

Religiosity Associated with Prolonged Survival in Liver Transplant Recipients

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We tested the hypothesis that religiosity (ie, seeking God's help, having faith in God, trusting in God, and trying to perceive God's will in the disease) is associated with improved survival in patients with end-stage liver disease who have undergone orthotopic liver transplantation. We studied a group of 179 candidates for liver transplantation who responded to a questionnaire on religiosity during the pretransplant psychological evaluation and underwent transplantation between 2004 and 2007. The demographic data, educational level, employment status, clinical data, and results of the questionnaire were compared with the survival of patients during follow-up, regardless of the cause of any deaths. Factorial analysis of responses to the questionnaire revealed 3 main factors: searching for God (active), waiting for God (passive), and fatalism. The consistency of the matrix was very high (consistency index = 0.92). Eighteen patients died during follow-up (median time = 21 months). In multivariate analysis, only the searching for God factor [hazard ratio (HR) = 2.95, 95% confidence interval (CI) = 1.05-8.32, $\chi^2 = 4.205$, $P = 0.040$] and the posttransplant length of stay in the intensive care unit (HR = 1.05, 95% CI = 1.01-1.08, $\chi^2 = 8.506$, $P = 0.035$) were independently associated with survival, even after adjustments for the waiting for God factor, fatalism, age, sex, marital status, employment, educational level, viral etiology, Child-Pugh score, serum creatinine level, time from the questionnaire to transplantation, donor age, and intraoperative bleeding. Patients who did not present the searching for God factor were younger than those who did, but they had shorter survival times ($P = 0.037$) and a 3-fold increased relative risk of dying (HR = 3.01, 95% CI = 1.07-8.45). In conclusion, religiosity is associated with prolonged survival in patients undergoing liver transplantation. *Liver Transpl* 16:1158-1163, 2010. © 2010 AASLD.

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Patients facing a serious illness such as advanced cancer, end-stage renal disease treated with hemodialysis, or human immunodeficiency virus infection often turn to God; this religiosity enables patients to better cope with the disease and improves their quality of life.¹⁻⁶ Surprisingly, increased spirituality/religiosity has positive effects on the progression of the disease. As a matter of fact, greater preservation of CD4 cells and better control of viral loads have been documented in patients showing an increase in religiosity after the diagnosis of human immunodeficiency virus.⁵ Whether religiosity also influences lifespan is currently being debated.

In the general population, religious practice appears to prolong lifespan; as a matter of fact, the risk of

death is significantly lower in those who frequently attend religious services versus those who do not.⁷⁻¹⁰ However, this association appears to be mediated by unhealthy habits (smoking, alcohol consumption, and a sedentary lifestyle) and social isolation; these factors are known to have a negative impact on prognosis and are less frequent in those who attend religious services.

In patients suffering from serious diseases, evidence of an association between religion, spirituality, and health is considered to be weak and inconsistent.¹¹ In a cohort of patients with depression and low social support who survived acute myocardial infarction, spirituality, frequency of church attendance, and frequency of prayer showed no significant correlation

Abbreviations: CI, confidence interval; HR, hazard ratio.

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TABLE 1. Questionnaire

Item	Affirmation	Score (Mean \pm Standard Deviation)
A	I sought God's help in dealing with the situation.	2.9 \pm 1.3
B	I trusted that God would handle the situation.	2.8 \pm 1.4
C	I tried to find the lesson from God in the event.	2.2 \pm 1.3
D	I let God solve my problem for me.	2.1 \pm 1.4
E	I accepted that the situation was not in my hands but in the hands of God.	2.5 \pm 1.4
F	I focused on the divine world rather than on the problems of this world.	1.7 \pm 1.1
G	I waited for God to provide solutions to my problems.	2.0 \pm 1.2
H	With God's help, I was able to see the situation in a different light.	2.7 \pm 1.3
I	I took control over what I could, and I let God help me with the rest.	2.9 \pm 1.4
J	The thought that we have a destiny helped me to see the situation in a new way, so things seemed to me more under control.	3.1 \pm 1.3
Mean		2.5 \pm 1.3

NOTE: The responses were coded as follows: 1 = not at all, 2 = a little, 3 = somewhat, 4 = considerably, and 5 = very much.

