Symptoms And Function During The Early Recovery Period Following Orthotopic Liver Transplantation Surgery

by

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A thesis submitted in conformity with the requirements for the Degree of Doctor of Philosophy

Graduate Department of Nursing Science

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Abstract

**Background:** Following OLT surgery, studies have focused more on long-term patient-reported outcomes, and less on those amenable to earlier intervention. The few early recovery period studies documented pain, mood changes, fatigue and functional limitations, but did not explore fully the relationships between these symptoms and function. This study examined the relationships of pain, mood, fatigue and fatigue impact and function in the early postoperative period, and explored the relationship between patients’ function and the fatigue and fatigue impact of primary caregivers. **Method:** A prospective, descriptive correlational repeated-measures design was used to collect data at baseline postoperatively, then at 4, 8 and 12 weeks upon discharge using the Brief Pain Inventory-Short Form, Profile of Mood States-Short Form, Modified Fatigue Impact Scale and the Human Activity Profile (HAP). Data for caregiver fatigue and fatigue impact were also collected. **Results:** Patients (N = 58) were on average 54 (10.4) years old, mostly male (66%), married (77%) and 65% had untreated viral, alcohol-induced or autoimmune liver disease. The 23 primary caregivers were on average 56.5 (7.85) years old, female (71%) and life partners of patients (88%). Linear regression analysis found no significant association between pain, mood, fatigue and function. Fatigue impact explained 11% of the variance in the patients’ HAP adjusted activity scores (AAS; $\eta_p^2 = .11$). No significant
association was found between the fatigue and fatigue impact of caregivers and the function of patients. Throughout follow-up, patients reported their worst pain upon movement in the moderate range. At 12 weeks, 22% reported moderate to severe pain upon movement, 28% reported moderate to extreme fatigue levels, and 21% reported fatigue impact often or almost always. Baseline HAP-AAS scores were low, but improved throughout follow up. At 12 weeks, patients’ mean HAP-AAS scores suggested functional impairment. Caregiver fatigue and fatigue impact scores were in the moderate range at baseline, and in the mild range by 12 weeks.

**Conclusion:** Future interventional studies are needed pre- and postoperatively, to minimize fatigue impact and evaluate the outcomes of these interventions on the postoperative function. More caregivers are also required to determine their fatigue and fatigue impact during the early recovery period, to support them during the early recovery period.
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CHAPTER 1: INTRODUCTION AND PROBLEM STATEMENT

The prevalence of liver cirrhosis and incidence of its complications, including end-stage liver disease (ESLD), are expected to increase over the next 10 to 20 years (Baxter & Smerdon, 2000; Davis, Albright, Cook, & Rosenberg, 2003; Wong, McQuillan, McHutchinson, & Poynard, 2000). Rates of acute hepatitis C virus (HCV) infections are increasing and injection drug use accounted for 63% of newly reported acute HCV cases with known risk factor information (Public Health Agency of Canada, 2009). Consequently, the need for liver transplantation surgery, the only treatment for ESLD, is also expected to increase (Baxter & Smerdon, 2000; Davis et al., 2003). Orthotopic liver transplantation (OLT) surgery, a procedure whereby a whole liver is removed from a deceased donor and transplanted into the recipient, is an established treatment for Canadians aged 19 to 66 years living with ESLD. Between 1999 and 2008, 4,217 liver transplantation surgeries were performed in Canada, with 80% being OLT (Canadian Institute for Health Information [CIHI], 2010). More Canadian males (64%) than females underwent liver transplantation, with the predominant cause in adults over 35 years being attributed to the hepatitis C virus (HCV; CIHI, 2010). Other common indications include untreatable hepatitis B, acute liver failure, hepatic carcinoma, cholestatic liver disease, and alcohol induced liver cirrhosis (O’Leary, Lepe, & Davis, 2008; Rugari, 2010; Russell, Feurer, Wisawatapnimit, Salonomn, & Pinson, 2008). The one- and five-year survival rates for Canadian liver transplant recipients are estimated at 85-95% and 80% respectively, which are due largely to advancements in surgical techniques and posttransplant immunosuppressant regimens (Hong et al., 2002; University Health Network (UHN), 2011).

Organ donor allocation is contingent on the candidate’s disease severity, urgency for transplantation and physiological suitability of the donor’s liver to the recipient’s body. The
mean \((M)\) length of hospital stay following liver transplantation is typically 13(16) days, and most patients are discharged within two weeks (Smith et al., 2009; Washburn, Meo, Halff, Roberts & Feng, 2009). The estimated cost of liver transplantation in Canada in 1998, from the date of wait-listing to the second anniversary of transplantation, was approximately $121,732 per patient (Taylor et al., 2002); more recent costs have not been estimated but are likely higher.

The trajectory of care during the early recovery period (i.e., less than three months) following hospital discharge includes strict adherence to immunosuppressant regimens, as well as frequent medical follow-up to monitor and manage organ rejection. Moreover, complications resulting from liver transplantation in the first 90 postoperative days are associated with recipients’ preoperative condition, quality of the donor liver and surgical technique, initial graft function, perioperative anesthetic used, and intensive care management (Mueller, Platz, & Kremer, 2004). During this time, 24% - 70% of recipients will develop acute cellular rejection necessitating high-dose corticosteroids; clinical features include jaundice, abdominal pain, malaise, and fever (Adair & Toogood, 2011; Dousset et al., 1998; European FK 506 Multicenter Liver Study Group, 1994; Wiesner et al., 1998). Therefore, the typical symptomatology of OLT recipients during the early postoperative recovery period is complex and multidimensional, and needed further examination.

**Symptoms and Function Following OLT Surgery**

As survival rates have improved, there is increasing interest among clinicians to understand patient-reported outcomes of surgery, including function. To date, the majority of data pertaining to postoperative function was reported in studies of health-related quality of life (HRQL). The focus was mainly on long-term limitations in function, from 1 year to over a decade following surgery (Beyer et al., 1999; Eshelman et al., 2010; Jones, 2005; Lasker,
Sogolow, Short, & Sass, 2011; Leyendecker et al., 1993; Ratcliffe et al., 2003; Rodrigue, Nelson, Reed, Hanto & Curry, 2010; Russell et al., 2008; Younoussi et al., 2000). These studies suggested that long-term functional outcomes were suboptimal. A tenable explanation for this may be significantly impaired function among OLT recipients in the early recovery period. However, the natural course of recovery, including early postoperative engagement in usual everyday physical, social and role-related activities, was not well-examined. Moreover, data describing functional status in the early recovery period were derived via generic HRQL measures which focused on global aspects of functioning. Data particular to specific functional limitations were largely unavailable. Thus, although there was a suggestion that long-term functional outcomes were suboptimal, limited data described the naturalistic trajectory of recovery and functional status, as well as the variables that may have mediated function in the early postoperative recovery period. Clearer understanding of these trends could enable clinicians to deliver timely interventions that may prevent long term functional limitations.

In addition to functional limitations, pain, mood changes, and fatigue were identified frequently as problems during the immediate postoperative period or the early recovery period following discharge (Chui, Chen, & Cheng, 2009; DiMartini et al., 2011; Donovan et al., 1997; Jones, 2005; Ko et al., 2012; Krasnoff et al., 2005; Lasker et al., 2011; Leyendecker et al., 1993; Moore, Burrows, & Hardy, 1997; Moretti, Robertson, Newhall, Clavien, & Gan, 2002; Ratcliffe et al., 2002; Rodrigue, Nelson, et al. 2010; Russell et al., 2008; Wang et al., 2012; Younoussi et al., 2000). These symptoms may have impacted function in the postoperative period, yet their effects were examined at only a cursory level, yielding limited data.

Pain was identified as a problem following OLT surgery, but was not assessed using comprehensive and standard measures; therefore little was known about pain severity and related
interference in the early recovery period. As well, general mental health following OLT surgery was found to be suboptimal compared to the healthy normative samples of generally well populations (Lasker et al., 2011; Ratcliffe et al., 2002; Saab et al., 2008; Saab et al., 2011; Wang et al., 2012). Specific mood states could not be determined from these studies, as mood was measured using mostly HRQL measures. Only six studies examined specific mood states in early recovery period. The prevalence of anxiety (20% - 43% of patients) and depression (17% - 45%) was evident during (and beyond) the early recovery period in these studies (Bonsel et al., 1992; Guimaro et al., 2011; Russell et al., 2008; Lasker et al., 2011; Leyendecker et al., 1993). However, poor methodological quality, including small sample sizes and reliance on cross-sectional study designs, precluded clear understanding of postoperative trends in negative mood states. More information was needed to inform interventions designed to address symptom management comprehensively.

Finally, fatigue may be a major problem following OLT surgery for up to ten years or more (Aadahl, Hansen, Kirkegaard, & Groenvold, 2002; Beyer et al., 1999; Lasker et al., 2011; Leyendecker et al., 1993; Van den Berg-Emons et al., 2006). Although liver transplantation reduces the fatigue associated with ESLD, OLT recipients continue to describe post-transplant fatigue which does not decrease over time (Gross et al., 1999). As the majority of research focused on long-term outcomes, the patterns of fatigue were less clear during the early postoperative recovery period. Although Moore et al. (1997) suggested that OLT recipients had levels of fatigue similar to the general population and that trends of fatigue were consistent during the early recovery period, the majority of cross-sectional studies found that fatigue was common and reported as moderate to severe (Lasker et al., 2011; Leyendecker et al., 1993; Rodrigue, Nelson et al., 2010). However, interpretations of the outcomes of fatigue and its
related impact during the early recovery period were limited by the heterogeneity of measures used, or poor methodological quality, including reliance on cross-sectional study designs, which did not provide prospective data to understand the trends of fatigue. Although the prevalence of fatigue was established, conclusions about individual variability were equivocal. Therefore, further validation of the available data was necessary, including the examination of fatigue and its related impact during the early recovery period. Identification of such trends through a repeated measures design study will better inform the timing of future interventions that address fatigue and its related impact during the early recovery period.

Although pain, negative mood states, and fatigue could limit function, no comprehensive examination of these potential inter-relationships was found using standard, reliable, and valid measures. Two cross-sectional studies found correlations between function and either depression or fatigue (Lasker et al., 2011; Rodrigue, Nelson, et al., 2010). However, inferences about causality were not possible in the absence of a longitudinal design. Nonetheless, the preliminary data suggested that negative mood states and fatigue may have a cumulative negative impact on function during the early recovery period. A prospective, repeated measures study design was used in this study to provide a clearer understanding of the association between pain, negative mood states, fatigue and its related impact, and function during the early recovery period.

Liver transplantation surgery impacts not only OLT recipients, but also their primary caregivers (Cohen, Katz, & Baruch, 2007; Weng et al., 2011). Most transplant programs require that OLT recipients have a social support system postdischarge in order to manage their lifestyle changes (London Health Sciences Centre, 2008; Rodrigue, Nelson, Reed, Hanto & Curry, 2010). Although any adult may be a primary caregiver, it is usually a spouse residing with the patient, who provides essential assistance with daily activities and social support (Rodrigue, Nelson et
Caregiving demands are highest in the first year following OLT surgery. As patients undergo lifestyle changes which impact their emotional well-being and quality of life, caregivers also experience significant stress and fatigue in the waiting period prior to OLT surgery and the fatigue continues during the recipient’s early recovery period (Miyazaki et al., 2010; Rodrigue, Nelson et al., 2010). Caregivers have reported higher levels of fatigue when their perception of the health of the OLT recipient is poor (Rodrigue, Nelson et al., 2010). Whether this perceived health status is linked to the OLT recipient’s functional status remained unknown. Therefore, further research was required to examine the relationship between the OLT recipients’ function in the early recovery period following discharge and their primary caregivers’ fatigue and its related impact during this time.

In summary, there was some preliminary evidence to suggest that the functional status of OLT recipients is suboptimal in the long term following surgery. Pain, negative mood states, and fatigue (level and impact) have been identified as problems in the long term following surgery. Yet, prospective data about trends of these symptoms in the early postoperative recovery period were limited. Moreover, the interrelationships of the symptoms and function during the early recovery period were not well understood. Further prospective examination was necessary to understand these interrelationships in order to develop appropriate interventions during this time period. Lack of prospective evidence during the early recovery period also makes it challenging for health care providers to develop timely and suitable interventions. Wilson and Cleary’s (1995) Model of Patient Outcomes suggests key inter-relationships between symptoms and function, and was used to guide the examination of symptoms and function in this study.
Problem Statement

The incidence of end-stage liver disease is increasing, and the need for liver transplantation surgery is expected to be on the rise over the next two decades. There was some preliminary evidence to suggest that liver transplant recipients experience functional limitations, as well as pain, negative mood states, and fatigue in the first three months following discharge. However, available data were insufficient to describe OLT recipients’ trajectory of functional recovery or its relationship to the severity of the reported symptoms. Primary caregivers of OLT recipients may also experience significant fatigue and its related impact during this time, yet available data did not describe their fatigue sufficiently or prospectively. Moreover, the relationship between the function of OLT recipients and their primary caregivers’ level of fatigue has not been described. Lack of prospective evidence during the early recovery period precluded development of appropriately timed and focused postsurgical interventions for OLTs recipients and their primary caregivers. Therefore, the purpose of this study was to examine prospectively the relationships between: (a) pain, negative mood states, fatigue (level and impact), and function among OLT recipients prior to hospital discharge, and at 4, 8 and 12 weeks postdischarge; and (b) OLT recipients’ function and the fatigue (level and impact) of their primary caregivers.
CHAPTER 2: LITERATURE REVIEW

This chapter provides an overview of orthotopic liver transplantation (OLT) surgery and related postsurgical complications, and the conceptual framework which directed examination of outcomes for this study. Evidence pertaining to pain, negative mood states, fatigue and its related impact, and function among OLT recipients prior to hospital discharge and up to three months postdischarge was reviewed and summarized. This body of evidence included 32 quantitative studies that used retrospective (five studies), prospective cohort (21 studies), and cross-sectional (six studies) study designs. As well, 2 qualitative studies had used semi-structured interviews to examine the experience of OLT surgery. Evidence pertaining to fatigue and its related impact on OLT recipients’ primary caregivers was summarized and evaluated. This chapter concludes with a review of an adapted version of Wilson and Cleary’s (1995) model of patient outcomes as the conceptual framework that guided examination of variables in this study.

OLT Surgery

End-stage liver disease (ESLD), caused by acute or chronic liver failure, is an irreversible form of liver cirrhosis. An estimated 20% of patients with chronic hepatitis will develop liver cirrhosis (Alter et al., 1992; Seeff., 1997). A leading cause of ESLD is the hepatitis C virus (HCV), affecting 242,000 to 300,000 (0.8%) Canadians and 3% of the population worldwide. Other known predictors of ESLD include alcohol-induced liver cirrhosis, the hepatitis B virus (HBV), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis. Liver transplantation surgery, using liver grafts donated by live or deceased donors, is the only viable treatment for ESLD. In 2009, 405 liver transplants were performed in Canada (CIHI, 2010). Of these, 72% were due to ESLD from viral hepatitis and alcohol-induced liver cirrhosis (CIHI, 2010; Remis, 2007). By 2030, approximately 45% of Canadians with chronic
HCV will develop ESLD, thereby leading to an increased need for liver transplantation (Davis, Alter, El-Sareq, Polynard, & Jennings, 2010; Remis, 2007). OLT surgery involves (a) extraction of the diseased liver and inferior vena cava, (b) a brief anhepatic phase, and (c) implantation of a whole deceased donor liver graft as well as a donor inferior vena cava (Eghtesad, Kadry, & Fung, 2005; Vieira de Melo et al., 2011). The OLT surgical technique includes a bilateral, subcostal incision with an upper midline extension through the xiphoid process (Makowka et al., 1988). Recovery from surgery includes a 24 to 48-hour admission to an intensive care unit (ICU) for immunosuppressive therapy, sedation, and mechanical ventilation for most patients (Glanemann, Busch, Neuhaus, & Kaisers, 2008). Following ICU discharge, OLT recipients continue to recover on a general ward, gradually increasing their ability to perform everyday activities. The average length of hospital stay is approximately fourteen days (Smith et al., 2009). Outpatient follow-up typically involves weekly transplant clinic visits for the first month, biweekly visits for the next 2 months, then monthly visits for the next 5 months (A. Healy, personal communication, May 3, 2011).

Complications Following OLT Surgery

Complications from OLT surgery are common and may present in the peri-operative period or following hospital discharge. Although incidence rates vary, reported complications in the first 90 days included (a) biliary leakage and stenosis (2.3%-50%; Akamatsu, Sugawara, & Hashimoto, 2010; Mueller et al., 2004); (b) bleeding requiring re-operation (4%; Jung et al., 2012); (c) neuropathologies such as encephalopathy, headaches, cerebrovascular disorder, infection, peripheral nerve damage, immunosuppressant-induced toxicity (8-47%; Adams et al., 1987; Burkhalter, Starzl, & Van Thiel, 1994; Lewis & Howdle, 2003; Lopez et al., 1992; Martinez, Estol, & Faris, 1988; Pujol et al., 1994; Starzl et al., 1978; Stein, Lederman, Vogt,
Carey, & Broughan, 1992; Sterzi et al., 1994; Stracciari & Gaurino, 2001); (d) malnutrition resulting in parenteral feeding (13.9%), insulin-dependent diabetes mellitus, and severe physical limitations (9.1%; Shankar et al., 2011). Factors influencing incidence rates of postoperative complications include the OLT recipients’ pre-operative health, quality of the transplanted liver, and technical aspects of the surgical procedure (Keefe, 2001; Murray & Carithers, 2005; Rudow & Goldstein, 2008).

Hospital readmission following discharge from OLT surgery has been reported to range from 33%-46% (Pereira, Bhattacharya, Carithers, Reyes, & Perkins, 2012; Shankar et al., 2011). Significant physiological and sociodemographic predictors of hospital readmission between 30-90 days following surgery were reported in two retrospective studies (Pereira et al., 2012; Shankar et al., 2011). They included (a) HCV infection; (b) creatinine >1.9umol/L; (c) albumin < 3.6g/L; (d) blood transfusions >1200ml; (e) postsurgical complications such as arrhythmias, biliary or vascular complications, hemodynamic instability requiring prolonged ICU stay, gastrointestinal bleeding, and/or infections; and (f) high school level education or lower (Pereira et al., 2012; Shankar et al., 2011).

In addition to postoperative complications, there was some emerging evidence which suggested that OLT recipients also experienced a constellation of postoperative symptoms including pain, mood changes, fatigue and its related impact, and functional limitations during the first three months following OLT surgery (Bonsel et al., 1992; Bryan et al., 1998; Chiu at al., 2009; De Bona et al., 2000; DiMartini et al., 2011; Donovan et al., 1997; Elliott, Frith, Pairman, Jones, & Newton, 2011; Eshelman et al., 2010; Foroncewicz et al., 2011; Geeverghese et al., 1998; Guimaro et al., 2011; Jones, 2005; Ko et al., 2012; Lasker et al., 2011; Leyendecker et al., 1993; Milan et al., 2011; Moore et al., 1997; Moretti et al., 2002; Naden et al., 2011; Ordin et al.,
2011; Pelgur, Atak, & Rose, 2009; Perez-San Gregorio et al., 2005; Perez-San-Gregorio et al., 2010; Pieber et al., 2006; Ratcliffe et al., 2002; Rodrigue, Nelson, Reed, Hanto & Curry, 2010; Russell et al., 2008; Saab et al., 2008; Saab et al., 2011; Van den Berg-Emons et al., 2006; Wang et al., 2012; Younoussi et al., 2000). The following section provides a review of the available data pertaining to these postoperative symptoms and function during their early recovery period.

**Pain Within 3 Months Following OLT Surgery**

Orthotopic liver transplantation (OLT) recipients have reported pain in the early postoperative period (i.e., within three months following surgery) in sixteen studies, that included a total of 1076 participants (see Appendix A). Fourteen quantitative studies employed various study designs to examine pain in this time period (Bonsel et al., 1992; Donovan et al., 1997; Ko et al., 2012; Krasnoff et al., 2005; Milan et al., 2011; Moretti et al., 2002; Ordin et al., 2011; Perez-San Gregorio et al., 2010; Pieber et al., 2006; Ratcliffe et al., 2002; Russell et al., 2008; van den Berg Emons et al., 2006; Wang et al., 2011., Younoussi et al., 2000). As well, one retrospective study had documented pain in OLT recipients who presented to the emergency department within 30 days following discharge (Unterman et al., 2009). In two qualitative studies, participants had described postsurgical physical discomfort during the first six weeks postoperatively (Jones, 2005; Naden et al., 2011). These studies were reviewed by timing of outcome measurement, including pain in the first 72 hours postoperatively, and at 4, 6, 8 and 12 weeks following discharge. Study limitations were examined with a view to informing this study.

**Pain at 72 Hours Postoperatively**

Immediately following surgery, four studies reported mild to moderate pain intensity ratings among OLT recipients; study designs and measures varied (Donovan et al., 1997; Ko et al., 2012; Milan et al., 2011; Moretti et al., 2002). Donovan et al. (1997, N = 13) examined pain
prospectively every 6 hours for the first 3 days (72 hours) following surgery, and found mild daily average pain ratings of mean (M) 1.8(.3) – 2(.1)/5 on a Likert scale ranging from 0 to 4. Ko et al. (2012, N = 44) reviewed retrospectively clinical records of the first 3 postoperative days, and reported mild to moderate daily median pain ratings (Mdn 0 (0, 2) – 62(48, 72)) using the visual analogue scale (VAS) ranging from 0 to 100. Milan et al. (2011, N = 34), reviewed retrospectively clinical records every hour for the first 24 hours postoperatively, and reported mild to moderate median pain (Mdn 1-2/3) pain ratings at 24 hours on a Likert scale ranging from 0 to 3. Finally, Moretti et al. (2002, N = 10), also reviewed retrospectively clinical records at five time points (i.e., 6, 12, 24, 48, and 72 hrs postoperatively), and reported mild mean pain ratings ranging from 0.5-1.0 on a 4-point rating scale. Aside from measuring pain intensity, all studies examined cumulative analgesic dosing as a proxy for pain. With the exception of 17 OLT recipients who received an additional regional analgesia intervention (Milan et al., 2011), cumulative analgesic expressed as morphine-equivalent (mg) delivered through patient-controlled analgesia systems ranged from 60mg to 90mg over the first 72 hours postoperatively in the four studies. While two of the four studies concluded that pain was not a major issue for the majority OLT recipients, considerable methodological limitations precluded generalization of their results. For example, a key limitation in three of the four studies was the use of self-developed rating scales to measure pain intensity; the reliability and validity of neither of these measures were addressed (Donovan et al., 1997; Milan et al., 2011; Moretti et al., 2002). Secondly, it was unclear from these same studies whether reported pain ratings were obtained for patients at rest or upon movement. As well, worst pain ratings in the previous 24 hours were not reported in any of the studies. Pain is a multidimensional experience that can be described by pain location, severity, temporality, and impact (National Institutes of Health, 1986). Accurate
assessment and diagnosis of pain are necessary first steps for the provision of effective treatment. Moreover, best practice guidelines recommend that these dimensions of postoperative pain be addressed with the use of a comprehensive, valid, and reliable pain measure (Registered Nurses Association of Ontario, 2002, 2013).

**Pain Within 3 Months Following Discharge**

Eleven studies reported pain among OLT recipients up to 3 months postdischarge. These studies included a retrospective chart review (Unterman et al., 2009), and 10 prospective studies that had used three separate health-related quality of life (HRQL) measures (Bonsel et al., 1992; Krasnoff et al., 2005, Ordin et al., 2011, Perez-San Gregorio et al., 2010; Pieber et al., 2006; Ratcliffe et al., 2002; Russell et al., 2008; Van den Berg-Emons, et al., 2006; Wang et al., 2012; Younoussi et al., 2000).

Unterman et al. (2009, N = 118) reviewed retrospectively clinical records of OLT recipients who had presented to the emergency department within 30 days after discharge. Approximately one third (36%) reported abdominal pain and gastrointestinal discomfort as chief complaints; 16% had wound infections and abscesses that may have been painful as well.

Pain was reported up to three months postdischarge in the 10 prospective quantitative studies using various health-related quality of life measures. These included the bodily pain (BP) scale of the Medical Outcomes Survey Short Form (SF-36; Ware & Sherbourne, 1992), the pain dimension of the Nottingham Health Profile (Hunt & McEwan, 1980) or the EuroQol 5D (EQ-5D) pain/discomfort scale The SF-36 BP scale included two items that assessed pain magnitude and interference; respondents recalled each item over the previous 4 weeks from the time of survey (Ware & Sherbourne, 1992). The BP scale was scored on a scale of 0 to 100, with 100 representing the best possible health (Hopman et al., 2000). The Nottingham Health Profile pain
domain included eight items that assessed presence or absence of pain requiring, categorical yes/no responses; respondents indicated whether each item reflected their current status. This domain was scored on a scale of 0 to 100, with 100 representing the worst possible problem (Hunt & McEwan, 1980). The EuroQol 5D (EQ-5D) pain/discomfort scale comprised 3 items which defined 3 levels of severity from 1 (better quality of life) to 3 (worse quality of life imaginable) at the time of survey (EuroQol, 1990).

Eight prospective studies used the same SF-36 measure. Of these, two longitudinal studies reported mild range pain intensity scores $M_{BP} = 83.98$ and $81$ respectively (Perez-San Gregorino et al., 2010 and Pieber et al., 2006), whereas three other longitudinal studies found moderate range pain scores of $M_{BP} = 66$, $54$ and $58$ respectively (Krasnoff et al., 2005; Ratcliffe et al., 2002; Russell et al., 2008). As well, three cross-sectional studies reported mild range pain scores $M_{BP} 72.7(28.5)$, $M_{BP} 72.65(18.63)$ and $M_{BP} = 73$ respectively (Van den Berg-Emons et al., 2006; Wang et al. 2012; Younoussi et al., 2000). It is unclear from these eight studies whether pain intensity was assessed at rest or upon movement. Also, study end-points varied; at 3 months postoperatively, Perez-San Gregorio et al. (2010) used 2 separate measures of pain for the same sample, reporting contrasting results. While the SF-36 BP scale found mild range pain scores, the pain/discomfort scale of the Euroqol 5D HRQL measure found mild to moderate range pain scores for the same sample. At 1-2 months, Pieber et al. (2006), reported mild range pain scores, similar to the normative sample (Hopman et al., 2000).

Krasnoff et al. (2005, $N = 50$), collected their data in an out-patient transplant clinic, and Ratcliffe et al. (2002, $N = 455$) used a postal survey at 3 months postoperatively (response rate 37%), whereas Russell et al. (2008, $N = 104$) recruited a convenience sample at 1 and 3 months postoperatively and reported a combined mean aggregate score. Although Russell et al.
examined pain at 1 month, they did not report the result, thus providing no comparative data as to whether pain had improved or worsened by 3 months. In the cross-sectional studies, Younoussi et al. (2000, \( N = 22 \)) surveyed participants who were at 2 to 23 months postoperatively at the time of survey (\( Mdn \) 4 months), Wang et al. (2012, \( N = 60 \)) surveyed those at 2 months to up to five years post OLT surgery, while Van den Berg-Emons et al., (2006, \( N = 96 \)) recruited participants who were between 53 days and 15.4 years post-transplant at the time of survey. In contrast to studies that used the SF-36 HRQL measure, two additional longitudinal studies, used the a separate HRQL measure, namely the Nottingham Health Profile, found mild range pain scores of \( M \) pain = 9 (18) and 18.44 (16.2) respectively (Bonsel et al., 1992 & Ordin et al., 2011). At 3 months, Bonsel et al. (1992) found that restrictions on the mobility dimension correlated most with the presence of bone pain (\( r = .57 \)), on the pain dimension with the presence of bone pain (\( r = .61 \)) and backache (\( r = .67 \)). Ordin et al. (2011, \( N = 65 \)), surveyed their sample in the outpatient transplant clinic at 3 months, and found that those with more severe disease at the time of transplantation also reported more pain 3 months postoperatively. Overall, four of the nine studies suggested that pain was a problem at 3 months postdischarge (Krasnoff et al., 2005; Perez-San Gregorio et al., 2010; Ratcliffe et al., 2002; Russell et al., 2008), while five others concluded that pain was minimal during the first 3 postoperative months. Despite the multiple measurement occasions, drawing conclusions about the trends in pain intensity during the early recovery period was challenging, in part, due to lack of standard measures. Unmanaged postsurgical pain during this time could become a persistent problem (Kehlet & Jensen, 2006); therefore further examination is needed to establish pain patterns more clearly.

In summary, there was limited evidence describing pain in the early recovery period following OLT surgery. Study end points varied, ranging from 24 and 72 hours postoperatively
to 4, 6, 8 or 12 weeks postdischarge. There was also the problem of the use of heterogeneous measures and study designs that precluded clear comparison of study results, which made it difficult to make inferences about overall trends in pain during the early recovery period for OLT recipients. Four studies identified pain as a problem in the immediate postoperative recovery period, and reported mild to moderate pain. Ten studies examined pain up to three months postdischarge, and reported mild to moderate pain. Although these studies described pain as a problem, assessment was limited to pain intensity ratings only, and it was not clear whether pain was assessed with movement. As well, no study examined other characteristics of pain, such as location or interference, during the immediate postsurgical period and up to 3 months postdischarge. Finally, the available data are further limited in terms of generalizability due to small samples (Bonsel et al., 1992; Donovan et al., 1997; Moretti et al., 2002; Perez-San Gregorino et al., 2010, Pieber et al., 2006; Younoussi et al., 2000), low response rates (Ratcliffe et al., 2002), and insensitive measurement biases (Donovan et al., 1997; Milan et al., 2011Moretti et al., 2002).

Accordingly, this study addressed the existing limitations in the assessment of pain within 3 months following discharge from OLT surgery, which included a lack of valid and reliable measures, as well as lack of observation pain during the early postoperative recovery period. This study employed an established, multidimensional pain measure as well as used a repeated measures study design.

**Mood Within 3 Months Following OLT Surgery**

The available evidence suggests that negative mood may be another problematic symptom for OLT recipients. To date, 18 quantitative studies, including 1422 participants in total, have reported a number of negative moods (e.g., anxiety, depression, anger, and fear)
during hospitalization or up to three months postdischarge (Appendix B). Of these, two retrospective studies documented anxiety and depression in the immediate postoperative period and up to 59 days during hospitalization (Chiu et al., 2009; Perez-San Gregorio et al., 2005).

Fifteen prospective studies used various study designs and measures to examine these variables up to three months postdischarge (Bonsel et al., 1992; Di Martini et al., 2011; Eshelman et al., 2010; Guimaro et al., 2011; Lasker et al., 2011; Leyendecker et al., 1993; Moore et al., 1997; Perez-San Gregorio et al., 2005; Pieber et al., 2006; Ratcliffe et al., 2002; Riether et al., 1992; Rodrigue, Nelson, Reed, Hanto & Curry, 2010; Russell et al., 2008; Van den berg-Emons, 2006; Younoussi et al., 2000). The results and methodological limitations were reviewed with a view to informing the current study.

**Mood During Hospitalization**

Chiu et al. (2009, N = 30) retrospectively reviewed clinical records of a small sample of OLT recipients to examine the prevalence of mood disorders during hospitalization. All participants were hospitalized for more than two months due to postoperative complications. The *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994) was used to diagnose mood disorders based on data obtained from clinical records. The authors determined that 2 of 30 participants had anxiety, and another two had depression between 5 and 59 days postoperatively. Perez-San Gregorio et al. (2005, N = 48) retrospectively reviewed clinical records that included the Hospital Anxiety and Depression Scale (HADS) to compare anxiety and depression symptoms while OLT recipients were in the ICU and upon transfer to a non-ICU ward. This scale included 14 items that screened for current anxiety (HADS-A) and depression (HADS-D); each item was measured on a 4-point Likert scale. Mild levels of anxiety, $M_{HADS-A} = 7.08$ vs. $5.64 \ (p < .097)$ and depression $M_{HADS-D} =$
4.53 vs. 3.11 ($p = .005$) were evident across both settings respectively. However, a small sample in one study (Chiu et al., 2009) and unclear timing of outcome measurement of both studies challenged the generalizability of outcomes clearly for OLT recipients who are typically discharged within 2 weeks following surgery.

**Mood Within 3 Months Following Discharge**

Changes to mental health following discharge after OLT surgery may be attributable to certain immunosuppressant medications, as well as the demands of adjusting to a new lifestyle that include potential surgical complications, adherence to strict medication regimens and medical surveillance, as well as the universal threat of organ rejection (Bravata, Olkin, Barnato, Keeffe, & Owens, 1999; Heinrich & Marcangelo, 2009; Riveter, Smith, Lewinson, Cotsonis, & Epstein, 1992). Mood disorders and general mental health states were examined in sixteen quantitative studies; study designs and measures varied. These studies were reviewed by outcome, including depressive symptoms, anxiety, negative mood states, and general mental health, spanning the first three months postdischarge.

**Depressive symptoms.** Depressive symptoms were reported in seven studies (Bonsel et al., 1991, $N = 46$; Di Martini et al., 2011, $N = 167$; Guimaro et al., 2011, $N = 24$; Lasker et al., 2011, $N = 100$; Perez-San Gregorio et al., 2010, $N = 27$; Riether et al., $N = 61$; Russell et al., $N = 104$), that used various study designs and five different measures (Appendix B). These measures included the Centre for Epidemiologic Studies Depression (CES-D; Radloff, 1977), a 20-item measure which screened for depressive symptoms; participants recalled each item over the week preceding the administration of the survey (Lasker et al., 2011; Russell 2008); The HADS (Zigmond & Snaith, 1983), (Guimaro et al., 2011); the Beck Depression Inventory (BDI; Beck et al., 1961), a scale that includes 21 items; participants recalled the severity of item over the
previous two weeks (Di Martini et al. 2011; Guimaro et al., 2011; Riether et al., 1992); the European Quality of Life Depression (EQ-5D; EuroQol Group, 1990) anxiety/depression scale, a 3-item measure that the severity of anxiety or depression at the time of survey, (Perez-San Gregorino et al., 2010), and the Self-rating Depression Scale (SDS; Zung & Durham, 1965), a 20-item measure that required participants to recall each item over the previous several days (Bonsel et al., 1992).

Patterns of depressive symptoms during the first three months following OLT surgery were difficult to identify. Findings from five longitudinal studies suggested that OLT recipients had mild (Riether et al., 1992, Russell et al., 2008; $M_{\text{CES-D}} = 10(10)$ and $M_{\text{BDI}} = 8.3(7.2)$ respectively); moderate (Bonsel et al., 1992, Perez-San Gregorio et al., 2010; $M_{\text{SDS}} = 43$ and $M_{\text{anxiety/depression}} = 1.26$ respectively); or mild to severe (Di-Martini et al., 2011, $\text{BDI} = 0$ to 20) levels of depressive symptoms at 3 months. Russell et al. (2008, $N = 104$, 74% male) examined depression in a convenience sample at 1 and 3 months, reporting 25% to be at risk for mild depression $M_{\text{CES-D}} = 10(10)$; using a combined mean aggregate score. However, since only the mean aggregate CES-D score was provided, it is unclear whether depressive symptoms had worsened or improved by 3 months. DiMartini et al. (2011; $N = 167$) prospectively examined depression among individuals who had undergone OLT surgery due to alcohol-induced liver cirrhosis. At 3 months at least 19% had high BDI scores, suggestive of high levels of depressive symptoms. A cross-sectional study of females with primary biliary cirrhosis (Lasker et al., 2011, $N = 75$) concluded that about 40% were at risk for major depression ($M_{\text{CES-D}} = 14.9(11.1)$) however, only 3% ($n = 4$) were less than three months postoperatively (Lasker et al., 2011), and the data may not reflect the true prevalence of depressive symptoms in the early recovery period. In one retrospective study that used 2 separate measures, mild ($M_{\text{HADS-D}} = 4.83(3.24)$) or
moderate ($M_{BDI} = 12.27 (5.14)$) levels of depression were noted for the same sample (Guimaro et al., 2011). These authors concluded that depressive symptoms were observed more frequently from the BDI (50% of the sample) compared to the HADS-D (16.7%) measure, suggesting a possible insensitive measurement bias. Although symptom severity varied among the studies that examined depression during the early recovery period, findings suggested that depressive symptoms were evident in a large number of OLT recipients during the early recovery period. However, a decision on the timing of an intervention was not possible from these studies, because individual patterns of depressive symptoms during the early recovery period could not be discerned. Differences in the outcomes could have been influenced by sex, variability in measures (Bonsel et al., 1992; Guimaro et al., 2011; Lasker et al., 2011; Perez-San Gregorio et al., 2010; Russell et al., 2008), and/or the disease-specific characteristics that were reported in 2 studies study (Lasker et al., 2011; DiMartini et al., 2011). Because depressive symptoms may fluctuate during the early recovery period, individual variability in depressive symptoms was more suitably observed using a repeated-measures design. Repeated observations were necessary not only to describe the natural history of depressive symptoms more clearly, but also to identify appropriate timing of future interventions, if needed for depression.

