal and heart transplantation. No reviews have been published on medication adherence in liver transplant patients specifically.

Health-related quality of life (HRQOL) is also recognised as an important patient-reported outcome. Solid organ transplantation remains a chronic condition which can have a high impact on the daily life and well-being of the patient.<sup>35-36</sup> For liver transplant patients specifically, health-related quality of life may well be influenced by long-term side effects of drugs, and by the status of the liver as '*de novo*' disease or recurrent disease may develop.<sup>37-39</sup>

## METHODS

The present review focuses on experience of symptoms related to side effects of immunosuppressive drugs, medication nonadherence and long-term health-related quality of life in adult liver transplant patients. The databases PubMed, PsychInfo, Cinahl, preCinahl, and the Cochrane Library, from 1966 to October 2008, were searched with the help of a medical librarian. A combination of following search terms was used: liver transplantation, liver transplant\*, compliance, non(-) compliance, non(-)adherence, adherence, concordance, symptom experience, symptom frequency, symptom distress, subjective side effects, subjective adverse effects, quality of life, general health status, long-term. Further selection criteria were English language publications and focusing on adult patients. Excluded were articles that focused on living donation. The articles found on all of the topics were screened and in addition to this search strategy the references of the publications were searched for additional publications. In total we found 41 publications on the three subjects: six studies on symptom experience, 14 studies with the main focus on medication

nonadherence and 21 studies on long-term HRQOL. From the 21 studies on long-term HRQOL five studies that were published after the latest meta-analysis were selected for this review.

## SYMPTOM EXPERIENCE

Symptom experience is a critical post-transplant outcome and it provides the transplant field with valuable information regarding the benefit and burden of immunosuppressive regimens as perceived by the patients.<sup>8</sup> Symptom experience refers to the patient's subjective experience of side effects related to immunosuppressive drugs and it can be divided in perceived symptom occurrence (cognitive part of symptom experience) and perceived symptom distress (emotional part of symptom experience).<sup>8-12</sup> Symptom occurrence is described along the dimensions of frequency, duration and severity of perceived side effects of immunosuppressive medications. Symptom distress, expressing the emotional burden related to side effects, demonstrates how patients are affected in daily life by these symptoms.<sup>5</sup> Many clinical symptoms may not be perceived by the patients as very distressing, and also the level of distress may differ in patients.<sup>20</sup> For instance, the patients may worry more about skin alterations, sexual disorders, depressive symptoms and stomach complaints than about hypertension or renal impairment. The amount of perceived distress was found to be related to health-related quality of life and to nonadherence in heart, renal and lung transplant recipients.<sup>9-23</sup> Kidney transplant recipients with a higher level of symptom occurrence and symptom distress for instance had a higher rate of nonadherence.<sup>19</sup> More 'drug holidays' as a measure of nonadherence and a higher level of symptom occurrence and distress was related to a worse quality of life in lung transplant recipients.<sup>23</sup> It is important to find evidence about symptom experience in liver transplant patients for three reasons: (1) healthcare workers must be informed that symptom occurrence and/or a higher level of perceived distress may worsen the patient's well-being and that it may lead to nonadherence, (2) it can be used to educate the patient and his/her relatives about the side effects of immunosuppressive medications and (3) it can be used in developing new drugs and in prescribing existing immunosuppressive medications based on patients' preferences.<sup>20,40</sup> Only a few studies were retrieved that report on symptom experience after liver transplantation.<sup>40-45</sup> Foley *et al.*<sup>41</sup> report a low score on occurrence of symptom frequency and perceived distress in 26 liver transplant recipients. Most frequently reported symptoms were fatigue, bodily appearance, excessive hair growth and overeating. However, the sample was rather small and the response rate was only 59%. Karam *et al.*

assessed 'Measures of Disease', more specifically physical symptoms and severity of symptom distress, in 126 liver, 229 renal and 113 heart transplant recipients as part of long-term quality-of-life-assessment.<sup>44</sup> The 'Measures of Disease' reported by the transplant patients were significantly worse than in the general population, with the worst score for renal transplant patients. The symptom distress score for psychological symptoms revealed that renal transplant recipients had a worse HRQOL than liver transplant recipients. However, limited specifications about the symptoms were provided.

