ORIGINAL ARTICLE

Pretransplant Depression, Antidepressant Use, and Outcomes of Orthotopic Liver Transplantation

Shari S. Rogal,[1] Douglas Landsittel,[3] Owen Surman,[4] Raymond T. Chung,[5] and Anna Rutherford[2]
[1]Department of Internal Medicine and [2]Division of Gastroenterology and Hepatology, Brigham and Women's Hospital, Boston, MA; [3]Division of General Internal Medicine, University of Pittsburgh, Pittsburgh, PA; and [4]Department of Psychiatry and [5]Division of Gastroenterology and Hepatology, Massachusetts General Hospital, Boston, MA

Depression is a common problem among patients awaiting organ transplantation, but little is known about the impact of depression and its treatment on the outcomes of liver transplantation. In this retrospective cohort analysis, we studied all patients over 18 years of age who underwent liver transplantation during a 5-year period (2004-2008) at a single center. Among 179 recipients, 65 patients had depression, as defined by a health care provider assessment, before transplantation. Depression was defined as past or active depression or an adjustment disorder. The associations between pretransplant depression and various outcomes (time to death, graft failure, first acute cellular rejection episode, first infection, and first rehospitalization) were assessed. In the entire sample, more patients with depression required posttransplant psychiatric care (37% versus 18%); the adjusted hazard ratio was 2.28 (1.27-4.11). The rates of other outcomes, including hospital readmission, acute cellular rejection, graft failure, mortality, and infection, were similar for patients with depression and patients without depression. Among those with depression, patients on antidepressants at the time of transplantation had acute cellular rejection less frequently than those not taking antidepressants (13% versus 40%); the adjusted hazard ratio was 0.14 (0.03-0.62). The rates of other outcomes were similar between these 2 groups. These data indicate that depression affects posttransplant psychiatric morbidity but not other medical outcomes of liver transplantation. Pharmacological treatment of depression may significantly reduce the incidence of acute cellular rejection in patients undergoing liver transplantation. However, future prospective studies of mental health and liver transplantation are required to definitively assess the effects of antidepressant medications on medical outcomes. *Liver Transpl 17:251-260, 2011.* © **2011 AASLD.**

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The number of people with cirrhosis (not decompensated) in the United States is estimated to be 400,000.[1] Orthotopic liver transplantation is one of the definitive treatments for such patients. The selection of patients for transplantation is complex and varies among centers. Although a psychiatric evaluation is nearly universal in the screening process for liver transplantation, it is unclear what role mental health comorbidities and their treatments play in the outcomes of liver transplantation.

Abbreviations: DRI, donor risk index; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MGH, Massachusetts General Hospital; MICU, medical intensive care unit; N/A, not applicable; UNOS, United Network for Organ Sharing.

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Address reprint requests to Shari Rogal, M.D., M.P.H., Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Presbyterian University Hospital, Mezzanine Level, C Wing, 200 Lothrop Street, Pittsburgh, PA 15261. Telephone: 412-648-9115; E-mail: shari.rogal@gmail.com

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Mental health issues are common among patients with advanced liver disease. One study showed that of 73 patients listed for transplantation, 17% had symptoms of depression, and 33% had symptoms of anxiety.[2] The rates are likely higher for patients with substance-related liver disease and those who are not on a transplant list. In another study of 71 patients, 66% with alcohol-related liver disease and 32% with non–alcohol-related liver disease met criteria for affective disorders.[3] In addition to affective disorders, patients with liver disease suffer from delirium, encephalopathy, psychiatric side effects of interferon therapy, and substance abuse. All these factors confound the measurements of psychiatric disease and complicate care.

Despite the high prevalence of mental health issues among patients with liver disease, there is little information concerning the ways in which mental health before transplantation affects the outcomes of transplantation. Most studies have investigated psychosocial outcomes after transplantation. One study found that poor mental health before transplantation was predictive of alcohol recidivism.[4] Another study assessed pretransplant mental health and medical outcomes among recipients of liver transplantation. This study investigated a variety of psychosocial factors in a combined group of liver, heart, and lung transplant recipients and found that pretransplant medication nonadherence predicted late acute rejection; moreover, living without a stable relationship predicted graft loss, but anxiety and depression did not predict poor outcomes.[5]

Studies of heart transplant recipients point to a significant role for pretransplant psychiatric factors in outcomes. Among heart transplant recipients, premorbid psychiatric disease was found to predict the need for postoperative psychiatric intervention,[6] and pretransplant suicide attempts, poor adherence to medical recommendations, previous drug or alcohol rehabilitation, and depression significantly predicted attenuated survival times.[7] However, another study found no difference in mortality by pretransplant mental health status when patients were selected for medical adherence.[8]

Although little is known about pretransplant mental health and outcomes of liver transplantation, posttransplant depression is associated with unfavorable medical outcomes among patients with other types of transplants. Among recipients of bone marrow transplants, depression after transplantation increased posttransplant mortality.[9] Among renal transplant recipients, posttransplant depression was associated with increased graft failure, a return to dialysis, and death.[10] This study did not assess pretransplant mental health. Among heart transplant recipients, depression after transplantation was associated with coronary artery disease but not mortality.[11]

Even though we know that mental health disorders are common and psychosocial factors have been suggested to play a role in outcomes, there is limited research addressing how pretransplant mental health affects posttransplant outcomes in those receiving liver transplants. The purpose of this exploratory study was to assess whether the outcomes after liver transplantation differed for patients with a history of depression before transplantation. We hypothesized that in patients undergoing liver transplantation, those with a previous diagnosis of depression would have less favorable outcomes than those without depression. We also hypothesized that the treatment of depression with antidepressant medications would attenuate these less favorable outcomes in the subgroup of patients with depression.