**Anxiety.** Symptoms of anxiety and/or fear were also reported in six studies that used different study designs and measures (Bonsel et al., 1992; $N = 46$; Guimaro et al., 2011, $N = 24$; Lasker et al., 2011; $N = 75$; Perez-San Gregorio et al., 2010, $N = 27$; Riether et al., 1992, $N = 61$; Russell et al., 2008, $N = 104$). These measures included The State-Trait Anxiety Inventory (Spielberger 1983), which included 40 items, 20 each allocated to each of the Anxiety – S subscale measuring feelings of anxiety “at this moment” and Anxiety-T subscale assessing the frequency of feelings “in general” (Bonsel et al., 1992; Riether et al., 1992); the HADS anxiety
subscale (Zigmond & Snaith, 1983) of 7 items measured on a 4-point Likert scale, (Guimaro et al., 2011); the Beck Anxiety Inventory (Beck et al., 1988) of 21 items, each measured on a 4-point Likert scale and recalled over the past four weeks (Russell et al., 2008); The EuroQol anxiety/depression scale of 3 items, assessing the presence or absence of “none”, “moderate” or “severe” anxiety or depression each, at the time of survey (San-Perez Gregorio et al., 2010); and an investigator developed measure of 5 items that measured fear/anxiety, whose psychometric properties were not described in detail (Lasker et al., 2011).

Study findings did not identify clear trends in the severity of anxiety in the first three months following hospital discharge. At 3 months, mild levels of anxiety were evident in two longitudinal studies with small samples that used the State-Trait Anxiety Inventory (Bonsel et al., 1992, $M_{STAI} T = 34$; Riether et al., 1992, $M_{STAI} T = 35.7(13.2)$, $M_{STAI-S} = 35.6(10)$), while moderate levels of anxiety were evident in a third study with a larger sample (Russell et al., 2008, $M_{BAI} = 10(7)$) that used for the Beck Anxiety Inventory the same time period; the authors concluded that anxiety was a problem for 20% of their sample. An additional longitudinal study that used the EuroQOL 5-D HRQL measure concluded that mild to moderate levels of anxiety were evident in their sample at 3 months (Perez-San Gregorio et al., 2010, $M_{anxiety/depression} = 1.26$). In contrast, Guimaro et al. (2011) retrospectively reviewed clinical records OLT recipients who were within 3 months post OLT surgery, and found that anxiety was not a clinical problem for their sample ($M_{HADS-A} = 7.33(5.14)$). Finally Lasker et al (2011) used a self-developed measure of 5 items to assess fear and anxiety, but did not provide the results. While this measure was pretested in a sample of healthy volunteers ($\alpha = .88$), it was not validated in OLT recipients or other patients. The measure assessed only anxiety and fear related to the possibilities of organ rejection, infection, pain, or death, versus measurement of symptoms
of anxiety generally. OLT recipients also have anxiety related to their health, ability to return to their daily activities, and gainful employment (Jones, 2005; Rodrigue et al., 2011). Lasker et al. concluded that anxiety continued to be a clinical problem beyond the early recovery period, yet anxiety was not examined sufficiently during the early recovery period.

Severity of anxiety symptoms varied in the first three months following OLT surgery, and a decision on the timing of an intervention was not possible from the findings of these studies, because individual patterns of anxiety symptoms could not be discerned. While one study measured anxiety at 1 and 3 months postoperatively, a combined mean aggregate anxiety score was reported, precluding an understanding of whether anxiety had improved or worsened by 3 months (Russell et al., 2008). Two additional studies either did not identify the number of OLT recipients (Guimaro et al., 2011), or had few participants (Lasker et al., 2011; n = 4) within three months post OLT surgery. Additionally, differences in the outcomes of the symptomology of anxiety could have been influenced by sex, the different study designs and measures that were used (Bonsel et al., 1992; Guimaro et al., 2011; Lasker et al., 2011; Perez-San Gregorio et al., 2010; Riether et al., 1992; Russell et al., 2008), or lack of an established measure (Lasker et al., 2011). Therefore, the extent to which anxiety was a problem for OLT recipients during the early recovery period remained unclear. This study addressed the identified limitations by examining anxiety using an established measure. As well, because anxiety could fluctuate during the early recovery period, detection of individual patterns of anxiety was more suitably determined through the repeated-measures study design used in this study.

**Negative mood states.** Measures that examined more than one negative mood state were used in two studies i.e. in a longitudinal (Moore et al., 1997) and a cross-sectional (Rodrigue, Nelson, et al., 2010) design. Both used the Profile of Mood States Survey (POMS;
McNair, Lorr, & Droppleman, 1971) to assess the intensity of transient and fluctuating negative mood states. The POMS included 65 items that measured six distinct negative mood states, including anxiety, depression, and anger. Results differed between these studies. Moore et al. found that anxiety, depression, and anger were not a clinical problem during the early recovery period postdischarge, whereas Rodrigue, Nelson, et al. (2010) reported mild anxiety, depression, and anger during the same period.

In their longitudinal study, Moore et al. (1997, \(N = 41\)) compared negative mood states among OLT recipients (\(n = 23\)), liver disease patients (\(n = 10\)), and matched healthy controls (\(n = 10\)) in a clinic setting at 1 and 3 months. On both occasions, when compared to the liver disease and healthy control groups, OLT recipients reported significantly less anxiety, \(F(2, 41) = 8.33, p < .001\) versus \(F(2, 41) = 10.19, p < .001\). They also reported less depression, \(F(2, 41) = 4.52, p < .05\) versus \(F(2, 41) = 4.08, p < .05\). Finally, OLT recipients also had less anger, \(F(2, 41) = 5.64, p < .01\) versus \(F(2, 41) = 6.73, p < .01\). These results suggested that anxiety, depression, and anger were not clinical problems following OLT surgery. Although their study was designed to detect specifically within-subject trends in negative mood states, Moore et al. had not performed a power analysis to detect the effect size of the findings between the first and any subsequent data collection time point. Consequently, their findings may have been overestimated and required further validation.

Rodrigue, Nelson, et al. (2010, \(N = 95\)), used the POMS in a cross-sectional study to survey participants at less than three months to up to three years postdischarge. Unlike Moore et al. (1997), they found mild anxiety, depression, and anger in their sample. However, only 3% (\(n = 4\)) of the sample was at less than three months postdischarge. These data were insufficient to
describe negative mood states or yield statistically significant inferences about severity at less than three months postdischarge.

Instead of the POMS, Leyendecker et al. (1993, N = 45) used the Mehrdimensional Stimungsfragebogen (MSF; Hecheltjen & Mertesdorf, 1973) to examine negative mood states in their cross-sectional sample. This measure included 58 items that measured the intensity of negative moods. Participants were at 3 to 19 months (M 9 months) postdischarge at the time of survey. Moderate to severe anxiety and anger were found in 43% and 53% of participants respectively, and moderate depressive symptoms were found in 45%. Data pertaining to reliability and validity of the MSF were not provided, however, and the number of participants surveyed at 3 months was unclear. Hence, generalizations about the severity and prevalence of depression, anxiety, and anger at 3 months after surgery for OLT recipients, based on this particular sample, were not possible.

Leyendecker et al. (1993), Moore et al. (1997), and Rodrigue, Nelson, et al. (2010) all suggested that negative mood states fluctuate in terms of intensity following OLT surgery. However, methodological limitations pertaining to the use of cross-sectional study designs (Leyendecker et al., 1993; Rodrigue, Nelson et al., 2010) and the lack of power analysis (Moore et al., 1997) precluded a precise assessment of the intensity and trends in depression, anxiety, and anger in OLT recipients who were less than three months postdischarge. Negative mood states have been known to impact function negatively in the long term following solid organ transplantation surgery (Goetzmann et al., 2008), yet conclusions about their intensity and impact during the early recovery period following OLT surgery were not possible. Thus, further study was necessary to understand the extent to which negative moods were problematic for
OLT recipients during the early recovery period, so that a decision on timely and appropriate future interventions could be made.

**General mental health.** In addition to specific negative mood states that were reported for OLT recipients during the early postoperative recovery period, general mental health states were observed in nine studies (N = 4 cross-sectional, N = 5 longitudinal) that used the SF-36 health survey (Eshelman et al., 2010; Lasker et al., 2011; Perez-San Gregorio et al., 2010; Pieber et al., 2006; Ratcliffe et al., 2002; Russell et al., 2008; Van den Berg-Emons, 2006; Wang et al., 2012; Younoussi et al., 2000). Four studies examined overall mental health using the SF-36 mental component summary (MCS) score (Ware & Sherbourne, 1992). The other five studies also assessed specific attributes of mental health via the SF-36 scales for mental health (MH scale) and role-emotional (RE scale). The MH scale included five items that assessed psychological distress and well-being; the RE scale included three items which assessed role limitations due to emotional problems. Each scale was scored on a scale of 0 to 100, with 100 representing the best possible health; respondents recalled each item over the four weeks preceding the time of survey (Ware & Sherbourne, 1992). Canadian normative data for these scales were derived from a prospective cohort study involving 9,423 randomly selected men and women aged 25 years or more living in the community (M MCS = 51.7(9.1); M MH = 77.5(15.3); M RE = 84.0(31.7); Hopman et al., 2000).

In nine studies using the SF-36 mental health measure, overall mental health, reported as the MCS or MH scale was similar to (Eshelman et al., 2010; N = 65, M MCS = 48; Pieber et al., 2006 N = 15, M MH = 79; Perez-San Gregorio et al., 2010 N = 27 M MH = 74.4; Russell et al., 2008; Younoussi et al., 2000 N = 22; M MCS = 49) or lower than (Ratcliffe et al., 2002, N = 455, M MH = 69.83; Van den Berg-Emons et al., 2006, N = 96, M MH = 71.7(19.3); Wang et al.,
2012, N = 60, M MH = 72.87(19.32); Lasker et al., 2011, N = 75, M MCS = 46.2 (11.7)) the age-
and sex-standardized Canadian norms (Hopman et al., 2000). The MH and RE scale results of
three longitudinal studies suggested that OLT recipients had moderate limitations in role-related
activities due to their mental health at 1 and/or 3 months postoperatively (Pieber et al., 2006;
Ratcliffe et al., 2002; Russell et al., 2008) compared to the Canadian norms (Hopman et al.,
2000). Additionally, Lasker et al. (2011), in a cross-sectional sample, also showed that moderate
depressive symptoms, anxiety, and fear were correlated significantly with the MCS result, \( r (73) = -0.805, p = .00 \) and \( r (73) = 0.32, p = .006 \), respectively, suggesting that these moods impacted
OLT recipients’ mental health negatively up to 17 years postoperatively.

While five studies of these nine studies reported that the mental health of OLT recipients
was comparable to the normative sample (Hopman et al., 2000), generalizability of their findings
were limited due to small samples, an unknown number of participants in the early recovery
period, and a possible sex bias (Lasker et al., 2011; Pieber et al., 2006; Perez-San Gregorio et al.,
2010; Van Den Berg Emons et al., 2006 & Younoussi et al., 2000). On the whole, mental health
scores of OLT recipients at 3 months following surgery were lower compared to the age- and
sex-standardized Canadian norms in four of the nine studies (Lasker et al., 2011; Ratcliffe et al.,
2002; Russell et al., 2008; Van den Berg-Emons et al., 2006). The examination of negative mood
states using the SF-36 MH scale, however, was limited to depression and anxiety. Therefore,
studies that examined negative mood using the SF-36 measure may not describe sufficiently the
range and intensities of negative mood states that OLT recipients experience during the early
recovery period. OLT recipients had also identified fear and anger as problems during the early
recovery period following OLT surgery (Jones, 2005; Leyendecker et al., 1993). Findings
reported by Lasker et al., Leyendecker et al., Ratcliffe et al., and Russell et al. supported a future
more comprehensive examination of negative mood states to determine their range, severity and intensity during the early recovery period following OLT surgery. Such assessment was a necessary first step toward effective management.

In summary, a growing body of research demonstrated that mood can be negatively affected during the early postoperative recovery period following OLT surgery. However, generalizations that could be drawn from these data were limited by heterogeneity in study designs (longitudinal vs. cross-sectional vs. retrospective) and measures used. Study end points also varied, ranging from 5 days postoperatively to 4, 6, 8, 12 weeks and up to 17 years postdischarge. Anxiety and depression were identified as problems prior to discharge ($N = 2$ studies), or up to three months postdischarge ($N = 4$ studies); however trends of anxiety could not be determined. Two studies reported a range of negative mood states as problems up to three months postdischarge, and three other studies reported that OLT recipients had poor general mental health scores during this period. Rates of anxiety and depressive symptoms were higher postdischarge than during hospitalization. Despite these data, questions remain about the persistence, variety, and severity of negative mood states during the early postoperative recovery period.

Although most studies have focused on examining general mental health states or mood disorders such as anxiety or depression, the results of two studies that used the POMS to comprehensively measure negative mood states (Moore et al., 1997; Rodrigue, Nelson, et al., 2010) suggested that negative mood states may not be problematic following OLT surgery. However, data from these studies were limited due to small samples, and provided insufficient evidence to inform whether clinical management of these mood states was necessary. Because assessment of the severity and trends of negative mood states is a necessary first step toward
treatment, this study was needed to corroborate data from these studies. Generalizability of early recovery period outcomes of all mood-related studies was limited due to small samples (Chiu et al., 2009; Leyendecker et al., 1993; Moore et al., 1997; Pieber et al., 2006; Perez-San Gregorio et al., 2010; Rodrigue, Nelson, et al., 2010; Van den Berg-Emons et al., 2006; Younoussi et al., 2000), a low response rate (Ratcliffe et al., 2002), lack of a standard measure (Lasker et al., 2011), high losses to follow up (Bonsel et al., 1992; Riether et al., 1992), and a sex bias (Lasker et al., 2011). Given the identified limitations, this study further examined the severity and trends of negative mood states during the early recovery period so that a decision on timing of future interventions could be more suitably determined for the early postoperative recovery period.

**Fatigue and Fatigue Impact Within 3 Months Following OLT Surgery**

OLT recipients reported fatigue, its related impact, and/or reduced vitality up to three months following discharge in 10 studies with a total of 1021 participants (Lasker et al., 2011; Moore et al., 1997; Perez-San Gregorio et al., 2010; Pieber et al., 2006; Ratcliffe et al., 2002; Rodrigue, Nelson, et al., 2010; Russell et al., 2008; Van den Berg-Emons et al., 2006; Wang et al., 2012; Younoussi et al., 2000). These studies used either the same SF-36 vitality (VT) scale as proxy for fatigue, or a disease-specific measure to examine fatigue or its related impact (see Appendix C).

Vitality was reported in seven quantitative studies that used the same SF-36 VT scale (Pieber et al., 2006; Perez-San Gregorio et al., 2010; Ratcliffe et al., 2002; Russell et al., 2008; Van den Berg-Emons et al., 2006; Wang et al., 2012; Younoussi et al., 2000); disease-specific measures were additionally used in 2 of these studies. The Younoussi et al. study had used the fatigue dimension (FA) of the Chronic Liver Disease Questionnaire (CLDQ; Younoussi et al., 1999) while Van den Berg-Emons et al. (2006) had used the Fatigue Severity Scale (Krupp et al.,...
1989) and the Multidimensional Fatigue Inventory (MFI-20; Smet et al., 1995) to measure the intensity and nature of fatigue. Moderate range VT scores were reported in all seven studies, $M_{VT} = 43 – 66.54(18.30)$, suggesting low energy and high fatigue (Pieber et al., 2006; Perez-San Gregorio et al., 2010; Ratcliffe et al., 2002; Russell et al., 2008; Van den Berg-Emons et al., 2006; Wang et al., 2012; Younoussi et al., 2000). The SF-36 VT scale included four items that measured energy and fatigue (Ware & Sherbourne, 1992). This VT scale was scored on a scale of 0 to 100, with 100 representing highest levels of vitality (Hopman et al., 2000). Respondents recalled each item over the 4 weeks preceding the time of survey (Ware & Sherbourne, 1992). Four of these studies used a longitudinal design. Pieber et al. (2006, $N = 15$) and Perez-San Gregorio (2010; $N = 27$), examined vitality at 1-2 and 3 months postoperatively respectively, and did not describe their survey distribution method, whereas Ratcliffe et al. (2002, $N = 455$) used a postal survey at 3 months (response rate 37%). Russell et al. (2008, $N = 107$, 74% male) recruited a convenience sample and provided a combined mean aggregate VT score for 1 and 3 months. These studies did not describe trends of vitality sufficiently during the early postdischarge period, nor did they report a specific result for fatigue. It was unclear whether fatigue improved or worsened during this time. It was necessary, therefore, to validate these findings and further determine the trends of fatigue during the early recovery period using a disease-specific measure, and a prospective, repeated measures study design.

In a cross-sectional study, Younoussi et al. (2000, $N = 22$) used the CLDQ to survey a cross-sectional sample of participants at 2 to 23 months postdischarge ($Mdn$ 4 months). In addition to reduced vitality, these participants also reported moderate fatigue via the fatigue (FA) dimension of the CLDQ survey. This FA scale included 7 items that assessed fatigue severity (Younoussi et al., 1999). Items were scored on a scale of 1 to 7, with 7 representing the worst
possible fatigue (Younoussi et al., 1999). Respondents recalled each item over the 2 weeks preceding the time of survey (Younoussi et al., 1999). Wang et al. (2012) also found reduced vitality among their sample who were at 2 months to 5 years postoperatively at the time of survey. As well, Van den Berg-Emons et al. (2006) recruited participants who were between 52 days and 15.4 years post-OLT surgery, in an out-patient clinic. In addition to reduced vitality, fatigue was reported by 66% of the participants, and 44% of the sample experienced severe fatigue. Scores for physical fatigue and reduced activity were significantly higher than the scores of reduced motivation and mental fatigue. Fatigue severity was reported via the Fatigue Severity Scale. This is a 9-item measure; each item was scored on a scale of 0 to 7, with 7 representing worst possible fatigue (Krupp et al., 1989). The MFI-20 is a self-report measure of 20 items, divided into one general fatigue scale and four different “nature of fatigue” scales. Each scale consisted of 4 items with a 5-point response format. Subscale scores ranged from 4 to 20, with higher scores representing more fatigue (Smets et al., 1995). Despite differences in study designs and measures, all seven studies reported low range vitality scores (Pieber et al., 2006; Perez-San Gregorio et al., 2010; Ratcliffe et al., 2002; Russell et al., 2008; Van den Berg-Emons et al., 2006; Wang et al., 2012; Younoussi et al., 2000). In the majority of studies, however, the SF-36 VT scale measured fatigue and energy, but did not provide information specific to fatigue; therefore, specific characteristics of fatigue, including its severity and impact, could not be discerned from them. While Van den Berg-Emons et al. (2006) and Younoussi et al. (2000) had also used disease specific measures to understand the severity and nature of fatigue, the number of participants at 3 months or less in their respective studies was not specified, therefore limiting the generalizability of their findings to the early recovery period.
Three additional studies examined fatigue; each used a different self-report measure (Lasker et al., 2011; Moore et al., 1997; Rodrigue, Nelson, Reed, Hanto & Curry, 2010). In a longitudinal study, Moore et al. (1997, N = 41) used the POMS to compare fatigue among OLT recipients (n = 23), liver disease patients (n = 10), and matched healthy controls (n = 10) in a clinic setting at 1 and 3 months postdischarge. They reported fatigue via the POMS fatigue-inertia scale (McNair et al., 1971). This scale included eight items that measured fatigue severity; participants recalled each item over the preceding 24 hours. At 1 month, moderate fatigue was found in all three groups, and no between-group differences in fatigue severity were found, $F(2, 41) = 2.06, p > .05$. At 3 months, OLT recipients’ fatigue was reduced significantly compared to the liver disease and healthy control groups, $F(2, 41) = 10.36, p < .001$. Although Moore et al. found improvement in OLT recipients’ fatigue at 3 months, they had not performed a power analysis to detect the effect size of the findings between the first and any subsequent data collection time point. Consequently, their findings may have been overestimated and require further validation.

Two further studies used cross-sectional designs to examine fatigue and its related impact (Lasker et al., 2011; Rodrigue, Nelson et al., 2010). In both studies, OLT recipients reported moderate to high fatigue that affected their physical function negatively. Lasker et al. (N = 100) compared fatigue outcomes of three groups of females (a) waiting for OLT surgery (n = 25) (b) after OLT surgery from less than three months (n = 4) to (c) those over seventeen years postdischarge at the time of survey (n = 75). Fatigue was assessed with the Fatigue Impact Scale (FIS; Fisk et al., 1994). This scale included 40 items which assessed fatigue severity and related impact. Each item was scored on a scale of 0 to 4, with 4 representing an extreme problem. Respondents recalled the extent to which fatigue was problematic over the month preceding the
time of the survey. Moderate fatigue was found in 18% of OLT recipients, $M$ FIS = 46.4 (34.8) and was associated negatively with cognitive (concentration, memory, and organization of thoughts), physical (motivation, effort, stamina, and coordination), and psychosocial (emotions, workload, and coping) functioning. However, Lasker et al.’s cross-sectional design did not permit an understanding of individual changes in fatigue over time. Moreover, the impact of OLT surgery on fatigue during the early recovery period remains unclear.

In the final study, Rodrigue, Nelson, et al. (2010, $N = 95$) surveyed participants at less than three months ($n = 3$) to up to three years postdischarge. Fatigue was assessed via the Multidimensional Fatigue Inventory Symptom Short Form. This measure included 30 items with five subscales, including general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor (Stein, Martin, Hann, & Jacobsen, 1998). Each item was scored on a scale of 0 to 4, with 4 representing an extreme problem; participants recalled each item over the week preceding the time of the survey. Compared to Lasker et al. (2011), the majority (72%) of Rodrigue, Nelson et al.’s., (2010) sample had high fatigue severity; 65% experienced fatigue for 5 or more days per week. OLT recipients with severe fatigue had greater mood disturbance ($OR = 1.06, p = .04$, 95% CI [1.02, 1.10]), suggesting that fatigue had a negative impact on mood. Both Lasker et al. and Rodrigue, Nelson et al., (2010) identified fatigue and its related impact as major problems after OLT surgery. However, in each study, fewer than 5% of the sample was within the three month postdischarge period. Consequently, neither study had sufficient data to accurately assess fatigue or its related impact during the early recovery period postdischarge. As well, neither Lasker et al. nor Rodrigue, Nelson et al. addressed the possible confounding effects of common comorbidities within the first few months following transplantation (e.g., diabetes or primary
disease recurrence) on outcomes of fatigue. Recognizing these limitations, both studies’ authors recommended further longitudinal examination to observe fatigue.

In summary, 10 studies suggested that low sense of vitality, fatigue and its related impact were problems for OLT recipients at 4, 8, and 12 weeks postdischarge; however, data from these studies could not be compared due to heterogeneity in study methods or designs. Despite these differences, data from seven studies indicated moderate to high fatigue or reduced vitality as significant problems for a large number of participants postdischarge. Only one study had observed within-subject variation in fatigue up to three months postdischarge, suggesting that fatigue was no longer an issue at 3 months. Generalizability of outcomes to the early recovery period was limited due to small samples (Pieber et al., 2006; Perez-San Gregorio et al., 2010; Lasker et al., 2011; Moore et al., 1997; Rodrigue, Nelson et al., 2010; Wang et al., 2012; Younoussi et al., 2000) and a sex bias (Lasker et al., 2011). All of these limitations, pertaining to the assessment of fatigue and its related impact in the early recovery period postdischarge, were addressed in this study using a standard measure for greater precision.

**Function Within 3 Months Following OLT Surgery**

Function has been defined in a number of ways, including functional status, functional impairment, functional ability, physical function, physical health, functional capacity, functional performance, activities of daily living (ADLs), health status, and quality of life (Fawcett, Tulman, & Samarel, 1995; Richmond, McCorkle, Tulman, & Fawcett, 1997). In this study, *function* was defined as the ability of OLT recipients to perform activities according to the following dimensions of day-to-day activity: (a) physical (ADLs: bathing, grooming, feeding) and instrumental ADLs (IADLs: shopping, cooking, cleaning), (b) social (activities involving
interaction with the community and/or family); and (c) role (activities involving work or other daily responsibilities; Wilson & Cleary, 1995).

Postoperative function was examined primarily following hospital discharge, and was reported in 16 studies (Beyer et al., 1999, \( N = 38 \); Bonsel et al., 1992, \( N = 46 \); Eshelman et al., 2010, \( N = 65 \); Foroncewicz et al., 2011, \( N = 11 \); Geervarghese et al., 1998, \( N = 100 \); Krasnoff et al., 2005, \( N = 50 \); Lasker et al., 2011, \( N = 75 \); Leyendecker et al., 1993, \( N = 45 \); Perez-San Gregorio et al., 2010, \( N = 27 \); Pieber et al., 2006, \( N = 15 \); Ratcliffe et al., 2002, \( N = 455 \); Rodrigue, Nelson, et al., 2010, \( N = 94 \); Russell et al., 2008; Van den Berg-Emons et al., 2006, \( N = 96 \); Wang et al. 2012; \( N = 60 \); Younoussi et al., 2000, \( N = 22 \)), predominantly using self-report measures (Appendix D). Self-report measures included the SF-36 physical functioning (PF), role-physical (RP) and social functioning (SF) scales, or the physical component summary (PCS) measure (Eshelman et al., 2010; Lasker et al., 2011; Ratcliffe et al., 2002; Rodrigue et al., 2010; Russell et al., 2008; Younoussi et al., 2000), the CLDQ activity (AC) domain (Younoussi et al., 2000), The Nottingham Health Profile Mobility Scale (Bonsel et al., 1992), the Karnovsky Performance Status (Bonsel et al., 1992), the Dutch National Health Survey on Health Problems (Bonsel et al., 1992), the Borg Scale of self-exertion (Foroncewicz et al., 2011), the Physical Activity Scale for the Elderly (PASE; Krasnoff et al., 2005), and the Alltag Questionnaire (Leyendecker et al., 1993). Objective measures of function included the 6-minute walk test (Beyer et al., 1999; Foroncewicz et al., 2011), the Incremental Cycle Ergometer Protocol (Pieber et al., 2006), and the Step-Counter (Krasnoff et al., 2005).

**Function During Hospitalization:**

One study prospectively examined function using the 6 minute walk-test (6MWT) at 7 and 14 days postoperatively (Foroncewicz et al., 2011, \( N = 11 \)). At 7 days, OLT recipients
walked 326.7 meters, representing half of the walking distance compared to the normative sample (Casanova et al., 2011), and 421 meters at 14 days postoperatively, representing more than two-thirds of the distance achieved by the normative sample. On both measurement occasions, OLT recipients achieved shorter walking distances compared to individuals diagnosed as living with class II heart failure \( M = 562(30) \) meters (Lipkin, Scriven, Crake, & Poole-Wilson, 1986). The Borg Scale (Borg, G., 1982) was also used by Foroncewicz et al. to determine self-perception of exertion. Participants rated their self-perception of exertion between mild and moderate levels. Normative data for the 6MWT were derived from a recent international study of healthy adults between the ages of 40 and 80 years (Casanova et al., 2011, \( N = 444 \)).

Generalizability of findings from Foroncewicz et al. may be limited, however, due to the small sample that was examined.

**Function Within 3 Months Following Discharge:**

Findings from four studies suggested that OLT recipients had poor function one month after surgery (Eshelman et al., 2010; \( M_{PCS} = 33 \)), with some improvement at 1 to 3 months (Pieber et al., 2006; Ratcliffe et al., 2002; Russell et al., 2008; \( M_{PF} = 62.4, 52 \) and 50(27) respectively). However, at 3 months, OLT recipients still had difficulty walking, climbing stairs, and lifting or carrying groceries (Ratcliffe et al., 2002; \( M_{RP} = 24 \)). They also accomplished less than what they would have liked, and were obligated to reduce the amount of time spent on work or other activities because of health problems (Ratcliffe et al., 2002). Over a third (35%) of participants in one study also reported difficulty coping with ADL (Leyendecker et al., 1993), and almost half of the participants in another study reported that they were unable to carry out daily activities or were disabled (Geevarghese et al., 1998). In a separate study Krasnoff et al.,
(2005) found that OLT recipients reported less physical activities than sedentary individuals who were 10 years older (Washburn et al., 1993).

From the available data, function was examined using used cross-sectional study designs in almost one third of OLT recipients (Lasker et al., 2011; Leyendecker et al., 1993; Rodrigue et al., 2010; Van den Berg-Emons et al., 2006; Wang et al. 2012; Younoussi et al., 2000), making it difficult to determine or describe function in the early recovery period. Two cross-sectional studies noted that fewer than 5% of their study participants were surveyed within three months following discharge (Lasker et al., 2011; Rodrigue et al., 2010), and three others did not specify the number of participants who were surveyed at less than 3 months postoperatively (Leyendecker et al., 1993; Van den Berg-Emons et al., 2006; Wang et al., 2012; Younoussi et al., 2000). Moreover, one study’s sample comprised females only, making generalization across sexes difficult (Lasker et al., 2011). Findings also suggested that functional limitations lingered beyond the early postsurgical recovery period and that the recovery of function may be gradual and prolonged (Lasker et al. 2011; Leyendecker et al., 1993; Rodrigue et al. 2010). Moreover, measures used to assess function did not provide sufficient detail about the activities that OLT recipients were able to perform, or why function had decreased, leaving unanswered questions about physical and social activities. Poor physical functioning interfered considerably with OLT recipients’ social activities in three studies (Ratcliffe et al. 2002, $M$ SF = 64; Rodrigue, Nelson et al. 2010, $M$ SF = 44 – 49; Russell et al. 2008, $M$ SF = 63(30)) and one other study reported minimal impact (Younoussi et al. 2000; $M$ SF = 80).

Three studies reported function among OLT recipients using different objective measures, and all concluded that OLT recipients had poorer function compared to normative samples (Beyer et al., 1999; Krasnoff et al., 2005; Pieber et al., 2006). Beyer et al., (1999)
reported improvement in participants’ walking distance over a 6 minute period. At 3 months, OLT recipients were able to walk $M = 555(23)$ meters, representing an average increase of 59 meters compared to 1 month; yet at 3 months, their walking distance was considerably lower compared to healthy individuals $M = 683(8)$ meters, and slightly lower compared to individuals diagnosed as living with class II heart failure $M = 562(30)$ meters (Lipkin, Scriven, Crake, & Poole-Wilson, 1986). Krasnoff et al., (2005) used the step-counter method to determine the number of steps OLT recipients walked per day. At 2 months, OLT recipients walked significantly fewer steps per day ($M = 4550.1 (2910.2)$) compared to healthy samples ($M = 6559 (2956)$ steps/day; Turdor-Locke et al., 2002), and achieved similar scores compared to individuals with disabilities and chronic illness. Finally Pieber et al. (2006), used an incremental cycle ergometer protocol to determine exercise endurance of OLT recipients. At 1-2 months postoperatively, there was no difference in exercise performance compared to performance prior to OLT surgery, suggesting that OLT surgery did not result in significantly improved physical capacity. Similar to studies that used subjective measures of function, all three studies that used objective measures of function also concluded that OLT recipients were limited in their physical capacity, however OLT recipients’ ability to carry out usual daily activities could not be determined from these studies.

The majority of data pertaining to function was reported in studies that used different measures of health-related quality of life. Eshelman et al. (2010), Lasker et al. (2011), Perez-San Gregorio et al. (2010), Pieber et al. (2006), Ratcliffe et al. (2002), Russell et al. (2000), Rodrigue et al. (2010), Van den Berg-Emons et al. (2006), Wang et al. (2012) and Younoussi et al. (2000) all used the SF-36 to measure outcomes of physical, role and social functioning, showing significantly poor physical function during the early recovery period postdischarge. The PCS
measure and PF, RP and SF scales of the SF-36 that were used to assess the function of OLT recipients provided a broad assessment of physical, role and social functioning. Additionally, the PF only assessed a limited number of activities, which included: (a) vigorous activities such as participating in strenuous sports and lifting heavy objects, (b) moderate activities, such as: moving a table, vacuuming, bowling or playing golf as well as lifting or carrying groceries, and (c) more basic activities including: climbing one to several flights of stairs, bending, kneeling, stooping, walking one block to over a mile, and bathing and dressing. While limitations in vigorous or moderate activities can be expected following major abdominal surgery, surgery itself may further affect the functional status of OLT recipients, whose preoperative functional status is significantly poor (Eshelman et al. 2010; Russell et al. 2008; Younoussi et al. 2000) and whose ability to perform usual day-to-day activities during the early recovery period may be further limited. Thus, the trajectory of the recovery of postoperative function, and in particular the ability of OLT recipients to perform ADL and IADL during the early recovery period, could not have been sufficiently gleaned from the range of activities assessed via generic measures such as the SF-36. Further, the SF-36 physical functioning scales have been shown to be less sensitive to discrete changes in function in patient groups other than OLT recipients (Herzberg et al., 2010; Parry et al., 2012), and in individuals who have undergone major orthopedic surgical interventions (Busija et al., 2008). Additionally, four studies used measures that were limited in scope, and therefore did not provide a broader understanding of the ability of OLT recipients to engage in usual daily activities. Thus, this study examined the physical, role and social function of OLT recipients during the early recovery period in more detail by using a more comprehensive measure of function, and a repeated-measures design to determine trends of function during this period.
Relationships Between Pain, Mood, Fatigue, and Function

Although function during the early recovery period following OLT surgery may be influenced by pain, mood changes, or fatigue, these relationships were not sufficiently examined. No study was found that examined the impact of pain on function for these patients. Two cross-sectional studies explored the relationships of fatigue and function or fatigue and depression.

Lasker et al. (2011) found that fatigue explained 20% of the variance in physical function in their sample, $M$ PCS = 46.7 (11.18), $R^2 = .199$, $F (2, 73) = 24.12$, $p < .001$. The authors established a correlation between fatigue and physical functioning; females with moderate to severe fatigue experienced poor function. However, their statistical model included data from those living with ESLD as well as those who had undergone OLT surgery. Consequently, the specific impact of fatigue on function of OLT recipients remains unknown. Lasker et al. also found that fatigue and depression explained 24% of the variance in function for the entire sample, indicating that these symptoms impacted function negatively before and following OLT surgery, Adj $R^2 = .24$, $F (2, 92) = 5.9$, $p = .017$. However, the impact of fatigue and depression on function specifically following surgery was not reported. Additionally, colinearity was detected ($r = .72$), suggesting that although fatigue was a predictor of the PCS score, part of the fatigue score was influenced by depression. Between-group differences, such as presurgery severity of ESLD or postsurgery severity of organ rejection were not measured which may have confounded their results. Thus, the reported variance in function due to fatigue or depression following surgery could not be estimated reliably for OLT recipients. As well, Lasker et al. recommended examination of other variables that may mediate the recovery of postoperative function. This study used a repeated measures design to corroborate these findings.
Rodrigue, Nelson, et al., (2010) found that participants with high fatigue had significantly lower physical function \((t = 3.9, p < .001)\), more difficulty with role-related activities \((t = 4.2, p < .001)\), and greater limitations in social activities \((t = 3.4, p < .001)\), when compared to those with less fatigue. Fatigue interfered considerably with general activity, work, and enjoying life, but fatigue interfered less with self-care and relationships with others. These data suggested that high fatigue had a negative impact on function. However, only 5% \((n = 4)\) of participants were at less than three months postdischarge; these data were not sufficient to assess fatigue precisely or yield clinically significant inferences about fatigue impact on function for those less than three months postdischarge. Although Lasker et al. (2011) and Rodrigue, Nelson, et al. (2010) found associations between depression, fatigue, and function, inferences pertaining to causality were limited due to their cross-sectional study designs. Nonetheless, these symptoms were implicated as having a negative impact on the functional status of OLT recipients and merited further study.