with mortality or recurrence of nonfatal myocardial infarction.¹² Conversely, in a group of elderly patients undergoing heart surgery, a lack of social participation and religious strength and comfort were independently correlated with the risk of dying at 6 months.¹³ In patients with renal failure on hemodialysis, spirituality appeared to be associated with longer survival; however, these data suggest that the effects of spirituality could be mediated by better social support.¹⁴ On the other hand, certain forms of religiosity may increase the risk of death, as shown in ill elderly patients who have experienced a religious struggle with their illness, even after adjustments for baseline health, mental health status, and demographic factors.¹⁵

With these considerations in mind, we tested the hypothesis that religiosity (ie, seeking God's help, having faith in God, trusting in God, and trying to discern God's will even in the disease) improves the survival of patients with end-stage liver disease who have undergone orthotopic liver transplantation. We also investigated the possible effects of demographic variables, educational level, employment, and physical variables on patient survival.

PATIENTS AND METHODS

Questionnaire on Religiosity

Candidates for liver transplantation routinely undergo a psychological evaluation that is designed to help patients deal with this particularly difficult period and that is part of every transplant workup.¹⁶ Because during the interview some patients reported a profound return to religion and spirituality, in 2003, we began administering a questionnaire on religiosity to patients who agreed to participate in this study.

The items on the questionnaire, developed by Tix and Frazier,¹⁷ describe several ways of coping through the search for God, and they are shown in Table 1. For each item, the patient was asked how much he or

she had been practicing such behavior with respect to coping with the difficulties of the transplant. Responses were coded according to a 5-point score (1 = not at all, 2 = a little, 3 = somewhat, 4 = considerably, and 5 = very much). With respect to the original questionnaire, the last item was modified to explore the belief in destiny as a way of coping.

The results of the questionnaire were blinded to the team of doctors who had to decide whether or not to refer a patient for liver transplantation; thus, therapeutic decisions were independent of the assessment of the patient's religiosity.

Patients

In order to collect a homogeneous patient population for treatment, we selected candidates for liver transplantation who responded to the questionnaire on religiosity and had received a transplant between January 2004 and December 2007. In every patient, cadaveric liver transplantation was performed with cold ischemia. From this group of 197 transplant patients, 18 were excluded from the analysis because they responded to the questionnaire incompletely. Thus, the study was performed with a total of 179 patients (129 males and 50 females) with a mean age of 52 \pm 9 years. Indications for liver transplantation were viral hepatitis in 122 patients (68%; 53 had hepatocellular carcinoma), alcoholic liver disease in 31 (17%), autoimmune hepatitis in 12 (7%), hepatocellular carcinoma without the virus in 4 (2%), polycystic liver disease in 3 (2%), metabolic liver disease in 2 (1%), and other liver diseases in 5 (3%). The median Child-Pugh score^{18,19} was 8.1.

Follow-Up

After transplantation, patients were enrolled in a clinical follow-up program, and medical visits were scheduled for 1 week, 3 months, and 6 months after transplantation and then every 6 months for 2 years and

every 12 months thereafter. Patients who did not show up for the check-up visits were contacted by telephone. In the case of no response, a patient's general practitioner or the local demographic registry was queried. None of the enrolled patients were lost to follow-up.

Endpoint

The only endpoint of the study was patient survival, regardless of the cause of any deaths. The protocol of this observational cohort study was approved by the local ethics committee.

Statistical Analysis

Continuous variables were expressed as means and standard deviations, and categorical variables were expressed as percentages. The answers to the questionnaire were analyzed by factor analysis, which is a statistical method developed in psychometrics and frequently used in different sciences. This analysis assumes that several unobserved variables together represent another unobserved variable. Specifically, factorial analysis evaluates the variability among observed variables (in our case, the scores of the answers to the questionnaire) and searches for possible combinations. The information obtained about the interdependencies between the observed variables is used to reduce their number to a lower number of underlying, unobserved variables called factors. In our study, this operation was carried out with a mathematical procedure called the principal component method. The first principal component (factor 1) accounts for as much of the variability in the data as possible, and each following component (factors 2 and 3) accounts for as much of the remaining variability as possible. Finally, arbitrary names are assigned to the main factors; these are based on the items of the questionnaire with the greatest loading. The factorability of the correlation matrix (which expresses the validity of the factor analysis) was examined with the Kaiser-Meyer-Olkin measure of the sampling adequacy test and Bartlett's test of sphericity. To calculate the factor scores for each patient, we used the Anderson-Rubin method.