PATIENTS AND METHODS

In this pilot study, a retrospective cohort analysis was performed through the extraction of data from the charts of all patients over 18 years of age who underwent primary orthotopic liver transplantation at Massachusetts General Hospital (MGH) from January 2004 to December 2008. Recipients were assessed for mental illness before transplantation and for the outcomes of transplantation. Approval by the MGH institutional review board committee was obtained for this project. Because there were no identifiers linking patients to records and because the analysis and data collection were retrospective in nature, the need for consent from individual patients was waived.

Patients' mental health data were collected from the charts, which included histories of depression and other psychiatric comorbidities. Depression was defined on the basis of a psychiatric assessment or a diagnosis referenced in the chart notes by a treating physician. Structured measurements of psychiatric disease were not available for patients at our center. We determined the occurrence of depression on the basis of assessments performed before transplantation. We did not differentiate between classifications of depression and included patients with minor and major depression, adjustment disorders, and mixed anxiety and depression both in the past and in the present. Antidepressant use was ascertained via the medication list at the time of admission for transplantation; computerized notes from the hospitalization and/or psychiatric records were used.

Baseline characteristics were assessed for patients with and without depression. Race and ethnicity were self-defined and were abstracted from data provided by the patients to hospital registration. Race was collapsed into white and nonwhite for further analyses. Ethnicity was independent of race and was defined as Hispanic or non-Hispanic. Education was self-reported and was categorized as less than high school, high school graduate, or college or more than college, and it was taken from registration data provided by the patients. Age was defined as age at the time of transplant. Marital status was taken from the registration data or from the hepatology notes when it was not available from hospital registration data. Its categories were single, married, living with a partner, widowed, and divorced, and they were collapsed into married or living with a partner versus unmarried/no

partner for modeling purposes. At our center, there is a requirement for abstinence from drugs and alcohol for at least 6 months before transplantation. A history of previous drug abuse was collected. A history of tobacco use was also collected; its categories were none, past, and present, and these were collapsed into ongoing versus not ongoing for analysis. The Model for End-Stage Liver Disease (MELD) score was the score collected by the transplant surgery service for its report to the United Network for Organ Sharing (UNOS) at the time of transplant. The donor risk index (DRI) was calculated with data provided by UNOS: donor age, cause of death (anoxia, trauma, or cerebrovascular accident), cold time in hours, organ location (local, regional, or national), donor race (African American, white, or other), donor height in centimeters, and donation after cardiac death. This risk score was calculated with the formula described by Feng et al.[12] Renal transplantation was defined as concomitant transplantation. In order to categorize patients by the degree of illness at the time of transplantation, we assessed whether the patients were in the intensive care unit at the time of transplantation. For patients who had more than 1 liver transplant in the designated time period, data from the first liver transplant were used in the study. The etiology of liver disease was that listed in the primary hepatologist's assessment of the patient. This was then further classified into alcohol-related and non–alcohol-related liver disease because of data showing that those with alcohol-related liver disease have both better transplantation outcomes and more psychiatric comorbidities than other patients with liver disease. Hepatocellular carcinoma (HCC) was listed distinctly from other etiologies of liver disease and was based on the diagnosis in hepatology assessments. The mean follow-up time for each group was also assessed.

Outcomes included infection within 1 year of transplant and readmission to the hospital within 1 year of transplant. Other outcomes were collected until death or December 31, 2009. Infection was defined as the time from transplantation to the first acute infectious illness necessitating antibiotic treatment or hospitalization. Readmission was defined as the time of first hospitalization after discharge from transplant admission and was collected from discharge summaries and transplant surgery notes, which were used to ascertain outside-hospital admissions. The time to the first acute rejection episode was, in the majority of cases, defined by a positive biopsy result. Four of the patients were empirically treated for acute rejection without a biopsy sample being obtained, and these were included in this outcome. None of the patients were noted to have more than 1 acute rejection episode within the study period. Graft failure was based on the UNOS definition of graft failure and included the need for retransplantation or death. Death was ascertained by a chart review and was confirmed with data reported to UNOS. Psychiatric morbidity was defined as a requirement for increased care with the addition of therapy, medication, or hospitalization and was collected from electronic charts to assess the time from transplantation to one of the aforementioned events.

The data were analyzed with the R statistical package (version 2.10.1).[13] The primary objectives of these analyses were to determine whether pretransplant depression worsens clinical outcomes and whether outcomes differ with the use of antidepressant medications in those with depression. A secondary analysis was performed to assess differences in outcomes when those labeled with past depression were excluded and only actively depressed recipients were assessed.

In the primary analysis, patients with depression and patients without depression before transplantation were compared.