In a cross-sectional study of living donor liver transplant (LDLT) recipients, Elliott & Firth et al. (2011; \(N = 103\), 64% male), examined the relationship between function and fatigue using separate measures, and showed that postoperative function was significantly lower in their sample than reported by other studies. Demographic and disease-related characteristics of this LDLT recipient sample were similar to those of OLT recipients. Participants were at less than two months to over thirteen years postdischarge \((Mdn 3\text{ years})\). Functional impairment was broad based. The majority of participants \((77\%)\) had difficulty with rudimentary activities such as reaching, gripping, climbing five stairs, eating, standing up from an armless straight chair, grooming, dressing, or arising. Function was measured using the Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire survey (Cella et al., 2007). This survey included 20 items that assessed activities such as personal care, ADLs, and
locomotor activities; respondents recalled each item over the week preceding the time of survey.

Fatigue impact was measured with the FIS (Fisk et al., 1994). Fatigue severity was associated independently with functional impairment (FIS Beta .727, $p < .0001$), indicating that higher levels of fatigue impacted function negatively. Elliott et al. argued that the LDLT recipients’ levels of function were comparable to those with advanced chronic liver disease and far from being normal following liver transplant surgery. As well, they proposed that function following liver transplant surgery may have been overstated in prior studies that had used primarily generic measures to assess broader outcomes of function (Aberg et al., 2009; Brownick & Saab, 2009; Desai et al., 2008; Santos et al., 2008; Van den Berg-Emons et al., 2006). Elliott et al. uncovered important data showing that functional limitations following liver transplant surgery may be more extensive than previously thought; thus they recommended further study of function following surgery. Their findings supported the use of a more comprehensive measure to understand more clearly the rudimentary levels of function during the early recovery period postsurgery.

In summary, although OLT recipients expected that receipt of a liver transplant would improve their ability to participate in activities (Holzner et al., 2001; Rodrigue et al., 2011) they consistently reported functional limitations during the early recovery period following OLT surgery. Although the early postoperative recovery period is a critical time in the restoration of optimal function, this period has largely been overlooked for OLT recipients. Possible complications following major abdominal surgery can be reduced when actions are taken that support a more rapid return to normal levels of function (Kehlet, H., & Dahl, J. 2003). These actions include the initial management of symptoms such as pain and fatigue, which are physiological responses to surgery and may contribute to limitations in function (Fearon et al.,
Sixteen quantitative studies described postoperative functional outcomes in the first three months postdischarge. Study end points varied at 4, 8, or 12 weeks; however, due to heterogeneity in measures and study designs it was difficult to compare the results to discern trends of physical, role and social function during the early recovery period. Results of the reviewed studies varied depending on study design and measures. Six studies used the SF-36 to describe function; OLT recipients consistently reported poor physical and social functioning and challenges with role-related activities. In contrast, two studies, each using a different measure, showed that OLT recipients engaged in ADLs with minimal difficulty. These conflicting outcomes may have been due in part to the use of measures with varying degrees of sensitivity to discrete changes in physical function, such as performance of basic day-to-day activities. Overall, the assessment of function postdischarge was limited largely to studies that used generic measures that examined a limited number of activities, and may not have sufficiently detected subtle changes in function.

Two studies also suggested that fatigue or depressive symptoms were correlated negatively with function; however, causal inferences were not possible because these data were derived from cross-sectional designs. Further, both studies had a limited number of participants at less than 3 months postdischarge, thereby limiting data that could be used to make clinically valuable inferences. Generalizability of findings to the early recovery period may be further restricted due to small samples (Foroncewicz et al., 2011; Jones et al., 2005; Perez-San Gregorio et al., 2010; Pieber et al., 2006; Lasker et al., 2011; Rodrigue, Nelson, et al., 2010; Younoussi et al., 2000), sex bias (Lasker et al., 2011), and a low response rate (Ratcliffe et al., 2002). OLT recipients’ postoperative functional status was researched in this longitudinal study that (a) used a more comprehensive measure of function; (b) reported more precisely trends in function during
the first three months after surgery; and (c) used a more robust design to understand the relationships of pain, negative moods, and fatigue (level and impact) on function.

In addition to the quantitative studies that were examined, two qualitative studies using semi-structured interviews were also reviewed (Appendix E). Jones (2005, \( N = 20 \)) conducted interviews with participants individually at 6 weeks in a clinic setting, the majority (75%) being male. Key themes arising from content analysis were pain and surgical discomfort, limitations in ADLs, and the need for greater assistance needed from family members to perform ADLs. Participants also expressed fear of organ rejection, depression, anxiety about the ability to afford medical expenses, and belief of being burdensome to their families due to limitations in physical activity. Naden et al., (2011, \( N = 15 \)), interviewed participants who had not been discharged since OLT surgery, and were between 18 and 43 days postoperatively. Major themes resulting from their Hermeneutic analysis suggested that pain intensity varied among participants, from little pain to significant pain. Participants experienced *comedowns* during rejection of the transplanted liver, which were associated with depressive low spirit. Participants also described inability to cope with their own feelings, especially if additional surgeries were necessary to manage postoperative transplant complications. These data support results from quantitative studies that have also described pain, negative mood states, and limitations in function as problems in the early recovery period postdischarge (Lasker et al., 2011; Moore et al., 1997; Ratcliffe et al., 2002; Rodrigue, Nelson et al., 2010; Russell et al., 2008; Younoussi et al., 2000).

**Primary Caregiver Fatigue and Fatigue Impact Within 3 Months Following OLT Surgery**

Caregivers to OLT recipients provide essential support following hospital discharge, assisting them with self-care, strict medication routines, and frequent medical follow-up (Bryan et al., 1998). In an exploratory cross-sectional pilot study, spouses or common-law partners
reported fatigue and vitality up to three months following OLT recipients’ discharge (Rodrigue, Nelson, Reed, Hanto & Curry (2010); Appendix F). Fatigue was measured using the POMS Short-Form (POMS-SF; Shacham, 1983) fatigue-inertia subscale; this subscale included five items that measured fatigue intensity. The authors also used the SF-36 V2 vitality (VT) scale as a proxy for fatigue (Ware, Snow, Kosinski, & Gandek, 1993). This scale included four items that examined fatigue and energy. The authors compared the fatigue and vitality of caregivers to individuals who were listed candidates for OLT surgery \((n = 49)\) to that of caregivers to OLT recipients \((n = 37)\). Both groups had similar demographic characteristics; the majority (>75%) of caregivers in each group were female.

The fatigue of caregivers to OLT surgery candidates was similar to the fatigue of caregivers to OLT recipients. Both groups reported moderate fatigue, \(M_{\text{fatigue-inertia}} = 9.9 (5.5)\) and \(8.05 (4.6)\) respectively (Rodrigue, Nelson, Reed, Hanto & Curry (2010). Following surgery, caregivers to OLT recipients had greater fatigue compared to the age- and sex-standardized normative sample the sample was a random selection of 432 adult men and women living in the community (Nyenhuis, Yamamoto, Luchetta, Terrien, & Paramentier, 1999; McNair, Lorr & Droppleman, 1981). Rodrigue, et al.’s findings suggested that fatigue continued to be a problem for caregivers during the recipients’ early recovery period postdischarge. Both groups of caregivers also had similar levels of vitality, \(M_{\text{VT}} = 49 (12)\) and \(M_{\text{VT}} = 50 (13)\) respectively, that were similar to the age- and sex-standardized normative sample, \(M_{\text{VT}} = 50 (10)\), (Ware, Kosinski & Dewey, 2000), indicating that they had minimal problems with fatigue and energy. However the fatigue-inertia subscale is a specific measure of fatigue, whereas the SF-36 V2 VT scale is a measure of fatigue and energy and does not provide a specific result for fatigue. Moreover, the fatigue and vitality results may have been influenced by the authors’ data
analysis methods. Rodrigue et al. made an \textit{a priori} decision not to adjust for multiple comparisons because their study was designed to identify clinically important variables that could be examined in a larger study. Consequently, their findings may have been overstated and require further validation.

In summary, fatigue was identified as a problem for caregivers of OLT recipients following hospital discharge, although the time period on average was 26 (21) months postdischarge (Rodrigue, Nelson, Reed, Hanto & Curry, 2010). This sample yielded no conclusions about earlier outcomes of fatigue, nor within-subject variation in fatigue, and only limited inferences could be made about trends in fatigue or its related impact. Generalizability of findings to the early recovery period was further restricted due to the small sample and the unknown number of caregivers during the early recovery period.

\textbf{Summary and Synthesis of Literature Review}

Improving survival rates and the increasing need for OLT surgery provided an impetus to better understand patient-reported outcomes following OLT surgery. A significant amount of research has described HRQL outcomes and other outcomes of surgery, including graft functioning and rejection, infections, and development of comorbid conditions. However, pain, negative mood states, and fatigue (level and impact) may also be problematic in the immediate postoperative period and/or the early recovery period postdischarge. Also, OLT recipients consistently have described limitations in physical functioning. Despite a growing body of literature describing these symptoms and function, significant methodological limitations in available studies precluded a comprehensive understanding of these symptoms and function, as well as the relationships of these symptoms and function in the immediate postoperative period and up to 3 months following discharge.
While pain, negative mood states, fatigue (level and impact) and limitations in functional status were documented for the early recovery period, there were corresponding gaps in research, including lack of clarity on pain intensity at rest and upon movement, trends in negative mood states and fatigue (level and impact), as well as ADLs and IADLs measures of function. Although pain was rated as mild to moderate in hospital and moderate following discharge, a clear assessment of pain severity and interference using standard measures was not found. Negative mood states were reported more frequently following discharge than during hospitalization; yet their trends and intensity were not examined to any degree during either time period using comprehensive standard measures. Fatigue was also described as a persistent problem following discharge that impacted function and mood negatively. Fatigue studies reported mainly on outcomes beyond the early recovery period, leaving a lack of understanding about fatigue in the early postoperative recovery period. Functional limitations reported by OLT recipients up to 3 months postdischarge were described largely using generic measures, or a limited range of specific measures. Neither of these measures examined performance of ADLs and IADLs comprehensively, and some generic measures may not have been sufficiently sensitive to detect discrete changes in function during the early recovery period. Consequently, questions persisted as to the precise levels of function during the early postdischarge period and needed to be addressed. Overall, clear gaps remained in the understanding of these symptoms, their severity, and their relationships to OLT recipients’ function during the early recovery period. Although limitations in function may have been attributable to other complications that were described following OLT surgery, it remained unknown whether pain, negative mood states, and fatigue also impeded the recovery of function during the early recovery period.
To better understand trends in pain, negative mood states, fatigue, and function during the early recovery period, and to determine the strength of the correlations of each of these symptoms with function, a prospective, repeated measures study design was needed. Examination of these relationships has direct implications for clinical practice. OLT recipients can be better prepared to manage pain, negative mood states, and fatigue and its related impact, and thus possibly decrease the burden of these symptoms on their function during the early postsurgical recovery period and possibly long-term adverse consequences. Before a decision on delivering an intervention could be made, however, a clearer assessment of these symptoms and their trends was necessary.

Further, postoperative functional outcomes of OLT recipients may also have an impact on the fatigue level of their primary caregivers. Primary caregivers provide essential support to OLT recipients during the early recovery period following discharge. Limited yet important evidence suggested that caregivers of OLT recipients experienced significant fatigue during this time. Limitations in OLT recipients’ function may necessitate increased support from their respective primary caregivers, which may explain caregivers’ reports of greater fatigue. This relationship between OLT recipients’ function and primary caregivers’ fatigue merited further exploration, because it has direct implications for clinical practice. Like OLT recipients, primary caregivers can also be better prepared for the postdischarge recovery phase by understanding the levels of the recipients’ function that can be expected following discharge.

In conclusion, this study was needed to address the identified limitations in the assessments of pain, negative mood states, fatigue, fatigue impact, and function; and to examine the relationships of these symptoms and function in OLT recipients during the immediate postoperative period and early recovery period postdischarge. To improve the validity of future
findings, this study used (a) a standardized and established measure to examine each symptom and function more precisely, and (b) a repeated-measures study design that examined the extent to which trends in symptoms influenced trends in function. This study aimed to extend the current understanding of the impact of pain, negative mood states, fatigue (level and impact) and function in OLT recipients, as well as their primary caregivers’ fatigue. Outcomes of this study can be used to guide a future intervention to help OLT recipients manage their symptoms and improve functional outcomes during the early recovery period.

A Conceptual Model of Patient Outcomes

The conceptual model that provided direction for this study was adapted from Wilson and Cleary’s (1995) conceptual model of patient outcomes. The primary research question examined individual interrelationships of pain, mood, fatigue, and fatigue impact on OLT recipient function. The secondary exploratory research question in this study examined the relationship between OLT recipients’ level of function and the fatigue and fatigue impact among their respective primary caregivers.

Overview of the Model of Patient Outcomes

The original model proposed by Wilson and Cleary (1995) conceptualized the relationships of clinical variables to overall HRQL, and intervening variables that mediate these relationships (Figure 1). This model integrated two paradigms of health, namely clinical and social science, and links biological factors to patient-reported HRQL. The clinical paradigm is primarily of interest to clinicians and scientists, focusing mainly on pathological processes, disease causation, and objective measurement of bodily function. The social science paradigm focuses on health perceptions of the patient, patient function, and patient interpretation of symptoms, which may or may not be measured physiologically. Measures of health in this model
are considered to exist on a continuum of five distinct levels. At the first level are the biological and physiological variables related to the function of cells (e.g., liver enzyme levels and organ systems). At the second level of the continuum are symptoms, conceptualized as a patient’s perception of an abnormal physical, emotional, or cognitive state. When symptoms are assessed, the focus shifts from cells and organs to the individual as a whole. The relationship between biological and physiological variables and symptoms is complex, and significant abnormalities in biological and physiological states may exist without the patient having any symptoms (Wilson & Cleary, 1995). The third level of the continuum is function. Measures of function assess an individual’s ability to perform particular defined tasks. The four domains of function that are commonly measured are physical function, role function, social function, and psychological function. At the fourth level of the continuum are general health perceptions, which include the individual’s subjective rating of physical and mental health. General health perceptions can be strong indicators of an individual’s use of health care services. At the final level of the continuum, overall HRQL is determined by an individual’s subjective assessment of self-satisfaction with life, within the contexts of a specific physiological state, symptom experience, function, and general health perception (Sprangers et al., 2010; Wilson & Cleary, 1995).
Wilson and Cleary (1995) also proposed that characteristics of the individual, such as preferences, values, personality, and motivation, impact various measures of health along the continuum. Characteristics of an individual’s environment, including psychological and social support, also affect certain measures of health along the continuum. In summary, the model of patient outcomes identifies five distinct levels of health measures along a continuum, postulating dominant causal relationships and inputs from an individual’s environment and personal characteristics. The model encourages a broader understanding of health outcomes.
An Adaptation of the Conceptual Model of Patient Outcomes

The conceptual model that provided direction for examination of variables in this study was adapted from Wilson and Cleary’s (1995) conceptual model of patient outcomes. This model was adapted successfully in studies examining symptoms and function in individuals with end-stage renal disease (Frank, Auslander, & Weissgarten, 2004; Kring, 2008) and those undergoing total knee arthroplasty (Wilson, 2011). As well, it was adapted to understand the impact of peer support following coronary artery bypass graft (Parry, 2009) and tested with individuals living with heart failure (Heo, Moser, Riegel, Hall, & Christman, 2004).

In this study, the model was adapted to conceptualize relationships of symptoms and function, as well as characteristics of an individual’s environment that are proposed to mediate these relationships (Figure 2). In the adapted model, caregivers were considered an integral part of the OLT recipient’s environment, and therefore were expected to provide essential physical, social, and psychological support to OLT recipients during the early recovery period following surgery. Therefore, it was anticipated that OLT recipients’ function could affect caregiver fatigue (level and impact). Biological and physiological variables, general health perceptions, overall HRQL, and characteristics of the individual were not examined in this study, and therefore were excluded from the adapted model.

**Symptoms.** This study examined, pain, mood, and fatigue (level and impact) during the first three months following OLT surgery. Pain is a subjective, multidimensional experience, and is often perceived as an indicator that something is wrong. OLT recipients reported pain in the first three months following surgery (Jones 2005; Ratcliffe et al., 2002; Russell et al., 2008; Saab et al., 2011), yet pain severity and related interference during this time were not described clearly. The Brief Pain Inventory Short Form (BPI-SF) severity scales measured pain severity in this study (Cleeland & Ryan, 1994). OLT recipients have previously reported negative mood states in the early postsurgical recovery period (Bryan et al., 1998; Pelgur et al., 2009; Rodrigue, Nelson, et al., 2010), which may be attributable to physical problems such as surgery and related
complications (Jones, 2005). The POMS-SF, a comprehensive measure of negative mood states (Shacham 1983), was used in this study. OLT recipients have also reported fatigue following OLT surgery. Fatigue has been identified as a persistent problem following OLT surgery and may be attributable to ESLD (Van den Berg-Emons et al., 2006). However, fatigue had not been measured in the early recovery period following the removal of the diseased liver and subsequent transplantation of a new liver. The POMS-SF fatigue-inertia scale and the Modified Fatigue Impact Scales (MFIS; Ritvo et al., 1994) were used to examine fatigue comprehensively in this study.

**Function.** Wilson and Cleary (1995) referred to function as an individual’s ability to perform certain activities, and posited that symptom status is an important determinant of function. In this study, function was defined as (a) physical (ADLs) and instrumental (IADLs), (b) social (activities involving interaction within the community and/or family), and (c) role (activities involving work or other daily responsibilities). Function was measured using the Human Activity Profile (HAP; Daughton et al., 1982). The HAP was used to measure function across all domains, including ADLs, IADLs, social, and role-related activities.

**Characteristics of the Environment.** Characteristics of one’s environment, including social and psychological supports, affect function (Wilson & Cleary, 1995). In this study, the caregiver was considered to be a source of social and psychological support, and thus part of the OLT recipient’s environment. OLT recipients rely, routinely, on their caregivers for support following surgery (Jones, 2005; Rodrigue, Nelson, et al., 2010). Following OLT surgery, caregivers also report increased caregiving demands, including emotional and instrumental caregiving tasks (e.g., rendering emotional support, accompanying the OLT recipient to medical appointments, attending to dietary requirements, and assuming extra roles and duties at home
(Cohen et al., 2007; Rodrigue, Nelson, et al., 2010). Based upon the suppositions of the Wilson and Cleary Model, and the available evidence, the adaptation of the model for this study postulates that OLT recipients’ function could impact fatigue of their respective primary caregivers. Caregiver fatigue was measured using the POMS-SF fatigue-inertia scale (Shacham 1983), and caregiver fatigue impact was measured using the MFIS (Ritvo et al., 1994).

In summary, an adaptation of the conceptual model of patient outcomes (Wilson & Cleary 1995) was used to guide examination of the interrelationships of the following variables in this study: pain, mood, fatigue (level and impact), and function in OLT recipients. As well, the relationship between OLT recipients’ function and the fatigue and related impact in their respective primary caregivers were examined.
CHAPTER 3: METHODOLOGY

Purpose

The primary purpose of this study was to examine the interrelationships of pain, mood, fatigue and fatigue impact, and the function of OLT recipients during the early recovery period following surgery. The secondary purpose was to determine whether there was a relationship between the fatigue, and fatigue impact of caregivers, and the function of OLT recipients within the same time period. This chapter reviews the research questions, a definition of terms, research design, sample and setting and the methods including the recruitment and the data collection procedures that were employed.

Research Questions

Primary Question

What is the impact of the orthotopic liver transplantation recipients’ pain, mood, fatigue (level and impact) on their function during the early postoperative recovery period?

Secondary Question

What is the impact of the orthotopic liver transplantation recipients’ function on their caregivers’ fatigue (level and impact) during the early postoperative recovery period?

Definition of Terms

Orthotopic liver transplantation (OLT) recipient was defined as an individual who had undergone liver transplantation surgery, and receiving a whole liver from a deceased donor (Eghtesad, Kadry, & Fung, 2005; Vieira de Melo et al., 2011).

Baseline was defined as the initial data collection point for the study, after discharge from the acute pain service (APS) while OLT recipients remained in hospital following surgery. Discharge from the APS typically occurred typically on the 4th or 5th postoperative day. Baseline
demographic data for the primary caregiver of OLT recipient were collected at this time, for those caregivers who were present at the time of recruitment.

*Early recovery period* was defined as the time from baseline (i.e., 4th or 5th day after surgery) during hospitalization, and then 4, 8, and 12 weeks following discharge. For the purposes of this study, this definition was applied to the OLT recipients and their respective primary caregivers.

*Primary caregiver* was defined as the individual who the OLT recipient identified as his or her most responsible care provider during the early recovery period. This was typically a spouse or close relative of the recipient, and was the individual who provided the most daily support required by the OLT recipient during the early recovery period (Rodrigue et al., 2010). Levels of support and care giving were not predefined as these were determined independently by each OLT recipient.

*Function* was defined as the OLT recipients’ ability to perform physical, social, and role-related activities (Wilson and Cleary, 1995). The Human Activity Profile Adjusted Activity Score (HAP-AAS) (Daughton, Fix, Kass, Bell & Patil , 1982) was used to measure the OLT recipients’ level of function.

*Pain* was defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (International Association for the Study of Pain, 2012; Merskey & Bodguk, 1994). The Brief Pain Inventory Short-Form (BPI-SF; Cleeland, 1991) numeric rating scales were used to measure the participants’ self-reports of pain at rest and upon movement. The BPI Interference subscale was used to measure pain-related interference.
Negative mood was defined as transient or persistent psychological distress experienced by participants and was measured using the POMS-SF developed by Shacham (1983).

Fatigue was defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities (Ritvo et al., 1997). The presence of fatigue was measured using the POMS-SF fatigue-inertia scale (Shacham, 1983). The impact of fatigue was measured using the Modified Fatigue Impact Scale (MFIS), which measured the physical, cognitive and psychosocial dimensions of fatigue (Ritvo, et al., 1997).

**Research Design**

A prospective, observational-correlational study using a repeated measures design was used. Outcome measures were obtained at baseline following surgery, and then at 4, 8, and 12 weeks following hospital discharge.

**Sample and Setting**

The target group included patients who underwent OLT surgery, and willing respective primary caregivers. The setting was a quaternary care, university-affiliated health science centre in South-Western Ontario and the largest centre for solid organ transplantation in Canada.

**Eligibility Criteria**

OLT recipients were included if they:

- had undergone OLT surgery, and were in hospital in stable medical condition;
- were 18 years and over;
- were able to speak, read and understand English;
- were able to provide informed consent;
- were scheduled for follow up at the outpatient transplant clinic at the study site; and
had ready access to a telephone for follow up data collection. OLT recipients were excluded if they had undergone previous organ transplantation.

Primary caregivers were included if they:

- were 18 years and over;
- were able to speak, read, and understand English;
- were identified by the OLT recipient as their respective primary caregiver; and
- had ready access to a telephone for follow up data collection.

**Methods**

**Participant Recruitment**

All patients awaiting OLT surgery were enrolled on the Organ Transplant Tracking Record (OTTR), database managed by the liver transplant team at the research site. While enrolled on the OTTR, patients were allocated pagers by the liver transplant team. Upon liver graft availability, a suitable patient was selected from the OTTR, contacted through their allocated pager, and given further instructions for immediate hospital admission in preparation for OLT surgery. Due to the unpredictable notification and timing of OLT surgery for successful candidates, formal participant enrolment took place once OLT recipients were in stable medical condition, postoperatively. The primary investigator (PI) was included in a group electronic mail notification that was disseminated immediately upon organ availability for a matched surgical candidate, and maintained a log of all patients who underwent OLT surgery.

Participants were recruited in three ways. First, a study brochure and introduction letter was mailed to those listed for OLT surgery (Appendix G) and their respective primary caregivers (Appendix H) at the time of study commencement, and to all those newly listed thereafter. Both information brochures described the purpose of the study, and possible follow up by the PI, for
consenting patients who undergo OLT surgery. Second, approved study flyers with the PI’s contact information, and study brochures were made available in the liver transplant clinic, to create awareness among patients who were listed for liver transplantation surgery, as well as their caregivers. Third, members of the APS, who care for all liver transplant patients postoperatively informed the PI of patients who were interested in further details of the study at the time that the APS transitioned the OLT recipient’s care to the attending team. These recruitment procedures prior to OLT surgery have been demonstrated to work well in previous longitudinal studies (Eshelman et al., 2010; Moore et al., 1997; Russell et al., 2008).

In this setting, OLT recipients’ postsurgical pain was managed by a specialized APS comprising two nurse practitioners (NP) and anesthesiologists. All members of this team were informed of this study and were supportive of it. The APS team as well as inpatient transplant unit nurses, were updated about the study regularly and were given a regular supply of study information brochures. Following OLT surgery, the APS NPs who were primarily responsible for the provision postoperative pain management plans for all OLT recipients, informed the PI of all patients who had undergone OLT surgery.

Upon discharge from the APS, the primary bedside nurse asked OLT recipients - those informed of the study preoperatively, and those not approached preoperatively due to illness, but now stable - if they were willing hear about participation in the study. The Confusion Assessment Method (CAM) (Inouye, et al., 1990) was used by the PI to establish the absence of cognitive impairment and ability to provide informed consent. If OLT recipients agreed to receive further information, they were given an oral and written explanation of the study by the PI. A written explanation was also given to the caregiver of the OLT recipient who was present at the time of recruitment, and all questions were discussed. Once all questions were answered
satisfactorily, and consent form were given to the OLT recipients (Appendix I) and their primary caregivers (Appendix J). In instances where the primary caregiver was not present, the PI contacted him or her, with the patient’s permission, via telephone to explain the study, and coordinated a mutually agreeable time to further discuss the study and obtain consent from those willing to participate. The PI confirmed eligibility of all those willing to participate by reviewing the inclusion and exclusion criteria with them carefully prior to obtaining informed consent. Entry to the study occurred if both OLT recipients and their willing primary caregivers: (a) expressed that they understood the study requirements and their rights, (b) were willing to participate, and (c) gave informed consent.

Data Collection

Baseline data collection. Following baseline study enrolment, demographic and outcome measures were collected, on average, on the 5th postoperative day following surgery. Demographic data for the primary caregivers were collected in person if they were present, or by telephone at a time convenient for them.

Follow-up data collection. Similar prior studies have achieved better response rates when study instruments were administered to OLT recipients in person. Telephone data collection was the second preferred method of administering study instruments to maximize opportunities for data collection (Moore et al. 1997; Pelgur et al. 2009; Saab et al. 2008). In order to minimize losses to follow-up, data were collected by the PI at the follow-up transplant clinic visits occurring at the 4th, 8th and 12th weeks following hospital discharge. The rationale for this time frame was based on current knowledge about the recovery process following hospital discharge; these time points were important in the clinical course of follow up surgical care which includes close monitoring of organ rejection and adherence to immunosuppression
medication regiments (A. Healy, personal communication, May 3, 2011). Also, most OLT recipients had recovered from surgery and were be able to complete the measures and the scheduled monthly clinic visits facilitated data collection in person. During the OLT recipients’ hospital stay, the PI was in continual contact with the liver transplant team to determine the participant’s discharge date and first scheduled out-patient appointment. The PI was also granted access to the appointment schedule for OLT recipients on the OTTR database. On the 4th, 8th and 12th week follow up appointments at the clinic, participants were given the study measures to be completed either during or following their visit as time and circumstances allowed. Data were collected (a) in person during the clinic visitation, or (b) via mailed study packages for those who did not want to complete their study packages in the clinic or (c) via telephone or mailed study packages if they were unable to attend their scheduled clinic visit or if their clinic appointment did not coincide with the data collection follow up time point. The average time for completion of data collection packages was 20 minutes in person or by telephone. Concomitantly, data from the primary caregiver were collected at the 4th, 8th and 12th weeks during scheduled clinic appointments. Telephone administration of data collection packages was completed for primary caregivers who did not attend the clinic appointment, or those who did not want the package mailed. The average time for completion of all caregiver measures was less than 7 minutes.

To minimize attrition at each postdischarge data collection point, the PI (a) reviewed the OTTR appointment schedule to confirm OLT recipient appointments 1 week and 48 hours prior to the scheduled appointment, (b) sent out mailed reminders to the OLT recipient and his or her primary caregiver of the subsequent data collection 2 weeks prior to their clinic visit and the expected time required to complete the measures, and (c) followed up with OLT recipients via
telephone for data collection if the appointment is rescheduled or cancelled. Patient flow through the study is illustrated in Figure 3.

**Table 1**

<table>
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<tr>
<th>Timing</th>
<th>Pre-OLT Surgery</th>
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<tr>
<td>OLT Surgery</td>
<td>Study brochures mailed to OLT recipient and primary caregiver</td>
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<td></td>
<td>Study brochures and flyer made available in pre-surgery clinic</td>
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**Post-OLT Surgery**

- OLT recipient approached by floor RN or APS NP
- Eligibility checked
- Written consent obtained
- Baseline data collected for OLT recipient (T0)
- Demographic data collected for primary caregiver
- Ineligible
- Refusal to participate

**Postdischarge Data Collection**

- Follow-up data collected at week 4 (T1), 8 (T2) and 12 (T3) for OLT recipient
- Data collection for primary caregiver at week 4 (T0), 8 (T1) and 12 (T2)

*Figure 3.* Schema of OLT recipient and primary caregiver flow through study.

**Instrumentation**

**Summary of measures.** Table 1 summarizes the measures that were used according to timing and outcome measure for OLT recipients and their primary caregivers:
Table 1

<table>
<thead>
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<th>Time, outcome variables and measures</th>
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<tbody>
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<td><strong>Time</strong></td>
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<td>Week 4, 8, and 12 following discharge</td>
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<tr>
<td>Caregivers: Fatigue</td>
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<td>Fatigue impact</td>
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</table>

**Baseline demographic information.** Baseline sociodemographic and medical data were collected using a general demographic questionnaire (GDQ) developed for the study (see Appendix K). In addition to the medical history, the GDQ asked OLT recipients to indicate their (a) age, (b) sex, (c) highest level of formal education, (d) marital status, (e) employment status, and (f) relationship to their primary caregiver. The GDQ measure for primary caregivers asked participants to indicate their (a) age, (b) sex, (c) highest level of formal education, (d) marital status, (e) employment status, and (f) relationship to their primary caregiver (see Appendix L).

**Outcome measures:** measures for function, pain, mood, fatigue (level and impact) are outlined below:

**Function.** Function was measured using the HAP (Daughton et al., 1982). The HAP (Appendix M) is a 94-item instrument that measures self-reported energy expenditure or physical
fitness and has been used widely among healthy and clinically ill patient populations (Daughton & Fix, 1982). The items are listed in ascending order according to energy requirements, such as getting out of bed to running 3 miles. Each activity is based on estimated metabolic equivalents (METs), with each successive question representing a slightly higher MET level. For each item on the scale, respondents were able to report their level of function by selecting one of three following choices: (a) whether they are still doing this activity, (b) have stopped doing this activity, or (c) never did this activity. Two scores could be determined: the maximum activity score (MAS) and the adjusted activity score (AAS). The MAS is the highest item number the respondent indicates he or she is still doing and represents the highest energy-requiring activity that the respondent is still performing. The AAS is the MAS minus the total number of activities below the MAS that the respondent has indicated that he or she has stopped doing. Potential scores for the AAS range from 0 to 94, with higher scores indicating higher levels of activity. The AAS was considered to be a measure of the respondent’s average daily activity and a more stable estimate of the OLT recipients’ daily activities and was used to represent their function (Daughton et al., 1982; Davidson & de Morton, 2007). The AAS can be further classified physical activity of each participant as (a) impaired (<53), (b) moderately active (53–74), or (c) active (>74) (Daughton et al., 1982).

Construct validity and utility for the HAP have been established across several patient groups, including those with chronic illnesses such as chronic obstructive pulmonary disease (COPD; Fix & Daughton, 1988; Neild, Hoo, Roper, Santiago, & Dracup, 2005), osteoarthritis and rheumatoid arthritis (Bennell et al., 2004; Bilek, Venema, Camp, Lyden, & Meza, 2005; Williams, Brand, Hill, Hunt, & Moran, 2010), end stage kidney disease and kidney transplantation (Daughton & Fix, 1988; Gallagher-Lepak, 1991; Johansen et al., 2001), and
allogeneic hematopoietic stem cell transplantation (Herzberg et al., 2010). The HAP has
demonstrated increased sensitivity to changes in activity level compared to those detected
through the SF-36 (Herzberg et al., 2010; Parry et al., 2012). Test-retest reliability estimates
were reported between.76 and.97 for the MAS and between.79 and.97 for the AAS (Davidson &
de Morton, 2007). Floor and ceiling effects are minimized due to the wide range of activities.
The HAP scores showed strong correlations with other instruments measuring physical function,
including the SF-36 (Baas, Fontana, & Bhat, 1997), the Minnesota Living with Heart Failure
Questionnaire (Baas et al., 1997) and the Sickness Impact Profile (Farrell, Gibson, & Helme,
1996), demonstrating evidence of strong convergent and discriminant validity (Davidson, 2007).
Construct validity for the HAP in OLT recipients can be generalized from that established in
other transplantation groups.

**Pain: BPI-SF.** Pain was measured using the BPI-SF (Cleeland & Ryan, 1994; Appendix
N). The BPI-SF is a short version of the original BPI and is a self-administered, well established
multidimensional pain measure designed to measure pain severity and impairment caused by
pain (Cleeland & Syrjala, 1992). The BPI-SF includes four ratings of pain severity (each were
measured at rest and upon movement), and seven items that measure the interference of pain.
Severity was recorded on 11-point numeric rating scales (NRS) ranging from 0 to 10, with higher
scores representing greater severity. The interference subscale measured the extent to which pain
interfered with everyday functions related to mood, walking, general activity, work, relations
with others and sleep. Each of these 7 items was scored from 0 to 10, for a total possible BPI
score of 0 to 60. The BPI-Interference was scored as a mean of the seven items. This mean was
used if more than 50% or four out of the seven items have been completed by the respondent
(Cleeland, 2009). The BPI-SF also contained supplemental items which enabled respondents to
indicate current treatments or medications they are receiving to treat their pain, the percentage of pain relief obtained in the past 24 hours from the treatments or medications, and the anatomical location of their pain on a body diagram.

The original BPI demonstrated strong construct validity and utility across divergent surgical groups including surgical oncology (Tittle, McMillan, & Hagan, 2003), orthopedic (Kapstad, Rokne, & Stavern, 2010; Watt-Watson, Chung, Chan, & McGillion, 2004; Wilson, 2011), coronary artery bypass graft (Gjeilo, Stenseth, Wahba, Lydersen, & Klepstad, 2007; Mendoza et al., 2004; Parry et al., 2010), thoracic (Ochroch et al., 2005; Ochroch, Gottschalk, Troxel, & Farrar, 2006), and major abdominal (Dicle, Karayurt, & Dirimese, 2009; Lin & Wang, 2005; Zalon, 2004) surgeries. Internal consistency reliability estimates for the overall BPI-SF have been reported between .77 and .87 (McDonald, Thomas, Livingston, & Severson, 2005; Zalon, 1999). The BPI has been used in the immediate postoperative period (Zalon, 1999) and up to 6 months following surgery (Mendoza et al., 2004; Watt-Watson et al., 2004). Construct validity of the BPI in OLT recipients was generalized from that established in surgical populations, particularly major abdominal surgeries.

**Negative mood states: POMS-SF.** Mood disturbance measured using the POMS-SF (Appendix O). The POMS-SF (Shacham, 1983) is a self-administered 30-item questionnaire with established use across a variety of healthy and ill patient groups (McNair et al., 1971; Shacham, 1983). It assesses transient, fluctuating feelings, and enduring affect states. The 6 original scales of the Profile of Mood States (POMS) instrument (McNair et al., 1971), namely anxiety-tension, depression-dejection, anger-hostility, confusion-bewilderment, vigour-activity and fatigue-inertia are retained in the POMS-SF. Respondents documented the degree to which each adjective applied to them on a 5-point Likert scale from 0 to 4, where 0 would indicate “not at all” and 4
would indicate “extremely”. Separate scores for each mood state were calculated by summing responses to each item in each of the 6 scales. A Total Profile of Mood States (POMS) score was calculated by summing the values of 4 of these six mood subscales; tension-anxiety, depression-dejection, confusion-bewilderment, anger-hostility; the fatigue-inertia subscale was excluded from the total POMS-score.

