



# Impact of psychiatric comorbidities on outcomes of elderly liver transplant recipients

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## ABSTRACT

**Objectives:** This study evaluated the impact of psychiatric comorbidities in liver transplant (LT) recipients aged  $\geq 65$  years (elderly) on length of hospital-stay (LOS), death, and a composite outcome of graft loss or death.

**Methods:** This retrospective study assessed impact of psychiatric comorbidities in 122 elderly LT recipients and a matched group of 122 LT recipients aged  $< 65$  years (younger). Associations were assessed using adjusted multivariable regression models.

**Results:** Among elderly, median age at LT was 68 years, most were males (62%), white (85%) and 61.7% had a history of any psychiatric diagnosis. Among younger, median age was 55, most were males (67.2%), white (77.5%) and 61.5% had any psychiatric diagnosis. Median LOS was 8 days for both groups. Among elderly, after a median follow-up of 5 years, 25.4% died and 29.5% experienced graft loss or death. History of adjustment disorder, history of depression, past psychiatric medication use, and pain prior to LT were associated with an increased risk of death or the composite graft loss or death. Perioperative use of SSRIs and lack of sleeping medication use were associated with longer LOS. Among aged  $< 65$ , after median follow-up of 4.7 years, 21 patients (17%) died and 25 (20%) experienced graft loss or death; history of depression, perioperative SSRIs or sleeping medications use was associated with increased mortality and graft-loss or death.

**Conclusion:** Six out of 10 patients among both elderly and younger cohorts had pre-LT psychiatric comorbidities, some of which adversely affected outcomes after LT.

## 1. Objective

Liver transplant (LT) is the only lifesaving option for patients with end-stage liver disease. In total, 152,597 patients have received LT since 1988 in the United States of America (US) and as of October 2017, 14,199 patients are awaiting LT (<https://www.unos.org>). Pre-transplant workup of LT candidates and post-transplant care of LT recipients is a highly complex process that is resource intensive and poses significant challenges to patients, their caregivers, and medical providers. There is increasing evidence that outcomes such as mortality and graft survival are comparable among younger and elderly LT recipients [1]. Mortality and graft survival is being increasingly studied and has been

reported among elderly LT recipients in the US [2–6], Taiwan [7], Japan [8], Ireland [9] and Turkey [10]. The increasing success of LT over the last two decades has fueled the demand for this surgery across all age groups, including elderly patients (age  $\geq 65$  years). As a result, LT recipient demographics have changed over the years. In 1988, only 1.7% of LT recipients in the US were older than 65-years of age, and this percentage has increased substantially to 18.7% in the U.S. in 2016 (<https://optn.transplant.hrsa.gov>), representing more than a 10-fold increase in the proportion of elderly patients undergoing LT [11]. As the number of persons aged 65 or older is expected to increase from 43.1 million in 2012 to 92.0 million by 2060 [12], demand for transplants among elderly will surely increase.

**Abbreviations:** ALD, alcoholic liver disease; LOS, length of hospital stay; LT, liver transplant; MELD, Model for End-Stage Liver Disease; SSRIs, selective serotonin reuptake inhibitors

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Chronic liver disease has been associated with multiple psychiatric comorbidities. While comorbidities such as depression may adversely impact clinical outcomes of LT [13,14], adequate treatment of depression likely improves and normalizes survival post-LT [15]. LT recipients of age  $\geq 65$  years at the time of LT have not been well-represented in these previous studies. Previous prevalence studies of psychiatric disorders among the elderly show a peak in the prevalence between 55 and 65 years of age, a low prevalence from 65 to 75 and then again an increase in prevalence among those 75 years and older [16]. Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions found that 11.4% of elderly study participants reported anxiety disorders, 6.8% had mood disorders, 3.8% had an active substance use disorder, and 14.5% reported at least one personality disorder during the previous year [17]. Thus, psychiatric disorders, especially depression and anxiety disorders, remain common among the elderly general population [18,19].

Whether depression or anxiety impacts outcomes of elderly LT recipients in a similar way to younger LT recipients remains an unanswered question. To our knowledge, no previous study has specifically investigated the impact of psychiatric comorbidities on outcomes in elderly LT recipients compared to younger LT recipients. The aim of this study is to address this gap in our understanding of LT outcomes.

## 2. Methods

### 2.1. Study patients

This study was conducted according to international ethical standards and approved by the Mayo Clinic Institutional Review Board (protocol #13-003177).

For the primary analysis, we performed a retrospective chart review of all 122 consecutive LT recipients who were  $\geq 65$  years old at the time of LT between January 1, 2010 and March 15, 2013 at Mayo Clinic, Jacksonville, Florida. Patients undergoing re-transplant or multi-organ transplant were excluded. In a secondary analysis, for comparison, we matched (by Model for End-Stage Liver Disease [MELD] score at LT [ $\pm 4$ ] and primary indication for LT) younger LT recipients who were  $< 65$  years old at LT and who underwent LT over the same time period as the older LT recipients to the older recipients in a 1:1 fashion (i.e. one younger recipient was matched to each older recipient). The last date of follow-up for any patient was January 25, 2018.

