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The effect of Liver Transplantation on the quality of life of the recipient’s main caregiver – a systematic review

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Abstract

Introduction
Liver transplantation (LT) is a transformative, life-saving procedure with life-long sequale for patients and their caregivers. The impact of LT on the patient’s main caregiver can be underestimated. We carried out a systematic review of the impact of LT on the Health Related Quality of Life (HRQL) of LT patients’ main caregivers.

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Methods
We searched 13 medical databases from 1996 to 2015. We included studies with HRQL data on caregivers of patients following LT then quality assessed and narratively synthesized the findings from these studies.

Results
Of 7076 initial hits, only five studies fell within the scope of this study. In general, they showed caregiver burden persisted in the early period following LT. One study showed improvements, however the other four showed caregiver’s levels of stress, anxiety and depression, remained similar or got worse post-LT and remained above that of the normal population. It was suggested that HRQL of the patient impacted on the caregiver and vice versa and may be linked to patient outcomes. No data was available investigating which groups were at particular risk of low HRQL following LT or if any interventions could improve this.

Conclusion
The current information about LT caregivers’ needs and factors that impact on their HRQL are not adequately defined. Large studies are needed to examine the effects of LT on the patients’ family and caregivers in order to understand the importance of caregiver support to maximise outcomes of LT for the patient and their caregivers.

Key Words
Liver transplant
Caregiver
Health related quality of life
Outcomes
Key Points:

1. Many Liver transplant caregivers showed increased caregiver strain post-transplant and it seems that their responsibilities did not reduce but rather changed post-operatively.

2. Current information levels about caregivers’ needs and factors that impact on their health related quality of life are not adequately defined.

3. Impairment of the caregivers health related quality of life may lead to worsening patient outcomes following liver transplant.

4. Increased professional intervention is necessary to improve the quality of life of both caregivers and that of the interrelated liver transplant patients

Abbreviations:

LT Liver Transplantation
HRQL: Health Related Quality of Life

Introduction

Liver transplantation (LT) transforms patients’ health taking them from being unlikely to survive 12 months to being given a life expectancy of over 10 years (1). However, in most patients, it removes one chronic health condition and replaces it with another. They move from having chronic liver disease to having to deal with the life-long effects of immunosuppression and sequale of complex, major surgery.

More than 26 000 liver transplants are performed throughout the world each year (2). Since more than half of patients are expected to survive 10 years or longer (1), there are an increasing number of long term survivors. The health-related quality of life (HRQL) of survivors following LT has been increasingly investigated (3-6) whereas the impact of LT on the patient’s partner or main caregiver has received little attention.
Issues potentially affecting caregivers include difficulties attendant upon caring for someone with a life-threatening illness, uncertainty while the patient is on the LT waiting list, adaptations required post-operatively and the long term concerns over complications and rejection (7). The effects of LT on the patient’s main caregiver need to be addressed in order to ensure their own health and well-being is maintained but additionally to ensure that they remain in a position to be able to continue to support the LT recipient throughout their recovery and deal with post transplantation challenges, thereby ensuring the best possible outcomes are achieved. A Spanish study evaluating social and family support for patients awaiting LT identified that the mean size of social network for liver transplant recipients was 12, ranging up to 30 people (8). While this may vary between cultures, it is clear that a single LT may impact upon a significant number of additional people. Finally, with the increasing use of living donor LT it is even more important to be able to provide patients and their caregiver’s with information regarding how their caregiver’s HRQL may be affected following a LT.

This systematic review examines the literature to assess what data is available to determine the effects of LT on the HRQL of the recipient's main caregiver and family.

Methods

Search terms
A search strategy was developed in MEDLINE (OVID). Validated terms for liver transplantation were combined with terms for carers (Supplementary Table 1). No language limits or study design filters were applied to the search strategy.

The MEDLINE search strategy was adapted for use in each of the other databases searched.
Data sources
The following databases were searched from January 1st 1996 to August 31st 2015: MEDLINE, MEDLINE In-Process, Applied Social Science Index and Abstracts (ASSIA), Cumulative Index to Nursing & Allied Health (CINAHL Plus), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Management Information Consortium (HMIC), Health Technology Assessment (HTA) database, PsycINFO, Social Science Citation Index and Social Care Online.