The POMS has been used to measure mood disturbance across divergent surgical groups, including liver donors (Ishizaki, Kaibori, Matsui, & Kwon, 2012; Shibata, Shimazaki, Sano, Kawasaki, & Arai, 2009) cardiac surgery patients (Elliott et al., 2010; Hedges & Redeker, 2008; Utriyaprasit & Moore, 2005), a small sample of OLT patients (Moore et al., 1997), as well as in patients with HCV (Moore et al., 1997; Singh, Gayowski, Wagener, & Marino, 1999; Von Wagner et al., 2006). Reported internal consistency and reliability estimates for the original POMS range from .63 to .96. Internal consistency reliability estimates for the POMS-SF subscales have been reported between .62 and .94, including in patients who had undergone bone marrow and kidney transplantations (Curran, Andrykowski, & Studts, 1995) and breast cancer patients receiving chemotherapy (DiLorenzo, Bovbjerg, Montgomery, Valdimarsdottir, & Jacobsen, 1999). The correlation between the subscales and the total score in POMS and POMS-SF was calculated at .84 (Curran et al., 1995). Construct validity of the POMS-SF in OLT recipients can be generalized from that established in other transplant groups.

Fatigue (Level and Impact): POMS-SF Fatigue-Inertia Scale, and Fatigue Impact:

Modified Fatigue Impact Scale. Fatigue level of OLT recipients and their caregivers was measured using the POMS-SF fatigue-inertia scale (Shacham, 1983; Appendix O (items 3, 18, 26, 29, 37)). This is a 5-item unidimensional, self-administered measure of fatigue comprising five adjectives and can be used alone (Whitehead, 2009). Respondents reported the degree to
which each adjective described them on a 5-point Likert scale. Possible scores ranged between 0 and 20 with higher scores indicating greater intensity of each state. Internal consistency reliability estimates for the fatigue-inertia scale have been reported between .89 and .94 in a variety of patient groups, including bone marrow and kidney transplantation (Curran et al., 1995).

Fatigue impact of OLT recipients and their primary caregivers was measured using the MFIS (Ritvo et al., 1994; Appendix P). The MFIS a shorter version of the original 40-item FIS, designed to measure the impact of fatigue on activities of daily living (Fisk et al., 1994; Appendix P). Internal consistency reliability estimates for the original FIS have been reported as ≥ .87 (Fisk et al., 1994). External validity has been established several groups of patients, including those with chronic fatigue (Fisk et al., 1994), multiple sclerosis (Fisk et al., 1994), COPD (Theander, Jakobsson, Jorgenson, & Unosson, 2009), primary biliary sclerosis (Prince, James, Holland, & Jones, 2000), chronic HCV infection (Elliott et al., 2010; Kramer et al. 2005) and liver transplant patients (Elliott et al., 2010; Lasker et al. 2011). The MFIS is a self-administered, multidimensional, 21-item scale which retains the three original FIS physical, cognitive, and psychosocial subscales. Respondents were asked to recall the perceived impact of fatigue on their ADLs over the previous 4 weeks on a 5-point Likert scale. Items of the MFIS can be aggregated into three subscales as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on an individual’s activities (Ritvo et al., 1994). The physical subscale comprises 9 items with possible scores ranging from 0 and 36, and the result is computed by adding raw scores of each item. The cognitive subscale comprises 10 items with possible scores ranging from 0 to 40, and the psychosocial functioning scale comprised 2 items with a possible total score ranging from 0 to 8. A global MFIS score can
range from 0 to 84 and is computed by adding the total score of each subscale. The MFIS has been used in healthy individuals and a variety of patient groups including those with chronic liver diseases (Biagini et al., 2008) and multiple sclerosis (Kos et al., 2003). Internal consistency reliability estimates for the MFIS are similar to the FIS, and have reported between: total MFIS = .8 and .96 (Fisk et al., 1994; Kos et al., 2003; Ritvo et al., 1994; Whitehead, 2009), physical subscale = .88 and .91 (Kos et al., 2003), cognitive subscale = .92 and .95 (Kos et al., 2003), and psychosocial subscale = .64 -.81 (Kos et al., 2003; Ritvo et al., 1994). Floor and ceiling effects have not been shown in the MFIS (Kos et al., 2003). Construct validity of the MFIS in OLT recipients and their respective primary caregivers can be generalized from that established in patients with liver disease and healthy individuals.

**Ethical Considerations**

Ethics approval was obtained from the Research Ethics Boards at the identified research site followed by the University of Toronto and the study period commenced October 11th 2013, ending September 2014. Participant confidentiality was maintained by ensuring that upon enrolment, all participants were assigned unique codes which corresponded with their names, and only the codes were documented on data collection instruments. Additionally, the PI successfully completed the *Principles–Good Clinical Research Practice* course (See Appendix Q), required of all investigators at the research site, in order to understand procedures related to conducting research and participant protection at the research site. All identifiable materials will be destroyed after 7 years, in accordance with the policies of the University of Toronto. No participant will be identified in any presentation or publication of study results.
Risks and Benefits

No direct or indirect risks were reported for OLT recipients or their respective primary caregivers who participated in similar observational studies. Accordingly, no direct or indirect risks were anticipated or occurred as a result of participating in this study. Participation in the study did not burden participants with any financial obligations. Participant burden was considered in the choice of the length of study measures selected. Participants were encouraged to take a break, if needed, while completing the study measures at each data collection time point. There were also no direct benefits anticipated for study participants. An indirect benefit from participating in this study may have been that of individual satisfaction felt by participants in the advancement of knowledge pertaining to function, pain, mood and fatigue among OLT recipients and fatigue among their respective primary caregivers during the early recovery period following OLT surgery.

Data Management and Security

The PI was responsible for all recruitment activities, data collection, and data storage. A database was designed specifically to assemble all study data. Study data were protected using several strategies. Paper copies of data collection records were locked in a secure cabinet accessible only to the PI. Participant contact information, signed consent forms and assigned study codes were stored separately and securely from the completed data collection records. The electronic database developed to assemble study data was stored on an encrypted device, requiring password access and was accessible only to select members of the research team, including the PI and biostatistician. Electronic files containing study data were decoupled from personal identifiers, and contained only the participants’ study identification (ID) codes. A crosswalk file with the study ID code and participant was kept in a secure location at the research
facilities and was not accessed by anyone other than the PI. Electronic data were backed up on a separate and secure universal drive available at the research facility.

**Sample Size and Data Analysis**

**Sample Size**

The primary analysis used a linear mixed effects model to measure the changes in pain, mood and fatigue, fatigue impact and function over time. Separate analyses were conducted to examine these changes in OLT recipients, and their caregivers (i.e., for fatigue). The mixed effects model included random effects to account for between and within subject correlation due to collecting up to three follow-up measurements per subject. In a simple study design with no covariates, a sample size of 58 achieved an 80% power to detect a medium-low effect size of .37 for two time points (i.e., Cohen’s $d = .37$ between the first and any subsequent time point) assuming a within-subject correlation of .70 and using a Bonferroni-corrected type I error of .017 (see Table 2 for example differences in outcomes based on different effect sizes).

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
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<tr>
<td><strong>Absolute Difference in Mean Score Between Two Time Points</strong></td>
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<tr>
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<tr>
<td>---</td>
</tr>
<tr>
<td>BPI-SF</td>
</tr>
<tr>
<td>POMS</td>
</tr>
<tr>
<td>MFIS</td>
</tr>
<tr>
<td>HAPS - MAS</td>
</tr>
<tr>
<td>HAPS-AAS</td>
</tr>
</tbody>
</table>

By collecting multiple measures per participant, the power to identify overall changes in the primary outcome over time increased. Using formulae suggested by Teerenstra, Moerbeek, van Achterberg, Pelzer, and Borm (2008), the required sample sizes to detect effect sizes
between .10 and 1.00 under various scenarios of within subject correlation are presented in Figure 4. As the correlation within individuals increases or as the observed effect sizes decrease, the sample size required decreases. Included in these estimates of sample size was an additional 30% to account for an expected loss due to disease relapse or death over the course of the study, consistent with trends at the study site and in similar published studies (Eshleman et al., 2010; Saab et al., 2011). Once the benefit of repeated measures and the disadvantage of loss-to-follow-up were taken into account, an 80% power to detect a small effect size of .25 in changes in pain, mood and fatigue was achieved with 58 participants. Therefore, for a desired sample size of 58, data were collected over a 12 month period, as anticipated.

**Analysis**

Data were analyzed using the IBM SPSS Statistics Software, version 22. The primary objective of the study, the correlation between pain, mood, fatigue and its related impact and function at 4, 8, and 12 weeks following discharge, compared to baseline, was determined using linear mixed models to account for the repeated measurements within OLT recipients. These models measured both the magnitude of the correlation between pain, mood and fatigue and function and the direction of the relationship. The aim of the primary research question was to describe the relationship between symptoms (pain, mood, fatigue (level and impact)) and the function of OLT recipients following surgery and in the first 12 weeks following discharge, while controlling for other covariates at all time points. To answer this question, a multiple linear mixed effects regression model was developed, accounting for repeated measures. This model was used to regress each independent variable on the dependent variable while including demographic and clinical covariates simultaneously. The dependent variable for the primary research question was function, and the independent variables were worst pain intensity upon
movement in the previous 24 hours, mood (operationalized as the POMS score), fatigue and fatigue impact. Covariates that were included were (a) age, (b) sex, (c) marital status and (d) diagnosis (i.e., indication for OLT surgery). Random effects for OLT recipients were included in the model, thereby accounting for within subject and between subject differences.

To address the research question, data initially were analyzed with descriptive statistics including measures of central tendency and dispersion for continuous variables. Frequencies and proportions were generated for categorical variables. Data were cleaned and checked for departures from normality. Multiple imputations were conducted to account for missing data, and an error rate of .001% was found for data entry, and data were corrected. The distribution of each continuous variable was assessed for outliers, defined as values greater than 1.5 times the interquartile range. No outliers of the raw data were found. Following analysis of residuals, data met the normality tests of kurtosis (0.17), skewness (0.002), as well as the Shapiro-Wilk test ($p = .412$). Regression diagnostics, specifically the variance inflation factor (VIF) tests, were also performed to determine colinearity. Initial VIF scores for worst pain upon movement in the previous 24 hours (WP-movement; 4.85) and pain interference (4.18), suggesting multicollinearity. WP-rest, which was also included in the regression model, was subsequently excluded from the adjusted regression model, resulting in a lower VIF score for pain interference (VIF = 2.64). Summary results for the variance inflation factors, and regression model assumptions for unadjusted regression modeling for each outcome on the explanatory variable are presented in appendix R. For significant factors in the model, effect size (partial eta-squared) is reported. Significant factors explaining the observed variance in function (HAP-AAS scores) included fatigue impact ($\eta^2_p = .11$) and time ($\eta^2_p = .40$).
The secondary objectives included an analysis of the relationships between the primary caregivers’ fatigue (POMS fatigue-inertia subscale) and fatigue impact (MFIS) and the OLT recipients’ function (HAP-AAS). Again, linear mixed models were used to examine these relationships while accounting for the dependency in measurements across times and recipient-caregiver dyads. Descriptive and summary statistics are reported using scores from the HAP administered to OLT recipients, and the POMS-SF and MFIS administered to their primary caregiver. Confounding factors were considered in the model but not evaluated formally. These included factors such as urgent surgical procedure following initial surgery and readmission to hospital. No statistically significant relationship was established between the primary caregivers’ fatigue and fatigue impact and OLT recipient’s function.
Feasibility

This study was supported by the identified research site’s Department of Anesthesia and Pain Management and the NP, Nurse Manager, Surgical Director of the Liver Transplant Program, Director of Surgical Services as well as the Director of the Gastrointestinal Program. To support recruitment rate for this study, a meeting was held with the Nurse Practitioner who is apprised of all patients enrolled on the OTTR, and who managed OLT patients postoperatively. The identified research facility performs a mean of 170 OLT surgeries annually, ranging between one to four surgeries on average per week. Following hospital discharge, all OLT recipients presented for follow up visitations to the outpatient transplant clinic weekly for 4 weeks, then biweekly for four occasions, and monthly thereafter. Based on the sample size estimation, 58 OLT recipients and their primary caregiver were required. Allowing for a 0-20% refusal rate, similarly to other longitudinal studies (Eshleman et al., 2010; Ratcliffe et al., 2002), ineligibility and lost opportunities, the anticipated recruitment rate for this study was achieved easily over a 12 month period. Table 3 depicts the projected timeline for the study.

Table 3

<table>
<thead>
<tr>
<th>Timeline over 12 month period</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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CHAPTER 4: RESULTS

This chapter presents the study results in 4 sections: (1) sociodemographic and clinical characteristics of OLT recipients, including their pain, mood, fatigue and fatigue impact, as well as function, (2) sociodemographic and clinical characteristics of the primary caregivers of OLT recipients, including their fatigue and fatigue impact; (3) results of the primary research question pertaining to the relationship of pain, mood, fatigue and fatigue impact with the function of OLT recipients, and (4) results of the secondary research question that examined the relationship between OLT recipients’ level of function and their primary caregivers’ level of fatigue and fatigue impact.

Sample

Recruitment

OLT Recipients. Seventy-five potentially eligible OLT recipients were approached following liver transplantation surgery. Of these, three refused to participate and the remaining 72 were assessed for eligibility. Of these, 12 were excluded; six could not speak, read or understand English, four had persistent postoperative delirium, and two required immediate transfer to the intensive care unit (ICU), precluding their participation. In total, 60 eligible OLT recipients consented to participate in the study, yielding 95% participation rate over the planned study recruitment period of nine months (see Figure 5).

Primary Caregivers. Of the 60 OLT recipients enrolled, 31 identified a potentially eligible caregiver who could be approached about participation in the study. Of the 31 caregivers approached, seven refused to participate for various reasons such as ‘not interested’ or ‘too busy’
The remaining 24 eligible primary caregivers consented to participate in the study (see Figure 6).

**Attrition**

**OLT Recipients.** Immediately following baseline data collection, two OLT recipients died in hospital. Complete follow up data were collected for all enrolled OLT recipients \((n= 58)\) at time 1. Rates of attrition were 2\% at follow up times 2 and 3; reasons for this attrition are outlined in Figure 5. Two additional OLT recipients were therefore recruited in order to meet the requirements of the sample size calculation.

**Primary Caregivers.** One caregiver enrolled in the study had to withdraw immediately before baseline data collection, due to the death of the OLT recipient she was caring for. Complete follow-up data were collected for all caregivers \((n = 23)\) at time 1. Eight percent attrition was observed at Time 2; reasons for this attrition are outlined Figure 6.
Approached for participation: N = 75
n = 3 refused, n = 12 ineligible (6 = language barrier, 4 = prolonged delirium, 2 = change in medical condition)

Consented to Participate
n = 60

Baseline Data Collection n = 60, (58 included in analysis)

Post Hospital Discharge Follow up

Time 1 Data Collection and Analysis n = 58
n = 2 losses to follow up (due to death)

Time 2 Data Collection and Analysis n = 57
n = 1 (did not complete measures due to illness)

Time 3 Data Collection and Analysis n = 57
n = 1 (did not complete measures due to financial and personal stress)

Figure 5 Flow of OLT Recipients through prospective data collection time periods.
Baseline Characteristics

OLT Recipients

Baseline sociodemographic and clinical characteristics of OLT recipients are presented in Table 4. The mean age of the sample was 54 (10.4) years and the majority were male (66%). On average, the majority were also married (77%), not working (68%), and had at least high school-level education (82%). Reasons for undergoing OLT surgery are reported in table 4. Most OLT recipients (65%) underwent surgery because of untreatable viral hepatitis (n = 20), alcohol-induced liver cirrhosis (n = 15), and autoimmune liver disease (n = 5). Sixty two percent (n=37)
reported at least one co-morbid condition, typically Type I or II diabetes (n=15, 25%) or upper GI disease (reflux, ulcer, or hernia, n=13, 22%); other co-morbidities are reported in Table 4.
Table 4. *Baseline Sociodemographic and Clinical Characteristics of OLT Recipients*

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<th>%</th>
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<td>Neurological disease (MS or Parkinson’s)</td>
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</table>

*Notes: MS = Multiple Sclerosis*
Primary Caregivers

The mean age of caregivers was 56.5(7.85) years and the majority were female (71%).

On average, the majority were the life partner of the OLT recipient (88%), currently employed (50%) and had at least high school-level education (88%). (See Table 5).

Table 5: Baseline Characteristics of Primary Caregivers

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<th>(%)</th>
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<td>8.3</td>
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<tr>
<td>Marital Status</td>
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<td></td>
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<tr>
<td>Married</td>
<td>20</td>
<td>83</td>
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<tr>
<td>Common-Law</td>
<td>3</td>
<td>12.5</td>
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<tr>
<td>Divorced</td>
<td>1</td>
<td>4.1</td>
</tr>
<tr>
<td>Relationship to OLT Recipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>Common-law spouse</td>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>Parent</td>
<td>3</td>
<td>12.5</td>
</tr>
</tbody>
</table>
Description of Symptoms and Function at Baseline and Follow-Up

Pain

Pain was assessed using numeric rating scales of the Brief Pain Inventory Short Form (BPI-SF). Each item was rated on a scale of 0 to 10, with higher scores representing greater pain intensity. The ‘worst pain’ (WP) and ‘least pain’ (LP) in the previous 24 hours, as well as pain intensity on the ‘average’ and ‘right now’ were all assessed at rest and upon movement, and are presented in Appendix S.

Mean BPI scores

Mean BPI scores are presented in Appendix S and Figures 7 to 10. At baseline, (i.e. postoperative day 5), average WP-rest and WP-movement scores in the previous 24 hours were in the moderate range. Both WP–rest ($F = 7.9, p <.001$) and WP-movement ($F = 8.0, p <.001$) improved significantly over time. Post hoc testing revealed that the most significant differences (representing a reduction in pain scores) were detected between baseline and 4 weeks post-discharge (Time 1). Scores for WP-rest were in the mild range across follow up time points, and scores for WP-movement remained in the moderate range throughout the course of follow up.

Mean baseline BPI pain interference scores (i.e., interference with mood, walking, sleep, enjoyment of activities, general activity, normal work and relations with other people) were in moderate range. Significant changes in pain interference scores were observed over time ($F = 13.0, p <.001$); this significant difference (representing a reduction in pain interference scores) occurred specifically between baseline and 4 weeks post discharge, with interference scores remaining in the mild range throughout the course of study follow up.
Figure 7: BPI NRS: **Worst Pain** at Rest and Upon Movement
T0 = Baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 12 weeks
*BPI = Brief Pain Inventory, NRS = Numeric rating scale (range 0-10)*

Figure 8: BPI NRS: **Least Pain** at Rest and Upon Movement
T0 = Baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 12 weeks
*BPI = Brief Pain Inventory, NRS = Numeric rating scale (range 0-10)*
**Figure 9: BPI NRS: Average Pain at Rest and upon Movement**
*T0 = Baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 12 weeks*
*BPI = Brief Pain Inventory, NRS = Numeric rating scale (range 0-10)*

**Figure 10: BPI NRS Pain Now at Rest and Upon Movement**
*T0 = Baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 12 weeks*
*BPI = Brief Pain Inventory, NRS = Numeric rating scale (range 0-10)*

### Frequencies of Moderate to Severe Pain

Table 6 presents frequencies of OLT recipients who reported moderate to severe pain intensity (i.e. BPI NRS ≥ 4/10) at all time points. At baseline, *WP-movement* was in the moderate to severe range for many (66%, n = 38). At 12 weeks post discharge, 22% of the sample (n = 12) also reported their *WP-movement* in the moderate to severe range, primarily along the surgical incision.
At baseline, moderate to severe pain interference was reported during general activity (n = 37, 62%), sleep (n = 30, 50%), walking (n = 29, 48%), and with mood (n = 29, 48%). At 12 weeks post discharge, more than one third of the sample also reported moderate to severe pain interference during normal work, (n = 23, 41%), general activity (n = 20, 36%), walking (n = 19, 34%), and sleep 20% (n = 12).

Table 6: Frequencies for OLT Recipients with moderate to severe surgical pain: BPI NRS Worst Pain upon Movement in Previous 24 hours

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N = 58)</th>
<th>T1 (N = 58)</th>
<th>T2 (N = 57)</th>
<th>T3 (N = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 to 6 / 10</td>
<td>4 (14%)</td>
<td>9 (16%)</td>
<td>14 (25%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>7 to 10/10</td>
<td>24 (41%)</td>
<td>17 (29%)</td>
<td>8 (14%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (66%)</td>
<td>26 (45%)</td>
<td>22 (39%)</td>
<td>12 (22%)</td>
</tr>
</tbody>
</table>

In summary, there were significant improvements in both WP-rest and WP-movement, as well as in pain interference at all follow up time points compared to baseline. However, WP-movement remained in the moderate range on average throughout the 12-week post-discharge period, and 22% of the sample reported moderate to severe pain. More than one fifth of the sample also reported pain interference with essential daily activities at 12 weeks.

**Mood**

Mood was assessed using the Profile of Mood States Short-Form (POMS-SF). Four of the six POMS-SF subscales were assessed at each data collection time point. These included the tension-anxiety (score range 0-24), depression-dejection (score range 0-32), confusion-bewilderment (score range 0-20) and anger-hostility (score range 0-28) subscales, with higher scores representing a greater problem. These four subscales were summed to represent negative mood (POMS score). The fatigue-inertia subscale of the POMS-SF was scored separately.
**Mean Scores for Anxiety, Depression, Confusion and Anger (POMS-SF)**

At baseline, 10% of the sample reported a history of clinical depression. Mean scores for each of the subscales as well as for the POMS score are presented in Appendix T and in Figures 11 and 12. Moderate levels of anxiety and depressive symptoms, as well as low levels of anger and confusion were evident at baseline. Significant reductions were noted in all negative mood states over time \((F = 19.2, p < .001)\); post-hoc analysis revealed that the most significant reduction in the combined negative mood states was observed at 4 weeks post-discharge. During the course of follow up, levels of confusion were consistently low at each follow up time point, whereas moderate to severe symptoms of depression \((n = 6, 10\%)\) and anxiety \((n = 8, 14\%)\) were noted by more OLT recipients at 12 weeks compared to depression \((n = 2, 3\%)\) and anxiety \((n = 2, 3\%)\) at 4 weeks. The highest levels of anger were also noted at 12 weeks post-discharge. Overall, mood scores were in the low range. OLT recipients reported their greatest improvement in negative mood states at 4 weeks following discharge, however more noted a greater frequency and intensity of anxiety and depressive symptoms at 12 weeks compared to at 4 weeks.
Figure 11: POMS-SF Subscales [Tension-Anxiety (range 0-24), Depression-Depression (range 0-32) and Anger-Hostility (range 0-28); T0 = Baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 12 weeks]; POMS-SF = Profile of Mood States Short Form

Figure 12: Confusion (range 0-20), Total POMS-SF Score (Sum of anger-hostility, anxiety-tension, depression-dejection and confusion-bewilderment subscales, range 0-104); T0 = Baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 12 weeks; POMS-SF = Profile of Mood States Short Form
Fatigue

Fatigue was assessed using the POMS-SF fatigue-inertia subscale. This subscale score was a sum of 5 items (score range 0 to 20), with higher scores representing greater fatigue.

Mean Fatigue Subscale Scores

Mean POMS-SF fatigue subscale scores are presented in Appendix U and Figure 13. At baseline, fatigue scores were in the moderate range, and remained in the mild to moderate range throughout the course of follow up. Significant changes in fatigue scores were detected over time ($F = 14.6, p < .001$); post-hoc testing revealed that the most significant difference (i.e. reduction in fatigue), was observed between baseline and 4 weeks (Time 1). However, more than 25% of the sample reported fatigue as a moderate to extreme problem at all follow up time points (T1, $n = 18$; T2, $n = 17$; T3, $n = 16$). Overall, a reduction was observed in fatigue at all follow up time points compared to baseline, however fatigue remained in the mild to moderate range throughout the course of follow up, with some OLT recipients experiencing moderate to extreme fatigue at 12 weeks post discharge.

Figure 13: Fatigue-Inertia Subscale (range 0 to 20)

POMS = Profile of Mood States (Short Form)

$T0 =$ Baseline, $T1 =$ 4 Weeks, $T2 =$ 8 Weeks, $T3 =$ 12 Weeks
Fatigue Impact

The Modified Fatigue Impact Scale (MFIS) was used to assess the impact of fatigue on OLT recipients’ physical, cognitive and psychosocial functioning. A possible composite score of the 3 subscales ranged from 0-84, with higher scores representing greater fatigue impact.

Mean Fatigue Impact Scores

Mean fatigue impact scale scores are presented in Appendix V and Figure 14. At baseline, mean fatigue impact were scores were reported in the moderate range, and remained in the mild to moderate range throughout the course of follow up. Significant changes in fatigue impact scores were detected over time ($F = 14.6, p < .001$); post-hoc testing revealed that the most significant difference (i.e. reduction in fatigue impact), was observed between baseline and 4 weeks post discharge (Time 1). At 12 weeks, 21% of the sample experienced the impact of fatigue “often” to “almost always”. Overall, low to moderate levels of fatigue impact were evident throughout the course of follow up for the sample on the whole, with a fifth experiencing moderate to severe fatigue impact at 12 weeks.

**Figure 14: Fatigue Impact Scores**

*MFIS = Modified Fatigue Impact Scale (range 0-84)*

*T0 = Baseline, T1 = 4 weeks, T2 = 8 weeks, T3 = 12 weeks*
Function

The Human Activity Profile (HAP) was used across time points to assess function. The adjusted activity score (AAS) of the HAP was reported to represent a measure of usual daily activities, and the best estimate of respondents’ average level of energy expenditure, in comparison with peers of same age and gender. The AAS score could be transformed into general fitness and activity classifications including: active (HAP AAS > 74), moderately active (HAP AAS = 53-74) or impaired lifestyle (HAP AAS < 53). The impaired classification was based on analyses of scores of healthy and physically impaired respondents, which indicated that all healthy respondents at every age reported an adjusted activity score above 52 (Daughton et al., 1982).

Mean Human Activity Profile Adjusted Activity Scores

Mean HAP AAS scores presented in Appendix W and Figure 15. At baseline, function scores were low, (M HAP AAS = 8.4(8.4)) and represented severe impairment. Improvement in function was noted throughout the course of follow up. Significant changes in function were observed over time (F = 182.8, p <.001); post-hoc testing revealed that these differences (i.e. improvement in function), were most significant between baseline and 4 weeks post discharge (Time 1), and then again between 4 and 8 weeks post-discharge (Time 2). At 12 weeks, however, the mean HAP-AAS score (M 48.2(18.1)) reported by OLT recipients still represented impaired function (Daughton et al, 1982).
Caregiver Fatigue and Fatigue Impact at 4, 8 and 12 weeks following OLT Recipients’ Discharge from Hospital

Fatigue

The POMS-SF fatigue-inertia subscale (range 0-20) was used to assess fatigue of primary caregivers, with higher scores representing a greater problem. Baseline measurements for caregivers were obtained at 4 weeks following the OLT recipients’ discharge from hospital. Mean fatigue subscale scores for caregivers are presented in Appendix X and Figure 16. At baseline, fatigue scores were in the moderate range. Significant differences were observed in caregiver fatigue scores over time ($F = 3.30, p = .047$); post-hoc testing revealed that the most significant difference was observed at 12 weeks when compared to baseline. By 12 weeks, fatigue subscale scores were in the mild range. Although fatigue for the sample on the whole had decreased over time, almost half ($n = 11, 48\%$) of the caregivers reported fatigue as a moderate
to extreme problem at baseline, and 35% ($n = 8$), and 24% ($n = 5$) at 8 and 12 weeks respectively.

![Figure 16: Caregiver Fatigue-Inertia Subscale Score (range 0-20)](chart.png)

**Figure 16: Caregiver Fatigue-Inertia Subscale Score (range 0-20)**

POMS SF = Profile of Mood States (Short Form)

$T0 =$ Baseline (4 weeks post OLT recipient discharge), $T1 = 8$ Weeks, $T2 = 12$ Weeks

**Fatigue Impact**

The Modified Fatigue Impact Scale (MFIS; score range 0-84) was used to assess the fatigue impact of primary caregivers, with higher scores representing a greater problem. Baseline MFIS scores were obtained at 4 weeks following the OLT recipients’ discharge from hospital. Mean scores for the MFIS of primary caregivers across time points are reported in Appendix Y and Figure 17. At baseline, scores for fatigue impact were in the moderate range, and had improved to the mild range by 12 weeks. Fatigue impact scores had reduced significantly at 12 weeks when compared to baseline ($F = 3.52, p = .04$). Overall, caregivers reported experiencing greater fatigue impact at 4 weeks following the OLT recipient’s discharge from hospital, and lesser fatigue impact by 12 weeks. However, at each time point, at least one third of caregivers reported a moderate to severe impact of fatigue ($T0 \ n = 18$, $T1 \ n = 10$, $T2 \ n = 8$).
Primary Research Question

*Relationship between pain, mood, fatigue and fatigue impact and function.*

The primary research question was: What is the impact of the orthotopic liver transplantation recipients’ pain, mood, fatigue (level and impact) on their function during the early postoperative recovery period? Pain intensity was measured using the numeric rating scales of the Brief Pain Inventory (Short Form), mood was assessed using the tension-anxiety, depression-dejection, anger-hostility and confusion-bewilderment subscales of the Profile of Mood States Short Form (POMS-SF), fatigue was assessed with the fatigue-inertia subscale of the POMS-SF, fatigue impact was assessed with the Modified Fatigue Impact Scale, and the Human Activity Profile was used to assess function.

As presented in Table 7, linear mixed effects model regression analysis revealed that *worst pain in the previous 24 hours upon movement*, pain interference, mood and fatigue were not significantly associated with function. Fatigue impact, however, was significantly associated with function: for each unit increase in fatigue impact, there was a -.30 unit decrease in function 95% CI [-0.42, -0.19]. In terms of the strength of this association, partial eta squared analysis revealed that fatigue impact also explained 11% of the variance in function (HAP-AAS; $\eta_p^2 =$...
Time was also significantly associated with function. Compared to baseline, function scores improved by 19.16, 95% CI [15.32, 23.00]; 28.97, 95% CI [24.90, 33.05], and 33.07, 95% CI [29.02, 37.12] units at time 1, 2 and 3 respectively. Overall, time explained 40% of the variance in function (HAP-AAS; \( \eta^2 = .40 \)).

Table 7. Regression Model 1.A: The Relationship Between OLT Recipients’ Pain Intensity, Mood, Fatigue, Fatigue Impact and their Function

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Slope Estimate (95% CI)</th>
<th>t-value (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>29.05 [7.31, 50.80]</td>
<td>2.68 (50)</td>
<td>.010</td>
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<tr>
<td>Worst pain upon movement in past 24 hrs</td>
<td>.00 [-0.66, 0.67]</td>
<td>.01 (156)</td>
<td>.995</td>
</tr>
<tr>
<td>Pain (BPI-SF Interference Scale)</td>
<td>-.87 [-1.80, 0.07]</td>
<td>-1.84 (156)</td>
<td>.068</td>
</tr>
<tr>
<td>Mood (POMS-SF Mood Score)</td>
<td>.03 [- .08, 0.13]</td>
<td>.55 (156)</td>
<td>.581</td>
</tr>
<tr>
<td>Fatigue (POMS-SF Fatigue-Inertia Subscale)</td>
<td>.03 [- .37, .42]</td>
<td>.13 (156)</td>
<td>.894</td>
</tr>
<tr>
<td>Fatigue Impact (MFIS)</td>
<td>-.30 [- .42, -.19]</td>
<td>-5.34 (156)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Point</th>
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<td>Baseline</td>
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<tr>
<td>1 (4 weeks post discharge)</td>
<td>19.16 [15.32, 23.00]</td>
<td>9.86 (156)</td>
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<tr>
<td>2 (8 weeks post discharge)</td>
<td>28.97 [24.90, 33.05]</td>
<td>14.04 (156)</td>
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<tr>
<td>3 (12 weeks post discharge)</td>
<td>33.07 [29.02, 37.12]</td>
<td>16.14 (156)</td>
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</table>

<table>
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<tr>
<th>Covariates</th>
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<th>p-value</th>
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</thead>
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<td>Age</td>
<td>-.02 (50)</td>
<td>.986</td>
</tr>
<tr>
<td>Sex (F vs M)</td>
<td>-.68 (50)</td>
<td>.502</td>
</tr>
<tr>
<td>Diagnosis</td>
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<tr>
<td>Hepatitis C</td>
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<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>-.44 (50)</td>
<td>.660</td>
</tr>
<tr>
<td>ETOH (alcohol-induced liver cirrhosis)</td>
<td>-.45 [-12.85, 3.71]</td>
<td>-1.11 (50)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>.18 [-13.90, 13.55]</td>
<td>-.03 (50)</td>
</tr>
<tr>
<td>Other</td>
<td>-1.81 (50)</td>
<td>.076</td>
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<td>Marital Status</td>
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<tr>
<td>- Single / Widowed</td>
<td>.43 (50)</td>
<td>.670</td>
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<tr>
<td>- Divorced / Separated</td>
<td>1.01 (50)</td>
<td>.318</td>
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<tr>
<td>- Married / Common-law</td>
<td>-</td>
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</table>

*Notes: BPI-SF = Brief Pain Inventory Short Form, POMS-SF = Profile of Mood States Short Form. MFIS = Modified Fatigue Impact Scale*
Secondary Research Question

Relationship between the Primary Caregivers’ Fatigue and Fatigue Impact, and the OLT Recipients’ Function

The secondary question for the study was: What is the impact of the orthotopic liver transplantation recipients’ function on their caregivers’ fatigue (level and impact) during the early postoperative recovery period? Fatigue of caregivers was measured using the POMS-SF fatigue-inertia subscale, and fatigue impact was measured using the Modified Fatigue Impact Scale. The function of OLT recipients was measured using the Human Activity Profile Adjusted Activity Score (HAP-AAS).

Two separate linear mixed effects models were developed to answer this question, one for fatigue level and one for fatigue impact. OLT recipients whose caregivers were enrolled in the study were included in each model. In the first model, the dependent variable was the caregivers’ fatigue, and the independent variable was their matched OLT recipients’ level of function (HAP-AAS score), while controlling for time. There was no statistically significant association found between the caregivers’ fatigue and the OLT recipients’ function (see Table 8). As well, time was not significantly associated with caregivers’ fatigue.

Table 8. Regression Model 1B: The Relationship Between Primary OLT Recipients’ Function and the Caregivers’ Fatigue Level

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Slope Estimate (95% CI)</th>
<th>t-value (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>7.09 [1.80, 12.37]</td>
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<td></td>
</tr>
<tr>
<td>OLT Recipients’ Function (HAP-AAS)</td>
<td>-.03 [-.13, .08]</td>
<td>-.49 (35)</td>
<td>.624</td>
</tr>
<tr>
<td>Time point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (4 weeks post OLT recipients’ hospital discharge)</td>
<td>0.0 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks post OLT recipients’ hospital discharge)</td>
<td>-1.34 [-4.30, 1.62]</td>
<td>-.92 (35)</td>
<td>.364</td>
</tr>
<tr>
<td>12 weeks post OLT recipients’ hospital discharge)</td>
<td>-2.78 [-6.06, 0.50]</td>
<td>-1.72 (35)</td>
<td>.095</td>
</tr>
</tbody>
</table>

Notes on Table: OLT = Orthotopic Liver Transplantation, HAP-AAS = Human Activity Profile Adjusted Activity Score
In the second model, the dependent variable was the caregivers’ fatigue impact, and the independent variable was their matched OLT recipients’ function (HAP-AAS score), while controlling for time. There was no significant association observed between the fatigue impact of primary caregivers and the function of OLT recipients (see Table 9). A statistically significant relationship was found, however between caregivers’ fatigue impact and time (see Table 9). Time—specifically at 3 months following OLT recipients’ discharge from hospital—was associated with a \(-9.75\) 95% CI \([-18.26, -1.24]\) unit reduction in the fatigue impact score of caregivers. These results suggest that the fatigue impact of primary caregivers is not associated with OLT recipients’ level of function, and that caregiver fatigue impact was in the mild range by 12 weeks following hospital discharge.