We assessed symptom experience in 108 adult liver transplant patients<sup>40</sup> with the 29-item Modified Transplant Symptom Occurrence and Symptom Distress Scale<sup>9,10,46</sup> and found that increased hair growth was the most frequent symptom in male and female recipients.

The most distressing symptom in women was excessive and/or painful periods, while in men this was impotence. Male and females did not differ with respect to symptom frequency, but overall symptom distress was more serious in women than in men. It was also shown that the most frequently reported symptoms do not necessarily cause the most perceived distress. Stomach, back and muscle complaints were listed in the Top Ten of most distressing symptoms for both sexes. Dividing the sample in a cohort with a short-term (1-4 years) and a long-term (5-18 years) follow-up, clear differences over time and between genders were noted. Women in the long-term cohort reported more cosmetic side effects. A decrease in symptom frequency and symptom distress was not seen in the long-term cohort. This might be explained by the fact that comorbidity from long-term immunosuppression increases through the years and by the effect of ageing, but this needs further investigation in future studies. No relationship was found between symptom experience and prednisolone nonadherence as measured with electronic monitoring.<sup>47</sup>

Drawing firm conclusions from these few studies on symptom experience, however, is difficult, because the studies used different measurement instruments, and the symptoms assessed were not always described in detail. Symptoms that cause distress may differ between men and women. Furthermore, no conclusions can be drawn about the relationship with different immunosuppressive regimens, nor about the relationship with medication adherence and HRQOL.

## NONADHERENCE WITH IMMUNOSUPPRESSIVE MEDICATION

Patients' adherence to immunosuppressive medications plays a key role in obtaining and maintaining a good clinical outcome. Fourteen studies on nonadherence

in adult patients after liver transplantation were retrieved.<sup>14,15,25,28,47-56</sup> Most of the studies that were published before 2000 included only small numbers of patients.

### Measurement of nonadherence

Measurement of medication nonadherence can be divided into direct and indirect methods.<sup>57</sup> Direct methods are: direct observation or measurement of a drug (metabolite) in blood or urine. Indirect methods are patient self-report, collateral report, pill counts, rates of prescription refills, assessment of clinical outcome, electronic medication monitors (EM), and measurement of physiological markers (i.e. heart rate of patients taking  $\beta$ -blockers).<sup>57-60</sup>

Adherence measurement methods in adult liver transplant adherence studies have been: monitoring blood levels of calcineurin inhibitors,<sup>15,20,25,48-51</sup> self-report,<sup>15,51-54</sup> collateral report,<sup>25</sup> retrospective chart review,<sup>14,51,55</sup> clinical outcome,<sup>25,28,49,51,55,56</sup> electronic monitoring (EM)<sup>47</sup> and appointment nonadherence.<sup>51</sup> The diagnostic accuracy of each method has been discussed extensively by several authors.<sup>57,59-62</sup> Recent research findings using cross validation and diagnostic research suggest that a combination of several measurement methods has higher sensitivity compared with using a single method.<sup>57,62</sup>

### Establishing nonadherence in clinical practice

In clinical practice a simple measure to establish suspected nonadherence, e.g. a patient is not responding to therapy, is by just asking the patient at a scheduled follow-up how often he/she could not take the medication as prescribed in the last four weeks and what caused this omission.<sup>57</sup> Another useful method is to contact the patient's pharmacy about refilling prescriptions<sup>57</sup> or to ask the patient to bring the medication along to a scheduled appointment with the physician or clinical nurse specialist.