Selection criteria
The following inclusion criteria were applied:
Population: caregiver or relative of patients aged 18 years or over following liver transplantation
Outcomes: health-related quality of life (HRQL) including quantitative (e.g. based on validated quality of life scales) or qualitative (e.g. obtained from interviews, focus groups etc) data.
Study design: no restrictions were applied.
Publication type: peer-reviewed publication

Study selection
Titles and abstracts were screened for relevance by one researcher (HY, TM-B, or CK) and checked by another (NM) based on the selection criteria above. Any disagreements were resolved through discussion or consultation with the wider research team (AY, IAR, RJ, AD, KA, AG, GJT).

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Full text articles were obtained for potentially relevant records and study selection was conducted (AY, IAR, GJT).

Quality Assessment
The methodological quality of included studies were assessed by two researchers (AY and IR) according to a previously described criteria for assessing study quality in systematic reviews of HRQL, disagreements were resolved with the senior author (GJT) (9). A 14 point check-list was adapted (Table 1). This has been used to previously grade studies as high, moderate or low quality on the basis of meeting 75%, 75-50% or less than 50% of points respectively (9,10).

Synthesis
Given heterogeneity in patient selection, study design, and HRQL data we conducted a narrative synthesis of findings from included studies.

Results
Five peer reviewed studies were included in the systematic review (see Figure 1 for study flow diagram). We conducted a broad search of the literature and only eight studies were identified as potentially meeting the inclusion criteria of the review. Of these, three were excluded after full text screening (two (11,12) were descriptive containing no quantitative or qualitative data, whilst a further one was a PhD dissertation (13)). Summary characteristics for included studies are provided in Table 2.

The identified studies varied considerably in terms of participant selection, were predominantly cross-sectional with one prospective study and employed both quantitative and qualitative methods. The marked differences in methodology made direct comparisons between results difficult. One study was graded as of high quality, two moderate and 2 poor quality (Table 3).
The study by Cohen and colleagues was the first study in this area and took the form of a cross-sectional survey, using the Caregiver Stress Questionnaire, of 24 care-givers carried out from 1-15 years following LT (14). Their objective was to determine psychological distress amongst caregivers following LT and hypothesized there may be differences between the sexes. They showed considerable ongoing caregiver burden, more so in women than men. They showed that a longer passage of time post-LT and a higher perception of caregiver workload or relational deprivation was correlated with depression whereas a sense of personal gain correlated inversely with depression. Hence the higher caregiving burden amongst women led to higher rates of depression. In their conclusions they discuss the possibility that psychosocial intervention could promote feelings of personal gain amongst caregivers which could reduce rates of depression. They argue that extended professional intervention could reduce stressors resulting in decreased caregiver distress and improvements in their physical and psychological well-being.

The study by Perez and colleagues included predominantly LT patients (78 patients), but also kidney (71 patients) and heart (17 patients) transplant recipients among the 166 patients investigated (15). Having been identified and consented pre-operatively, patients and their relatives were surveyed at two time points; on discharge from the intensive care unit and one year following discharge. Four different HRQL instruments were used with slight modifications. These were an in-house psychosocial survey, The Quality of Life Questionnaire (QLQ-C30; European Organization for Research and Treatment of Cancer [EORTC]), the Hospital Anxiety and Depression Scale (HADS) and the Leeds anxiety and depression scale. The main focus of the study was to analyse anxiety, depression and quality of life in transplant recipients and their closest relative shortly after transplant surgery. Results were not stratified by which organ was transplanted. They found high levels of post-transplant anxiety in patient’s caregivers and that levels of anxiety were strongly transmitted from the recipients to the family. They postulated that this may be because a poor psychological status may be mirroring a poor physical status i.e. the transplant may not be
They also concluded that the mood of the patient’s family could harm the patient, primarily because of a loss of support; for example, ignoring psychological disorders leading to neglect of filling prescriptions. This study also demonstrated that caregivers with high levels of anxiety immediately post-transplant were also more likely to experience feelings of anxiety and fear one year later. However, the authors also report that due to their selection bias, there was a lack of controls for sociodemographic factors or clinical variables and there were no pre-transplant caregiver assessments.