The multivariate analysis was conducted with Cox proportional hazard modeling, first with only depression as a covariate and then with adjustments for the variables that changed the coefficient for the outcome by more than 10%. This change-in-estimate cutoff approach is thought to yield better statistical properties when we are assessing for confounding in comparison with more general significance testing methods.[13] In addition, the overall clinical focus on depression status and treatment aligns more closely with this approach. The following were the potential confounders assessed in the modeling: age and MELD score at transplant (which were kept as continuous variables); gender; nonwhite race; Hispanic ethnicity; HCC status; ongoing tobacco use at the time of transplantation; history of past illicit drug use; concomitant transplantation of other organs; medical intensive care unit (MICU) stay before transplantation; married status (including those who were married or were living with a partner); education less than high school, high school graduate, and beyond high school; DRI; and alcoholic liver disease. In all cases, 95% confidence intervals were applied.

Analyses were then completed for patients with depression according to antidepressant use. The baseline characteristics of patients with depression were compared by antidepressant use with *t* tests for continuous variables (MELD score, DRI, and age). Chi-square tests were used for categorical variables.

Cox proportional hazard models were then used to assess the impact of antidepressant use on the analysis. This was done with a single model using dummy variables for patients with depression on antidepressants and for patients with depression not on antidepressants so that the differences from the baseline nondepressed group could be assessed. Patients on antidepressant medications without depression (3 in all) were included in the nondepressed group. Hazard ratios were generated for each of these groups in comparison with the nondepressed group. On the basis of evidence of potential confounding from changes of more than 10% to the point estimate, selected confounders were included in the final models. The number of death events was too small among those not on antidepressants to create final models for this outcome. Multivariate analyses were then performed between

depressed subjects on medications and depressed subjects off medications.

Kaplan-Meier curves were created to visualize and assess the timing of the outcomes in each of the groups (unmedicated and depressed, medicated and depressed, and nondepressed subjects).

Finally, a secondary analysis using chi-square testing was performed to assess the associations between depression and antidepressant use in patients with active depression or an adjustment disorder at the last assessment. The group of depressed patients was divided into patients with active depression and patients with past depression, and we assessed outcome rates by antidepressant medication use and nonuse. Patients with active depression included those with an active adjustment disorder or depression according to the chart or a psychiatric evaluation. Patients with past depression included those listed on the chart with past depression or a past adjustment disorder and those listed with depression on a problem list or in a note on the chart without further elaboration.

Multicollinearity in the final models was assessed with the variable inflation factor calculation.

RESULTS

From January 2004 to December 2008, 179 patients underwent primary orthotopic liver transplantation at MGH; 103 (57%) had no mental health problems, 28% had depression, 8% had depression and anxiety, 3% had anxiety alone, 2% had depression and posttraumatic stress disorder or another mental health problem, and 2% had other mental health issues (eg, anger disorder). Among the 65 patients from the group with mental health disorders who were classified as depressed (including those with other comorbid disorders), 54% had active depression, 15% had past depression, 17% had an active adjustment disorder, 9% had a past adjustment disorder, and 5% had depression not otherwise specified but listed as a diagnosis on the chart. Hereafter, recipients with past or present depression and/or an adjustment disorder will be called depressed.

In comparison with nondepressed transplant recipients, depressed recipients had more alcohol-related liver disease (37% versus 25%), had more illicit drug use in the past (35% versus 25%), and more frequently underwent simultaneous renal transplantation (17% versus 10%) (Table 1). There were fewer depressed patients in the MICU preoperatively (9% versus 14%). None of these differences were statistically significant. Although the MELD scores were statistically different between depressed and nondepressed patients (28 versus 30, $P = 0.02$), the difference was not deemed to be clinically meaningful. The other baseline characteristics were similar between the 2 groups. Table 2 illustrates that the majority of patients in the cohort had alcohol, hepatitis C, or a combination as the etiology of their liver disease, and depressed patients were more likely to have alcohol plus hepatitis C as an etiology (23% versus 10% in the nondepressed group). Other etiologies were similarly distributed between the groups.

Among depressed patients, those on antidepressants had a slightly lower average MELD score at transplant (26 versus 31, $P = 0.01$) and a shorter follow-up time of 29.6 versus 38.9 months ($P = 0.04$; Table 1). Those on antidepressants had a nonsignificantly lower DRI (1.293 versus 1.428), were less likely to be married (52% versus 68%), and were more likely to have a concomitant renal transplant (22% versus 8%). However, the other baseline characteristics were similar between depressed patients on and off antidepressants.

Comparing the nondepressed and combined depressed populations, we found no significant differences in rates of infection or readmission at 1 year or in rates of acute rejection, graft failure, or death (Table 3). However, depressed patients had increased posttransplant psychiatric morbidity in comparison with nondepressed patients (37% versus 18%). The hazard ratio was 2.28 for this comparison (95% confidence interval = 1.27-4.11). Regardless of medication use, those with depression did worse in terms of psychiatric morbidity than the nondepressed group (Table 3 and 4).

There were no differences in infection 1 year after transplantation between nondepressed, unmedicated and depressed, and medicated and depressed patients (Table 3 and 4), but the Kaplan-Meier curves crossed at 8 months, with both groups of depressed patients having more posttransplant infections than the nondepressed group (48% versus 39% at 1 year). This was not statistically significant.

Among depressed patients, those taking antidepressants had a lower rate of acute cellular rejection than unmedicated patients (13% versus 40%; Table 4). The group on medications had less acute rejection than the nondepressed group (13% versus 25%), and those with unmedicated depression had more acute rejection than the nondepressed group (40% versus 25%; Table 4). Although the overall Cox proportional hazard models did not yield statistically different results for the comparisons of the depressed groups and the nondepressed group (Table 3), the pairwise comparison of the depressed patients on medications versus the depressed patients off medications yielded an adjusted hazard ratio of 0.14 (0.03-0.62; Table 5).