### Prevalence of nonadherence

As the retrieved studies use different methodology it is not easy to derive a general nonadherence prevalence rate. Schweizer *et al.*<sup>15</sup> reported the first prospective adherence study (n=13) among adult liver transplant recipients. Nonadherence was suspected when unexplained decreases in cyclosporin blood levels were observed. Three of 13 liver transplant recipients were found to be nonadherent. In a retrospective study among 118 patients who had undergone liver transplantation for alcoholic liver cirrhosis, Berlakovich *et al.*<sup>28</sup> reported that 19 recipients (16%) were not within the target range of whole blood trough levels of the calcineurin inhibitor. This, however, in itself does not prove nonadherence. We studied prednisolone nonadherence with the use of electronic monitoring and found an overall high level of dosing adherence for prednisolone (median of 99%), except that

timing adherence, which describes 'the percentage of days that opening of the bottle was within three hours of the subject's chosen time of day to routinely take their prednisolone dose', was low in about one-third of the patients.<sup>47</sup> Dew *et al.*<sup>63</sup> analysed adherence after solid organ transplantation, and included seven liver transplant studies on medication nonadherence in her meta-analysis. Liver transplant recipients had a medication nonadherence rate of 6.7 cases per 100 patients per year (PPY) vs 15 cases per 100 PPY in heart transplant recipients and 36 cases per 100 PPY in renal transplant recipients.

The limited available evidence suggests that adherence for medication intake after liver transplantation seems to be good, and more favourable than in other transplant recipients. Nonadherence should of course also be evaluated in view of the possible clinical consequences of medication nonadherence.

### Clinical consequences of nonadherence

Medication nonadherence must have a measurable effect on the clinical outcome for it to be clinically relevant.<sup>64</sup> The ultimate goal is to develop a clinically relevant definition of nonadherence indicating the level of nonadherence that is connected with increased risk for poor clinical outcome. Review of nonadherence studies in renal transplant recipients revealed that nonadherence was associated with poor clinical outcome, e.g. rejection episodes and graft loss.<sup>29,65</sup> Research in heart transplant populations<sup>27</sup> with electronic monitoring showed that minor deviations from the dosing schedule were associated with increased risks of late acute rejection, graft loss, and mortality.

In a retrospective review by Mor *et al.*<sup>25</sup> in 375 liver transplant patients it was found that nonadherence accounted for 34.6% of late acute rejection episodes. In a retrospective study among 118 patients who had undergone liver transplantation for alcoholic liver cirrhosis, Berlakovich *et al.*<sup>28</sup> reported that late acute rejection differed significantly between the adherent patients (5% with acute rejection) and the nonadherent patients (22% with acute rejection). In our study concerning prednisolone nonadherence, we looked for a relationship between nonadherence and clinical outcomes during a two-year follow-up including liver tests, acute rejection episodes, changes in dosages of immunosuppression, hospital re-admissions, and patient and graft survival.<sup>56</sup> Except for a somewhat higher alkaline phosphatase in patients who were less adherent, no relationship between prednisolone nonadherence and clinical outcome parameters was found.<sup>56</sup> It is possible, however, that the level of nonadherence in our patient population was too low to be of clinical significance. O'Carroll *et al.*<sup>51</sup> conducted a retrospective audit in 435 Scottish patients who were beyond one year after LT. Approximately one out of 100 patients died from poor

adherence and nonadherence may have played a role in the development of chronic rejection.

These studies show on the one hand that medication nonadherence may have serious consequences for graft and patient survival. On the other hand the level of nonadherence must be substantial with abstinence of medication probably for many weeks.

### Economic consequences of nonadherence

Nonadherence with the immunosuppressive regimen has found to be associated with poor economic outcome, but has not been studied in adult liver transplant patients thus far.<sup>31-33</sup> Economic consequences, using data from the renal transplant literature, include higher healthcare costs among nonadherent patients in comparison with adherent patients in terms of hospital care, retransplantation, ambulatory care, nursing homes, productivity loss and 'out-of-pocket' expenses of patients and relatives.<sup>31-33</sup> On the other hand, when lifetime costs of adherent vs nonadherent renal transplant patients were compared, Cleemput *et al.*<sup>33</sup> found lower costs in nonadherent patients over lifetime, due to a shorter life span in nonadherent patients (i.e. a median survival of 12 vs 16 years). Yet quality adjusted life years (QALYs) were higher in adherent patients.<sup>33</sup>