The cross-sectional study by Rodrigue and colleagues investigated the main caregiver of 49 pre-operative and 37 post-operative (median 26 months) LT patients comparing the two groups to each other and to a normal population (16). Assessments were carried out for Quality of Life (SF-36), Life satisfaction (Quality of Life Inventory (QLI)), Mood (Profile of Mood States-Short Form (PoMSS)), Caregiver Strain (Caregiver Strain Index (CSI)) and Benefit (Caregiver Benefit Index (CBI)) and Social Intimacy (Miller Social Intimacy Scale (MSIS)). This is the most comprehensive study available with good descriptions of the methodology and results and was the only study graded as high quality (Table 3). The pre- and post-LT groups were well matched for demographics but no other details were listed. No attempt was made to adjust for patient factors therefore the results are potentially vulnerable to confounding. There were no significant differences between pre- and post-LT groups for quality of life, life satisfaction, caregiver strain or social intimacy and all were less than those of a normalised population other than caregiver strain which was increased in the LT groups. However there were suggestions, of, improvements (non-significant) in the post-LT group such as in life satisfaction (High life satisfaction: 18.9% vs. 8.2%) and some quality of life measures such as physical functioning and bodily pain (Table 4) which may have reached statistical significance with a larger study population. Interestingly, caregiver strain was 22% higher in the post-LT group although this did not reach statistical significance. Caregiver strain correlated with lower mental quality of life, lower life satisfaction and mood disturbance. In their conclusions the authors discuss the importance of educating caregivers.
about the long-term nature of their caregiving responsibilities and the effects LT will have on them and the patients they care for.

Weng and colleagues conducted a qualitative study on the post-operative stress levels experienced by the primary caregivers in the first six months following LT (17). Face-to-face interviews were carried out on a sample of only six participants. This study describes the complexities of the decision making process for living donor LT and how family dynamics, affected by both cultural and ethical considerations, impacted upon this. They describe the large amounts of stress experienced by caregivers due to factors such as the gap between expectation and actual experiences, the unstable process of LT, entanglement burden and difficult interactions with healthcare professionals. In addition, they found that LT caregivers felt the stress experienced interfered with their comprehension of information provided. They concluded that not enough consideration was given to caregivers and suggested ways the caregivers experience could be improved to maximise support to the recipient because of the vital role the caregiver plays in the transplant process.

Sirivatanauksorn and colleagues investigated both LT patients and their caregivers pre- (57 caregivers) and post-LT (59 caregivers) using the SF-36 translated into the Thai language (18). In contrast to the other studies, all aspects of HRQL from the SF-36 showed improvement with the majority being statistically significant. This was a cross-sectional study with the groups well matched for disease aetiology but very few other details are presented. More information in the methodology on factors such as participant selection would have been beneficial and unfortunately no data was presented on how long post-LT the survey was completed. The use of the same HRQL outcome measure allowed comparison with the SF-36 results from Rodrigue’s study (16) (Table 4), the markedly different scores and indeed the very high scores recorded (scores from SF-36 are on a 50 mean/10 standard deviation scale) in the study by Sirivatanauksorn raise further questions over the methodology.
Discussion

The support of patients' families and caregivers is an essential component to obtaining a successful outcome following transplantation (19, 20). However, this review demonstrates that to date the impact of LT on the patients' families and caregivers has not been significantly evaluated. Our extensive search resulted in only five peer-reviewed studies on this subject. Two of the main findings being the suggestion that impairment of the caregivers' HRQL led to worsening outcomes for the post-LT patient and secondly the persisting burden of caregiving responsibility following LT leading to decreased HRQL.

The study by Weng and colleagues included only six participants but their qualitative data demonstrated the huge stress experienced by living-donor LT patient's caregivers in the peri-transplant period (17). The study by Perez and colleagues reported that levels of both anxiety and depression in the patient impacted on caregivers and vice versa (15). They felt that the caregiver's mood could lead to harmful effects on the patient if there is loss of support. Indeed both these studies emphasised the importance of the main caregiver to the ultimate success of the transplant by supporting the recipient through the difficult early post-operative period. Mirroring this, it has been shown in renal transplantation that a strong correlation exists between social support and adherence to the complicated post-transplant immunosuppressant regime (21). Indeed it has been suggested in cardiothoracic transplantation that caregiver well-being should be monitored as it is an important risk factor for recipient mortality (22).

The studies by Cohen and Rodrigue both also demonstrated the high, persisting caregiver load following LT, impacting on caregivers' quality of life and mood and with an increased caregiver burden which itself may lead to depression (14,16). They both suggest that professional intervention is necessary to improve the quality of life of both caregivers and that of the interrelated LT patients. In contrast, the study by Sirivatanauksorn and colleagues demonstrated significantly improved levels of nearly all aspects of HRQL.
assessed post-LT (18). This is a short report and so it is difficult to be certain of the reasons for this. Length of time since the transplant and unknown components of the methodology may be factors but another may be cultural and ethical differences in the populations as suggested by Weng (17).