Readmissions over the course of the year did not differ statistically overall for the groups, but the Kaplan-Meier curve demonstrates that this was likely due to an initially large number of readmissions among all patients. At the end of the time period, both medicated and unmedicated depressed patients had more readmissions than the nondepressed group, although this was not statistically significant.

There was no significant difference in graft failure and death between the 3 groups of patients. However, there were trends toward more deaths and graft failure among the medicated depressed patients versus the unmedicated depressed patients (Table 4). The Kaplan-Meier curves (Fig. 1) demonstrate that the unmedicated and depressed patients had lower rates of death (8% versus 14%) and graft failure (16%

TABLE 1. Baseline Statistics for the Sample by Depression Status and Medication Use

	Depression (n = 65)	No Depression (n = 114)	*P* Value	No Antidepressants (n = 25)	Antidepressants (n = 40)	*P* Value
Age (years)	51.0 ± 9	52.8 ± 11	0.23	51 ± 12	51 ± 7	0.94
Gender						
Male	44 (68%)	84 (74%)	0.50	19 (76%)	25 (62%)	0.39
Female	21 (32%)	30 (26%)		6 (24%)	15 (37%)	
Race						
Caucasian	60 (92%)	95 (83%)	0.35	23 (92%)	37 (92%)	0.93
African American	3 (5%)	10 (9%)		1 (4%)	2 (5%)	
Asian American	2 (3%)	7 (6%)		1 (4%)	1 (2%)	
Other	0 (0%)	2 (2%)				
Hispanic ethnicity	8 (12%)	13 (11%)	0.95	3 (12%)	5 (12%)	0.77
Education*						
<High school	7 (13%)	9 (8%)	0.80	3 (12%)	4 (10%)	0.50
High school graduate	28 (51%)	53 (46%)		13 (52%)	15 (37%)	
>High school	20 (36%)	31 (27%)		7 (28%)	13 (32%)	
Social support						
Single	13 (20%)	18 (16%)	0.20	5 (20%)	11 (27%)	0.23
Married	38 (58%)	75 (66%)		17 (68%)	21 (52%)	
Living with a partner	0 (0%)	5 (4%)		0 (0%)	0 (0%)	
Divorced	10 (15%)	11 (10%)		1 (4%)	7 (17%)	
Widowed	4 (6%)	3 (3%)		2 (8%)	1 (2%)	
Tobacco use						
None	29 (45%)	63 (55%)	0.41	11 (44%)	19 (47%)	0.62
Past	24 (37%)	34 (30%)		11 (44%)	13 (32%)	
Ongoing	11 (17%)	16 (14%)		3 (12%)	8 (20%)	
Former illicit drug use	23 (35%)	28 (25%)	0.19	9 (36%)	14 (35%)	0.85
Other organ transplantation	11 (17%)	11 (10%)	0.28	2 (8%)	9 (22%)	0.24
Pretransplant MICU stay	6 (9%)	16 (14%)	0.50	2 (8%)	4 (10%)	0.89
MELD score	28 ± 6	30 ± 8	0.02	31 ± 7	26 ± 5	0.01
Alcohol-related liver disease	24 (37%)	28 (25%)	0.11	10 (40%)	14 (35%)	0.89
HCC	24 (37%)	38 (33%)	0.75	8 (32%)	16 (40%)	0.70
DRI	1.373 ± 0.35	1.386 ± 0.34	0.82	1.428 ± 0.37	1.293 ± 0.30	0.13
Length of follow-up (months)	33.3 ± 18.0	33.2 ± 19.7	0.943	38.9 ± 16.9	29.6 ± 17.9	0.04

NOTE: Data are presented as means and standard deviations or as numbers and percentages.
*The numbers do not equal the total because of missing values.

versus 25%) than the nondepressed group, and those on medications had higher rates of death (30% versus 14%) and graft failure (35% versus 25%) than the nondepressed group. Notably, the numbers of deaths were too small to adjust for potential confounders and too small to carry out Cox proportional hazards analyses, but the models for graft failure were nonsignificant. The patients on antidepressants who died had the following listed as causes of death: infection (4), neoplasm (2), recurrent liver disease (1), pulmonary hypertension (1), cerebrovascular accident (1), motor vehicle accident (1), cardiac arrest (1), and drug overdose on selective serotonin reuptake inhibitors and pain medicine (1).

Secondary analyses were conducted to assess the differences between patients labeled with active depression or an adjustment disorder and those with a history of depression, an adjustment disorder, or an unspecified diagnosis of depression on the chart, and they demonstrated that the results did not qualitatively change with the inclusion of only actively depressed patients, although the sample was underpowered to detect statistically significant differences in outcomes. However, death did reach statistical significance in the subgroup of actively depressed patients in univariate analysis, with 8 in the group on medications and 1 in the unmedicated group dying.

Comparing the groups of patients with ongoing or past depression, we found that 16 of 21 patients with past depression were on antidepressants, and their numbers looked similar to the numbers of those patients on medications who were classified with ongoing depression (Table 6). Similarly, the trends among the patients with past depression who were off medications reflected those of the actively depressed group who were off medications.

No evidence of multicollinearity was found within the final models.