**Table 9. Regression Model 1C: The Relationship Between OLT Recipients’ Function and Caregivers’ Fatigue Impact.**

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Slope Estimate (95% CI)</th>
<th>t-value (df)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>26.53 [16.89, 36.17]</td>
<td></td>
<td>.000</td>
</tr>
<tr>
<td>OLT Recipients’ Function (HAP-AAS)</td>
<td>.005 [-0.28, 0.29]</td>
<td>.04 (32)</td>
<td>.971</td>
</tr>
<tr>
<td>Time point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (4 weeks post OLT Recipients’ Hospital Discharge)</td>
<td>0.0 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 weeks post OLT Recipients’ Hospital Discharge)</td>
<td>-4.65 [-11.91, 2.60]</td>
<td>-1.31 (32)</td>
<td>.201</td>
</tr>
<tr>
<td>12 weeks post OLT Recipients’ Hospital Discharge)</td>
<td>-9.75 [-18.26, -1.24]</td>
<td>-2.33 (32)</td>
<td>.026</td>
</tr>
</tbody>
</table>

*Notes on Table: OLT = Orthotopic Liver Transplantation, HAP-AAS = Human Activity Profile Adjusted Activity Score*

**Summary of results**

There was one primary research question and one secondary research question in this study. The primary question examined the relationship between the OLT recipients’ pain, mood,
fatigue and fatigue impact and their postoperative function during hospitalization, and during the first 12 weeks following discharge from hospital. Linear mixed model regression analysis uncovered that there was no statistically significant relationship between OLT recipients’ worst pain upon movement and their function. However, OLT recipients experienced moderate pain upon movement during hospitalization and throughout the first 12 weeks following discharge, with 22% of the sample reporting moderate to severe ratings for worst pain upon movement at 3 months.

Overall, OLT recipients reported their symptoms of anxiety, depression and levels of psychological distress in the moderate range at baseline. Following discharge, an improvement was noted in overall levels of psychological distress over time. While confusion improved over time, moderate to severe symptoms of anxiety and depression were more frequently reported by OLT recipients at 12 weeks (14% and 10% respectively) compared to their first month after discharge when only 2% of the sample reported moderate to severe anxious and depressive symptoms. Linear mixed model regression analysis uncovered that there was no statistically significant relationship between OLT recipients’ mood and their function.

Additionally, fatigue and fatigue impact scores of OLT recipients were reported in the moderate range during hospitalization, and improved over time. The mean fatigue subscale scores and fatigue impact scores were lower throughout the course of follow-up compared to baseline, and were reported in the mild to moderate range by the sample on the whole. However at 3 months, 25% of the sample continued to report fatigue as a moderate to extreme problem. Moderate to severe fatigue impact was reported by 21% of the sample.

Scores representing the function of OLT recipients during hospitalization suggested severe impairment. Significant improvement was noted throughout the course of follow up.
However at 12 weeks post-discharge, the HAP-AAS score of participants was less than 53, classifying their function as impaired (Daughton et al., 1982). Linear mixed model regression analysis showed that fatigue impact was significantly associated with OLT recipients’ function and explained 11% of the variance in this outcome.

The secondary research question sought to examine the relationship between the function of OLT recipients and the fatigue (level and impact) of their primary caregivers. Caregivers reported their fatigue subscale score in the moderate range at baseline, with significant improvement (i.e., a reduction in fatigue) at all follow up time points. Their mean fatigue subscale score was in the mild range at 12 weeks. Similarly, caregivers’ fatigue impact was observed to be in the moderate range at 4 weeks, and had reduced significantly by at 12 weeks. Neither caregiver fatigue (level or impact) were significantly associated with OLT recipients’ function. Time, however, did predict the fatigue impact of caregivers, which was significantly lower by 12 weeks, and overall, caregivers reported low levels of the negative impact of fatigue by this time.

In summary, the results of this study suggest that function, as measured by the HAP-AAS (Daughton et al., 1982), was severely impaired at baseline, following OLT surgery. Although there was a statistically significant improvement in HAP-AAS scores by 12 weeks, these scores did remain below 53, indicating impaired function. Fatigue impact was significantly associated with function, explaining 11% of the variance in HAP-AAS scores. Pain, negative mood states and fatigue were not significantly associated with function, yet the summary data suggest that scores for each of these outcomes were in the higher range for some OLT recipients. Pain intensity upon movement, was in the moderate range (NRS ≥ 4/10) throughout the course of follow up; 22% of the sample reported moderate to severe pain intensity upon movement at 12
weeks. Negative mood states were experienced at moderate range at baseline, and had improved to the mild range throughout the course of follow up; yet symptoms of anxiety and depression were more frequently reported at 12 weeks than at 4 weeks. Fatigue and fatigue impact were experienced in the moderate range at baseline, and improved slowly following discharge; at 12 weeks, 28% of the sample experienced moderate to extreme fatigue levels, and 21% reported experiencing the negative impact of fatigue as “often” or “almost always”. Additionally, caregivers’ fatigue and fatigue impact was highest at 4 weeks after OLT recipients’ discharge and had improved by 12 weeks. Finally, neither the fatigue nor fatigue impact of primary caregivers was significantly associated with OLT recipients’ function.
CHAPTER 5: DISCUSSION

This chapter provides a discussion of the results in four major sections, in the context of relevant literature. The first section discusses the results related to the linear mixed effects regression model that was used to answer primary research question. These results will be discussed pertaining to the relationships between pain, mood, fatigue and fatigue impact and the function of OLT recipients. The second section discusses results of two separate regression models that were used to answer the secondary question concerning the fatigue and fatigue impact of primary caregivers, in relation to the OLT recipients’ function. The third section reviews the patterns of each symptom and function. Finally, strengths and limitations of this study will also be discussed.

The conceptual model that provided guidance for the examination of variables was adapted from Wilson and Cleary’s (1995) Conceptual Model of Patient Outcomes, which links biological variables to health related quality of life. The model was adapted to conceptualize the relationships between OLT recipients’ symptoms and function, as well as characteristics of their environment that mediated these relationships. Caregivers in the current study were considered to be part of the OLT recipients’ environment.

Primary Question: Relationships between pain, mood, fatigue, fatigue impact and function at baseline and during the first 12 weeks following discharge.

This is the first known study that prospectively examined postoperative pain, mood, fatigue and fatigue impact as well as OLT recipients’ functional status during hospitalization and up to 12 weeks following hospital discharge. The primary question was: What is the impact of the orthotopic liver transplantation recipients’ pain, mood, fatigue (level and impact) on their function during the early postoperative recovery period?
A multiple linear mixed effects regression model was used to answer this question. *Worst pain in the previous 24-hours upon movement (WP-movement)*, mood, and fatigue were not found to be significantly associated with OLT recipients’ function. Tenable explanations for the lack of a significant relationship between these symptoms and function may include choice of measures that were used for pain and function, as well as the low-range scores reported for negative mood states.

While a significant association between worst pain intensity (BPI- *WP-movement*), the BPI-interference subscale, and physical function (HAP-AAS) was not found in this study, OLT recipients did report moderate levels of pain interference at baseline ($M_{BPI-I} = 4.4 (2.9)$) with sleep, mood, and usual activities. However, the use of a more comprehensive measure versus the shorter could have accounted for the lack of a possible association. BPI-interference subscale scores had improved significantly by 12 weeks, and were reported in the mild range ($M_{BPI-I} = 2.3 (2.6)$). Pain interference has also been reported in other prospective studies involving outcomes of major abdominal surgeries. At 4 weeks following transverse rectus abdominis myocutaneous (TRAM) flap reconstruction surgery, Dell et al. (2008) reported mild pain in their sample, and also mild-range pain interference with items of the BPI-Interference subscale ($M$ pain interference - general activity = 2.5/10; $M$ pain interference – work = 3.6/10). It is not known if measures were taken at rest or on movement. In the current study, although pain-interference was in the mild range by 12 weeks post-discharge, it was in the moderate range at baseline during hospitalization, and may possibly have impeded functional recovery. Future studies could focus on better characterizing the relationship between pain and functional status during the hospitalization period following OLT surgery. Consideration should be given to more comprehensive measures of function that evaluate physical movement, essential daily activities
such as sleep, and affective states such as mood, which were affected by pain during hospitalization for this sample. Results from future studies could help to inform interventions aimed at reducing postoperative pain and its interference during the immediate postoperative period, and improve the quality of postoperative recovery.

Participants in the current study could have limited their activities due to the anticipation of moderate to severe postoperative pain with ambulation and other activities, thereby accounting for the lack of a significant association between pain and function. A growing body of knowledge suggests that kinesiophobia (that is, the fear of movement due to pain), may affect the quality of recovery among postoperative patients, and this has also been correlated with limitations in physical function (George et al., 2012). In this study, baseline scores for functional status indicated impaired function ($M$ HAP-AAS = 8.4(8.4)). These scores suggest that OLT recipients varied in their functional status, but many had difficulty with essential daily activities such as getting in and out of bed without assistance, and had stopped activities such as reading and watching television (Daughton et al., 1982). Inability to perform such instrumental daily activities could be due to physical deconditioning following major surgery in individuals known to have significant physical impairment preoperatively, or possibly due to fear of movement. More data are required to corroborate the baseline functional status scores reported in this study, and describe the extent to which pain contributes to the overall functional status postoperatively. Further prospective evaluation of the association between pain and function is necessary, to understand whether pain on movement contributes to low levels of functional status. Qualitative research is also necessary to better understand the experience of postoperative recovery, including the putative fear of pain and activity.
The relationship between mood and the functional status of OLT recipients in this study was also not statistically significant. Mean scores for the anxiety-tension, depression-dejection, confusion-bewilderment and anger-hostility subscales, as measured by the POMS-SF, were reported in the mild range throughout the course of follow up, and could explain, in part, their lack of contribution to the observed variance in the OLT recipients’ functional status scores during follow up (i.e., the HAP-AAS scores). The mild-range mood scores has been observed in this population previously, and may be explained by the evidence that the early recovery period following life-saving OLT surgery has been associated with feelings of relief, euphoria, and optimism of returning to a “normal life” (Holzner et al. 2001, Jones et al. 2005). Longer-term evaluations of OLT recipients recovery (i.e., those beyond 3 months post-surgery), suggest that such positive emotions are not necessarily long-lasting (Lasker et al., 2011; Guimaro et al., 2011).

Several cross-sectional studies have found significant associations between specific mood disorders and the functional status of OLT recipients. For example, in a cross-sectional study, Nickel et al. (2002) found that moderate-range depressive and anxiety scores, as measured by the Hospital Anxiety and Depression Scale $\beta = -4.72, p < .001$, explained 51% of the variance in the physical component summary score (PCS) of the SF-36 HRQL measure among those beyond 6 months following OLT surgery; age ($\beta = .350, p < .001$) and employment status ($\beta = -4.72, p < .001$) also explained their functional status. Lasker et al. (2011) confirmed these results when they examined a cross-sectional sample of female OLT recipients who were at less than three months to up to seventeen years postoperatively. They found that combined anxiety and depressive symptoms explained 24% of the variance ($R^2 = .24, p = .017$) in the SF-36 PCS scores. Cumulatively, data collected in the current study as well as studies involving OLT recipients up
to seventeen years postoperatively, suggested the impact of mood disorders such as depression and anxiety may be problematic beyond the early recovery period.

In the current study, the Profile Mood States Short-Form (POMS-SF) was used to examine the variety of negative mood states experienced by OLT recipients in the immediate postoperative period and the first three months post-discharge, versus using a disease specific measure limited to depression or anxiety. Available data describing negative mood states during these time periods were limited for OLT recipients. Results from this study indicated that the depression-dejection, and tension-anxiety subscale scores were in the mild range at 4, 8 and 12 weeks following discharge, although more participants reported these symptoms at 12 weeks (anxiety; \( n = 6, 10\% \); depression; \( n = 8, 14\% \)) than at 4 weeks (anxiety; \( n = 2, 3\% \); depression; \( n = 2, 3\% \)). These data confirm results of other studies that have shown that anxiety and depression appear to be more problematic at or beyond the first three months post-discharge for some (Lasker et al. 2011; Nickel et al. 2002). Evidence to-date is inconclusive about critical postoperative time points, during which transient such negative mood states could evolve to clinical mood disorders. Future prospective studies are necessary to observe the natural course of negative mood states, such as anxiety and depression, as well as their relationship with function over the long term. Longitudinal assessment is necessary to address the management of potential mood disorders and to minimize mood-related interference on OLT recipients’ functional status, should this be a problem long-term.

The relationship between fatigue (as measured by the POMS-SF fatigue-inertia subscale) and functional status (as measured by the HAP-AAS) of OLT recipients was also not statistically significant. The mean POMS-SF fatigue subscale scores remained in the mild range throughout the course of follow up, and contrary to what was expected, the data suggested that fatigue was
not a major problem in the early postoperative period. However, the fatigue-inertia subscale has only 5 items that assessed the perception and frequency of fatigue. Perhaps a measure, such as the well-established 21-item Modified Fatigue Impact Scale (MFIS), would provide a more comprehensive examination of other characteristics of fatigue, including fatigue impact on psychosocial and cognitive dimensions. Despite the limited number of items, the fatigue-inertia subscale was selected to reduce respondent burden with only 5 items and because it had been validated for OLT recipients previously (Moore et al. 1997). As data describing the natural course of fatigue in the early recovery period following OLT surgery are preliminary, future studies are still necessary. Multi-centre, larger scale studies need to consider using more comprehensive measures of fatigue, such as the MFIS, which measures the perception of fatigue as well as its’ impact.

As discussed earlier, fatigue impact as measured by the MFIS, was found to be significantly associated with function. Following linear regression, post-hoc analysis revealed that fatigue impact explained 11% of the observed variance in HAP-AAS scores (\(\eta_p^2 = .11, p < .0001\)). This result was similar to other studies that found fatigue impact on functional status to be problematic, although to a greater extent than what was observed in this study. For example, Lasker (2011) in a cross-sectional sample used the Fatigue Impact Scale (FIS) to examine fatigue of females up to 17 years following OLT surgery. Their step-wise linear regression model that included the SF-36, and found that the FIS scores explained 20% of the variance in the SF-36 physical component summary score (\(R^2 = .199, F(2, 73) = 24.12, p < .001\)).

Elliott et al. (2011) examined postoperative fatigue and functional status in another cross-sectional study involving liver transplant recipients up to thirteen years. Results of their regression model suggested that fatigue severity (as measured by the FIS) was independently
associated with the observed variance in functional impairment scores of the Patient-Reported Outcomes Measurement Information System and the Health Assessment Questionnaire (PROMIS-HAQ; \( \beta = .496, SE = .095, \beta = .727, p < .0001 \)); indicating that higher levels of fatigue negatively impacted function. They argued that the functional status of their sample was comparable to those with advanced chronic liver disease and was far from being normal following surgery. However, generalizations regarding the extent to which fatigue is problematic based on data from the current study and those of Lasker et al. (2011) and Elliott et al. (2011) are inconclusive due to the various measures of functional status used (HAP-AAS in this study, the SF-36 PCS used by Lasker et al., and the PROMIS-HAQ used by Elliott et al). A standardized approach is needed with respect to the selection and timing of outcome measures and measurement.

Given that just 11% of variance in function (HAP-AAS) was explained, it appears as though that based on the results of this study alone, an intervention to manage fatigue impact in the early postoperative period may not be warranted. However, the cumulative evidence reviewed suggests that fatigue remains a problematic symptom up to seventeen years following OLT surgery. For example in two cross-sectional studies, Lasker et al. (2011) found that fatigue explained 20% of the variance in physical function in females up to 17 years postoperatively, and Elliott et al. (2011) found that fatigue severity was associated independently with functional impairment (FIS Beta .727, p < .0001). However data for the early recovery period in both studies (i.e., at 3 months or less postoperatively) were limited. While inferences about the relationship between fatigue and functional status must be made with caution (due to the inherent limitations of cross-sectional studies to infer causality) the magnitude of the associations seems to imply that fatigue does determine, in part, functional status to varying degrees, consistently. Although the
functional status (HAP-AAS) of OLT recipients in this study was impaired at 12 weeks and was not explained by other symptoms or clinical or sociodemographic variables, it was explained, in part, by fatigue impact, consistent with what the literature suggests. Kehlet & Dahl (2003), argued that management of fatigue is an important part of postoperative recovery, and should be considered as part of comprehensive postsurgical recovery interventions. Therefore, a future educational intervention targeting fatigue postoperatively, embedded as part of a multifaceted postoperative recovery program could potentially minimize the negative impact of fatigue, and improve functional status for some OLT recipients.

**Secondary Question: Relationship between the Caregivers Fatigue and Fatigue Impact and OLT Recipients’ Function.**

Two separate multiple linear mixed effects regression models were used to answer this question. Neither the fatigue nor fatigue impact of caregivers was found to be significantly associated with their matched OLT recipients’ function. This study prospectively examined whether the fatigue (level and impact) of primary caregivers was associated with OLT recipients’ functional status in the first twelve weeks following discharge. Studies have shown that fatigue can be problematic for caregivers of these recipients and possibly for caregivers of other solid organ transplant recipients as well.

Rodrigue, Nelson, Reed, Hanto & Curry (2010) also used the POMS-SF fatigue-inertia subscale and the SF-36 vitality scale to describe caregiver fatigue in a larger cross-sectional study involving caregivers (N = 37) up to 2 years following OLT surgery. They concluded that higher levels of fatigue and lower levels of vitality were evident in their caregivers compared to other healthy adults (Hopman et al., 2000; Nyenhuis, Yamamoto, Luchetta, Terrien, & Paramentier, 1999). However, they did not delineate results for caregivers in the early recovery
period after hospital discharge. In a prospective study involving lung transplant recipients and their caregivers up to six months following surgery, Xu et al. (2012) showed that caregivers reported up to 30% of their daily activities were health-related; these included care for the recipient who could not always independently organize medications, monitor vital signs and blood glucose, prepare for and attend medical appointments, or exercise (Xu et al. 2012). However, the specific experience of caregiver fatigue related to the limitations in their lung transplant recipients’ functional status was not explored. Although preliminary research highlighting care giving experience to transplant recipients has suggested that fatigue can problematic, and that caregivers assume additional responsibilities, the extent to which caregiver fatigue and fatigue impact can be explained by OLT recipients’ functional status remains unclear. Data from the current study as well as those reported by Rodrigue, Nelson, Reed, Hanto & Curry (2010) should be regarded as preliminary, and suggest that the experience of caregiver fatigue following OLT surgery needs further exploration. The transition from hospital to the community is a critical period during which both OLT recipients and their caregivers are required to make lifestyle adjustments. The experience of caregivers could be further evaluated through qualitative as well as quantitative methods, to understand the changes in their fatigue over time, as well as to identify critical time points for future interventions, where appropriate.

An explanation for the lack of a significant relationship between the OLT recipients’ function and the fatigue (level and impact) impact of their primary caregivers could be the low-range scores that were observed for primary caregivers’ fatigue (level and impact) throughout the course of follow up. Although caregivers’ levels of fatigue (level and impact) were in the moderate range at baseline (i.e., at 4 weeks following OLT recipients’ hospital discharge), each outcome improved significantly throughout the course of follow up. These data suggest that
despite the impaired functional status of OLT recipients (HAP-AAS <53) throughout the course of follow up, neither the fatigue (level or impact) of caregivers was affected. However given the small sample of caregivers, conclusions about the proposed relationships would be premature. Future prospective studies involving larger samples of caregivers are still needed to corroborate the results of the present study. These studies should continue to consider comprehensive measures of fatigue such as the MFIS.

Although the fatigue and fatigue impact of caregivers were not associated with OLT recipients’ function, each outcome was significantly associated with time. Specifically, caregivers experienced less fatigue ($F = 3.30, p < .047$) and fatigue impact ($F = 3.522, p = .040$) at 12 weeks compared to their measures at 4 weeks following OLT recipients’ discharge. Mean scores for fatigue and fatigue impact were close to the moderate range at baseline, but remained in the mild range throughout the course of follow up. The results for caregivers are exploratory and must be interpreted with caution. As OLT surgery is an urgent versus elective surgical procedure, future educational interventions to help prepare caregivers can be provided while OLT recipients remain in hospital. Support for caregivers during this early recovery period is necessary. Future studies to understand the caregiver experience are still necessary to better understand their fatigue following OLT recipients’ transition from hospital to the community in order to deliver appropriate interventions.

In summary, the relationship between symptoms and function in this study are conceptualized according to an adapted model that was originally developed by Wilson and Cleary (1995). The adaptation of the model for this study postulates that symptoms of OLT recipients would impact their function, and that their function would in turn impact the fatigue and fatigue impact of their respective primary caregivers. These suppositions are partially
supported through regression analysis. The regression model designed to address the primary question revealed no statistically significant associations between worst pain in the previous 24 hours upon activity, negative mood, and fatigue of OLT recipients and their functional status. However the functional status of OLT recipients was partially explained by fatigue impact, and supports the conceptualization of the relationships between symptoms and function proposed by Wilson and Cleary (1995). Fatigue impact was found to have a statistically significant relationship with OLT recipients’ functional status, and explained 11% of the variance in the HAP-AAS scores. The secondary question in this study was also conceptualized according to the adapted conceptual model used in this study. OLT recipients were considered to have a relationship with their environment, and in the current study primary caregivers were considered to be part of the OLT recipients’ environment. However, results of linear regression analysis indicated that neither fatigue nor the fatigue impact of primary caregivers was found to have a statistically significant relationship with OLT recipients’ functional status. In contrast, time (specifically following OLT recipients’ discharge from hospital), was found to have a statistically significant relationship with caregivers’ fatigue and fatigue impact. By 12 weeks, caregivers had significantly less fatigue and fatigue impact compared to at 4 weeks following OLT recipients’ discharge from hospital. These data are important in deciding the most appropriate time for a future intervention.

**Trends of OLT Recipients’ Postoperative Pain, Mood, Fatigue and Function at Baseline and Follow-Up**

**Pain**

Despite not being significantly associated with OLT recipients’ function in this study, 66% of the total sample reported worst pain *at rest* (*WP-rest*) and *upon movement* (*WP-movement*) in
the previous 24 hours in the moderate range at baseline data collection. Mean postoperative pain intensity ratings of participants were more severe than in other OLT recipient samples that consistently reported mean pain intensity ratings in the mild range in first 72 hours postoperatively (Donovan et al., 1997; Moretti et al., 2002; Ko et al., 2012 & Milan et al., 2011). Differences in outcomes between this study and the others could be attributed to timing of outcome measurement, route of analgesia, lack of pain assessment upon movement, or choice of measure. In comparison, baseline measures in this study were generally obtained on postoperative day 5, wherein patients were considered in stable condition and transferred out of the intensive care unit. Additionally, 3 of these studies had not used a valid pain measure, and had possibly underestimated pain (Donovan et al., 1997; Moretti et al., 2002; Milan et al., 2011).

WP-movement was primarily reported in the surgical site throughout the course of follow-up and remained in the moderate-severe range for 45% at 4 weeks, 39% at 8 weeks, and 22% at 12 weeks. These findings suggested that pain was a consistent problem for OLT recipients up to 3 months postoperatively, which can have implications for long term pain. The development of chronic post-surgical pain (CPSP), has been a significant predictor of acute postoperative pain following cardiac, vascular and general surgery procedures (Choiniere et al., 2014; Gupta et al., 2011; Kehlet et al., 2006; Katz et al., 2009; Macrae et al., 2008).

Several prospective studies have concluded that pain intensity was in the mild range at 1 to 3 months (Bonsel et al. 1992., Ordin et al. 2011., Perez-San Gregorio et al. 2010; Pieber at al. 2006) and similar results were reported among cross-sectional samples at less than three months following OLT surgery (Wang et al., 2012, Van Den Berg-Emons et al. 2006., Wang et al. 2012., Younoussi et al. 2000). The contrasting results of pain outcomes between these studies and the current study could be explained, in part, by the choice of using HRQL binary measures. These
measures included the SF-36 bodily pain scale or the Nottingham Health Profile and EuroQOL pain subscales, and were used to detect only the presence of pain. Data pertaining to pain intensity in the current study were obtained using the more comprehensive rating scales of Brief Pain Inventory-Short Form, a disease-specific measure. In summary, pain remained a clinical problem at rest and upon movement postoperatively at baseline for OLT recipients in the current study. It was also a common problem during their transition from hospital to the community, particularly upon movement, and points to the need for future interventions that improve pain management overall. Future studies are needed to corroborate these results as well as evaluate self-management educational interventions that aim to improve pain management, especially upon movement throughout the early recovery period.

**Mood**

Despite the lack of a significant association between negative mood and OLT recipients’ functional status, changes in their patterns of anxiety and depression were observed over time. At baseline, moderate levels of psychological distress were evident. These findings were in contrast to two other studies that reported lower levels of psychological distress during hospitalization using different measures (Chui et al., 2009; Perez San-Gregorio et al. 2005). For example, Chui et al. (2009) retrospectively diagnosed anxiety and depression clinical mood disorders using the *Diagnostic and Statistical Manual of Mental Disorders–IV* criteria, reporting 6% prevalence for each. However, participants may have had transient negative mood states such as depressive and anxiety symptoms and may have been excluded because they not meet the DSM IV criteria. As well, Perez-San Gregorio et al. (2005) were not clear about their timing of outcome measurement and reported mild levels of anxiety and depression levels as assessed by the Hospital Anxiety and Depression Scale (HADS). This measure was specifically designed to detect the presence and
intensity of anxiety and depression, and excluded other negative mood states, whereas the POMS-SF (used in this study) was intended to provide a more comprehensive measure of transient negative mood states including anxiety, depression, confusion and anger.

Although the initial experience of negative mood states in this study had resolved for the majority following baseline measurement, symptoms of depression and anxiety were present for some at 12 weeks (anxiety; \( n = 6, 10\% \); depression; \( n = 8, 14\% \)). The prevalence of anxiety (20% - 43% of patients) and depression (17% - 45%) was evident during and beyond the early recovery period in other studies (Bonsel et al., 1992; Guimaro et al., 2011; Russell et al., 2008; Lasker et al., 2011; Leyendecker et al., 1993). However, data from these studies remain inconclusive about the early recovery period due to small samples, (Bonsel et al., 1992; Lasker et al., 2011; Leyendecker et al., 1993), and a focus on only those with alcohol induced liver cirrhosis (Guimaro et al., 2011). Additional data are necessary to understand the natural history of anxiety and depression using a more comprehensive measure, in the longer term, in future studies.

The body of knowledge documenting the negative mood states of OLT recipients, including results of this study, suggests that some OLT recipients may develop anxiety and depression beyond the early recovery period. Significant lifestyle adjustments that are necessary for coping with problems associated with immunosuppression, as well as the uncertainty of organ rejection may contribute to transient or ongoing depression and anxiety (Lasker et al. 2011; Wang et al. 2012). Frequent interaction with health care providers during the early postdischarge recovery period (i.e., clinic visits for follow-up monitoring) as well as greater social support during the first 12 weeks may have contributed to less overall psychological distress in that period. Future examination of patients’ mood when healthcare provider support is less and possibly caregiver support as well towards the end of the 3rd month is needed. Future prospective studies
that include long term follow-up are necessary to identify patterns of negative mood states at baseline, as well as beyond three months after surgery. Future studies could also consider the influence of immunosuppressant medications on mood and optimal period for health care provider support following surgery. Larger samples of OLT recipients would permit an analysis of possible clinical or sociodemographic characteristics that may contribute to the development of postoperative negative mood states and their association with physical function.

**Fatigue**

While fatigue was not significantly associated with function, mean scores for the POMS-SF fatigue-inertia subscale were in the moderate range at baseline, and lower throughout the course of follow-up. Nonetheless, fatigue scores were in the *moderate to extreme* range for 25% of the OLT recipients in this study at 12 weeks postdischarge. Longer term evaluations of the impact of OLT surgery suggest that fatigue remained problematic for up to seventeen years postoperatively, but the results remain inconclusive due to varying timing of outcome measurements (Lasker et al., 2011; Rodrigue, Nelson, Reed, Hanto & Curry., 2010; Van Den Berg-Emons et al., 2006), small samples (Lasker et al., 2011) and differences in measurement (Lasker et al., 2011; Van Den Berg-Emons et al. 2006). Nonetheless, based on the results of this study as well as previous studies, interventions to minimize fatigue could be introduced preoperatively and continue postoperatively. For example, eight previous studies have reported that non-pharmacological interventions for the management of fatigue such as psycho-education and psychological intervention have effectively reduced fatigue among adult patients who have undergone abdominal surgery or who live with chronic illnesses (Kahokehr et al., 2012; Sohng et al., 2003; Badger et al., 2005; Ream et al. 2006; Armes et al., 2007; Yesibalkan et al., 2009;
Weardem et al., 2010; Chan et al., 2011; Reif et al., 2012). A future educational intervention targeting fatigue postoperatively for OLT recipients could be evaluated as part of their recovery.

**Functional Status**

Collectively, results of this study as well as other reports support the use of clinical interventions in the immediate postoperative recovery period as well during the early post-discharge period to reduce fatigue levels and lessen their impact. More data are needed to identify those patients with higher fatigue levels that may continue long term. It is possible, that interventions provided to those waiting for OLT surgery, could improve their pre-operative fatigue levels which are often poor. Given the possibility of disease recurrence (such as viral hepatitis), graft rejection, or unresolved fatigue emanating from initial liver failure, interventions aimed at managing fatigue may be necessary for OLT recipients need to be considered at different times throughout the pre- and postsurgical periods.

Limitations in the functional status of OLT recipients, as measured by the HAP-AAS, were evident throughout the course of follow-up (including baseline) and are consistent with other reports that have documented lower levels of function among OLT recipients assessed with the SF-36 HRQL measure (Ware & Sherbourne 1992., Eshleman et al. 2010., Lasker et al. 2011., Perez-San Gregorio et al. 2010., Pieber et al. 2006., Ratcliffe et al. 2002., Russell et al. 2000., Rodrigue et al. 2010., Van den Berg-Emons et al. 2006., and Younoussi et al. 2000). Using the Patient-Reported Outcomes Measurement Information System, Health Assessment Questionnaire, a disease specific measure of function, Elliott et al. (2011) reported functional impairment in their sample of OLT recipients up to thirteen years postoperatively, which was also explained by severity of fatigue. Elliott et al. (2011) argued that generic HRQL measures may have overestimated OLT recipients’ functional status, as they assessed a limited number of
activities. This conclusion is further supported by the results of the current study. Although gradual improvement was noted in the mean scores for the HAP-AAS, data at 12 weeks suggested that function was impaired ($M_{\text{HAP-AAS}} = 48.2(18.1)$). The entire sample was still having difficulty with household activities, climbing stairs and coping with their grooming.

There are multiple potential implications for further evaluation and management of OLT recipients’ functional status. Results of the current study were based on a sample from one research facility, and this was one of the first studies to evaluate functional outcomes of OLT surgery across the early recovery period. Multi-centre studies involving larger samples are therefore required to corroborate these findings, as well as to understand the role of the severity of ESLD on posttransplant functional status. Possible non-pharmacologic interventions to manage fatigue and improve function could be considered while OLT recipients are waiting to receive a cadaveric liver, in order to maximize their physical conditioning pre-operatively. Comprehensive measures of functional status, such as the Human Activity Profile (Daughton et al., 1982), could be also used in future prospective studies to provide more nuanced evaluation of function to inform future interventions aimed at improving function in the pre-and postoperative period.

**Strengths**

There are several strengths noted in this study, which create confidence in the conclusions that can be drawn to support future research. First, robust methods were utilized to address limitations noted in previous studies. Second, a high participation rate (95%) was achieved from all possible OLT surgical candidates. A comprehensive approach to recruitment activities was used, that included mailed study brochures to all those listed on the liver transplant waiting list, posting of flyers in the liver transplant clinic for OLT surgery candidates and their
caregivers, provision of in-services for staff nurses on the unit for the post-surgical recruitment activities. Thirdly, assiduous follow up procedures were undertaken, in which data collection included a variety of methods to maximize opportunities for participation, minimize losses to follow up as well as ensure standardized data collection time points. These included primarily, follow up in the outpatient clinic if it coincided with the data collection time point, or telephone administration of the questionnaire where clinic appointments were not scheduled or were unattended. The option of a mailed survey with a self-addressed stamped envelope was also offered. At any given follow-up time point, fewer than 2% of the sample did not complete data collection.

Fourth, measurement bias was minimized through choice of standard measures to assess pain, mood, fatigue (level and impact), and function. These measures may have also improved assessment of discrete changes noted in each of the symptoms and function; the latter may have been overlooked in studies that used HRQL to assess the same variables. Linear mixed effects regression models that were used accounted for repeated measures and also adjusted the model to limit confounding biases that could have resulted in colinearity; prior studies considered such statistical adjustments to a lesser extent.

Fifth, a specific study database was developed for the study, using SPSS. Data were entered by the PI, and logic and range checks were completed, to assess for departure of data from normality. Following completion of data entry, 25% of the data were manually cross-checked between the original data collection package and the corresponding SPSS data entry. An error rate of < 0.1% was found, and errors were corrected. Finally, this study was also strengthened by the use of a model that guided the examination of clinical variables using logical and previously tested relational propositions.
Limitations

While this study had several strengths, there may have been potential sources of bias that affected study outcomes. First, the entire cohort was recruited from a single academic health science centre in Ontario, and was limited to English-speaking individuals. Care practices for OLT recipients at this site may be dissimilar to others, resulting in potential selection bias. It may have also under-represented groups such as Aboriginal Canadians, among whom the rates of hepatitis have been reported to be higher (Public Health Agency Canada of Canada, 2011). A future multi-centre site involving liver transplant recipients in general would minimize selection bias. Secondly, fewer than 40% of the potential caregivers were recruited, potentially resulting in a sample bias, and the majority (71%) were female. Third, participants may have underreported problematic symptoms or overstated positive aspects of their symptoms and function, thereby subjecting the results of this study to social desirability bias. Data were collected during the early recovery period following life-saving liver transplantation surgery, which was a significant motivator for participants. OLT recipients may have presented themselves in a more positive light and underreported the intensity of their symptoms and ability to perform activities of daily living, to acknowledge the resource intensive medical intervention that had prolonged their lives. As well, the majority of data were collected in person or via telephone. These factors may have contributed to social desirability bias, which has been identified as a concern in empirical studies that have relied on self-report measures (DeMaio., T., 1984; Schwarz & Oyserman., 2001; Holbrook, A., Green, M. & Krosnick, J. 2003; Nolte S., Elsworth, G. & Osbourne, R. 2013) and could have affected this sample. Fourth, while the intention of the study was to study pain in the early recovery period, pain intensity in the peri-operative period (i.e., within the first 72 hours)
was not assessed should be considered in future studies. Intense pain in the peri-operative period has been known to influence long term pain problems (Kalso et al. 2001., Katz et al., 1996).
CHAPTER 6: SUMMARY, IMPLICATIONS, CONCLUSION

The prevalence of liver cirrhosis and incidence of related complications, including end-stage liver disease (ESLD), are expected to increase over the next ten to twenty years (Baxter & Smerdon, 2000; Davis, Albright, Cook, & Rosenberg, 2003; Wong, McQuillan, McHutchinson, & Poynard, 2000). End-stage liver disease is irreversible and associated significantly with functional debility prior to liver transplantation (Eshelman et al., 2010; Russell et al., 2008; Younoussi et al., 2000). To date, the recovery of the functional status of OLT recipients postoperatively has been determined primarily by studies that have examined HRQL. These studies have concluded that although HRQL improves following transplantation, OLT recipients continue to experience functional limitations in the long term (Beyer et al., 1999; Eshelman et al., 2010; Jones, 2005; Lasker, Sogolow, Short, & Sass, 2011; Leyendecker et al., 1993; Ratcliffe et al., 2003; Rodrigue, Nelson, Reed, Hanto & Curry, 2010; Russell et al., 2008; Younoussi et al., 2000). Programs to address recovery of function post-transplantation focus mainly on heart and lung transplant recipients, whereas resources to address the recovery of OLT recipients are limited (Trojetto et al. 2011). Few studies have examined the natural course of the recovery of postoperative function of OLT recipients during hospitalization and during the first 3 months at home after surgery. Symptoms such as pain, negative mood states, fatigue, and fatigue impact have been reported by OLT recipients, however the extent to which these symptoms affected the postoperative recovery of function had not been examined to any great degree.