The times that elapsed between transplantation and death in the 2 groups of patients were compared with the log-rank test and Breslow's test, and the results were displayed as Kaplan-Meier curves.

To identify which variables contributed significantly to the prediction of survival, we used the Cox proportional hazards regression model. The following variables were tested: age (continuous variable), sex, marital status (married or not married), educational level [categorized as low (mandatory school) or high (high school or university)], occupation (categorized as managers, employees, workers, or other), type of liver disease (viral or not viral), Child-Pugh score (continuous variable), serum creatinine level (normal/abnormal), time from the questionnaire to transplantation (con-

TABLE 2. Factors That Emerged from Factorial Analysis

Item	Factor 1: Seeking God	Factor 2: Awaiting God	Factor 3: Fatalism
A	0.84	0.25	0.10
B	0.69	0.39	0.27
C	0.59	0.29	0.46
D	0.43	0.76	0.15
E	0.71	0.46	0.17
F	0.30	0.73	0.21
G	0.30	0.85	0.13
H	0.78	0.31	0.27
I	0.81	0.34	0.13
J	0.20	0.18	0.93

NOTE: Items with a loading greater than 0.5 are bolded.

tinuous variable), donor age (continuous variable), time of ischemia of the graft (continuous variable), posttransplant length of stay in the intensive care unit (continuous variable), units of red blood cells transfused (continuous variable), and factors that emerged from the factor analysis (expressed as dummy variables). The predictors of survival were initially identified by univariate analysis. Independent predictors of survival were identified by multivariate analysis with a forward procedure of inclusion of variables.

A 2-tailed *P* value less than 0.05 was considered to be significant. All tests were conducted with SPSS version 13.0.

RESULTS

The scores of responses to the items of the questionnaire are shown in Table 1. Note the considerable variability in the scores of the different items (the mean fluctuated between 1.7 and 3.1) and the large standard deviation, which suggested considerable variability in the religiosity of the studied population.

Factorial analysis performed for the scores of responses revealed the presence of 3 factors, as shown in Table 2. Taking into account the items with higher loadings in the 3 factors, we named the first factor "searching for God" (active), the second factor "waiting for God" (passive), and the third factor "fatalism." The consistency of the matrix was very high (consistency index according to the Kaiser-Meyer-Olkin test = 0.92). Bartlett's test of sphericity indicated that the matrix was not an identity matrix ($\chi^2 = 1203.3$, $P < 0.001$).

During the follow-up period (median = 21 months), 18 of the 179 patients died; the annual death rate was 3.25%. According to univariate analysis, only the searching for God factor, age, educational level, length of stay in the intensive care unit, and intraoperative bleeding were associated with survival, as shown in Table 3, whereas the waiting for God factor, fatalism, gender, marital status, occupation, viral liver disease,

TABLE 3. Predictors of Survival in Univariate Analysis

Variable	HR	95% CI	χ^2	P Value
Age (years)	1.06	1.00-1.13	3.99	0.046
Sex (male)	1.94	0.56-6.71	1.10	0.29
Marital status (married)	0.97	0.28-3.35	0.01	0.96
Educational level (high)	2.65	0.99-7.08	3.80	0.051
Occupation (managers)	0.82	0.48-1.41	0.50	0.48
Liver disease (nonviral)	0.66	0.22-2.00	0.55	0.46
Child-Pugh score	1.01	0.86-1.24	0.01	0.91
Serum creatinine level (mg/dL)	1.87	0.54-6.53	0.97	0.32
Time from the questionnaire to transplantation (months)	0.97	0.89-1.06	0.35	0.56
Donor age (years)	1.01	0.98-1.04	0.49	0.48
Cold ischemia of the graft (minutes)	0.99	0.99-1.00	0.72	0.39
Length of the posttransplant intensive care unit stay (days)	1.05	1.02-1.08	8.76	0.003
Intraoperative bleeding (units of red blood cells transfused)	1.11	1.02-1.20	6.19	0.013
Searching for God factor (absent)	3.01	1.07-8.45	4.36	0.037
Waiting for God factor (absent)	0.67	0.26-1.70	0.70	0.40
Fatalism factor (absent)	1.15	0.46-2.90	0.09	0.76