DISCUSSION

We have shown in this retrospective cohort analysis that, among patients with a history of depression before transplantation, there was an increase in

TABLE 2. Etiology of Liver Disease by Depression Status

Etiology of Liver Disease	Depression (n = 65)	No Depression (n = 114)
Hepatitis C only	21 (32%)	38 (33%)
Alcohol only	8 (12%)	16 (14%)
Hepatitis C and alcohol	15 (23%)	11 (10%)
Acute liver failure	2 (3%)	4 (4%)
Hepatitis B	2 (3%)	7 (6%)
Nonalcoholic fatty liver disease	1 (1%)	4 (4%)
Alpha-1-antitrypsin deficiency	1 (1%)	4 (4%)
Cryptogenic	3 (5%)	3 (3%)
Primary sclerosing cholangitis	1 (1%)	8 (7%)
Autoimmune hepatitis	1 (1%)	5 (4%)
Other*	10 (15%)	14 (12%)

NOTE: In addition to the cited diagnoses, HCC was found in one-third of the patients in each category. Data are presented as numbers and percentages.
*_Other_ includes Caroli disease, primary biliary cirrhosis, hemochromatosis, sarcoidosis, polycystic liver disease, and combinations of these.

psychiatric morbidity 1 year after transplantation that required stepped-up treatment or hospitalization. This highlights the importance of screening patients for depression before transplantation and following them closely. The other medical outcomes were notably similar for patients with and without depression before transplantation.

Patients with depression were more likely, though not statistically so, to have a history of alcohol use and illicit drug use in the past, were more likely to have a combined etiology of hepatitis C and alcohol for their liver disease, and were more likely to have alcohol-related liver disease in general. This was not surprising because substance abuse and affective disease are clearly linked in patients with liver disease. In a study of 71 patients, 66% with alcohol-related liver disease and 32% with non–alcohol-related liver disease met criteria for affective disorders.[3] In past studies, up to 40% of those with alcohol-related liver disease had a history of illicit drug abuse.[14] This connection highlights the importance of screening those with hepatitis C and alcohol-related liver disease for affective disorders in the transplant setting.

A recent review of psychiatric disease and transplantation recommends that patients with depression not be excluded from transplantation but rather be treated similarly to the rest of the population, preferably with medication and psychotherapy, often over long periods of time.[15] Transplantation psychiatric intervention is optimal with pretransplant secondary prevention and postoperative continuity of care. Failure of adequate treatment is not uncommon and can

TABLE 3. Cox Proportional Hazard Models for Depression Versus No Depression and Liver Transplant Outcomes

	Depressed Versus Nondepressed: Unadjusted	Depressed Versus Nondepressed: Adjusted*	No Antidepressants Versus Nondepressed†	Antidepressants Versus Nondepressed†
Infection at 1 year	1.29 (0.82-2.05), $P = 0.27$	1.29 (0.82-2.05), $P = 0.27$	1.18 (0.60-2.29), $P = 0.63$	1.74 (0.96-3.17), $P = 0.07$
Readmission at 1 year	1.19 (0.81-1.75), $P = 0.37$	1.19 (0.81-1.75), $P = 0.37$	1.00 (0.58-1.73), $P = 1.0$	1.34 (0.86-2.10), $P = 0.20$
Acute rejection	0.90 (0.48-1.69), $P = 0.75$	0.90 (0.48-1.69), $P = 0.75$	1.33 (0.61-2.90), $P = 0.47$	0.34 (0.10-1.14), $P = 0.08$
Graft failure	1.06 (0.59-1.90), $P = 0.85$	1.37 (0.50-3.77), $P = 0.54$	0.73 (0.15-3.50), $P = 0.70$	2.14 (0.67-6.80), $P = 0.20$
Death	1.14 (0.58-2.26), $P = 0.69$	1.27 (0.28-5.86), $P = 0.76$	N/A	N/A
Psychiatric morbidity	2.28 (1.27-4.11),‡ $P = 0.01$	2.28 (1.27-4.11),‡ $P = 0.01$	2.65 (1.22-5.71),‡ $P = 0.01$	2.36 (1.27-4.75),‡ $P = 0.02$

NOTE: Hazard ratios and P values are presented; the values within parentheses are 95% confidence intervals.
*Graft failure and death were adjusted for MELD, MICU, DRI, and education.
†The hazard ratios were adjusted as follows: graft failure for education, MELD, MICU, and DRI; infection and psychiatric morbidity for MELD and DRI; and acute rejection for age, DRI, MICU, and education.
‡Significant to the $P < 0.05$ level.

TABLE 4. Outcomes by Depression Status and Antidepressant Use

	No Depression (n = 114)	Depression (n = 65)	*P* Value*	No Antidepressants (n = 25)	Antidepressants (n = 40)	*P* Value*
Infection at 1 year	44 (39%)	31 (48%)	0.27	11 (48%)	20 (53%)	0.35
Readmission at 1 year	68 (60%)	43 (66%)	0.37	16 (64%)	27 (68%)	0.37
Acute rejection	28 (25%)	15 (23%)	0.75	10 (40%)	5 (13%)	0.04†
Graft failure	29 (25%)	18 (28%)	0.85	4 (16%)	14 (35%)	0.10
Death	21 (14%)	14 (12%)	0.69	2 (8%)	12 (30%)	0.05
Psychiatric morbidity	21 (18%)	24 (37%)	0.01†	10 (40%)	14 (33%)	0.90

NOTE: Data are presented as numbers and percentages.
**P* values were obtained by unadjusted Cox proportional hazard modeling.
†Statistically significant to the 0.05 level.