Primary caregivers of OLT recipients, most often spouses, contribute significantly to the postoperative recovery process, especially following hospital discharge. Primary caregivers assist with strict medication regimens, activities of daily living and accompanying OLT recipients to frequent medical appointments. Preliminary data suggested that primary caregivers
have experienced fatigue and lower vitality (Rodrique, Nelson, Reed, Hanto & Curry (2010)) compared to other healthy adults (Hopman et al. 2000). However it was unclear whether caregiver fatigue was related to the functional status of OLT recipients. This study aimed to examine the (1) relationships between OLT recipients’ pain, mood, fatigue and fatigue impact and their function at baseline postoperatively, and then at 4, 8 and 12 weeks post-discharge, and (2) relationship between caregivers’ fatigue and fatigue impact and OLT recipients’ function at 4, 8 and 12 weeks following discharge. OLT recipients’ pain at rest and upon movement was measured using rating scales of the BPI-SF that assessed worst, least, average in the previous 24 hours, as well as pain now; negative mood states were measured using the Profile of Mood States – Short Form (POMS-SF), fatigue was measured using the fatigue-inertia subscale of the POMS-SF, and was scored separately. Fatigue impact was measured using the Modified Fatigue Impact Scale (MFIS), and functional status was measured with the Human Activity Profile - Adjusted Activity Score (HAP-AAS). Caregiver fatigue was measured using the POMS-SF fatigue-inertia subscale, and caregiver fatigue impact was measured using the MFIS.

The mean age of the sample was 54 (10.4) years and the majority were male (66%). On average, the majority were also married (77%), not working (68%), and had at least high school-level education (82%). Most OLT recipients (65%) underwent surgery because of untreatable viral hepatitis (n = 20), alcohol-induced liver cirrhosis (n = 15), and autoimmune liver disease (n = 5). Sixty two percent (n=37) reported at least one co-morbid condition, typically Type I or II diabetes (n=15, 25%) or upper GI disease (reflux, ulcer, or hernia, n=13, 22%). The mean age of caregivers was 56.5(7.85) years and the majority were female (71%). On average, the majority were the life partner of the OLT recipient (88%), currently employed (50%) and had at least high school-level education (88%).
Function of OLT recipients was the primary outcome for the study, as measured by the HAP-AAS. Independent variables proposed to explain function included pain, mood, fatigue and fatigue impact. Distributions of each variable were assessed using measures of central tendency, including means and standard deviations for continuous variables, and frequencies and proportions for categorical variables. Linear mixed effects regression models were used to evaluate the relationships between the dependent and independent variables in each question, with significant relationships detected at $p \leq .05$.

Throughout the course of follow up (including baseline), worst pain upon movement in the previous 24 hours (WP-movement) remained in the moderate range, and ranged from $M$ BPI NRS = 6.1 (3.0) at baseline, to $M$ BPI NRS = 4.0 (3.7) at 12 weeks post-discharge. At 12 weeks, 22% of the sample reported WP-movement in the moderate to severe range. Mean scores for anxiety-tension and depression-dejection subscales of the POMS-SF were in the moderate range at baseline. These had improved to the mild range throughout the course of follow up and were more frequently reported at 12 weeks compared to at 4 weeks. Mean scores for the fatigue-inertia subscale (POMS-SF) were in the moderate range at baseline, and had improved to the mild range throughout the course of follow up. However at 12 weeks, 25% of the sample continued to report fatigue as a moderate to extreme problem. Fatigue impact scores (MFIS) were in the moderate range at baseline, and had improved to the mild range throughout the course of follow up, with moderate to severe fatigue impact reported by 21% of the sample at 12 weeks. Mean scores for functional status (HAP-AAS) indicated severe impairment at baseline ($M$ HAP-AAS = 8.4(8.4)). HAP-AAS scores greater than 53 have been reported by individuals classified as healthy. Even though the HAP-AAS in this study had improved gradually by 12 weeks they remained in the impaired range ($M$ HAP-AAS < 53), indicating that OLT recipients had difficulty with basic
activities of daily living such as walking and climbing stairs. Mean scores for the fatigue-inertia subscales and the fatigue impact (MFIS) scale of primary caregivers were each in the moderate range at 4 weeks post-discharge, and had improved to the mild-range by 12 weeks.

Linear mixed effect regression model analysis found that WP-movement, mood, and fatigue were not associated with OLT recipients’ functional status. Fatigue impact was significantly associated with function, and explained 11% of the observed variance in the HAP-AAS scores (HAP-AAS; \( \eta_p^2 = .11 \)). Neither the fatigue nor fatigue impact of caregivers had a significant association with OLT recipients’ functional status; however, time did explain the observed variance in caregivers’ fatigue impact scores. That is, time — specifically 12 weeks following OLT recipients’ discharge from hospital, compared to at 4 weeks post discharge — was associated with a -9.75 95% CI [-18.26, -1.24] unit reduction in the fatigue impact score of caregivers.

**Implications for Research**

Future research of OLT recipients will focus on: 1) the qualitative examination of the experience of postoperative recovery related to adequate pain management and the related fear of activity, 2) a longitudinal assessment of the symptoms of anxiety and depression from 3 month post-discharge to 1 year, 3) interventions to reduce fatigue to improve functional status and physical conditioning both prior to and following liver transplantation surgery, and 4) a qualitative examination of caregivers in order to better understand their levels of fatigue and fatigue impact following hospital discharge.

A future study needs to focus on a more critical examination of the experience of recovery from OLT surgery, with a particular focus on better pain management to reduce the fear of pain. It is unclear from this study whether functional scores were low due to fear of movement.
related to inadequate management and intense pain, or whether OLT recipients were actually not able achieve optimal functional levels due to pre-operative deconditioning. A more in-depth examination of pain should also be considered in future research, as postoperative pain intensity, duration and qualities collectively have longer-term implications in the development of persistent pain problems. Research designs could include both qualitative and quantitative methods, and continue to use comprehensive measures of pain.

While recipients’ initial experience of moderate symptoms of depression, anxiety, confusion and anger at baseline had resolved throughout the course of follow up for many OLT recipients, a small group continued to experience symptoms of anxiety and depression at 12 weeks. In several studies, these symptoms have been more problematic in the longer term (DiMartini et al., 2011, Nickel et al., 2002; Leyendecker et al., 1993; Lasker et al., 2011), although the progression of these symptoms to persistent clinical mood disorders remains unknown. A naturalistic long-term observational study over the course of 1 year postoperatively using specific depression and anxiety measures would help to identify critical time points at which future interventions can be provided for those who need them.

Results of this study are consistent with others who suggest that functional status is poor prior to OLT surgery (Eshelman et al., 2010; Russell et al., 2008; Younoussi et al., 2000). While slight improvement is noted postoperatively, it remains impaired compared to age- and sex-matched normative samples (Hopman et al. 2000). It will be important to determine which interventions could improve patients’ physical conditioning prior to surgery, increase functional capacity and accelerate their recovery process following surgery.

Finally, data describing the experience of caregivers’ fatigue and fatigue impact in this study as well as others are limited due to a small sample. Overall results suggested that, while
Caregivers experienced mild to moderate levels of fatigue and fatigue impact at baseline (i.e., at 4 weeks following the OLT recipients’ discharge from hospital), by 12 weeks, both fatigue and fatigue impact were not significantly problematic. However, due to the small number of enrolled caregivers, future multi-centre studies involving a larger sample are needed to understand their fatigue and fatigue impact levels more clearly.

Implications for Practice

Implications for future clinical practice relate to 1) improving pain control especially during activity and supporting increased activity after surgery to prevent complications and possible persistent pain problems, 2) discussing with caregivers the ways they have managed fatigue related to the recipient’s health issues prior to surgery and their relevance after discharge from hospital. Summary results of the trends in NRS scores for this sample, particularly upon movement, suggested that pain was not well controlled. Throughout the course of follow up, ratings for the WP-movement were in the moderate range, with 22% of the sample describing moderate to severe surgical pain. Unmanaged acute pain prevents optimal activity for recovery and could transition to a persistent longer term problem (Choiniere et al., 2014; Gupta et al., 2011; Kehlet et al., 2006 & Katz et al. 2009). Data from this study could be immediately used to provide education to the interprofessional teams caring for these patients postoperatively. Focus groups with team members about strategies to improve overall pain assessment and management, function, and mood could be used to decide on future interventions. Future interventions focusing on patient education could also focus on pain assessment and management strategies after surgery.

Caregivers remain an integral part of the OLT recipients’ recovery process, and account for up to 30% of their daily activities in the care of OLT recipients post-discharge (Xu et al,
Results describing their levels of fatigue are limited at present. Results from this study suggest that caregivers experience most fatigue at 4 weeks following the OLT recipients’ transition from hospital to home. Others have reported that caregivers have longer term fatigue, for up to 2 years (Rodrigue, Nelson, Reed, Hanto & Curry (2010)). Given the small sample of caregivers that were enrolled in this study, results to inform educational interventions should be done cautiously. Discussions with caregivers about their experience and needs could help to validate findings and facilitate and further our understanding of the caregiver burden following OLT surgery.

Conclusions

The main purpose of this study was to examine the relationships between pain, mood, fatigue (level and impact) and the functional status of OLT recipients during hospitalization and up to 12 weeks post-discharge. A significant association was detected between fatigue impact and functional status, wherein 11% of the variance in functional status scores (HAP-AAS) was explained by fatigue impact. Pain intensity was not significantly associated with functional status, however 22% of the sample reported moderate to severe pain intensity upon movement at 12 weeks after surgery. Future prospective interventional studies are needed pre and postoperatively, to minimize fatigue impact and evaluate the outcomes of these interventions on the postoperative function of OLT recipients. Multi-centre, longitudinal longer-term observational studies are required to determine critical time points at which anxiety and depression may develop, as well as their impact on OLT recipients’ functional status. These studies could help to identify critical time points for future interventions. Due to the small number of caregivers in this study, additional data are still required describing the experience of
the fatigue and fatigue impact of caregivers, and the relationship of these clinical variables with OLT recipients’ functional status.
References


Ware, J., Bayliss, W., Rogers, M., Kosinski, M., Tarlov, A. (1996). Differences in 4-year health outcomes for elderly and poor, chronically ill patients treated in HMO and fee-for-service systems. *Journal of the American Medical Association, 276* (13), 1039-1047.


Appendix A: Quantitative Studies of Pain in the First 3 Months Following OLT Surgery

<table>
<thead>
<tr>
<th>Author/Date/Country</th>
<th>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</th>
<th>Sample (Characteristics /Setting)</th>
<th>Measures/ Validity and reliability</th>
<th>Primary outcomes /secondary outcomes</th>
<th>Relevant outcome(s) and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonsel et al. / 1992/ Netherlands</td>
<td>Prospective / To document quality of life pre and post orthotopic liver transplantation / cross-sectional and longitudinal (pre-tx, then at 3 months (mo))</td>
<td>N = 46 (31 male, 15 female) aged 42.6(11.1) years / community (n = 18 in cross-sectional and n = 14 in longitudinal)</td>
<td>QOL / Nottingham Health Profile Pain Scale / valid, reliable</td>
<td>At 3 mo, mild pain ratings found using both study designs, pain subscale = 9(18) in cross-sectional group, and pain = 12 longitudinal group; significant correlation of pain dimension with presence of bone pain (r = .61) and back ache (r = 0.67)</td>
<td>Small samples; lack of a standard pain measure; assessment limited to presence or absence of pain</td>
</tr>
<tr>
<td>Donovan et al., / 1997/ USA</td>
<td>Prospective / To compare postoperative analgesic requirements of patients undergoing OLT surgery vs. liver resection for cancer / 12 data collection points (pain assessed q6h x 72 hours)</td>
<td>N = 23 (13 OLT aged 40(3) years, 10 controls aged 48(5)) /In-patient unit</td>
<td>Self-developed pain rating scale / not provided</td>
<td>Both groups had mild daily average pain ratings 1.8(0.3) – 2(0.1); OLT group used significantly less opioid</td>
<td>Unknown whether pain was measured at rest or upon movement</td>
</tr>
<tr>
<td>Ko et al. / 2012/ Korea</td>
<td>Retrospective / To determine the relationship between postoperative opioid requirements and severity of liver disease among OLT patients with high vs. low model of end-stage liver disease (MELD) scores/ 3 data collection points (postoperative days (POD) 1, 2 and 3)</td>
<td>N = 44 [n = 30 (25 males, 5 females aged 51.7(7.4) years with less severe liver disease MELD scores (MELD ≤20), and n = 14 (10 males and 4 females aged 53.9(5.3) years with more severe liver disease MELD scores MELD&gt;20)] / In-patient unit.</td>
<td>Visual analogue scale / valid, reliable</td>
<td>Patients with higher MELD scores (i.e., more severe liver disease) reported mild to moderate median VAS scores upon coughing across all time points, compared to patients with lower MELD scores (i.e., less severe liver disease), who reported mostly mild to median VAS scores across all time points upon coughing.</td>
<td>Less severe liver disease was associated with significantly higher post-operative pain intensity scores, and greater opioid requirements; retrospective, possible selection bias (excluded patients with histories of chronic pain)</td>
</tr>
<tr>
<td>Krasnoff et al. / 2005/ USA</td>
<td>Prospective, repeated measures/ To document health-related fitness, physical activity and physical HRQL over first 2 years post tx and compare outcomes between males and females / 4 data collection points (2(T0), 6(T1), 12(T2) and 24(T3)) mo postoperatively.</td>
<td>N = 50 (32 male, 18 female) aged 51.4(11.8 years) / community</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>BP = 66 at 2 mo</td>
<td>OLT recipients had moderate range pain scores and reported more pain than normative sample; no differences among males and females in pain outcomes</td>
</tr>
<tr>
<td>Milan et al / 2011/ United</td>
<td>Retrospective / to compare postoperative pain scores, morphine consumption and walking time in patients who received</td>
<td>N = 34 (n = 17 OLT recipients with TAP blocks, 10 male, 7</td>
<td>Investigator-developed pain rating scale / not</td>
<td>TAP group reported mild pain ratings and used less opioid, control group</td>
<td>Small sample, lack of standard pain measure; unknown whether pain was assessed at rest or upon movement;</td>
</tr>
<tr>
<td>Kingdom</td>
<td>transversus abdominis plane (TAP) blocks and intravenous (IV) morphine versus those who used IV morphine/data collected at 24 hours postoperatively</td>
<td>female aged 52.3(7.7) years; n = 17 historical controls, 12 male, 5 female aged 48.4(9.5) years / in-hospital</td>
<td>provided</td>
<td>reported moderate range pain ratings</td>
<td>reliability and validity of measures not provided</td>
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<tr>
<th><strong>Author/ Date/Country</strong></th>
<th><strong>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</strong></th>
<th><strong>Sample (Characteristics /Setting)</strong></th>
<th><strong>Measures/ Validity and reliability</strong></th>
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<th><strong>Relevant outcome(s) and Limitations</strong></th>
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<tbody>
<tr>
<td>Moretti et al. / 2002 / USA</td>
<td>Retrospective / To compare postoperative morphine use, analgesic efficacy and side effects in OLT vs. liver resection patients / 5 data collection points (at 6, 12, 24, 48 and 72 hrs postoperatively</td>
<td>N = 25 (10 OLT aged 44(10), 15 liver resection aged 58(10) / in-patient unit</td>
<td>4-point rating scale/ not provided</td>
<td>OLT recipients had mild average pain ratings across all time points, and used less morphine</td>
<td>Unknown whether pain was assessed at rest upon movement; Small sample, reliability and validity of measures not provided</td>
</tr>
<tr>
<td>Ordin et al. / 2011 / Turkey</td>
<td>Prospective, repeated measures / To investigate liver transplant recipients’ QOL and factors affecting it, before and 3 mo post tx</td>
<td>N = 65 (46 male, 19 female; aged 45.7(10.2) years</td>
<td>QOL – Nottingham Health Profile / Valid, Reliable</td>
<td>At 3 mo, mild range pain scores (pain subscale = 18.44(16.2))</td>
<td>Small sample of OLT recipients (n = 17 OLT), outcomes specifically for OLT recipients unknown; Lack of standard pain measure; assessment limited to presence or absence of pain</td>
</tr>
<tr>
<td>Perez-San Gregorio et al. / 2010 / Spain</td>
<td>Prospective, repeated measures / To compare HRQL in liver transplant patients pre and post-tx / 4 data collection points (Pre-tx (T0), then 3(T1), 6(T2) and 12(T3) mo post</td>
<td>N = 27 (19 male, 8 female), aged 51.67 years / community</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Pre-tx BP 65.16 3mo post-tx 83.98 (p&lt;.007)</td>
<td>Small sample, lack of standard pain measure; contrasting pain outcomes (SF-36 BP scale results indicated mild-range scores; EQ-5D scale results indicated mild-moderate range pain scores).</td>
</tr>
<tr>
<td>Pieber et al. / 2006 / Austria</td>
<td>Prospective, repeated measures / To evaluate endurance capacity, muscle strength and QOL before and post tx (Pre-tx (T0), 1-2 mo (T1), and after 3 years (T2) post tx</td>
<td>N = 15 (10 male, 5 female), aged 52.2 (11.1) years / community</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Pre-Tx BP 79 1-2 mo post tx 81</td>
<td>Small sample, OLT recipients report comparable BP scale scores to normative sample</td>
</tr>
<tr>
<td>Ratcliffe et al. / 2002 / England</td>
<td>Prospective, repeated measures / To assess pre and post transplantation HRQL of liver recipients / pre-tx (T0), 3 (T1), 6 (T2), 12 (T3) and 24 (T4) mo post tx</td>
<td>N = 455 (233 male, 222 female, aged 15 to &gt; 60 yrs; 68% &gt; 46 yrs); longest waiting time for OLT was 14 mo / mailed survey</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Pre-Tx BP 56.44 3 Mo Post Tx 57.55 (p &gt;.05)</td>
<td>No change in BP 3 mo following liver transplant (z = -.487, p = .626), patients experience more pain than normative sample. Possible sample bias (inability to adjust for non-responders in Tobit model); pain-related interference not specified. 37% survey response rate.</td>
</tr>
<tr>
<td>Author/Date/Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics /Setting)</td>
<td>Measures/ Validity and reliability</td>
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<tr>
<td>Russell et al. / 2008 / USA</td>
<td>Prospective, repeated measures / To (i) model the effects of pre and post-tx clinical covariates on individual post-tx SF-36 scales and summary components and (ii) Evaluate whether HRQOL profiles differ as a function of liver transplantation and Hep C Virus / 4 – pre-tx, (T0), 1(T1), 3(T2), 6(3) and 12(T4) mo post-tx</td>
<td>N = 104 with pre/post data, aged 53.5 (7.8) yrs, 73% male, 27% female, 51% Hep C Virus, 26% metabolic liver disease / clinic</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Pre-Tx 43 ± 24  Post Tx 54 ± 27 (p&lt;.001)</td>
<td>BP improved post-tx, pre-tx HCV infection had a negative impact on post-OLT BP (p = .010), history of ≥ 1 rejection episodes negatively affected BP (p = .007) Specific BP scale scores not provided for each occasion</td>
</tr>
<tr>
<td>Van den Berg-Emons et al. / 2006 / Netherlands</td>
<td>Cross-sectional / To assess severity of fatigue in liver transplant recipients / 1</td>
<td>N = 96 (n = 45 male, n = 51 female), aged 51.8(12.7) yrs. Time since transplant 52 days – 15.4 years / clinic</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>BP = 72.7(28.5)</td>
<td>BP scores comparable to normative sample; cross-sectional number of participants &lt; 3 mo postoperatively unknown,</td>
</tr>
<tr>
<td>Wang et al. / (2012) / China</td>
<td>Cross-sectional / To investigate HRQL post OLT surgery &gt; 2 months to up to 5 years postoperatively and compare to healthy controls and those with end stage liver disease/ 1</td>
<td>N = 60 post liver transplant aged 48.9(8.7) yrs, 95% male, 92% HCV, 3% HBV, 5% ETOH</td>
<td>HRQL – SF – 36, valid, reliable</td>
<td>BP = 72.65(18.63)</td>
<td>BP in mild range postoperatively; and lower compared to those waiting for transplant; cross-sectional; participants &lt; 3 months postoperatively unknown</td>
</tr>
<tr>
<td>Younoussi et al. / 2000 / USA</td>
<td>Prospective, cross-sectional / To measure the impact of OLT on patients’ HRQL / 2</td>
<td>N = 37 (25 male), aged 50.2 (12) yrs. Time since OLT 2-23 mo.</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>BP 52 72 (p&lt;.05)</td>
<td>BP improved compared to pre-tx Small sample, cross-sectional, pain data in early recovery period unclear, related interference unknown</td>
</tr>
</tbody>
</table>
### Appendix B: Quantitative Studies of Mood in the First 3 Months Following OLT Surgery

<table>
<thead>
<tr>
<th>Author/Date/Country</th>
<th>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</th>
<th>Sample (Characteristics/Setting)</th>
<th>Measures/Validity and reliability</th>
<th>Primary outcomes/secondary outcomes</th>
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<tr>
<td>Bonsel et al. / 1992 / Netherlands</td>
<td>Prospective / To document quality of life pre and post orthotopic liver transplantation / cross-sectional and longitudinal (pre-tx, then at 3 mo)</td>
<td>N = 46 (31 male, 15 female) aged 42.6(11.1) years / community</td>
<td>Anxiety - State-Trait Anxiety Inventory/valid, reliable</td>
<td>Similar levels of anxiety and depression using both study designs; Mile range anxiety scores (STAI= 34)</td>
<td>Small sample; (n = 18 in cross-sectional and n = 14 in longitudinal)</td>
</tr>
<tr>
<td>Chiu et al. / 2009 / Taiwan</td>
<td>Retrospective / Describe clinical characteristics of OLT recipients referred for psychiatric consultation during prolonged hospitalization due to complications / 1</td>
<td>N = 21 (16 male, 5 female, aged 53(8) years</td>
<td>Diagnosis made from chart review, symptoms classified according to DSM - IV</td>
<td>Depressive symptoms in 2 participants (2%); anxiety symptoms in 2 participants (2%)</td>
<td>Small sample, retrospective, unclear how many patients were recipients of deceased versus live liver donors; retrospective review possible affecting diagnosis, limited generalizability. Possible missing data. OLT recipients with typical length of stay not included in sample.</td>
</tr>
<tr>
<td>DiMartini et al. (2011) / USA</td>
<td>Prospective, repeated measures / describe patterns of depressive symptoms over first 12 months following liver x for ETOH / 4 (T0 = 3 mo postoperatively; T1 = 6 mo postoperatively; T2 = 9 mo postoperatively; T3 = 12 mo postoperatively)</td>
<td>N = 167 (84% male; aged 50(8) years;</td>
<td>Depressive symptoms; Beck Depression Inventory / Valid, reliable</td>
<td>3 groups identified: Group 1: consistently low depressive scores across all time points (n = 95); Group 2: initially low depressive scores that rose over time (n =</td>
<td>Limited to sample with history of ETOH; younger, unmarried pts and those with HCV more likely to experience problematic trajectories;</td>
</tr>
<tr>
<td>Author/ Date/ Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics /Setting)</td>
<td>Measures/ Validity and reliability</td>
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<tr>
<td>Eshleman et al. / 2010 / USA</td>
<td>Prospective / Observe mental and physical QOL over time in OLT recipients with and without alcohol-induced liver cirrhosis / T0 (before OLT surgery) T1 (1 mo post-tx), T2 (6 mo post tx)</td>
<td>N = 65 (n = 14 with alcohol-induced liver cirrhosis; n = 31 without), aged 54(14) / mailed survey</td>
<td>HRQL – SF-36 v2 /valid, reliable</td>
<td>MCS = 48</td>
<td>Mental health of entire sample similar to normative sample; sex characteristics of participants not described.</td>
</tr>
<tr>
<td>Guimaro et al. / 2011 / Brazil</td>
<td>Retrospective / To assess post-traumatic stress disorder, depression, anxiety and QOL among liver transplant recipients with acute liver failure / 1 (13.50 (13.80) mo postoperatively)</td>
<td>N = 24 (19 female, 5 male), aged 41.17(17.03) yrs / clinic n = 12 &lt; 5 mo post tx (Group A) n = 12 &gt; 5 years post tx (Group B)</td>
<td>Anxiety and Depression - HADS / Valid, reliable Depression – Beck Depression Inventory (BDI) / Valid, reliable</td>
<td>Group A HADS Anxiety 7.33(5.14) Depression 4.83 (3.24) BDI = 12.67(5.14)</td>
<td>Anxiety evident in 33% of entire sample, depression evident in 16.7-50% of entire sample, observed more when BDI used; possible insensitive measurement bias; Small sample &lt; 5 mo post op; unclear how many &lt; than 3 mo postoperatively</td>
</tr>
<tr>
<td>Lasker et al. / 2011 / USA</td>
<td>Cross-Sectional / To (i) examine demographic, biomedical, psychological, and social factors possibly related to QOL and to see whether these differed before and after LTx (ii) identify which factors were related to QOL outcomes, separately by group (iii)undertake multivariate analysis to identify factors that are critical for QOL and (iv)to compare national norms for Quality Metric’s SF-36, to demonstrate the status of this population before and following LTx / 2</td>
<td>N = 100 females with primary biliary cholangitis (n = 25 (aged 57.5 (8.1) yrs on waiting list and n = 75 (aged 58.8 (8.0) yrs) following LTx; &gt; 82% age ≥ 50 yrs / Online, mailed and in-person surveys. Time since LTx: &lt; than 1 year to &gt; than 17 yrs.</td>
<td>HRQOL – SF-36 / Valid, reliable CES-D / valid, reliable Fear/Anxiety scale / self-developed, not provided</td>
<td>MCS post-tx = 46.2 (11.7) years 14.9(11.1) Scores not provided</td>
<td>MCS scores lower than normative sample, suggesting problems with mental health. 39% of sample qualified for major depression based on CES-D cut-off scores. Trends in negative mood states unclear from cross-sectional design. Limited data for early recovery period (n = 4 less than 3 mo postoperatively)</td>
</tr>
<tr>
<td>Leyendecker et al. / 1993 / Germany</td>
<td>Cross-sectional / To describe physical and psychological status and complaints, ability to perform ADLS, quality of life / 1</td>
<td>N = 45 (26 male, 19 female, aged 46 years); Time since transplants 3-19 mo, mean 9 mo / mailed survey</td>
<td>Mood – Mehrdimensionaler Survey / not provided</td>
<td>43% had moderate to severe anxiety; 45% had moderate depressive; 53% had moderate</td>
<td>Prevalence of anxiety, depression and anger established, trends not identified. Limited generalizability (sample &lt; 3 mo after LTx)</td>
</tr>
<tr>
<td>Author/ Date/ Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics /Setting)</td>
<td>Measures/ Validity and reliability</td>
<td>Primary outcomes /secondary outcomes</td>
<td>Relevant outcome(s) and Limitations</td>
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<tr>
<td>Moore et al. / 1997 / Australian</td>
<td>Prospective / Controlled investigation of anxiety, mood, cognitive functioning, coping styles, relationship factors and QOL. / There would be (i) Reduced negative mood states tension/anxiety, depression, anger/hostility, fatigue and confusion, improved in vigour (ii) Improved QOL and physical well-being, appetite (iii) Well-being by return to work or other duties / Pre OLT (T0), 1 mo(T1), 3 mo(T2), 9 mo(T3) and 12 mo(T4) postoperatively.</td>
<td>N = 32, (22 male, 10 female) 44.19 (12.44) years / n = 10 controls with liver disease, n = 10 healthy volunteers</td>
<td>Mood States – POMs / Valid, Reliable</td>
<td>Anxiety – Depression</td>
<td>OLT recipients group had reduction in depression and anxiety, no change in LD or HC groups over time. Recommend to examine discrete episodes of anxiety which may be present following OLT. Did not account for multiple testing effects of their variables. Small sample.</td>
</tr>
<tr>
<td>Perez-San Gregorio / 2005 / Spain</td>
<td>Prospective / To (i) compare symptoms of anxiety and depression in the intensive care unit (ICU) and after discharge from ICU (ii) analyze the influence that mental health of close relatives of liver tx recipients has on symptoms of anxiety and depression of liver tx recipients in ICU and post-ICU / 2</td>
<td>N = 48 (34 male, 14 female) aged 51.15(8.57) years / in hospital</td>
<td>Anxiety and Depression – HADS / Valid, reliable</td>
<td>Anxiety ICU 7.08 Post-ICU 5.64 (p = .097)</td>
<td>Low levels of anxiety in and following ICU discharge; depression levels significantly lower after ICU discharge; timing of outcome measurement and length of stay in each area unknown; possible sex bias</td>
</tr>
<tr>
<td>Perez-San Gregorio et al. / 2010 / Spain</td>
<td>Prospective, repeated measures / To compare HRQL in liver transplant patients pre and post-tx / 4 data collection time points (Pre-tx (T0), then 3(T1), 6(T2) and 12(T3) mo post-tx</td>
<td>N = 27 (19 male, 8 female), aged 51.67 years / community</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Pre-Tx 3 Mo postTx MH 50.40 75.40 (p = .001) RE 35.06 77.77 SF 40.74 72.22 Anxiety/Depression Pre-Tx 3 Mo postTx 1.85 1.26 (p = .002)</td>
<td>Small sample, mental health improved post tx, however slightly lower scores than normative sample; mild to moderate levels of depression/anxiety evident at 3 mo</td>
</tr>
<tr>
<td>Perez-San Gregorio et al. / (2013) / Spain</td>
<td>Prospective, repeated measures / To compare the anxiety and depressive symptomology in hospital postoperatively (T0) and 12 months(T1) post tx</td>
<td>N = 34 (27 male, 7 female), aged 51.45(8.28) years / hospital and community</td>
<td>HADS – valid, reliable</td>
<td>T0 HADS – A = 5.04(3.85) HADS – D = 3.36(2.86)</td>
<td>Small sample, low levels of anxiety and depression at baseline, timing of measurement unclear</td>
</tr>
<tr>
<td>Pieber et al. / 2006 / Austria</td>
<td>To evaluate endurance capacity, muscle strength and QOL before and post tx (Pre-tx (T0), 1-2 mo (T1), and after 3 years (T2) post tx</td>
<td>N = 15 (10 male, 5 female), aged 52.2 (11.1) years / community</td>
<td>HRQL – SF-36 / Valid, reliable</td>
<td>Pre-Tx 1-2mo post tx MH 64 79 RE 46 80 SF 40 80</td>
<td>Small sample, OLT recipients reported similar mental health and social functioning but significantly more problems</td>
</tr>
<tr>
<td>Author/Date/Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics/Setting)</td>
<td>Measures/Validity and reliability</td>
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<tr>
<td>Ratcliffe et al. / 2002 / England</td>
<td>Prospective, repeated measures / To assess pre and post transplantation HRQL of liver recipients / pre-tx (T0), 3 (T1), 6 (T2), 12 (T3) and 24 (T4) mo post tx</td>
<td>N = 455 (233 male, 222 female, aged 15 to &gt; 60 yrs; 68% &gt; 46 yrs); longest waiting time for OLT was 14 mo / mailed survey</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>MH Pre-Tx 62.06 3 Mo Post 69.83 (p&lt;.001)</td>
<td>Mental health improved after OLT surgery but remained below normative sample. Specific negative mood states not identified.</td>
</tr>
<tr>
<td>Riether et al. / 1992 / USA</td>
<td>Prospective, repeated measures / To (i) document sickness related dysfunction and recovery in liver and heart tx candidates and recipients (ii) compare psychological and neurocognitive profiles of heart and liver tx candidates and recipients and (iii) assess usefulness of psychometric instruments / (i) OLT candidates will report more sickness-related dysfunction and have more neurocognitive deficits than heart tx (ii) heart tx recipients will report a better QOL and less medical disability (iii) anxiety and depressive symptoms will decrease, approaching normal values by 1 year post tx (v) neurocognitive deficits as measured by verbal learning, visual conceptual ability and visuomotor tracking ability will be correlated with electroencephalographic evidence of delirium or encephalopathy for liver tx patients / Pre-tx(T0), 3(T1), 6(T2) and 12(T3) mo post tx</td>
<td>N = 61 OLT candidates (33 male, 28 female), aged 45.8 (12.1) years / community</td>
<td>Depression – Beck Depression Inventory / reliable, valid Anxiety – Spielberger State-Trait Anxiety Inventory (STAI)</td>
<td>Depression Pre Tx 13.0(8.4) 3 Mo post Tx 8.3(7.2) (p&lt;.024) STAI – S Pre Tx 40.9(13.8) 35.6(16.0) STAI – T Pre Tx 37.4(12.9) 35.7(13.2)</td>
<td>High loss to follow-up among OLT recipients (n = 19 at 3 mo); mild levels of anxiety and depressive symptoms evident at 3 mo</td>
</tr>
<tr>
<td>Russell et al. / 2008 / USA</td>
<td>Prospective, repeated measures / To (i) model the effects of pre and post LTx clinical covariates on individual post-tx SF-36 scales and summary components and (ii) Evaluate whether HRQOL profiles differ as a function of liver transplantation and Hep C Virus / 4 – pre-tx, (T0), 1 (T1), 3 (T2), 6 (3) and 12 (T4) mo post-tx</td>
<td>N = 104 with pre/post data, aged 53.5 (7.8) yrs, 73% male, 27% female, 51% with Hep C Virus, 26% with metabolic liver disease / clinic</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Combined mean aggregate scores for 1 and 3 mo MH =71(22) RE = 66(42) MCS = 49(12) BAI = 10(7); mild to moderate anxiety</td>
<td>Prevalence of anxiety 20%, prevalence of depression 22% but SF-36 scores similar to those of normative sample. SF-36 may not be as sensitive to changes in affect as disease specific measures. Combined mean aggregate score provided for each</td>
</tr>
</tbody>
</table>
### Author/Date/Country

**Van den Berg-Emons et al. / 2006/Netherlands**  
**Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)**  
Cross-sectional / To assess severity of fatigue in liver transplant recipients / 1  
**Sample (Characteristics /Setting)**  
N = 96 (n = 45 male, n = 51 female), aged 51.8(12.7) yrs. Time since transplant 52 days – 15.4 years / clinic  
**Measures/Validity and reliability**  
HRQL – SF-36 / valid, reliable  
**Primary outcomes /secondary outcomes**  
MH = 71.7(19.3)  
RE = 73.0(39.9)  
**Relevant outcome(s) and Limitations**  
MH and RE scale scores lower than; cross-sectional number of participants < 3 mo postoperatively unknown, MH and RE in early recovery period unclear

**Wang et al. / (2012) / China**  
**Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)**  
Cross-sectional / To investigate HRQL post OLT surgery > 2 months to up to 5 years postoperatively and compare to healthy controls and those with end stage liver disease/ 1 /  
**Sample (Characteristics /Setting)**  
N = 60 post liver transplant aged 48.9(8.7) yrs, 95% male, 92% HCV, 3% HBV, 5% ETOH  
**Measures/Validity and reliability**  
HRQL – SF – 36, valid, reliable  
**Primary outcomes /secondary outcomes**  
MH = 72.87(19.32)  
**Relevant outcome(s) and Limitations**  
MH scores lower compared to healthy controls (MH 86.9(13.56); cross-sectional; participants < 3 months postoperatively unknown

**Younoussi et al. / 2000 / USA**  
**Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)**  
Cross-sectional / To measure the impact of OLT on patients’ HRQL / 2  
**Sample (Characteristics /Setting)**  
N = 22, aged 50.2 (12) yrs. Time since OLT 2-23 mo.  
**Measures/Validity and reliability**  
HRQL – SF-36 / valid, reliable  
**Primary outcomes /secondary outcomes**  
MCS = 49  
MH = 73  
RE = 85  
**Relevant outcome(s) and Limitations**  
Mental health similar to normative sample; small sample. Sex of participants not specified
### Appendix C: Quantitative Studies of Fatigue and Fatigue Impact in the First 3 Months Following OLT Surgery