TABLE 4. Patient Characteristics with Respect to Religiosity

	Seeking God	Not Seeking God	P Value
Number	89	90	
Age (years)	53 \pm 8	50 \pm 9	0.033
Male sex, n (%)	64 (72)	65 (72)	0.999
Married, n (%)	79 (89)	71 (79)	0.112
High educational level, n (%)	36 (40)	44 (49)	0.256
Managers, n (%)	4 (4)	6 (7)	0.759
Employees, n (%)	33 (37)	29 (32)	0.599
Workers, n (%)	27 (30)	35 (39)	0.296
Other, n (%)	25 (28)	20 (22)	0.464
Nonviral liver disease, n (%)	25 (28)	31 (34)	0.450
Child-Pugh score > 8, n (%)	40 (45)	32 (36)	0.259
Mild encephalopathy, n (%)	16 (9)	11 (6)	0.550
Time from the questionnaire to transplantation (months)	5.5 \pm 6.7	4.8 \pm 6.3	0.474

Child-Pugh score, serum creatinine, time that elapsed from the questionnaire to transplantation, and time of ischemia of the graft showed no association. According to multivariate analysis, only the searching for God factor [hazard ratio (HR) = 2.95, 95% confidence interval (CI) = 1.05-8.32, $\chi^2 = 4.205$, $P = 0.040$] and the length of stay in the intensive care unit (HR = 1.05, 95% CI = 1.01-1.08, $\chi^2 = 8.506$, $P = 0.035$), after adjustments for the waiting for God factor, fatalism, age, gender, marital status, occupation, educational level, and other clinical variables, were independently associated with survival.

Patients who reported a negative score for the searching for God factor were younger (Table 4) but had a greater risk of death from all causes that was 3 times higher than the risk for those who had positive values (HR = 3.01, 95% CI = 1.07-8.45).

The Kaplan-Meier curves, illustrated in Fig. 1, show higher survival rates in patients with a positive searching for God factor versus those with a negative factor ($P = 0.026$ by the log-rank test).

DISCUSSION

This study shows that liver transplant candidates with high religious coping (defined as seeking God's help, having faith in God, trusting in God, and trying to perceive God's will in the disease) have more prolonged posttransplant survival than patients with low religiosity. It is already known that religiosity permits one to cope better with the disease¹⁻⁶ and may influence its progression.⁵ This study shows that religiosity is associated with prolongation of lifespan, regardless of the cause of death. In a meta-analysis of 42 studies that surveyed nearly 126,000 people and controlled for sociodemographic and physical health status factors, active religious involvement (ie, religious attendance) was shown to increase the odds of being alive at follow-up by 26%.²⁰ At variance with this meta-analysis, we directly investigated the relationship between the individual and God, regardless of religious creed (Christian, Muslim, or other) and church attendance. The relationship that we considered is a personal encounter with God at a time when the

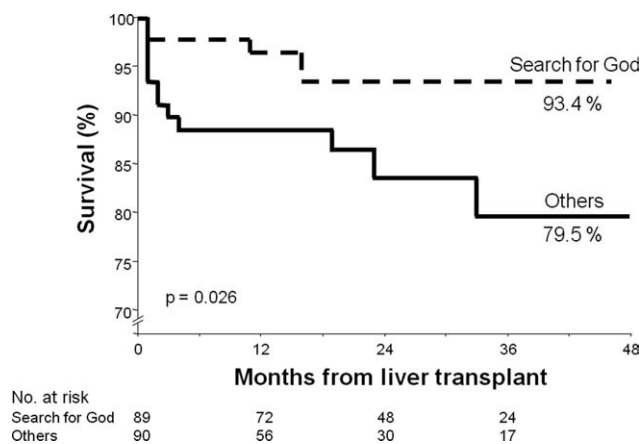


Figure 1. Kaplan-Meier survival curves for patients undergoing liver transplantation.

patient, unable to bear the painful reality, must come to term with his or her own existence and the mystery of life. Our questionnaire does not explore the relationship between religiosity and attending religious services or the kind of religious belief. Nevertheless, the psychological evaluation provided evidence that the relationship of the patients with God was primarily intimate and private in nature and was experienced with a religious sentiment derived from their cultural context. The individuality of such sentiment was reflected by the fact that it was often manifested outside the official religious institutions and communities; indeed, although many patients were part of the church community, others feeling such a strong religious drive often declared avoidance of the church or even (to some degree) disagreement with the institution.