TABLE 5. Cox Proportional Hazard Models for Antidepressant Use Versus No Antidepressant Use Among Depressed Recipients

	Hazard Ratio	Adjusted Hazard Ratio*
Infection at 1 year	1.42 (0.68-2.97), $P = 0.35$	1.99 (0.80-4.97), $P = 0.14$
Readmission at 1 year	1.32 (0.71-2.47), $P = 0.37$	0.34 (0.75-2.91), $P = 0.25$
Acute rejection	0.32 (0.11-0.93),† $P = 0.04$	0.14 (0.03-0.62),† $P = 0.01$
Graft failure	2.54 (0.83-7.71), $P = 0.10$	4.83 (0.41-56.44), $P = 0.21$
Psychiatric morbidity	0.95 (0.42-2.14), $P = 0.90$	0.91 (0.39-2.09), $P = 0.83$

NOTE: Hazard ratios and *P* values are presented; the values within parentheses are 95% confidence intervals.
*Hazard ratios were adjusted as follows: infection for MELD, age, race, and DRI; readmission for education; rejection for MELD, MICU, Hispanic ethnicity, renal transplant, and education; psychiatric morbidity for Hispanic ethnicity; and graft failure for MELD, age, MICU, education, renal transplant, and DRI.
†Significant to the 0.05 level.

be a result of patient nonadherence or professional intervention. Clinicians may be uncomfortable about prescribing medications in the setting of liver failure, so communication between the treating practitioner and the transplant team (including appropriately trained mental health professionals) can be of great benefit in achieving the appropriate dosing of antidepressants. Factors to be considered when safe and efficacious doses of antidepressants are being determined for patients with severe liver dysfunction include knowledge of drug-drug interactions with antirejection medications and the specific agents associated with hepatotoxicity. Specifically, there is a black box warning against the use of duloxetine in patients with hepatic failure, and nefazodone, trazodone, and venlafaxine have been associated with hepatotoxicity. Several elements help with safety monitoring, such as knowledge of and attention to evidence of toxicity and adverse events with specific agents, close follow-up of laboratory markers of toxicity, and use of serum levels of active medication metabolites. The determination of the aforementioned variables is routinely available when the team has access to consultation with dedicated transplant psychiatrists, pharmacologists, and hepatologists.

We expected that among recipients with depression, those who were on antidepressants would have improved outcomes. Our finding of reduced acute cellular rejection among depressed patients taking antidepressants could be a function of adherence to transplant-related medications and is consistent with other studies showing a correlation between adherence and acute rejection. Past research has shown that 57% of those who did not attend their appointments regularly experienced acute rejection in contrast to 2% of those who attended appointments, and this supports the notion that medical adherence mediates acute rejection.[16] One recent study found that medication nonadherence predicted increased late acute rejection among patients undergoing heart, liver, or lung transplantation.[5] Depression is one of many factors in medical nonadherence, which include age, distance from and access to the transplant center, active substance abuse, memory impairment, and some types of personality impairment. Butler et al.[17] found that depression was among the leading causes of decreased adherence among patients awaiting renal transplantation. Taking these findings together, we find that untreated depression may be associated with decreased adherence and thus acute rejection.

The typical posttransplant immunosuppressive regimen at our institution includes a calcineurin inhibitor (eg, cyclosporine or tacrolimus), an antiproliferative agent (eg, mycophenolate mofetil or azathioprine), and a steroid for up to 1 year post-transplant. Although

this study was not designed to assess medication adherence, a post hoc analysis showed no significant difference in tacrolimus levels at the time of rejection according to antidepressant use. This lack of difference may be due to a reduction in the goal medication level based on the time since transplantation or due to variable adherence to or variable doses of other unmeasured antirejection medications. An assessment of adherence should be a part of a future study on this topic. However, this relationship may be related to pathophysiological factors other than adherence. There could also be a relationship between untreated depression and modulation of the immune system because it has been postulated that depression is associated with increased activity of the hypothalamic-pituitary-adrenal axis and glucocorticoid resistance,[18] which makes rejection more likely.