### Risk factors for nonadherence

Knowing that nonadherence can have a negative impact on outcomes after transplantation, clinicians should be aware of possible risk factors for nonadherence so that adequate interventions can be undertaken. Reported risk factors in liver transplant patients are higher costs of medications,<sup>15</sup> age <40 years,<sup>47</sup> psychiatric disorders,<sup>14,15</sup> side effects of medications,<sup>14,15,51</sup> beliefs that medications were harmful,<sup>51</sup> and experiencing a large effect of the transplant on the patients' daily life.<sup>51</sup> More studies are needed to judge the influence of higher level factors related to the healthcare centre and healthcare providers. For example, in a multicentre study of renal transplant patients using electronic monitoring, associations were found between the transplant centre and adherence.<sup>66</sup> Another study showed that nonadherence rates were higher in the United States compared with Europe, and highlight that healthcare system factors, such as insurance coverage, are possibly an influencing factor of higher nonadherence rates in the USA.<sup>7,63,67-69</sup>

### Interventions

No intervention studies to enhance medication adherence in adult liver transplant patients have been published, to our knowledge. As nonadherence is a complex behaviour, usually not predictable and individual to every patient, it is difficult to develop effective strategies to enhance adherence.<sup>7,70</sup> Several reviews about interventions in other chronic illness patient populations have been published.<sup>71-74</sup>



One conclusion they have in common is that no 'magic bullet' was found and that very few effective interventions significantly affected clinical outcomes in the long term. Patient education is important and may include discharge teaching and introducing a self-medication programme.<sup>57,70</sup> Once-daily medication dosing and simplifying dosing so that it fits into the lifestyle of the patient may improve adherence.<sup>34,57,71,74</sup> Of further importance is investment in a good relationship between the healthcare professionals and the patient, with more frequent interactions with attention to adherence.<sup>57,71,74</sup> Additionally, this includes means of easy communication by phone or e-mail and broadening opening hours of the outpatient clinic to shorten waiting times.<sup>57</sup> Interventions need to be tailored to the individual patient. A combination of educational, behavioural and affective interventions seems to be most effective, but they are complex and labour-intensive.<sup>71,74</sup>

## LONG-TERM HEALTH-RELATED QUALITY OF LIFE

The World Health Organisation defined Health as '*a state of complete physical, mental and social well-being and not merely the absence of disease*'.<sup>75</sup> General HRQOL improves significantly from pre- to post-LT but most findings refer to a relatively short duration of follow-up.<sup>37-39</sup>

Long-term results indicate that HRQOL, after the initial improvement from pre- to post-LT, remains rather stable through the years and is not always negatively influenced by comorbidity and clinical side effects of medications.<sup>37-39</sup> Results show, however, that LT patients have significant deficiencies in most QOL areas when they are compared with healthy controls.<sup>40</sup> The impact of aetiology of liver diseases on HRQOL, such as alcoholic liver disease, HCV infection, acute liver failure, remains inconclusive with contradicting findings of HRQOL gains. The assumption was made by Tome *et al.*<sup>39</sup> that recurrence of disease, e.g. hepatitis C, and development of '*de novo*' diseases, e.g. diabetes mellitus, after LT might be of higher influence on a worsened HRQOL than the original aetiology of the disease.<sup>39</sup> In view of sexual functioning and employment more recent studies show that females tend to have a lower HRQOL compared with males. Sexual health was found to be unchanged after LT compared with the period before LT when data of longitudinal studies were combined. Employment rates varied considerably after transplantation.<sup>39</sup> Unemployment was predicted by age, longer duration of disability before LT, unskilled workers, lower income, and unemployment status.<sup>39</sup> Five new publications, one qualitative and four quantitative studies, assessing long-term HRQOL have been published since the most recent meta-analysis by Tome *et al.*<sup>36,39,76-79</sup> Median