<table>
<thead>
<tr>
<th>Author/Date/Country</th>
<th>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</th>
<th>Sample (Characteristics /Setting)</th>
<th>Measures/Validity and reliability</th>
<th>Primary outcomes /secondary outcomes</th>
<th>Relevant outcome(s) and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasker et al. / 2011 / USA</td>
<td>Cross-Sectional / To (i) examine demographic, biomedical, psychological, and social factors possibly related to QOL and to see whether these differed before and after LTx (ii) identify which factors were related to QOL outcomes, separately by group (iii) undertake multivariate analysis to identify factors that are critical for QOL and (iv) to compare national norms for Quality Metric’s SF-36, to demonstrate the status of this population before and following LTx / 2</td>
<td>N = 100 females with primary biliary cholangitis (n = 25 (aged 57.5 (8.1) yrs on waiting list and n = 75 (aged 58.8 (8.0) yrs following LTx; &gt; 82% of sample over aged ≥ 50 yrs / On-line, mailed and in-person surveys. Time since LTx: &lt; than 1 year to &gt; than 17 yrs</td>
<td>Fatigue – Fatigue Impact Scale (FIS) / Valid, reliable</td>
<td>80% of sample scored 80 or greater on the FIS, indicating “moderate” fatigue. Fatigue interfered negatively with cognitive, psychosocial and physical functioning.</td>
<td>Fatigue severity in early recovery period not sufficiently examined (n = 3 &lt; than 3 mo postoperatively). Results not generalizable to males.</td>
</tr>
<tr>
<td>Moore et al. / 1997 / Australia</td>
<td>Prospective / Controlled investigation of anxiety, mood, cognitive functioning, coping styles, relationship factors and QOL. / There would be (i) Reduced negative mood states tension/anxiety, depression, anger/hostility, fatigue and confusion, improved in vigour (ii) Improved QOL and physical well-being, appetite (iii) Well-being by return to work or other duties / 5 - Pre OLT (T0), 1 mo(T1), 3 mo(T2), 9 mo(T3) and 12 mo(T4) postoperatively.</td>
<td>N = 32, 22 male, 10 female, mean age 44.19 yrs ± 12.44 / community N = 10 controls with liver disease, N = 10 healthy volunteers.</td>
<td>POMS fatigue-inertia subscale Valid, Reliable</td>
<td>T1            T2</td>
<td>Fatigue 8.43(4.6)  5.69 (3.8)</td>
</tr>
<tr>
<td>Perez-San Gregorio et al. / 2010 / Spain</td>
<td>Prospective, repeated measures / To compare HRQOL in liver transplant patients pre and post-tx / 4 - (pre-tx (T0), then 3(T1), 6(T2) and 12(T3) mo post-tx</td>
<td>N = 27 (19 male, 8 female), aged 51.67 years / community</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Pre-Tx 25.07  3 Mo Post Tx VT 62.40(p = .000)</td>
<td>Small sample; vitality scores improved post tx, however lower compared to normative sample; specific results for fatigue not provided</td>
</tr>
<tr>
<td>Pieber et al. / 2006 / Austria</td>
<td>To evaluate endurance capacity, muscle strength and QOL before and post tx / 4 data collection points (pre-tx (T0), 1-2 mo (T1), and after 3 years (T2) post tx)</td>
<td>N = 15 (10 male, 5 female), aged 52.2 (11.1) yrs / community</td>
<td>HRQL – SF-36 / Valid, reliable</td>
<td>Pre-Tx 32  1-2 Mo Post Tx VT 53(p = .000)</td>
<td>Small sample; vitality scores improved post tx however significantly lower compared to normative; specific trends for fatigue not discernable</td>
</tr>
<tr>
<td>Author/ Date/ Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics /Setting)</td>
<td>Measures/ Validity and reliability</td>
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<tr>
<td>Ratcliffe et al. / 2002 / United Kingdom</td>
<td>Prospective, repeated measures / To assess pre and post transplantation HRQL of liver recipients / 5 - pre-tx (T0), 3 (T1), 6 (T2), 12 (T3) and 24 (T4) mo post tx</td>
<td>N = 455 (233 male, 222 female, aged 15 to &gt; 60 yrs; 68% &gt; 46 yrs); longest waiting time for OLT was 14 mo / mailed survey</td>
<td>HRQL SF-36 VT / valid, reliable</td>
<td>Pre-Tx  3 Mo Post Tx VT  30  47</td>
<td>Vitality scores improved post tx but significantly below normative sample. Specific result for fatigue not provided. Trends in recovery of fatigue not identifiable. Low response rate (37%)</td>
</tr>
<tr>
<td>Rodrigue et al. / 2010 / USA</td>
<td>Cross-sectional /To (i) characterize nature and severity of fatigue and sleep quality before and following OLT (ii) assess the relationship between fatigue and sleep quality and QOL and (iii)identify their multivariate correlates / Fatigue and sleep quality would be prevalent in patients before and after OLT, fatigue severity would be associated with low QOL, and psychological factors would be predictive of fatigue and sleep disturbance severity / T0 (before OLT), T1 (following OLT)</td>
<td>N = 110 candidates (52.1±8.1 yrs, 45% female, 50% had HCV, 34.5% ad alcohol-induced ESLD); Time to OLT 302(322.5) days N = 94 OLT (aged 55.0±10 yrs, 39% female; 52% HCV, 36% alcohol-induced ESLD); Time since OLT 760.8 (593.3) days</td>
<td>Multidimensional Fatigue Symptom Inventory Short Form / valid, reliable</td>
<td>72% had high fatigue severity; 65% had fatigue 5 or more days/week</td>
<td>Small sample &lt; 3 mo postoperatively (n = 3); OLT recipients with severe fatigue had greater mood disturbance (OR = 1.06, p = .04, 95% CI = 1.02-1.10)</td>
</tr>
<tr>
<td>Russell et al. / 2008 / USA</td>
<td>Prospective, repeated measures / To (i) model the effects of pre and post LTx clinical covariates on individual pre-tx SF-36 scales and summary components and (ii) Evaluate whether HRQOL profiles differ as a function of liver transplantation and Hep C Virus / 4 (pre-tx, (T0), 1 (T1), 3 (T2), 6 (3) and 12 (T4) mo post-tx)</td>
<td>N = 104 with pre/post data, aged 53.5 (7.8) yrs, 73% male, 27% female, 51% with Hep C Virus, 26% with metabolic liver disease / clinic</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Combined mean aggregate VT score = scores 43(26)</td>
<td>Combined mean aggregate score provided for vitality. Trends in vitality could not be determined. Specific results for fatigue not provided. Possible sex bias.</td>
</tr>
<tr>
<td>Van den Berg-Emons et al. / 2006 / Netherlands</td>
<td>Cross-sectional /To assess severity of fatigue in liver transplant recipients / 1</td>
<td>N = 96 (n = 45 male, n = 51 female), aged 51.8(12.7) yrs. Time since transplant 52 days – 15.4 years / clinic</td>
<td>Fatigue Severity Scale (FSS) / valid, reliable Multidimensional Fatigue Inventory (MFI-20)</td>
<td>FSS  = 4.66(1.56)</td>
<td>Scores for physical fatigue and reduced activity were significantly higher (more fatigue) than the scores on reduced motivation and mental fatigue subscale, 66% of patients experienced fatigue, and 44% of all patients experienced severe fatigue; SF-36 VT scores lower compared to normative sample; cross-sectional, number of participants &lt;3 mo postoperatively unknown</td>
</tr>
<tr>
<td>Author/ Date/ Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics /Setting)</td>
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<tr>
<td>Wang et al. / (2012) / China</td>
<td>Cross-sectional / To investigate HRQL post OLT surgery &gt; 2 months to up to 5 years postoperatively and compare to healthy controls and those with end stage liver disease/ 1 /</td>
<td>N = 60 post liver transplant aged 48.9(8.7) yrs, 95% male, 92% HCV, 3% HBV, 5% ETOH</td>
<td>HRQL – SF – 36, valid, reliable</td>
<td>VT = 66.54(18.30)</td>
<td>VT scores similar to normal healthy sample; cross-sectional; participants &lt; 3 months postoperatively unknown</td>
</tr>
<tr>
<td>Younoussi et al. / 2000 / USA</td>
<td>Cross-sectional / To measure the impact of OLT on patients’ HRQL / 2</td>
<td>N = 22, aged 50.2 (12) yrs. Time since OLT 2-23 mo.</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>VT = 54</td>
<td>Small sample; VT scores lower compared to normative sample; moderate level of fatigue. Sex characteristics not described</td>
</tr>
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</table>
### Appendix D: Quantitative Studies of Function in the First 3 Mo Following OLT Surgery

<table>
<thead>
<tr>
<th>Author/ Date/ Country</th>
<th>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</th>
<th>Sample (Characteristics/ Setting)</th>
<th>Measures/ Validity and reliability</th>
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<th>Relevant outcome(s) and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyer et al. / 1999 / Denmark</td>
<td>Prospective / To study the influence of OLT surgery on physical fitness during the first postoperative year / 4: T0 (Pre-OLT), T1 (1 mo), T2 (3 mo), T3 (6 mo), T4 (12 mo)</td>
<td>N = 38 (23 male, 15 female) average age 45 years / Clinic</td>
<td>6-minute walk test / valid, reliable</td>
<td>Baseline = 462(26) m T1 data not provided T2 - 555(23) meters</td>
<td>Walking distance improved at 3 mo compared to baseline; small sample, high loss to follow up (final data only available for 17 participants)</td>
</tr>
<tr>
<td>Bonsel et al. / 1992 / Netherlands</td>
<td>Prospective / To document quality of life pre and post orthotopic liver transplantation / cross-sectional and longitudinal (pre-tx, then at 3 mo)</td>
<td>N = 46 (31 male, 15 female) aged 42.6(11.1) years / community</td>
<td>Nottingham Health Profile Mobility Scale/ valid, reliable Karnovsky Performance Status (KPS) Scale / valid, reliable Activities of daily life (ADL) from Dutch National Survey on Health Problems / not provided</td>
<td>At 3 mo NHP Mobility subscale = 27 KPS scale = 70 ADL = 9.2(1.4)</td>
<td>Restrictions on mobility dimension of NHP correlated with presence of bone pain (r = 0.57); contrasting results of functioning - according to KPS scale, OLT recipients able to care for self however unable to carry out normal activity or do active work, whereas ADL dimension of Dutch Health Survey suggested that OLT recipients had similar ADL scores compared to normative sample; small samples with both study designs, (n = 18 in cross-sectional and n = 14 in longitudinal)</td>
</tr>
<tr>
<td>Eshelman et al. / 2010 / USA</td>
<td>Prospective / Observe mental and physical QOL over time in OLT recipients with and without alcohol-induced liver cirrhosis / T0 (before OLT surgery) T1 (1 mo post-tx), T2 (6 mo post tx)</td>
<td>N = 65 (n = 14 with alcohol-induced liver cirrhosis; n = 31 without), aged 54(14) / mailed survey</td>
<td>HRQL – SF-36 v2/ valid, reliable</td>
<td>PCS scores similar for both groups (PCS = 32 and 34).</td>
<td>Low function compared to normative sample, minimal improvement compared to pre-OLT; sex characteristics of participants not described. ADL and IADLS of OLT recipients unknown.</td>
</tr>
<tr>
<td>Foroncewicz et al. / 2011 / Poland</td>
<td>Prospective / To examine whether 6 minute walk test in combination with subjective rating of perceived exertion could be used to evaluate exercise capacity among liver transplant recipients / 2 (7 and 14 days postoperatively)</td>
<td>N = 11 (8 male, 3 female) aged 48.2 yrs / in-patient</td>
<td>6-min walk test (6MWT) / valid, reliable Borg Scale (self-perception of exertion)</td>
<td>Day 7 Day 14 6MWT 326.7m 421m Borg 8-12/20 8-11/20</td>
<td>Small sample; liver transplant recipients achieved half of the distance POD 7, and more than two thirds of the walking distance compared to normative sample on POD 14. Self-perception of exertion scores ranged between mild to moderate</td>
</tr>
<tr>
<td>Author/Date/Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics /Setting)</td>
<td>Measures/ Validity and reliability</td>
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<tr>
<td>Geevarghese et al / 1998 / USA</td>
<td>Prospective / To describe quality of life and physical functioning outcomes / 10 - Pre-tx(T0), 3mo(T1), 6mo(T2), 1yr (T3), 2 yrs(T4), 3yrs (T5), 4yrs (T6), 5 yrs(T7) 6 yrs (T8) post tx</td>
<td>N = 100 (68 male, 32 females), aged 46(1) years (range 14-64 years) / clinic</td>
<td>Karnovsky Performance Status Scale / valid, reliable</td>
<td>At 3 mo Able (80-100) 52% Unable (50-70) 41% Disabled (10-40) 7%</td>
<td>Over one third of sample requiring varying degrees of personal assistance with daily activities and unable to work; requiring frequent medical care; small sample requiring hospitalization; specific level of engagement with ADL/IADL unclear.</td>
</tr>
<tr>
<td>Krasnoff et al. / 2005 / USA</td>
<td>Prospective / To document the health related fitness, physical activity and physical HRQL over first 2 years post tx and compare outcomes between males and females / 4 data collection time points / 2(T0, 6(T1), 12(T2) and 24(T3) mo post tx.</td>
<td>N = 50 (32 male, 18 female), aged 51.4(11.8) years / community</td>
<td>HRQL – SF-36 / valid, reliable Physical Activity Scale for the Elderly (PASE) Step-Counter (steps per day)</td>
<td>At 2 mo PF = 60 RP = 60 94.9(63.3) 4559.1(2910.2)</td>
<td>Physical functioning scores significantly lower compared to normative samples; PASE scores lower compared to normative age sample; Step-counter scores similar to individuals with disabilities and chronic illness; females reported lower PASE and step-counter scores than males</td>
</tr>
<tr>
<td>Lasker et al. / 2011 / USA</td>
<td>Cross-Sectional / To (i) examine demographic, biomedical, psychological, and social factors possibly related to QOL and to see whether these differed before and after LTx (ii) identify which factors were related to QOL outcomes, separately by group (iii)undertake multivariate analysis to identify factors that are critical for QOL and (iv)to compare national norms for Quality Metric’s SF-36, to demonstrate the status of this population before and following LTx / 2</td>
<td>N = 100 females with primary biliary cholangitis (n = 25 (aged 57.5 (8.1) yrs on waiting list and n = 75 (aged 58.8 (8.0) yrs) following LTx; &gt; 82% of sample over aged ≥ 50 yrs / On-line, mailed and in-person surveys. Time since LTx: &lt; than 1 year to &gt; than 17 yrs</td>
<td>SF-36 PCS / Valid, reliable</td>
<td>PCS = 40.5(10) in OLT group</td>
<td>Function low up to 17 years post-tx. Function severity in early recovery period not sufficiently examined (n = 3 &lt; than 3 mo postoperatively). Trends in performance of ADLS and IADLSS of participants not described Fatigue explained 20% of variance in function. Results not generalizable to males. Depression explained 24% variance in whole sample (specific results for OLT recipients not provided)</td>
</tr>
<tr>
<td>Leyendecker / 1993 / Germany</td>
<td>Cross-sectional / To describe physical and psychological status and complaints, ability to perform ADLS, quality of life / 1</td>
<td>N = 45 (26 male, 19 female, aged 46 years); Time since transplants 3-19 mo, mean 9 mo / mailed survey</td>
<td>Alltag Questionnaire / not provided</td>
<td>33% had moderate problems with or could not cope with ADLS</td>
<td>Range of ADLS provided. Number of participants at 3 mo not specified, limited generalizability. Possible measurement bias.</td>
</tr>
<tr>
<td>Author/ Date/ Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics /Setting)</td>
<td>Measures/ Validity and reliability</td>
<td>Primary outcomes /secondary outcomes</td>
<td>Relevant outcome(s) and Limitations</td>
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<tr>
<td>Perez-San Gregorio et al. / 2010 / Spain</td>
<td>Prospective, repeated measures / To compare HRQL in liver transplant patients pre and post-tx / 4 data collection time points (Pre-tx (T0), then 3(T1), 6(T2) and 12(T3) mo post-tx</td>
<td>N = 27 (19 male, 8 female), aged 51.67 years / community</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>PreTx 3 Mo Post Tx PF 31.66 62.4(p = .000) RP 9.25 40.55(p=.004) SF 40.75 72.22(p=.000)</td>
<td>Small sample; poor physical function and difficulty with role-related activities at 3 mo compared to normative. Range of ADL and IADLs not provided.</td>
</tr>
<tr>
<td>Pieber et al. / 2006 / Austria</td>
<td>To evaluate endurance capacity, muscle strength and QOL before and post tx (Pre-tx (T0), 1-2 mo (T1), and after 3 years (T2) post tx</td>
<td>N = 15 (10 male, 5 female), aged 52.2 (11.1) years / community</td>
<td>HRQL – SF-36 / Valid, reliable</td>
<td>PreTx 1-2 Mo Post Tx PF 43 68 RP 20 30 SF 40 80 Exercise testing – Incremental cycle ergometer protocol ATVO2 10.3(3) 9.4(2.7) Watt at AT 39.4(16.5) 34.8(15.6) Peak Torque (Nm) 98.9(33) 95.7(33.4) Peak Torque (Nm/kg) 128.3(61.9) 136.6(38.9) Hand grip Strength 53.4(31.4) 47.1(13.1)</td>
<td>Small sample, physical functioning improved at 1-2 mo postoperatively however significantly lower compared to normative sample; exercise performance levels similar to pre-op levels.</td>
</tr>
<tr>
<td>Ratcliffe et al. / 2002 / United Kingdom</td>
<td>Prospective, repeated measures / To assess pre and post transplantation HRQL of liver recipients / pre-tx (T0), 3 (T1), 6 (T2), 12 (T3) and 24 (T4) mo post tx</td>
<td>N = 455 (233 male, 222 female, aged 15 to &gt; 60 yrs; 68% &gt; 46 yrs); longest waiting time for OLT was 14 mo / mailed survey</td>
<td>HRQL SF-36 / valid, reliable</td>
<td>At 3 mo PF = 55 RP = 24.77 SF = 64.77</td>
<td>Poor function and difficulty with role-related activities and social functioning at 3 mo. Range of ADLS or IADLS not provided. Earlier outcomes of function since surgery not measured.</td>
</tr>
<tr>
<td>Rodrigue et al. / 2010 / USA</td>
<td>Cross-sectional /To (i) characterize nature and severity of fatigue and sleep quality before and following OLT (ii) assess the relationship between fatigue and sleep quality and QOL and (iii)identify their multivariate correlates / Fatigue and sleep quality would be prevalent in patients before and after OLT, fatigue severity would be associated with low QOL, and psychological factors would be predictive of fatigue and sleep disturbance severity / T0 (before OLT), T1 (following OLT)</td>
<td>N = 110 candidates (52.1±8.1 yrs, 45% female; 50% HCV, 34.5% alcohol-induced ESLD); Time to OLT 302 (322.5) days</td>
<td>HRQL SF-36 / valid, reliable</td>
<td>Fatigue High Low (n = 72) (n = 23) PF 39 35 (p &lt;.001) RP 35 45 (p &lt;.001) SF 40 49 (p &lt;.001)</td>
<td>Entire sample had poor functioning post OLT surgery. Fatigue had a significant negative impact on function. Small sample of participants in early recovery period (n = 4). Trends in function not understood. ADLS and IADLS not sufficiently described.</td>
</tr>
<tr>
<td>Author/Date/Country</td>
<td>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</td>
<td>Sample (Characteristics/Setting)</td>
<td>Measures/Validity and reliability</td>
<td>Primary outcomes/secondary outcomes</td>
<td>Relevant outcome(s) and Limitations</td>
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<tr>
<td>Russell et al. / 2008 / USA</td>
<td>Prospective, repeated measures / To (i) model the effects of pre and post LTx clinical covariates on individual post-tx SF-36 scales and summary components and (ii) Evaluate whether HRQOL profiles differ as a function of liver transplantation and Hep C Virus / 4 – pre-tx, (T0), 1 (T1), 3 (T2), 6 (3) and 12 (T4) mo post-tx</td>
<td>N = 104 with pre/post data, aged 53.5 (7.8) yrs, 73% male, 27% female; 51% Hep C Virus, 26% metabolic liver disease / clinic</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>Combined mean aggregate score for all measurement occasions</td>
<td>Poor function, low compared to normative sample. Trends in function not identifiable. Possible sex bias.</td>
</tr>
<tr>
<td>Van den Berg-Emons et al. / 2006/Netherlands</td>
<td>Cross-sectional / To assess severity of fatigue in liver transplant recipients / 1</td>
<td>N = 96 (n = 45 male, n = 51 female), aged 51.8(12.7) yrs. Time since transplant 52 days – 15.4 years / clinic</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>PF = 67.8(24.1) RP = 53.4(44.2)</td>
<td>Poorer physical function scores compared to SF-36 scores of normative sample; trend in recovery of physical function unclear postoperatively; due to cross-sectional design, number of participants &lt; 3 mo post-tx unknown</td>
</tr>
<tr>
<td>Wang et al. / (2012) / China</td>
<td>Cross-sectional / To investigate HRQL post OLT surgery &gt; 2 months to up to 5 years postoperatively and compare to healthy controls and those with end stage liver disease/ 1</td>
<td>N = 60 post liver transplant aged 48.9(8.7) yrs, 95% male, 92% HCV, 3% HBV, 5% ETOH</td>
<td>HRQL – SF – 36, valid, reliable</td>
<td>PF = 79.23(18.29)</td>
<td>PF scores lower compared to healthy sample; trend in recovery of physical function over time unclear; cross-sectional; participants &lt; 3 months postoperatively unknown</td>
</tr>
<tr>
<td>Younoussi et al. / 2000 / USA</td>
<td>Cross-sectional / To measure the impact of OLT on patients' HRQL / 2</td>
<td>N = 22, aged 50.2 (12) yrs. Time since OLT 2-23 mo.</td>
<td>HRQL – SF-36 / valid, reliable</td>
<td>PCS = 41 PF = 62 RP = 47 SF = 80 CDLQ AC = 5.3</td>
<td>Poor function, low SF-36 scores compared to normative sample. Minimal difficulty with social functioning. Trends in function not identifiable. ADLS not clearly described. CDLQ AC domain suggests that activity level comparable to those living with chronic liver disease. Small sample.</td>
</tr>
</tbody>
</table>
### Appendix E: Qualitative Study Describing Pain, Mood, Fatigue, and Function 3 Months Following OLT Surgery

<table>
<thead>
<tr>
<th>Author/Date/Country</th>
<th>Study Design/Purpose / Setting / number of measurement occasions</th>
<th>Sample / Setting</th>
<th>Relevant Outcomes/Limitations</th>
</tr>
</thead>
</table>
| Jones et al. / 2005 / USA | Qualitative, content analysis method / What is the post-transplant experience of liver organ experience as assessed at 3 points of time during the first year of recovery? / Initial face to face interviews in out-patient follow up clinic, then via telephone / 6 weeks (T1), 6 mo (T2), and 12 mo (T3) post-surgery. | N = 20, 15 male mean age 43 yrs, 5 female mean age 43 yrs; N = 12 married | Major themes at 6 weeks:  
1. Physical  
   - Physical Health: post-surgical physical discomfort, organ rejection, concern with current health  
   - Medication Side Effects: Some reports of medication side effects (hirsutism, moon face)  
   - Level of Functioning: Low level, limited activities of daily living  
2. Psychological  
   - Emotions: Post-transplant euphoria, fear of organ rejection, depression  
3. Social  
   - Resources: Importance of having inpatient social support from family, medical personnel  
4. Economic  
   - Healthcare Costs (some concern)  
5. Spiritual  
   - Awakening and reawakening of spirituality (transplant is a miracle)  
Limitations: Possible recall bias, small sample |
| Naden et al. / 2011 / Norway | Qualitative / Exploratory, hermeneutic / How do patients experience their hospital stay after liver transplantation? | N = 15 (12 male, 3 female) 43.7 yrs / in hospital | Major themes at 28.3 (range18-43) days post-transplant in hospital  
1. Physical Discomfort:  
   - Varied experiences, where some participants had little pain, while others had significant pain. Some described feelings of fatigue associated with pain  
2. Comedowns experienced during rejection of transplant  
   - Half of the sample experienced rejection, and experienced frustration and had associated depressive low spirit  
3. Other psychological/mental reactions  
   - Inability to cope with their own feelings; additional surgeries to manage postoperatively complications after OLT surgery was mentally challenging and associated with depressive thoughts  
Limitations: small sample, unclear how many participants had significant pain |
### Appendix F: Study of Fatigue in Caregivers to OLT Recipients Less Than 3 Months Following Surgery

<table>
<thead>
<tr>
<th>Author/ Date/ Country</th>
<th>Study purpose (Design, Research Questions/Hypotheses/Number of measurement occasions)</th>
<th>Sample (Characteristics /Setting)</th>
<th>Measures/ Validity and reliability</th>
<th>Primary outcomes /secondary outcomes</th>
<th>Relevant outcome(s) and Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodrigue et al. / 2011 / USA</td>
<td>Cross-sectional / To determine quality of life and psychosocial functioning of spouse/partner caregivers before and after liver transplantation</td>
<td>N = 86 (n = 49 pre OLT caregivers, aged 55(9) years, 76% female; n = 37 post OLT caregivers, aged 55(9) years, 84% female). Time since OLT 26(21) mo.</td>
<td>HRQL SF-36 / valid, reliable</td>
<td>VT score: Pre-OLT 49(12) Post OLT 50(13) Fatigue-Inertia score: Pre-OLT = 9.9(5.5) Post OLT = 8.05(4.6)</td>
<td>Both groups had similar vitality scores, that were similar to the normative sample. Higher fatigue was found with the disease specific measure. No differences in fatigue were found among caregivers before and after surgery. Small sample.</td>
</tr>
</tbody>
</table>
Appendix G: Study Information for OLT Recipients

What Happens to Everyday Activities, Pain, Mood, and Fatigue in the Early Recovery Period After Liver Transplantation Surgery?

What is the study purpose?

- A team of researchers are trying to understand the recovery period for liver transplant recipients during hospitalization and after they are discharged from hospital.

- This study is designed to understand how liver transplant recipient’s function, pain, mood and fatigue may change after hospital discharge from liver transplantation surgery.

- A secondary aim of the study is to understand how the level of function of the liver transplant recipient during the early recovery period affects the level of fatigue of their primary caregiver.

Who qualifies?

- Any liver transplant recipient who receives their donated liver from a deceased donor, and (1) is a resident of Ontario (2) is over 18 years of age (3) speaks fluent English and (4) is being followed by the University Health Network transplantation follow-up clinic.

Caregivers of liver transplant recipients who agree to participate in this study may also be qualified to participate in this study if they (1) are a residents of Ontario (2) are over 18 years of age and (3) speak fluent English.

What is involved?

- Before you are discharged from the hospital, the researcher will ask you for your consent to participate in this study. She will answer any questions you may have.

- If you agree to participate in the study, she will give you a questionnaire that will take about 20-30 minutes to complete.
**What is involved?**

- When you come to see your transplant doctor in the clinic on the 4th, 8th, and 12th week after discharge, the researcher will give you the same questionnaires that will take between 30 minutes to complete.

- Caregivers who agree to participate in this study will be asked to complete a questionnaire that will take about 10 minutes before the liver transplant recipient is discharged from the hospital. If the caregiver accompanies the recipient to their scheduled clinic appointment at the 4th, 8th, and 12th week following discharge, they will be asked to complete the same questionnaire at these appointments that will take approximately 10 minutes to complete.

**Why should I participate?**

- Liver transplant recipients' return to everyday activities, and management of symptoms such as pain, changes in mood and fatigue, and the fatigue of their primary caregivers have not been well studied in the first three months after liver transplantation. Your participation in this study will help healthcare providers understand this recovery period better for both liver transplant recipients and their primary caregivers.

- New knowledge may help us improve our clinical practice, and inform future liver transplant recipients on how to improve their activity levels and manage their symptoms better after hospital discharge, as well as help us better prepare future caregivers for this time period.

**Who can I contact for questions?**

You may contact:

Salima S. J. Ladak  
(416) 416-340-4800  
extension 2772

OR  
E-mail her at Salima.Ladak@uhn.on.ca
Appendix H: Study Information for Primary Caregivers

What Happens to Everyday Activities, Pain, Mood, and Fatigue in the Early Recovery Period After Liver Transplantation Surgery?

What is the study purpose?

- A team of researchers are trying to understand the recovery period for liver transplant recipients during hospitalization and after they are discharged from hospital.

- This study is designed to understand how liver transplant recipient’s function, pain, mood and fatigue may change after hospital discharge from liver transplantation surgery.

- A secondary aim of the study is to understand how the level of function of the liver transplant recipient during the early recovery period affects the level of fatigue of their primary caregiver.

Who qualifies?

- Any liver transplant recipient who receives their donated liver from a deceased donor, and (1) is a resident of Ontario (2) is over 18 years of age (3) speaks fluent English and (4) is being followed by the University Health Network transplantation follow-up clinic.

- Caregivers of liver transplant recipients who agree to participate in this study may also be qualified to participate in this study if they (1) are a residents of Ontario (2) are over 18 years of age and (3) speak fluent English.

What is involved?

- Before you are discharged from the hospital, the researcher will ask you for your consent to participate in this study. She will answer any questions you may have.

- If you agree to participate in the study, she will give you a questionnaire that will take about 20-30 minutes to complete.
What is involved?

- When you come to see your transplant doctor in the clinic on the 4th, 8th, and 12th week after discharge, the researcher will give you the same questionnaires that will take between 30 minutes to complete.

- Caregivers who agree to participate in this study will be asked to complete a questionnaire that will take about 10 minutes before the liver transplant recipient is discharged from the hospital. If the caregiver accompanies the recipient to their scheduled clinic appointment at the 4th, 8th, and 12th week following discharge, they will be asked to complete the same questionnaire at these appointments that will take approximately 10 minutes to complete.

Why should I participate?

- Liver transplant recipients' return to everyday activities, and management of symptoms such as pain, changes in mood and fatigue, and the fatigue of their primary caregivers have not been well studied in the first three months after liver transplantation. Your participation in this study will help health care providers understand this recovery period better for both liver transplant recipients and their primary caregivers.

- New knowledge may help us improve our clinical practice, and inform future liver transplant recipients on how to improve their activity level and manage their symptoms better after hospital discharge; as well as help us better prepare future caregivers for this time period.

Who can I contact for questions?

You may contact:

Salima S. J. Ladak  
(416) 416-340-4800  
extension 2772  
OR  
E-mail her at  
Salima.Ladak@uhn.on.ca
Appendix I: OLT Recipient Consent Form

Date ______/_____/_____
Day   Mo   Year

Participant Study Number

LIVER TRANSPLANT RECIPIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: Symptoms and Function During the Early Recovery Period following Orthotopic Liver Transplantation Surgery

NAME OF PRINCIPAL INVESTIGATOR: Kathryn Nichol, RN, PhD

NAME OF STUDENT PRINCIPAL INVESTIGATOR (Student PI): Salima S. J. Ladak, RN(EC), MN, PhD Candidate

CONTACT INFORMATION STUDENT PI:
Salima S. J. Ladak, RN(EC), MN, PhD Candidate
Toronto General Hospital
200 Elizabeth Street
3 EN - Department of Anesthesia and Pain Management
Toronto, Ontario
M5G-2C4
(416) 340-4800 ext 2772
Salima.ladak@uhn.on.ca

INTRODUCTION:

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

BACKGROUND/PURPOSE:

Liver transplantation surgery is on the rise in Canada, however there is little scientific evidence that explains the ability of liver transplant recipients level of function (ability to perform usual daily activities) in the first three months following surgery. There is some scientific evidence suggesting that symptoms such as pain, mood changes and fatigue may be potential problems during the first three months after liver transplant recipients go home from hospital. However, the impact of these symptoms on ability of liver transplant recipients’ function has not been
clearly described. It is also not clear whether the ability of liver transplant recipients’ level of function affects the fatigue of their primary caregivers. You have been asked to participate in a study that is designed to better understand the impact of these symptoms on your level of function while you are in the hospital and when you go home from the hospital after your transplantation surgery. The study will also look at whether there is a relationship between your level of function and your primary caregiver’s fatigue. Information from this research study will be used to develop future treatments that help liver transplant recipients manage these symptoms and improve their ability to perform usual daily activities.

**STUDY DESIGN:**
Questionnaires will be given to study participants at 4 different time points during the first 3 months after liver transplantation surgery to understand their pain, mood, fatigue and ability to perform usual daily activities. You will be given 2 questionnaires while you are in hospital, and 1 questionnaire at the 4th, 8th and 12th week follow-up clinic appointment after you leave the hospital. 58 liver transplant recipients at University Health Network and their caregivers will be enrolled in this study.

**PROCEDURES:**
1. The study will involve completing questionnaire booklets. You will be asked to complete 2 questionnaire booklets while you are in the hospital on the 4th or 5th day after your liver transplantation surgery. The first questionnaire booklet will ask you about your personal and medical information and the second questionnaire booklet will ask you about your level of activity, pain, mood and fatigue. These booklets will take about 35 minutes to complete.
2. You will be asked to complete the second questionnaire booklet again at your 4th, 8th and 12th week scheduled outpatient clinic appointment at the transplant clinic. This questionnaire will take approximately 30 minutes to complete. You will be given a private space in the clinic to complete this questionnaire at each clinic appointment. You can choose to complete the questionnaire before or after your clinic appointment.
3. If you are unable to complete the questionnaire at your scheduled clinic appointments outlined above, you can take the questionnaire home, and the PI will follow up with a phone call so that you can complete the survey with her over the telephone. During the telephone call, the PI will read the questions to you and you will provide her with your responses, which she will document on her copy of the same questionnaire. If you are not available at the time the PI calls you, she will follow up the following day and the day after that if necessary.
4. If you are unable to attend the clinic appointment, the PI will contact you by telephone up to 2 times. She will read the questions to you over the telephone.
5. Two weeks before each clinic appointment, the PI will send a reminder letter via mail and remind you by telephone again at 48 hours before your appointment that you will be asked to complete the study questionnaire at your upcoming clinic appointment.
VOLUNTARY PARTICIPATION and WITHDRAWAL FROM THE STUDY:

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and change your mind later. You may refuse to answer any question you do not want to answer. You may leave the study at any time without affecting your medical care. If you decide to leave the study, the information that was collected before you leave the study will still be used in order to help answer the research question. No new information will be collected without your permission. We will give you new information that is being learned during the study that might affect your decision to stay in the study.

RISKS:

There are no medical risks if you take part in this study, but being in this study may make you feel uncomfortable. You may refuse to answer questions or stop the questionnaire at any time if there is any discomfort.

BENEFITS:

Participation in this study will not give you any direct benefit, however your participation may benefit future liver transplant recipients by educating them on what they can expect regarding pain, mood and fatigue and their ability to perform usual daily activities during the early recovery period following surgery.

CONFIDENTIALITY:

If you agree to join this study, the study investigator and her team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could identify you and includes your:

- Name, address
- Medical records that include your information on the types of medical conditions you have.
- The information that is collected for the study will be kept in a locked and secure area by the study investigator for 10 years.

Only the study team will be allowed to look at your records. The University Health Network Research Ethics Board and/or the University of Toronto Research Ethics Board may come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure that the study is following proper laws and guidelines. All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may
come from this study. Your name will be made anonymous and replaced with an identification number on all completed questionnaires.

COSTS:
You will not have to pay for any of the questionnaire booklets involved with this study. You will not be reimbursed for your time involved with this study.

RIGHTS AS A PARTICIPANT
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.
By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

CONFLICT OF INTEREST
The study investigators have an interest in completing this study. Their interests should not influence your decision to participate in this study. You should not feel pressured to join this study.

QUESTIONS ABOUT THE STUDY
If you have any questions, concerns or would like to speak to the study team for any reason, please call Salima S. J. Ladak at (416) 340-4800 extension 2772. If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (UHN REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything you discuss will be kept confidential.

CONSENT
This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to take part in this study.

<table>
<thead>
<tr>
<th>Print Study Participant’s Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

(You will be offered a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

<table>
<thead>
<tr>
<th>Print Name of Person Obtaining Consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
Appendix J: Primary Caregiver Consent Form

CAREGIVER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: Symptoms and Function During the Early Recovery Period following Orthotopic Liver Transplantation Surgery

NAME OF PRINCIPAL INVESTIGATOR: Kathryn Nichol, RN, PhD

NAME OF STUDENT PRINCIPAL INVESTIGATOR (Student PI): Salima S. J. Ladak, RN(EC), MN, PhD Candidate

CONTACT INFORMATION STUDENT PI:
Salima S. J. Ladak, RN(EC), MN, PhD Candidate
Toronto General Hospital
200 Elizabeth Street
3 EN - Department of Anesthesia and Pain Management
Toronto, Ontario
M5G-2C4
(416) 340-4800 ext 2772
salima.ladak@uhn.on.ca

INTRODUCTION:
You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish including your friends, family, and family doctor. Participation in this study is voluntary.