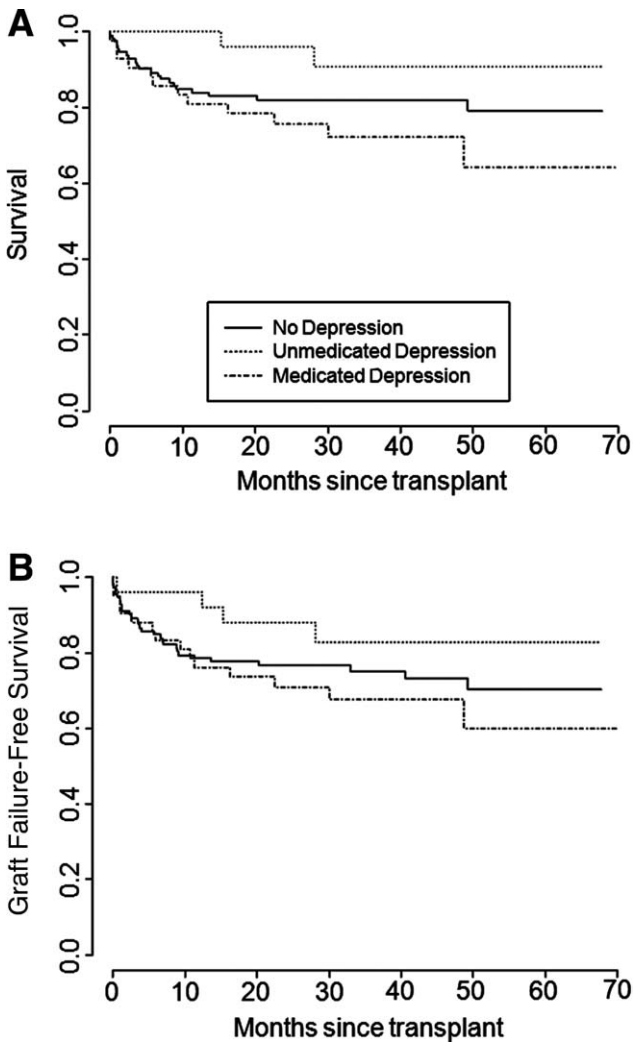

Figure 1. Kaplan-Meier curves for (A) death and (B) graft failure by depression status and antidepressant use.

Although depressed patients did not differ in acute rejection from nondepressed patients, this was possibly due to the decreased amount of acute rejection among patients on antidepressants in this sample because medicated patients had nonsignificantly less acute rejection than nondepressed patients. Interestingly, none of the 3 patients on antidepressant medications for reasons other than depression experienced acute rejection. An unmeasured effect of psychiatric medications on antirejection medication metabolism may account for this, or taking an antidepressant may be a marker for adherence to other transplant-related recommendations. Although it is possible that the changes in outcomes for patients with depression based on antidepressant use are mediated by newly diagnosed psychiatric issues, the lack of significant differences in psychiatric morbidity between those on medications and those off medications suggests that psychiatric medication use instead of posttransplant psychiatric morbidity mediates this difference.

An unexpected finding of this study was a trend toward increased mortality among those on antidepressants versus those not taking antidepressants. The number of depressed patients who suffered mortality was too small to allow for adjustments for potential confounders, and no conclusions can be drawn from this result. Although this is potentially quite important and some evidence suggests an increased rate of death among those on antidepressants[19] that is potentially mediated by increased bleeding or hepatotoxicity,[15] in this study, the number of outcomes was too small to be considered stable. Given the causes of death of recipients in this study (as listed in the Results section), we find it difficult to implicate

TABLE 6. Outcomes by Depression Status and Medication Use

	Ongoing Depression and No Medications (n = 20)	Ongoing Depression and Medications (n = 24)	Past Depression and No Medications (n = 5)	Past Depression and Medications (n = 16)
Infection at 1 year	10 (50%)	11 (46%)	1 (20%)	9 (56%)
Readmission at 1 year	13 (65%)	15 (63%)	3 (60%)	12 (75%)
Acute rejection	7 (35%)	4 (17%)	3 (60%)	1 (6%)
Graft failure	3 (15%)	9 (38%)	1 (20%)	5 (31%)
Death	1 (5%)	8 (33%)	1 (20%)	4 (25%)
Psychiatric morbidity	9 (45%)	6 (25%)	1 (20%)	8 (50%)

NOTE: Data are presented as numbers and percentages.

antidepressant medications as the cause of the overall increased rate of death. There was 1 recipient on antidepressant medications for whom a drug overdose was the cause of death. Although there is literature indicating that suicide is increased among young people on selective serotonin reuptake inhibitors, more recent findings have indicated that this is likely not the case in those over 25 years of age,[20] as was the case for this recipient. However, this relationship warrants further investigation in a prospective trial because antidepressant use may be a marker of more severe illness at the baseline in this observational study.

The increased rates of psychiatric morbidity for patients with a history of depression and the decreased rates of acute rejection for those with depression on antidepressants highlight the importance of appropriate perioperative teaching, psychiatric intervention, and chronic care for transplant recipients. Patients should be educated about the importance of adherence to required psychiatric treatment. Patients at risk may benefit from an increased frequency of visits to the transplant clinic and from screening for major life stress, substance abuse, and altered mental status. Use of standardized self-testing for depression is another consideration. Communication between the transplant team and the treating psychiatrist can be helpful.

Although this study is unique in its assessment of antidepressant use and medical outcomes, it is an exploratory study with several limitations. These include the small numbers of patients and outcomes (especially death and graft failure), which limit our ability to interpret the analysis of these outcomes in terms of antidepressant use. Also, the multiple comparisons made in this study limit the interpretability even in the setting of small *P* values.

At our institution, patients with a history of psychiatric disease, hepatitis C, HCC, or substance abuse are typically referred for psychiatric assessment. There is no formal protocol for psychiatric follow-up; however, patients are considered for transplantation only if a psychiatrist deems their condition stable and has a plan for ongoing care. Future studies could benefit from the use of standardized psychiatric instruments to diagnose depression in the entire sample and by the standardization of follow-up. In this study, the definition of depression included people with past depression and comorbid anxiety, and anxiety could have played a significant and independent role in outcomes. There was no differentiation between diagnostic categories of depression or the timing of depression because of a lack of information on the chart in terms of psychiatric symptoms at the time of transplant. Given the high rate of recurrence of depression in the general population and the vulnerability of patients to relapse at times of stress, we thought that patients with a history of pretransplant depression would benefit from treatment with medications. Although we cannot speak about the severity of preoperative depression because of a lack of data, we interpreted the data as demonstrating that patients taking antidepressants were gaining benefit in functional capacity.