The cross-sectional studies of caregivers of patients with end-stage liver disease on the LT waiting list gives greater insight into the potential challenges faced by caregivers following a LT (23-27). The study by Miyazaki and colleagues demonstrated a quarter of caregivers did not feel adequately informed or prepared prior to transplant, to provide the best care for the patient. Indeed more than half of caregivers had reduced, or given up, their employment, three-quarters showed signs of depression and more than half showed signs of significant stress (23). Interestingly, the authors showed a correlation between caregiver burden and certain disease aetiologies although none of the studies in the present systematic review were sufficiently powered to be able to determine if this persisted post-LT. Many LT caregivers and indeed LT health professionals may feel that the caregiving role and caregiver’s psychological stress will lessen post-transplant. However, the studies by Rodrigue and Cohen would suggest this is not the case: Many LT caregivers showed increased caregiver strain post LT and it seems that their responsibilities did not reduce but rather changed post-operatively (14, 16). It may be predicted that the first year post-LT is the most challenging but the study of Rodrigue had a median follow-up of 26 months and Cohen’s study up to 15 years post-LT with data to suggest problems may increase over time. Further research into the long-term effects seems warranted.

Other data is available from investigating other solid organ transplants for the effects on patients’ caregivers. This intelligence may be relevant given the common issues surrounding life-threatening illnesses, long term conditions, transplantation and life-long immunosuppression which are quite different to other areas of caregiver research. For example, a study of 73 spouses of lung transplant recipients carried out by Rodrigue’s group.
again showed caregivers had significantly decreased quality of life following transplantation compared to controls, with considerable strain and emotional distress (28). They did show that a small number of spouses experienced interpersonal benefits and personal growth following the transplant and so interventions could perhaps be designed to increase the number of spouses who may benefit in this way. Similarly, a systematic review in heart transplantation demonstrated that social support is a strong contributor to long-term post-transplant health (29). However the lives of heart transplant recipient’s carers were shown to change markedly following a transplant: A qualitative study of 11 caregivers demonstrated the caregivers’ primary focus became the care of the transplant recipient but this resulted in high levels of anxiety and distress due to uncertainty about prognosis in addition to concerns regarding various home, work, financial, family and personal issues (30). Incidence of depression and anxiety amongst a study of 242 caregivers of cardiothoracic transplant patients was shown to steadily increase throughout the first 3 years post-transplant (31). This group felt this was explained by acute stress around the time of surgery moving towards ongoing chronic stressors relating to transplant complications and the psychosocial status of the recipient. Furthermore, they felt caregivers at risk should be identified early to allow interventions to improve their HRQL to maximize positive outcomes for the entire family following the transplant. In LT it has been suggested that there are certain caregiver characteristics that may predispose to stress post-LT and so earlier identification of these may allow earlier intervention to reduce this impact (32).

Conclusion
More research is needed to understand the LT caregiver’s experience in more depth with qualitative research perhaps key initially to determine which HRQL and well-being assessments are most relevant to their experience. Once the full impact of LT on patient’s families and caregivers is ascertained, health and social care providers will have the appropriate intelligence to develop services to personalize, target and maximize services to meet their specific needs. The information identified by this systematic review shows that
the current information levels about caregivers' needs and factors that impact on their HRQL are not adequately defined. However, it is clear that not all caregivers have identical needs and that support packages need to be tailored to the individual with some of the available data suggesting that this may vary significantly between different cultures. This situation is by no means unique to LT and in other settings it has been shown that investing in care support packages provides significant societal return on investment through enhanced social and mental health and continued employment (33).

Large scale and longitudinal studies to examine the effects of LT on the patients' family and caregivers are urgently needed. To generate robust data these studies must evaluate both LT factors including disease aetiology, severity, complications, comorbidities as well as patient and caregiver socio-demographic characteristics. Armed with this information, LT services will be significantly better placed to achieve their goals of enhancing the quality of life of LT patients and their families and caregivers.

Acknowledgements
We gratefully acknowledge Melissa Harden for assistance with searching; Thirimon Moe Byrne, Huiqin Yang, and Claire Khouja for assistance with screening of titles and abstracts - all from the Centre for Reviews and Dissemination from York University.

References

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15. Perez San Gregorio, M.A., A. Martin Rodriguez, J. Perez Bernal, Psychological

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differences of patients and relatives according to post-transplantation anxiety.