BACKGROUND/PURPOSE:
Liver transplantation surgery is on the rise in Canada and following surgery, primary caregivers to liver transplant recipients provide significant physical and emotional support to the recipient during their early recovery period. However, there is little scientific evidence that describes the relationship between liver transplant recipient’s pain, mood and fatigue and their level of function (ability to perform usual daily activities). As well, there is limited evidence that describes impact of the liver transplant recipients’ level of function and the impact of this
function on the fatigue of their primary caregivers. You have been asked to participate in a study that is designed to better understand the relationship between the liver transplant recipients’ level of function and the fatigue of their primary caregiver. Data from this research study will be used to develop future interventions that better prepare caregivers of liver transplant recipients for the early recovery period.

**STUDY DESIGN:**
A questionnaire will be given to study participants at 4 different time points during the first three months after liver transplantation surgery to understand their pain, mood, fatigue and ability to perform usual daily activities. 58 liver transplant recipients at University Health Network and their caregivers will be enrolled in this study.

**PROCEDURES:**
1. The study will involve the completion of 2 questionnaire booklets. The first questionnaire will ask you about your personal information. You may complete this questionnaire before the liver transplant recipient goes home from the hospital. This questionnaire will take about 10 minutes to complete.
2. The second questionnaire will ask you about your fatigue. You will be asked to complete this questionnaire on the liver transplant recipient’s 4th, 8th and 12th week scheduled outpatient clinic appointments at the transplant clinic. The questionnaire will take approximately 10 minutes to complete.
3. You will be granted a private space in the clinic to complete this questionnaire, and may complete the questionnaire before or after the liver transplant recipient’s appointment.
4. If you are unable to complete the questionnaire at each of the scheduled clinic appointments outlined above, you may take the questionnaire home. The PI will follow up with a phone call so that you can complete the questionnaire with her over the telephone. During the telephone call, the PI will read the questions to you and you will provide her with your responses, which she will document on her copy of the same questionnaire. If you are not available at the time the PI calls you, she will follow up the following day and the day after that if necessary.
5. If you are unable to accompany the liver transplant recipient to the clinic appointment, the PI will contact you by telephone up to 2 times. She will read the questions to you over the telephone.
6. Two weeks before each clinic appointment, the PI will send a reminder letter via mail and remind you by telephone again at 48 hours before the liver transplant recipient’s clinic appointment that you will be asked to complete the study questionnaire at the upcoming clinic appointment.

**VOLUNTARY PARTICIPATION and WITHDRAWAL FROM THE STUDY:**
Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and change your mind later. You may leave the study at any time without it affecting you or the care that the liver transplant recipient receives. You will not be required to provide an explanation for leaving the study. You may refuse to answer any question you do not want to answer. If you decide to leave the study, the information that was collected before you
leave the study will still be used in order to help answer the research question. No new information will be collected without your permission. We will give you new information that is being learned during the study that might affect your decision to stay in the study.

**RISKS:**
There are no medical risks if you take part in this study, but being in this study may make you feel uncomfortable. You may refuse to answer questions or stop the questionnaire at any time if there is any discomfort.

**BENEFITS:**
Participation in this study will not give you any direct benefit, however your participation may benefit caregivers of future liver transplant recipients by educating them on what they can expect regarding their level of fatigue and its relationship to the level of function of the liver transplant recipient during the early recovery period following surgery.

**CONFIDENTIALITY:**
If you agree to join this study, the study investigator and her team will collect the personal information they need for the study. Personal information is any information that could identify you and includes your:
- Name, address
- The information that is collected for the study will be kept in a locked and secure area by the study investigator for 10 years.

Only the study team will be allowed to look at your records. The University Health Network Research Ethics Board and/or the University of Toronto Research Ethics Board may come to the hospital to look at the study records and at your personal information to check that the information collected for the study is correct and to make sure that the study is following proper laws and guidelines. All information collected during this study, including your personal information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study. Your name will be made anonymous and replaced with an identification number on all completed questionnaires.

**COSTS:**
You will not have to pay for any of the questionnaire booklets involved with this study. You will not be reimbursed for your time involved with this study.

**RIGHTS AS A PARTICIPANT**
If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost.

By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.
CONFLICT OF INTEREST
The study investigators have an interest in completing this study. Their interests should not influence your decision to participate in this study. You should not feel pressured to join this study.

QUESTIONS ABOUT THE STUDY
If you have any questions, concerns or would like to speak to the study team for any reason, please call Salima S. J. Ladak at (416) 340-4800 extension 2772. If you have questions about your rights as a research participant or have concerns about this study, please call the Chair of the University Health Network Research Ethics Board (UHN REB) or the Research Ethics office number at (416) 581-7849. The REB is a group of people who oversee the ethical conduct of research studies. The UHN REB is not part of the study team. Everything you discuss will be kept confidential.

CONSENT
This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to take part in this study.

Print Study Participant’s Name ___________________________ Signature ___________________________ Date ___________________________

(You will be offered a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person Obtaining Consent ___________________________ Signature ___________________________ Date ___________________________
Appendix K: OLT Recipient General Demographic Questionnaire

RECIPIENT STUDY

DEMOGRAPHIC QUESTIONNAIRE

Study ID No. ____________________________

Today’s Date (DD/MM/YR) ____________________________

1. Sex: 
   
   □ 01 Male
   
   □ 02 Female

2. Participant Age _________________

3. Date of Surgery
   Year  Month  Day

4. Please indicate your current marital status: (Mark ONE only):
   □ 01 Single  □ 02 Common-Law  □ 03 Married
   □ 04 Divorced  □ 05 Widowed  □ 06 Separated

5. Please indicate your current employment status (Mark ONE only):
   □ 01 Employed Full Time  □ 02 Employed Part Time  □ 03 Currently not Employed
   □ 04 Self-Employed  □ 05 Retired  □ 06 Homemaker
   □ 07 Other
   ____________________________
6. Please indicate the highest education you have attained (Mark ONE only):

☐ 01 Less than high School
☐ 02 High School
☐ 03 College
☐ 04 Trade School
☐ 05 Undergraduate Degree
☐ 06 Graduate Degree
☐ 07 Did not complete
   College or University

7. The section below will be completed by study investigator.
   Reason for Liver Transplantation (Mark ONE)

☐ 01 Hepatitis C
☐ 02 Hepatitis B
☐ 03 Hepatocellular Carcinoma
☐ 04 Primary biliary cirrhosis
☐ 05 Alcohol-induced liver cirrhosis
☐ 06 Primary sclerosing cholangitis
☐ 07 Autoimmune Hepatitis
☐ 08 Cystic Fibrosis
☐ 09 Other: Please list_______________________

8. Co-Morbidities: (To be completed by study investigator; mark all that apply).

☐ 01 Stroke or TIA
   00
   01
☐ 02 Arthritis
   00
   01
☐ 03 Peripheral vascular disease
   00
   01
☐ 04 Osteoporosis
   00
   01
☐ 05 COPD, acquired ARDS or emphysema
   00
   01
☐ 06 Diabetes type I and II
   00
   01
- 07 Asthma
  - 00
  - 01

- 08 Neurological disease (MS or Parkinson’s)
  - 00
  - 01

- 09 Depression
  - 00
  - 01

- 010 Hearing Impairment (hard of hearing even with hearing aids)
  - 00
  - 01

- 011 CHF
  - 00
  - 01

- 012 Upper GI disease (hernia, ulcer, reflux)
  - 00
  - 01

- 013 MI
  - 00
  - 01

- 014 Angina
  - 00
  - 01

- 015 Anxiety or panic disorders
  - 00
  - 01

- 016 Visual Impairment (cataracts, glaucoma, macular degeneration)
  - 00
  - 01

- 017 Degenerative disc disease (back disease, spinal stenosis or severe back pain)
  - 00
  - 01

- None
  - 00
  - 01
Appendix L: Primary Caregiver General Demographic Questionnaire

DEMOGRAPHIC STUDY

PARTICIPANT QUESTIONNAIRE

Study ID No.

Today’s Date (DD/MM/YR)

1. **Sex:**
   - 01 Male
   - 02 Female

2. **Participant Age:** ________________

3. **Please indicate your current marital status:** (Mark ONE only):
   - 01 Single
   - 02 Common-Law Spouse
   - 03 Married
   - 04 Divorced
   - 05 Widowed
   - 06 Separated

4. **Please indicate your relationship with liver transplantation recipient** (Mark ONE only)
   - 01 Spouse
   - 02 Common-Law Spouse
   - 03 Sibling
   - 04 Parent
   - 05 Friend

5. **Please indicate your current employment status** (Mark ONE only):
   - 01 Employed Full Time
   - 02 Employed Part Time
   - 03 Currently not Employed
   - 04 Self-Employed
   - 05 Retired
   - 06 Homemaker
   - 07 Other

6. **Please indicate the highest education you have attained** (Mark ONE only):
   - 01 Less than high School
   - 02 High School
   - 03 College
   - 04 Trade School
   - 05 Undergraduate Degree
   - 06 Graduate Degree
   - 07 Did not complete College or University
Appendix M: Human Activity Profile

RECIPIENT STUDY
BASELINE QUESTIONNAIRE

Study ID No.

Today’s Date: (DD/MM/YEAR)

Instructions: Please check each activity according to these directions:

Check column 1 (“Still Doing this Activity”) if:

You completed the activity unassisted the last time you had the need or opportunity to do so

Check Column 2 (“Have Stopped Doing this Activity”) if:

You have engaged in the activity in the past, but you probably would not perform the activity today even if the opportunity should arise

Check Column 3 (“Never Did this Activity”) if:

You never engaged in the specific activity
<table>
<thead>
<tr>
<th>Activity</th>
<th>Still doing this activity</th>
<th>Have stopped doing this activity</th>
<th>Never did this activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Getting in and out of chairs or bed (without assistance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listening to the radio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading books, magazines, or newspapers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Writing (letters, notes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working at a desk or table</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing (for more than one minute)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing (for more than five minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing or undressing (without assistance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Getting clothes from drawers or closets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Getting in or out of a car (without assistance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dining at a restaurant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Playing cards/table games</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking a bath (without assistance)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putting on shoes, stockings, or socks (no rest or breaks needed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attending a movie, play, church event or sports activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking 30 yards (27 meters)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking 30 yards (non-stop)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing/undressing (no rest or break needed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using public transportation or driving a car (99 miles or less)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using public transportation or driving a car (110 miles or less)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooking your own meals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washing or drying dishes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putting groceries on shelves</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ironing or folding clothes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dusting/polishing furniture or polishing cars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Showering</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing six steps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing six steps (non-stop)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing nine steps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climbing twelve steps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking ½ block on level ground</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RECIPIENT STUDY
BASELINE QUESTIONNAIRE

Today’s Date: (DD/MM/YEAR)

<table>
<thead>
<tr>
<th></th>
<th>Still doing this activity</th>
<th>Have stopped doing this activity</th>
<th>Never did this activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.</td>
<td>Walking ½ block on level ground (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33.</td>
<td>Making a bed (not changing sheets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34.</td>
<td>Cleaning windows</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35.</td>
<td>Kneeling or squatting to do light work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.</td>
<td>Carrying a light load of groceries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.</td>
<td>Climbing nine steps (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.</td>
<td>Climbing twelve steps (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39.</td>
<td>Walking ½ block uphill</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40.</td>
<td>Walking ½ block uphill (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41.</td>
<td>Shopping (by yourself)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42.</td>
<td>Washing clothes (by yourself)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>43.</td>
<td>Walking one block on level ground</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44.</td>
<td>Walking two blocks on level ground</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45.</td>
<td>Walking one block on level ground (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46.</td>
<td>Walking two blocks on level ground (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47.</td>
<td>Scrubbing (floors, walls, or cars)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48.</td>
<td>Making beds (changing sheets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49.</td>
<td>Sweeping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50.</td>
<td>Sweeping (five minutes, non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51.</td>
<td>Carrying a large suitcase or bowling (one line)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52.</td>
<td>Vacuuming carpets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53.</td>
<td>Vacuuming carpets (five minutes non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54.</td>
<td>Painting (interior/exterior)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55.</td>
<td>Walking six blocks on ground level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56.</td>
<td>Walking six blocks on level ground (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57.</td>
<td>Carrying out the garbage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>58.</td>
<td>Carrying a heavy load of groceries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>59.</td>
<td>Climbing 24 steps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60.</td>
<td>Climbing 36 steps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61.</td>
<td>Climbing 24 steps (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>62.</td>
<td>Climbing 36 steps (non-stop)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### BASELINE QUESTIONNAIRE

**Today’s Date: (DD/MM/YEAR)**

<table>
<thead>
<tr>
<th></th>
<th>Still doing this activity</th>
<th>Have stopped doing this activity</th>
<th>Never did this activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>63.</td>
<td>Walking one mile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>64.</td>
<td>Walking one mile (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65.</td>
<td>Running 110 yards (100 meters) or playing softball/baseball</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66.</td>
<td>Dancing (social)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67.</td>
<td>Doing calisthenics or aerobic dancing (5 minutes non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68.</td>
<td>Mowing the lawn (power mower, not riding mower)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>69.</td>
<td>Walking two miles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70.</td>
<td>Walking two miles (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71.</td>
<td>Climbing 50 steps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72.</td>
<td>Shovelling, digging, spading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>73.</td>
<td>Shovelling, digging, spading (5 minutes non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74.</td>
<td>Climbing 50 steps (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75.</td>
<td>Walking three miles or golfing 18 holes without riding a cart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76.</td>
<td>Walking three miles (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>77.</td>
<td>Swimming 25 yards</td>
<td></td>
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<tr>
<td>78.</td>
<td>Swimming 25 yards (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79.</td>
<td>Bicycling one mile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80.</td>
<td>Bicycling two miles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81.</td>
<td>Bicycling one mile (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82.</td>
<td>Bicycling two miles (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83.</td>
<td>Running or jogging ¼ mile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84.</td>
<td>Running or jogging ½ mile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85.</td>
<td>Playing tennis or racquetball</td>
<td></td>
<td></td>
</tr>
<tr>
<td>86.</td>
<td>Playing basketball (game play)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>87.</td>
<td>Running or jogging ¼ mile (non-stop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88.</td>
<td>Running or jogging ½ mile (non-stop)</td>
<td></td>
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</tr>
<tr>
<td>89.</td>
<td>Running or jogging one mile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90.</td>
<td>Running or jogging two miles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>91.</td>
<td>Running or jogging three miles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>92.</td>
<td>Running or jogging one mile in 12 minutes or less</td>
<td></td>
<td></td>
</tr>
<tr>
<td>93.</td>
<td>Running or jogging two miles in 20 minutes or less</td>
<td></td>
<td></td>
</tr>
<tr>
<td>94.</td>
<td>Running or jogging three miles in 30 minutes or less</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix N: Brief Pain Inventory (Short Form)

Recipient Study
Baseline Questionnaire

Study ID No.

Today's date: 

[Day] [Month] [Year]

The questions in this package will ask you about your pain, mood, fatigue and level of physical function. Each section has instructions to guide you on how to respond to the questions.

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these every day kinds of pain today?

Yes
No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most

3. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours at REST

0 1 2 3 4 5 6 7 8 9 10

No Pain

Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours with MOVEMENT

0 1 2 3 4 5 6 7 8 9 10

No Pain

Pain as bad as you can imagine
5. Please rate your pain by circling the one number that best describes your pain at its LEAST in the last 24 hours at **REST**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

6. Please rate your pain by circling the one number that best describes your pain at its LEAST in the last 24 hours at **MOVEMENT**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. Please rate your pain by circling the one number that best describes your pain on the AVERAGE at **REST**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. Please rate your pain by circling the one number that best describes your pain on the AVERAGE with **MOVEMENT**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Please rate your pain by circling the one number that tells how much pain you have **RIGHT NOW** at **REST**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10. Please rate your pain by circling the one number that tells how much pain you have **RIGHT NOW** with MOVEMENT.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>Pain as bad as you can imagine</td>
</tr>
</tbody>
</table>

11. What treatments or medications are you receiving for your pain? (Please mark all that apply)

- [ ] 001 Acetaminophen (e.g. Tylenol®)
- [ ] 002 Anti-inflammatory medication (e.g., Ibuprofen, Advil®, Celebrex®)
- [ ] 003 Anticonvulsant that helps to manage nerve injury pain (e.g. Pregabalin®, Gabapentin®)
- [ ] 004 Opioid – Dilaudid® (hydromorphone)
- [ ] 005 Opioid - Percocet®, or Oxycodone
- [ ] 006 Opioid - Morphine
- [ ] 007 Opioid - Fentanyl patch
- [ ] 008 Opioid - Tramacet® or Tramadol
- [ ] 009 Opioid - Codeine
- [ ] 010 Ice packs
- [ ] 011 Heat therapy (e.g. heating blanket, heat pack)
- [ ] 012 Music therapy
- [ ] 013 Guided imagery
- [ ] 014 Acupuncture
- [ ] 015 Cognitive behavioral therapy
- [ ] 016 Medicinal marijuana
- [ ] 017 Over-the-counter topical rubs (e.g., Rub A535®, Robaxacet®)
- [ ] 018 Muscle relaxants (e.g., Robaxacet®, Baclofen®)
- [ ] 019 Physiotherapy
- [ ] 020 Exercise
- [ ] 021 Herbal medications
- [ ] 022 Transcutaneous Electric Nerve Stimulation
- [ ] 023 Other: ______________________________________________________

12. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

<table>
<thead>
<tr>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Relief</td>
<td>Complete Relief</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Recipient Study

#### Baseline Questionnaire

- **Today’s Date (DD/MM/YEAR)**

13. Circle the one number that describes how, the past 24 hours, pain has interfered with your

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) General Activity</strong></td>
<td>Does not Interfere</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(b) Mood</strong></td>
<td>Does not Interfere</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(c) Walking ability</strong></td>
<td>Does not Interfere</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(d) Normal work (this includes both work outside the home and housework)</strong></td>
<td>Does not Interfere</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(e) Relations with other people</strong></td>
<td>Does not Interfere</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(f) Sleep</strong></td>
<td>Does not Interfere</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(g) Enjoyment of life</strong></td>
<td>Does not Interfere</td>
<td>Completely interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix O: Profile of Mood States (Short Form)

RECIPIENT STUDY
BASELINE QUESTIONNAIRE

Today’s Date (DD/MM/YEAR)

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle ONE answer to the right, which describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases:

0 = not at all
1 = a little
2 = moderately
3 = quite a bit
4 = extremely

1. Tense…………………0  1  2  3  4
2. Angry………………..0  1  2  3  4
3. Worn out……………0  1  2  3  4
4. Unhappy…………….0  1  2  3  4
5. Lively…………………0  1  2  3  4
6. Confused…………….0  1  2  3  4
7. Peeved………………0  1  2  3  4
8. Sad…………………..0  1  2  3  4
9. Active…………………0  1  2  3  4
10. On Edge…………….0  1  2  3  4
11. Grovely…………….0  1  2  3  4
12. Blue…………………0  1  2  3  4
13. Energetic……………0  1  2  3  4
14. Hopeless……………0  1  2  3  4
15. Uneasy………………0  1  2  3  4
16. Restless……………0  1  2  3  4
17. Tired…………………0  1  2  3  4
18. Bored………………..0  1  2  3  4
19. Hoeless……………..0  1  2  3  4
20. Discouraged…………0  1  2  3  4
21. Resentful……………0  1  2  3  4
22. Nervous……………0  1  2  3  4
23. Misable……………0  1  2  3  4
24. Cheerful……………0  1  2  3  4
25. Bitter………………0  1  2  3  4
26. Exhausted…………0  1  2  3  4
27. Anxious……………0  1  2  3  4
28. Helpless……………0  1  2  3  4
29. Weary………………0  1  2  3  4
30. Bewildered………0  1  2  3  4
31. Furious……………0  1  2  3  4
32. Full of pep…………0  1  2  3  4
33. Worthless…………0  1  2  3  4
34. Forgetful……………0  1  2  3  4
35. Vigorous……………0  1  2  3  4
### BASELINE QUESTIONNAIRE

#### Study ID No. 

<table>
<thead>
<tr>
<th>#</th>
<th>Question</th>
<th>Options</th>
<th>Options</th>
<th>Options</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Unable to concentrate</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Fatigued</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Annoyed</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Uncertain about things</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Bushed</td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Today’s Date (DD/MM/YEAR)

[Blank]
Appendix P: Modified Fatigue Impact Scale

<table>
<thead>
<tr>
<th>Study ID No.</th>
<th>Study ID No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE QUESTIONNAIRE</td>
<td>BASELINE QUESTIONNAIRE</td>
</tr>
<tr>
<td>Today’s Date (DD/MM/YEAR)</td>
<td>Today’s Date (DD/MM/YEAR)</td>
</tr>
</tbody>
</table>

The following is a list of statements that describe the effects of fatigue. Please read each statement carefully, then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. Please answer every question. If you are not sure which answer to select, choose the one answer that comes closest to describing you.

Because of my fatigue in the past 4 weeks…

<table>
<thead>
<tr>
<th>Statement</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have been less alert</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. I have had difficulty paying attention for long periods of time</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I have been unable to think clearly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I have been clumsy and uncoordinated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I have been forgetful</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I have had to pace myself in my physical activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I have been less motivated to do anything That requires physical effort</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. I have been less motivated to participate in social activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. I have been limited in my ability to do things away from home</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. I have trouble maintaining physical effort for long periods of time</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. I have difficulty making decisions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>12. I have been less motivated to do</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
</tr>
<tr>
<td></td>
<td>Anything that requires thinking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13. My muscles feel weak</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. I have been physically uncomfortable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. I have had trouble finishing tasks</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>that require thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I have had difficulty organizing my</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>thoughts when doing things at home</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>or at work</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. I have been less able to complete tasks</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>that require physical effort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. My thinking has been slowed down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. I have trouble concentrating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. I have limited my physical activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. I have needed to rest more often or</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>for longer periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Certificate of Training

UHN Good Clinical Research Practice – Principles

Toronto, Ontario

This is to certify that

Salima Ladak

Successfully completed the above course fulfilling a total of 5 contact hours on

February 24, 2012

VanessaSpeers, Manager, CRP
### Appendix R: Regression Diagnostics

**Primary Model: Function as a Result of Independent Variables**

<table>
<thead>
<tr>
<th>Proposed Predictors</th>
<th>Full model</th>
<th>Model after removal of collinear items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIF scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pain (BPI Pain Interference Scale)</td>
<td>4.18</td>
<td>3.17</td>
</tr>
<tr>
<td>- Worst Pain in past 24 hrs (rest)</td>
<td>3.89</td>
<td>Removed as was discussed at Committee</td>
</tr>
<tr>
<td>- Worst Pain in past 24 hrs (movement)</td>
<td>4.85</td>
<td>2.29</td>
</tr>
<tr>
<td>- Mood (POMS-SF Mood Score)</td>
<td>2.66</td>
<td>2.30</td>
</tr>
<tr>
<td>- Fatigue (POMS SF-Fatigue Subscale)</td>
<td>2.18</td>
<td>2.12</td>
</tr>
<tr>
<td>- Modified Fatigue Impact Scale(MFIS)</td>
<td>2.10</td>
<td>2.04</td>
</tr>
<tr>
<td>- Timepoint*</td>
<td>1.20</td>
<td>1.21</td>
</tr>
<tr>
<td>- Age</td>
<td>1.34</td>
<td>1.37</td>
</tr>
<tr>
<td>- Sex (F vs M)</td>
<td>1.21</td>
<td>1.22</td>
</tr>
<tr>
<td>- Diagnosis*</td>
<td>1.05</td>
<td>1.04</td>
</tr>
<tr>
<td>- Marital Status*</td>
<td>1.33</td>
<td>1.35</td>
</tr>
<tr>
<td><strong>Residual analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Skewness</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>- Kurtosis</td>
<td>0.13</td>
<td>0.08</td>
</tr>
<tr>
<td>- Shapiro-Wilk test for normality (p-value)</td>
<td>0.519</td>
<td>0.507</td>
</tr>
</tbody>
</table>

*Maximum VIF across categorical levels
### Appendix S: OLT Recipients’ Pain at Baseline and During the First 3 Months Following Hospital Discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time 0 (Baseline) (n = 58)</th>
<th>4 weeks (Time 1) (n = 58)</th>
<th>8 weeks (Time 2) (n = 57)</th>
<th>12 weeks (Time 3) (n = 57)</th>
<th>Crude analysis for differences over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPI, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F-value</td>
</tr>
<tr>
<td>Worst pain in previous 24 hours at rest (NRS)</td>
<td>5.0 (3.3)</td>
<td>3.4 (3.1)++</td>
<td>3.0 (3.3)</td>
<td>2.8 (3.2)</td>
<td>7.9</td>
</tr>
<tr>
<td>Worst pain in previous 24 hours with upon movement (NRS)</td>
<td>6.1 (3.0)</td>
<td>4.7 (3.5)+++</td>
<td>3.9 (3.3)+</td>
<td>4.0 (3.7)</td>
<td>8.0</td>
</tr>
<tr>
<td>Least amount of pain at rest in previous 24 hours (NRS)</td>
<td>1.9 (2.3)</td>
<td>1.1 (1.7)+</td>
<td>0.9 (1.9)</td>
<td>1.0 (1.9)</td>
<td>4.5</td>
</tr>
<tr>
<td>Least amount of pain upon movement in previous 24 hours (NRS)</td>
<td>3.4 (2.7)</td>
<td>2.4 (2.4)+</td>
<td>1.8 (2.3)</td>
<td>1.9 (2.5)</td>
<td>6.4</td>
</tr>
<tr>
<td>Pain on the average at rest (NRS)</td>
<td>3.2 (2.5)</td>
<td>2.1 (2.4)++</td>
<td>2.0 (2.3)</td>
<td>1.8 (2.1)</td>
<td>7.8</td>
</tr>
<tr>
<td>Pain on the average upon movement (NRS)</td>
<td>4.3 (2.6)</td>
<td>2.9 (2.5)++</td>
<td>2.7 (2.6)</td>
<td>2.8 (2.9)</td>
<td>7.0</td>
</tr>
<tr>
<td>Pain now at rest (NRS)</td>
<td>2.5 (2.5)</td>
<td>1.6 (2.2)+</td>
<td>1.2 (1.2)</td>
<td>1.0 (2.0)</td>
<td>8.0</td>
</tr>
<tr>
<td>Pain now upon movement (NRS)</td>
<td>3.6 (3.0)</td>
<td>2.1 (2.4)++</td>
<td>1.9 (3.0)</td>
<td>1.6 (2.7)</td>
<td>7.4</td>
</tr>
<tr>
<td>Pain relief from analgesics in previous 24 hours</td>
<td>6.5 (3.0)</td>
<td>6.1 (3.4)</td>
<td>6.1 (3.4)</td>
<td>5.8 (3.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Pain-related interference in previous 24 hours</td>
<td>4.4 (2.9)</td>
<td>2.7 (2.7)+++</td>
<td>2.2 (2.7)</td>
<td>2.3 (2.6)</td>
<td>13.0</td>
</tr>
</tbody>
</table>

*Results are presented as means and standard deviations (SD)*  
*Notes on Table* (BPI – Brief Pain Inventory; NRS = Numeric Rating Scale, (+ = p <.05, ++ = p<.01, +++ = p<.001; Bonferroni adjusted). Each time point was compared to previous follow up.*


Appendix T: OLT Recipients’ Mood at Baseline and During the First 3 Months Following Hospital Discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time 0 (Baseline) (n = 58)</th>
<th>Time 1 (4 weeks) (n = 58)</th>
<th>Time 2 (8 weeks) (n = 57)</th>
<th>Time 3 (12 weeks) (n = 57)</th>
<th>Crude analysis for differences over time*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude analysis for</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>differences over time*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POMS Subscales, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension-Anxiety</td>
<td>10.1 (7.4)</td>
<td>4.2 (4.0)***</td>
<td>4.7 (4.3)</td>
<td>5.4 (5.3)</td>
<td>21.2 &lt; .001</td>
</tr>
<tr>
<td>Depression-Dejection</td>
<td>9.4 (9.4)</td>
<td>3.8 (5.6)***</td>
<td>3.9 (6.3)</td>
<td>4.8 (6.9)</td>
<td>11.9 &lt; .001</td>
</tr>
<tr>
<td>Anger-Hostility</td>
<td>7.9 (8.0)</td>
<td>3.8 (4.5)***</td>
<td>3.7 (5.0)</td>
<td>4.4 (5.1)</td>
<td>8.5 &lt; .001</td>
</tr>
<tr>
<td>Fatigue-Inertia</td>
<td>11.9 (5.6)</td>
<td>8.4 (4.8)***</td>
<td>7.5 (5.0)</td>
<td>7.3 (4.5)</td>
<td>14.6 &lt; .001</td>
</tr>
<tr>
<td>Confusion-Bewilderment</td>
<td>6.7 (5.2)</td>
<td>3.4 (3.4)***</td>
<td>3.4 (3.6)</td>
<td>3.1 (3.5)</td>
<td>15.1 &lt; .001</td>
</tr>
<tr>
<td>Vigour-Activity</td>
<td>8.5 (5.7)</td>
<td>8.9 (5.0)</td>
<td>11.0 (5.2)+</td>
<td>11.1 (5.2)</td>
<td>5.4 .001</td>
</tr>
<tr>
<td></td>
<td>- POMS Score**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34.2 (27.6)</td>
<td>15.6 (15.0)***</td>
<td>15.7 (16.7)</td>
<td>17.8 (18.8)</td>
<td>19.2 &lt; .001</td>
</tr>
</tbody>
</table>

Results are presented as mean and (standard deviation). Profile of Mood States Short Form (POMS-SF); (+ = p < .05, ++ = p < .01, +++ = p < .001; Bonferroni adjusted). Note: POMS-SF total mood score = (anxiety/tension + depression/dejection + anger/hostility + confusion/bewilderment subscales; excludes the fatigue-inertia subscale). Each time point was compared to the previous follow up.
Appendix U: OLT Recipients’ Fatigue at Baseline and During the First 3 Months Following Hospital Discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time 0 (Baseline) (n = 58)</th>
<th>Time 1 (4 weeks) (n = 58)</th>
<th>Time 2 (8 weeks) (n = 57)</th>
<th>Time 3 (12 weeks) (n = 57)</th>
<th>Crude analysis for differences over time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (POMS-SF Fatigue-Inertia Subscale)</td>
<td></td>
<td>8.4 (4.8)**</td>
<td>7.5 (5.0)</td>
<td>7.3 (4.5)</td>
<td>14.6</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.9 (5.6)</td>
<td>8.4 (4.8)**</td>
<td>7.5 (5.0)</td>
<td>7.3 (4.5)</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Profile of Mood States Short-Form (POMS-SF) Fatigue – Inertia subscale; Results are presented as mean and (standard deviation) (+ = p <.05, ++ = p<.01, +++ = p<.001; Bonferroni adjusted). Each time point was compared to previous follow up.
### Appendix V: OLT Recipients’ Fatigue Impact at Baseline and During the First 3 Months Following Hospital Discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time 0 (n = 58)</th>
<th>Time 1 (n = 58)</th>
<th>Time 2 (n = 57)</th>
<th>Time 3 (n = 57)</th>
<th>Crude analysis for differences over time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue impact (MFIS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>45.4(20.4)</td>
<td>31.2(15.0)++</td>
<td>26.3(14.7)</td>
<td>25.4(17.9)</td>
<td>26.4 &lt;.001</td>
</tr>
</tbody>
</table>

*Modified Fatigue Impact Scale (MFIS); Results are presented as mean and (standard deviation); (+ = p <.05, ++ = p<.01, +++ = p<.001; Bonferroni adjusted). Each time point was compared to previous follow up.
Appendix W: OLT Recipients’ Function at Baseline and During the First 3 Months Following Hospital Discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time 0 (n = 58)</th>
<th>Time 1 (n = 58)</th>
<th>Time 2 (n = 57)</th>
<th>Time 3 (n = 57)</th>
<th>Crude analysis for differences over time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function (HAP AAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f-Value</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.4(8.4)</td>
<td>32.1(15.3)+++</td>
<td>44.0(17.8)+++</td>
<td>48.2(18.1)+</td>
<td>182.8</td>
</tr>
</tbody>
</table>

The Human Activity Profile (HAP) Adjusted Activities Score (AAS) at each time point. Results are presented as mean and (standard deviation). (+ = p < .05, ++ = p < .01, +++ = p < .001; Bonferroni adjusted). Each time point was compared to previous follow up.
Appendix X: Fatigue of Primary Caregivers During the First 3 Months Following OLT Recipients’ Discharge From Hospital

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline (n = 23)</th>
<th>Time 1 (n = 23)</th>
<th>Time 2 (n = 21)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (POMS-SF Fatigue-Inertia Subscale)</td>
<td></td>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.6 (5.3)</td>
<td>7.3 (5.0)</td>
<td>6.0 (4.1)</td>
<td>3.30</td>
</tr>
</tbody>
</table>

Profile Of Mood States Short-Form (POMS-SF); Results are presented as mean and (standard deviation). (+ = p < .05, ++ = p < .01, +++ = p < .001). Each time point was compared to previous follow up. Note: only significant difference was between 12 weeks and baseline (Bonferroni adjusted p = 0.048)
Appendix Y: Fatigue Impact of Primary Caregivers During the First 3 Months following OLT Recipients’ Discharge from Hospital

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline (n = 23)</th>
<th>Time 1 (n = 23)</th>
<th>Time 2 (n = 21)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue Impact (MFIS)</td>
<td></td>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>29.0 (11.9)</td>
<td>22.1 (14.7)</td>
<td>18.3 (14.8)</td>
<td>3.52</td>
</tr>
</tbody>
</table>

Modified Fatigue Impact Scale (MFIS); Results are presented as mean and (standard deviation). Each time point was compared to previous follow up. Note: only significant difference was between 12 weeks and baseline (Bonferroni adjusted $p = .046$)
Table 10. Bivariate Correlations between Pain, Mood, Fatigue, Fatigue Impact, Function and OLT Recipient Sample Characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Worst pain (rest)</th>
<th>Worst pain (mvmt)</th>
<th>Mood</th>
<th>Fatigue</th>
<th>Fatigue Impact</th>
<th>Function (AAS)</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Marital Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain interference</td>
<td>0.67+++</td>
<td>0.70+++</td>
<td>0.65+++</td>
<td>0.51+++</td>
<td>0.57+++</td>
<td>-0.46+++</td>
<td>-0.07</td>
<td>-0.05</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>Worst pain (rest)</td>
<td>0.79+++</td>
<td>0.41+++</td>
<td>0.37+++</td>
<td>0.46+++</td>
<td>-0.35+++</td>
<td>-0.08</td>
<td>0.06</td>
<td>0.11</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Worst pain (mvmt)</td>
<td>0.37+++</td>
<td>0.28+++</td>
<td>0.43+++</td>
<td>-0.37+++</td>
<td>-0.13+</td>
<td>0.14+</td>
<td>0.03</td>
<td>0.11</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td>---</td>
<td>0.68+++</td>
<td>0.64+++</td>
<td>-0.45+++</td>
<td>-0.01</td>
<td>-0.01</td>
<td>0.11</td>
<td>0.14+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Impact</td>
<td>---</td>
<td>0.61+++</td>
<td>-0.43+++</td>
<td>0.03</td>
<td>0.06</td>
<td>0.07</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function (AAS)</td>
<td>---</td>
<td>---</td>
<td>0.05</td>
<td>-0.004</td>
<td>0.06</td>
<td>-0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>---</td>
<td>---</td>
<td>-0.20+++</td>
<td>-0.01</td>
<td>-0.33</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Age</td>
<td>---</td>
<td>---</td>
<td>-0.09</td>
<td>0.23</td>
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</tr>
<tr>
<td>Diagnosis*</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>-0.06</td>
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<td></td>
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</tr>
<tr>
<td>Marital status*</td>
<td>---</td>
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<td>---</td>
<td>---</td>
<td></td>
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<td></td>
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</tbody>
</table>