follow-up ranged from 4.4 years to more than 15 years after LT. The main findings of these studies are that varying levels of physical and psychosocial disability may persist for many years after LT, although patients describe having productive and meaningful lives with a positive outlook despite remaining uncertainty about the future.<sup>36</sup> Physical impairment led to significantly lower employment<sup>76</sup> but did not have an impact on satisfaction and self-care.<sup>77</sup> Long-term HRQOL did not seem to be related to the level of clinically observed comorbidity<sup>77</sup> or to the use of calcineurin inhibiting drugs.<sup>78</sup> Job rehabilitation in the first year after LT had a positive influence on long-term HRQOL.<sup>78</sup> Age above 60 years, female gender and post-transplant complications as recurrent disease and osteoporosis were associated with poorer physical functioning.<sup>79</sup> These new studies also report a lower HRQOL than in the general population. In three of the four quantitative studies the SF-36<sup>80</sup> was used as a generic instrument to measure HRQOL<sup>76,78,79</sup> and one study also used a disease specific questionnaire.<sup>79</sup>

In summary, so far recent HRQOL studies add evidence in that QOL remains satisfactory in the long term after LT, but lower compared with that of the general population. Although some of the recent studies on long-term HRQOL contribute to earlier assumptions that overall long-term HRQOL does not seem to be affected by the level of comorbidity and that female patients experience a worse HRQOL compared with men, more studies on long-term HRQOL after LT are needed to gain more understanding.

## CONCLUSIONS

The present review focused on three important patient-reported outcomes in adult liver transplant patients, i.e. perceived subjective side effects of immunosuppressive drugs (i.e. symptom experience), medication nonadherence and long-term health-related quality of life. Clearly, these entities are interrelated but have often been studied separately.

We found that self-reported symptom experience in liver transplant recipients has not been studied extensively. Differences between different immunosuppressive regimens have not been explored so far in this respect. Also the relationship between symptom experience and medication adherence and HRQOL needs further study. Special attention should be paid to the level of perceived symptom distress and its impact on the daily life of the patient as a high level of distress might lead to nonadherence and worse HRQOL, as experienced in kidney, heart and lung transplant patients.

Medication nonadherence as measured to date seems to be infrequent, but if present may have serious consequences. Important risk factors included age <40 years, and side effects of medications.<sup>15,47,51</sup> More studies are needed to gain more insight into clinically relevant nonadherence and to judge the influence of the healthcare centre and healthcare providers. More studies into the prevalence of medication nonadherence and corresponding risk factors are needed before appropriate intervention studies can be developed. Evidence from studies in chronically ill patients and other organ transplant patients show us that there is not one single effective intervention available and that a combination of multidimensional and multi-level interventions may be effective for long-term results to enhance adherence.<sup>71,74</sup> This is an important area for future research, yet the clinical consequences of nonadherence in liver transplant patients should also determine if this is a priority.

Results show that long-term HRQOL is satisfactory, but it is below the level of the general population. These results must be interpreted with caution as HRQOL benefits after liver transplantation may have been overstated due to variables such as selection bias (e.g. exclusion of severely ill and deceased patients), too many short-term studies, and suboptimal methodology.<sup>39</sup> In addition, HRQOL will also be affected by cultural, economic and social factors which are difficult to incorporate in research.<sup>38,39,81</sup> In studying HRQOL from the perspective of patient-reported outcomes it is recommended to use both a disease-specific questionnaire and a generic questionnaire. The former detects disease-specific changes and the latter allows comparison of results with other groups of patients with chronic diseases. Presently we lack data on the influence of recurrence of disease and of 'de novo' diseases in adult liver transplant patients. Also gender differences should be given more attention.

## RECOMMENDATIONS

Two main recommendations can be made. Firstly it is important that assessment of adherence is an integrated part of the treatment plan of the patient, and poor adherence should always be considered when a patient is not responding to therapy.<sup>57</sup> Secondly, physicians should be aware of the possible influence of subjective side effects of immunosuppressive drugs on medication adherence and of the impact of corresponding distress on the daily life of the patient. In the future, medication regimens should not only be based on clinical data alone, but, when possible, also on subjective patient-reported outcomes.

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