Consideration was given to the inclusion of only patients with a diagnosis of active depression in the study; however, the majority of the patients who were labeled with past depression were on antidepressant medications (16 of 21 patients), and this indicated that they were actively being treated for depression and could not be fairly classified as nondepressed. Additionally, the timing of the psychiatric analyses was nonuniform, so there was concern about misclassification bias if the patients with past depression were included in the nondepressed group. There were insufficient data to determine the severity or timing of mood disorders, so these patients were included. Those with inactive psychiatric disease had outcome rates that were strikingly similar to those of their counterparts with active disease, so all were included. A future study would benefit from uniform assessment timing with standardized instruments both before and after transplantation.

The lack of randomization in this observational study means that the differences based on treatment may be functions of unmeasured confounders. An important unmeasured confounder is psychotherapeutic treatment of depression. This variable was not used because of the difficulty in tracking the frequency of psychotherapy visits retrospectively in the referral center setting. The generalization of the study findings is limited because a single center participated in this effort. Individual centers have different ways of evaluating, screening for, and treating depression in patients with advanced liver disease who are being evaluated for liver transplantation.[15]

In summary, this study assessed medical outcomes with respect to pretransplant psychiatric comorbidities and antidepressant use for patients undergoing orthotopic liver transplantation. Our results suggest that patients with pretransplant depression may benefit from treatment with antidepressants, and this treatment may reduce rates of acute rejection after liver transplantation. The results of this study suggest that depression as a diagnosis or symptom complex is insufficient to determine adverse effects on the posttransplant prognosis, although patients with pretransplant psychiatric illness should be monitored for increased posttransplant psychiatric morbidity. Future studies of mental health and liver transplantation are needed to definitively assess the effects of antidepressant medications on medical outcomes.

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REFERENCES

1. Everhart JE, ed. Digestive Diseases in the United States: Epidemiology and Impact. Washington, DC: US Government Printing Office; 1994. NIH publication 94-1447.
2. Guimaro MS, Lacerda SS, Karam CH, Ferraz-Neto BH, Andreoli PB. Psychosocial profile of patients on the liver transplant list. Transplant Proc 2008;40:782-784.

3. Ewusi-Mensah I, Saunders JB, Wodak AD, Murray RM, Williams R. Psychiatric morbidity in patients with alcoholic liver disease. Br Med J (Clin Res Ed) 1983;287:1417-1419.
4. Kelly M, Chick J, Gribble R, Gleeson M, Holton M, Winstanley J, et al. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. Alcohol Alcohol 2006;41:278-283.
5. Dobbels F, Vanhaecke J, Dupont L, Nevens F, Verleden G, Pirenne J, De Geest S. Pretransplant predictors of posttransplant adherence and clinical outcome: an evidence base for pretransplant psychosocial screening. Transplantation 2009;87:1497-1504.
6. Maricle RA, Hosenpud JD, Norman DJ, Woodbury A, Pantley GA, Cobanoglu AM, Starr A. Depression in patients being evaluated for heart transplantation. Gen Hosp Psychiatry 1989;11:418-424.
7. Owen JE, Bonds CL, Wellisch DK. Psychiatric evaluations of heart transplant candidates: predicting posttransplant hospitalizations, rejection episodes, and survival. Psychosomatics 2006;47:213-222.
8. Skotzko CE, Rudis R, Kobashigawa JA, Laks H. Psychiatric disorders and outcome following cardiac transplantation. J Heart Lung Transplant 1999;18:952-956.
9. Loberiza FR Jr, Rizzo JD, Bredeson CN, Antin JH, Horowitz MM, Weeks JC, Lee SJ. Association of depressive syndrome and early deaths among patients after stem-cell transplantation for malignant diseases. J Clin Oncol 2002;20:2118-2126.
10. Dobbels F, Skeans MA, Snyder JJ, Tuomari AV, Maclean JR, Kasiske BL. Depressive disorder in renal transplantation: an analysis of Medicare claims. Am J Kidney Dis 2008;51:819-828.
11. Dew MA, Kormos RL, Roth LH, Murali S, DiMartini A, Griffith BP. Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation. J Heart Lung Transplant 1999;18:549-562.
12. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006;6:783-790.
13. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2010.
14. DiMartini A, Dew MA, Javed L, Fitzgerald MG, Jain A, Day N. Pretransplant psychiatric and medical comorbidity of alcoholic liver disease patients who received liver transplant. Psychosomatics 2004;45:517-523.
15. Surman OS, Cosimi AB, DiMartini A. Psychiatric care of patients undergoing organ transplantation. Transplantation 2009;87:1753-1761.
16. De Geest S, Dobbels F, Martin S, Willems K, Vanhaecke J. Clinical risk associated with appointment noncompliance in heart transplant recipients. Prog Transplant 2000;10:162-168.
17. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. Transplantation 2004;77:769-776.
18. Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. Prog Neuropsychopharmacol Biol Psychiatry; doi:10.1016/j.pnpbp.2010.04.011.
19. Smoller JW, Allison M, Cochrane BB, Curb JD, Perlis RH, Robinson JG, et al. Antidepressant use and risk of incident cardiovascular morbidity and mortality among postmenopausal women in the Women's Health Initiative study. Arch Intern Med 2009;169:2128-2139.
20. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880. doi: 10.1136/bmj.b2880.