Chart reviews included baseline patient characteristics of age, sex, race, MELD score, body mass index (BMI) at listing, and primary indication for LT. In addition, we recorded any history of smoking, illicit drug use, alcohol consumption, hepatic encephalopathy, lactulose use, gastrointestinal bleeding, hypertension, diabetes mellitus, and stroke. The three primary outcomes were length of hospital stay (LOS) after LT, death, and a composite outcome of graft loss or death. Of note, our composite outcome of graft loss or death simply refers to graft loss, as graft loss is defined as either graft failure or death with a functioning graft. As is commonly done in the transplant literature, we chose to utilize a more detailed description of the outcome in order to enhance the clarity of our analyses. These three outcomes were chosen to examine potential post-transplant morbidity or mortality associated with pre-transplant psychopathology in the elderly.

### 2.2. Data collection

All potential liver transplant candidates had a comprehensive psychosocial assessment. They met with an experienced team of social workers exclusively working with transplant patients. Prior to listing for LT, all LT recipients also underwent a comprehensive psychiatric evaluation conducted by experienced American Board of Psychiatry and Neurology certified psychiatrists in the subspecialty of Psychosomatic Medicine/Consultation & Liaison Psychiatry, who were embedded in the Transplant Center and experienced in conducting pre-transplant

psychiatric evaluations. These psychiatrists evaluated all LT candidates prior to listing using semi-structured interviews. Diagnostic and Statistical Manual of Mental Disorders IV Text Revised (DSM-IV-TR) [20] terminologies were used in describing clinical disorders. A focused and comprehensive assessment followed the same template including the same factors for all potential LT candidates. The template included social support, psychological health, lifestyle factors (drugs and alcohol use, compliance, health lifestyle and ability to sustain lifestyle changes) and understanding of transplant process and need for follow up. A comment about appropriateness for listing was included in each psychiatric consultation report. This format ensured consistent evaluation and afforded an opportunity to readily abstract data during chart reviews.

Information about baseline psychiatric comorbidities was collected from the pre-transplant psychiatric evaluations conducted by the Transplant Psychiatry service. Pre-transplant social work assessment notes were reviewed as well. Baseline variables included past and current DSM-IV-TR psychiatric disorders, previous and current psychiatric treatments and medications, and family history of psychiatric illness. Liver disease related data was collected from transplant gastroenterology service notes. Further information, such as perioperative use of psychotropic medications, pain prior to LT, and presence of hepatic encephalopathy, was extracted from the inpatient admission notes from the LT service at the time of LT.

### 2.3. Statistical analysis

Continuous variables were summarized using the sample median and interquartile range (IQR). Categorical variables were summarized using number and percentage of patients. Baseline characteristics and psychiatric comorbidities were compared between the two age groups using a paired Wilcoxon signed rank test or a paired McNemar's test, where the lack of independence that was introduced by the 1:1 matched design was taken into account. The Kaplan-Meier method was used to estimate the cumulative incidences of death and graft loss, or death after LT, where censoring occurred at the date of last follow-up.

Separately for the age  $\geq 65$  years at LT and age  $< 65$  years at LT groups, associations between baseline psychiatric comorbidities and the separate outcomes of death and graft loss or death after LT were evaluated using single variable (i.e., unadjusted) and multivariable Cox proportional hazards regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Again, separately for the age  $\geq 65$  years at LT and age  $< 65$  years at LT groups, associations between baseline psychiatric comorbidities and LOS after LT were examined using single variable and multivariable negative binomial regression models [2]. Multiplicative effects and 95% CIs were estimated and are interpreted as the multiplicative increase on mean LOS.

All multivariable models were adjusted for any baseline non-psychiatric characteristic that was associated with the given outcome with a P value  $< 0.05$ . Additionally, for significant associations between psychiatric comorbidities and outcomes, we examined the sensitivity of our multivariable regression results to further additional individual adjustment (i.e. including only one more variable in the model at a time) for all baseline non-psychiatric characteristics that were not adjusted for in the initial multivariable model. Baseline non-psychiatric characteristics and psychiatric comorbidities that occurred in five or fewer patients were not evaluated in the Cox proportional hazards and negative binomial regression analyses due to their rare occurrence.

In exploratory analysis, we tested for differences between the age  $\geq 65$  years at LT and age  $< 65$  years at LT groups regarding associations between psychiatric comorbidities and outcomes using the aforementioned multivariable Cox and negative binomial regression models. A marginal models approach (Cox regression) and a generalized estimating equation approach (negative binomial regression) were taken to account for the dependence between matched pairs, and where models were adjusted for all variables that had been adjusted for in

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