Table 1. Criteria list for assessing the methodological quality of studies on quality of life among liver transplant patient caregivers

Positive criteria if;

A. Socio-demographic and medical data is described (e.g., age, race, employment status, educational status etc.)

B. Inclusion and/or exclusion criteria are formulated

C. The process of data collection is described (e.g., interview or self-report etc.)

D. The aetiology of liver disease is described

E. The results are compared between two groups or more (e.g., healthy population, pre-transplant group etc.)

F. Mean or median and range or standard deviation of time since diagnosis or treatment is given

G. Participation and response rates have to be described and have to be more than 75%

H. Information is presented about patient/disease characteristics of responders and non-responders or if there is no selective response

I. A standardized or valid quality of life questionnaire is used

J. Results are not only described for quality of life but also for the physical, psychological and social domain

K. Mean, median, standard deviations or percentages are reported for the most important outcome measures

L. An attempt is made to find a set of determinants with the highest prognostic value

M. Patient signed an informed consent form before study participation

N. The degree of selection of the patient sample is described

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**Table 2. Summary of the studies identified for this review**

<table>
<thead>
<tr>
<th>Authors (date)</th>
<th>Main aim</th>
<th>Brief Methods</th>
<th>Country</th>
<th>Sample size of LT Caregivers</th>
<th>Brief results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen (2007) (14)</td>
<td>Assess psychological distress and perceived health of family caregivers of LT recipients.</td>
<td>Cross sectional. The Caregiving Stress Questionnaire was given to a sample of caregivers from 1-15 years post-LT</td>
<td>Israel</td>
<td>24</td>
<td>Caregiver burden and stress persisted after LT. This was worse for women than men and caregiver burden was associated with an increased risk of depression.</td>
</tr>
<tr>
<td>Perez (2008) (15)</td>
<td>Assess anxiety and depression in transplant patients and their families</td>
<td>Four questionnaires (An in-house psychosocial study, QLQ-C30, HADS, Leeds anxiety Scale) comparing anxiety and depression immediately after and 1 year post transplantation</td>
<td>Spain</td>
<td>78 LT (from a group of 166 transplant patients)</td>
<td>Anxiety and depression immediately after transplant was associated with post-transplant outcomes. High anxiety in patients just after transplant was associated with increased anxiety in patients and relatives 1 year after transplant.</td>
</tr>
<tr>
<td>Rodrigue (2009) (16)</td>
<td>To examine caregiver strain and psychological functioning of caregivers post-LT.</td>
<td>Cross sectional. Four questionnaires (SF-36, PoMSS, CSI, CBI, MSIS) of caregivers of patients pre- and post-LT.</td>
<td>USA</td>
<td>86</td>
<td>Low quality of life, mood, and depression scores which persisted (non-significantly) post-LT with an increased caregiver burden. Almost all measures of HRQL were below a matched non-caregiver population</td>
</tr>
<tr>
<td>Weng (2011) (17)</td>
<td>Assess caregiver stress during postoperative stage following LDLT</td>
<td>Qualitative study with semi-structured face-to-face interviews 6 months post-LT</td>
<td>Taiwan</td>
<td>6</td>
<td>Stress was associated with a gap between expectations and experiences of primary caregivers</td>
</tr>
<tr>
<td>Sirivatanauksorn (18)</td>
<td>Analysis of pre-versus post-LT HRQL in patients and their spouses/caregivers</td>
<td>Cross-sectional. A questionnaire of caregivers pre- and post-LT using SF-36</td>
<td>Thailand</td>
<td>116</td>
<td>LT improved HRQL of spouses and caregivers</td>
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<td>Author</td>
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<td>Cohen (14)</td>
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<td>Sirivatanauksorn (18)</td>
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Table 3
Quality Assessment of studies.
White boxes indicate a positive score for each of the 14 criteria A-N (Table 1)
Table 4 Comparison of carer’s pre and post-transplant SF-36 subscale scores reported by Rodrigue (16) and Sirivatanauksorn (17).

<table>
<thead>
<tr>
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<th>Pre-LT Caregiver</th>
<th>Post-LT Caregiver</th>
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<tbody>
<tr>
<td></td>
<td>Rodrigue</td>
<td>Sirivatanauksorn</td>
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<tr>
<td>Physical Functioning</td>
<td>50.2</td>
<td>68.4</td>
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<td></td>
<td>51.4</td>
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<td>Role-Physical</td>
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<td></td>
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<td>Bodily Pain</td>
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<td>73.2</td>
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Figure 1: PRISMA 2009 Flow Diagram: impact of liver transplantation on carers or family of patients

Records identified through database searching (n = 7,076)

Records screened (n = 7,076)

Full-text articles assessed for eligibility (n = 8)

Studies included in narrative synthesis (n = 5)

Records excluded (n = 7,068)

Full text articles excluded, with reasons (n = 3):
- descriptive studies with no quantitative or qualitative data (n=2)
- PhD thesis (n=1)