

# Original Research Reports

## Depression and Liver Transplant Survival



William Meller, M.D., Nicole Welle, M.D., Kristen Sutley, M.D., Steven Thurber, Ph.D.

**Background:** *Patients who underwent liver transplantation and experienced clinical depression have heretofore evinced lower survival rates when compared to nondepressed counterparts. Objective:* *To investigate the hypothesis that transplant patients who seek and obtain medical treatment for depression would circumvent the prior reduced survival findings. Methods:* *A total of 765 patients with liver transplants were scrutinized for complications following transplantation. Further, 104 patients experienced posttransplant depression as manifested by diagnosis and treatment by medical personnel. Survival analyses were conducted comparing hazard and survival curves for these selected individuals and the remainder of transplant patients. Results:* *Contrary to prior data and consistent with the aforementioned hypothesis, median survival durations, survival curves, and hazard functions*

*(controlling for age and prolonged posttransplant survival for the depressed patients were better.*

**Conclusion:** *The improved survival for the depressed patients may simply be related to an amelioration of depressed symptoms via antidepressant medications. However, this interpretation would only be congruent with reduced hazard, not elevated survival, beyond the norm (median) for other transplant participants. Assuming the reliability and generalization of our findings, perhaps a reasonable and compelling interpretation is that combined with the effectiveness of antidepressant medications, the seeking and receiving treatment for depression is a type of proxy measure of a more global pattern of adherence to recommended posttransplant medical regimens.*

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**Key words:** liver transplants, depression, survival analysis, compliance.

### INTRODUCTION

Investigations on patients who underwent organ transplantation (meta-analyses) suggest that the quality of life for patients generally improves. Corresponding data for psychologic health and adjustment, however, are not as definitive.<sup>1</sup> Specific to liver transplants, the extant studies suggest high rates of patient depression, beginning with published rates of 60% for patients awaiting transplant<sup>2</sup> and 30–40% for patients who underwent liver transplantation.<sup>3–5</sup> Moreover, increasing evidence suggests not only that depression is a

component of posttransplant maladjustment but importantly, this emotional condition also has a

Received June 18, 2016; revised September 5, 2016; accepted September 6, 2016. From the Department of Psychiatry (WM, NW, KS), University of Minnesota, Minneapolis, MN; Minnesota Department of Human Services (ST), Child and Adolescent Behavior Health Services, Willmar, MN. Send correspondence and reprint requests to Steven Thurber, Ph.D., Child and Adolescent Behavior Health Services, Minnesota Department of Human Services, 1701 Technology Drive NE, Willmar, MN 56201; e-mail: steven\_thurber@yahoo.com

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negative effect on liver transplant survival rates.<sup>3-6</sup> As a case in point, DeMartini *et al.*,<sup>4</sup> using Cox proportional hazard modeling, showed that Beck depression scores were stronger predictors of reduced posttransplant survival rates than age, hospital length of stay, or Model for End-Stage Liver Disease (meld) scores.

It follows that effective treatment of depression may improve transplant outcome. In a cohort of 167 posttransplant patients, Rogal *et al.*<sup>5</sup> reported that treatment of depression may reduce acute cellular rejection, and in a remarkable study with the same cohort, Rogal *et al.*<sup>7</sup> showed that depressed patients treated with adequate antidepressant medication enjoyed similar transplant survival to nondepressed patients. Inadequately treated depressed patients, however, showed decreased survival time periods.<sup>5</sup>

Given these aggregate findings on depression, we compared posttransplant survival in patients prescribed antidepressant medications ( $N = 104$ ) in relation to the remainder of 765 transplant recipients.

## METHOD

Important liver transplant data germane to the current investigation were gathered and maintained by members of the Transplant Services Care Team, University of Minnesota Medical School, Twin cities. A transplant team social worker was responsible for contacting patients at least once every 6 months posttransplant, to ascertain any health-related concerns and evaluate mental and emotional adjustment problems.

Data related to the duration from the time of transplant to either patient death or the termination of the study were gathered from 869 transplant patients with surgeries occurring over a 20-year period (from 1993–2013); the collection of data continued until the year 2015.

Survival analysis involves several possible approaches to data analysis, each of which is related to (A) the timing and (B) the likelihood of events (e.g., death). The appropriate method of survival analysis for a given study depends on whether timing, likelihood, or both are deemed important. Following this determination, the selected survival analysis procedure should conflate with whether or not group differences (e.g., depressed vs nondepressed) or other covariates are hypothesized to influence survival rates.<sup>8</sup>

The Kaplan-Meier survival model yields a comparison between 2 groups in relation to survival rates.

The groups are compared with reference to “survival curves” that plot the probability of an event occurring (e.g., death of a participant) in relation to the time duration (from the start of the investigation to a termination point). Statistical tests using the Kaplan-Meier approach include whether group differences are obtained earlier (i.e., closer in time to the transplant date) or later in the survival curve. The “earlier” significance test is termed “Breslow,” whereas the “later” statistical test is the “Log Rank.” A statistical comparison is also made in the middle portion of the curve termed “Tarone-Ware Test.”<sup>9</sup>

The Cox proportional hazards survival model provides procedures for evaluating the effects of covariates that may affect the hazard function. Unlike the Kaplan-Meier method, the Cox procedure evaluates the hazard or risk of dying following transplant. The Cox approach yields a “hazard ratio” similar to the “odds ratio” in logistic regression. A significant hazard ratio of more than 1 indicates an increasing probability of death, whereas a hazard ratio of less than 1 represents a decreasing risk with declivities in the covariate of interest. Importantly, the Cox proportional hazards survival approach allows statistical control over variables that might constitute alternative explanations for a hazard hypothesis of focal interest.<sup>8</sup> Kaplan-Meier survival procedures were first computed followed by Cox regression.

## RESULTS

Demographic information on the 2 groups of transplant patients is presented in [Table 1](#). As noted, the individuals who sought medication differed by sex, mean age, and rates of diagnostic precursors to liver transplantation. No differences in racial classifications were found. Univariate Kaplan-Meier survival analyses indicated that indeed females evinced longer time to death durations, as did persons of younger age at the time of liver transplantation. These 2 variables, sex and age, were therefore controlled in subsequent analyses.

Inspection of the survival curves in [Figure 1](#) indicates better survival rates for participants who sought and received antidepressive medications (the more elevated the curve, the greater the probability of survival). The figure also reveals separation between the 2 groups that increases with time duration, with the greatest separation occurring at later points in the curve comparisons.

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