Factorial analysis showed that not all ways in which a patient may turn to God are associated with prognostic benefit; instead, only those related to active searching, grouped together in factor 1, are associated with prognostic benefit. A more passive attitude (eg, the types grouped in factor 2) is not associated with any prognostic advantage. This is also true for an attitude of trust in fate (expressed in factor 3). Thus, the results show that it is faith in God, rather than in a generic destiny, that is associated with patient survival. One patient reported the following: "I recovered my life by the will of someone up there who loves me. I knew I was in God's hands, I had great faith in Him, I was with Him. This closeness made me feel strong and calm."

The possible underlying physiological mechanisms linking religiosity with survival are not known to us. In previous studies, various mechanisms have been hypothesized to explain the relationship between religiosity/spirituality and health, such as neuroendocrine activation, psychoneuroimmune pathways, cardiac autonomic control, metabolic balance, social support, and healthy living habits.²¹⁻²⁴ Although we are aware of this uncertainty regarding the physiological mechanisms, we are inclined to believe that the relationship between religiosity and prognosis is not

one of mere association; instead, faith as a way of coping is a real resource for seriously ill patients and helps to improve their prognosis. In situations in which patients face a serious physical illness, they discover a new way of looking at themselves and explore inner aspects and spiritual horizons; this could create a sense of hope, new stimuli for the mind, and energy.

The resources offered by spiritual factors constitute a topic that is poorly investigated and used in modern medicine, as if a sort of collective amnesia existed.²⁵ A review of 2348 studies published in the 4 most important psychiatric journals between 1978 and 1982 in fact revealed that only 2.5% of these studies had analyzed spiritual or religious variables.²⁶ A later review of the same journals between 1991 and 1995 revealed an even lower percentage (1.2%).²⁷ Similarly, spiritual and religious variables were investigated in only 1.1% of studies in the field of internal medicine.²⁸ The reasons for this amnesia can be traced back to the separation between medicine and religion that occurred over the last few centuries after millennia of shared history.²⁹ Furthermore, medical practice seems to be increasingly geared toward a technological model based on delivering services rather than caring for the patient as a whole and considering not only physical but also psychological, social, and spiritual aspects.³⁰ Despite medicine's lack of interest in religion, 90% of the world's population today is involved in some form of religion or spirituality. Finally, 90% of Americans dealt with the stress of September 11, 2001 by a return to religion.³¹

Our study also investigated the relationship between educational level and occupation and patient survival after liver transplantation. In the United States, educational level has been shown to be a determinant of access to and outcome after kidney transplantation.^{32,33} However, these disparities in access to transplant do not apply to our population, in which all the studied patients were already under evaluation for liver transplantation at the same center. Taking into account the data for 14,814 recipients of liver transplants from 1987 to 2001 in the United Network for Organ Sharing database, researchers found that education had only a marginal influence on the outcome; survival was lower in those with only a high-school education versus those who had graduated from college.³⁴ In our study, educational level was associated with survival only in the univariate analysis ($P = 0.051$). In agreement with previous studies,³⁵ our study also showed no association between occupational status and survival after liver transplantation.

This study, however, does have several limitations. First, the spirituality questionnaire was administered before transplantation, and we have no data regarding the spirituality of patients before the illness and during continuing care. Thus, we did not investigate whether an increase in religiosity occurs when the diagnosis is communicated to the patient or when the patient faces stressful situations (eg, being or not being placed on the waiting list for transplantation).

Moreover, we did not explore in detail the relationship between religiosity and attending religious services or the kind of religious belief. Additional limitations of this study are the low number of patients and consequently the low number of events during the follow-up. Finally, the results collected in this study concern a population of severely ill patients; thus, the conclusions that we have reached cannot necessarily be extrapolated to other groups of patients with different illnesses and different degrees of illness severity.

In conclusion, this study shows that in candidates for liver transplantation, actively seeking God is associated with better survival after transplantation.

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