

Depression and Anxiety Symptoms in Patients With Cirrhosis: A Prospective Study Before and After Liver Transplantation

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ABSTRACT

Background. Timely identification of possible psychiatric symptoms and/or disorders, such as depression and anxiety, in liver cirrhosis and liver transplant patients is important. This study aimed to determine whether patients with both liver cirrhosis and liver transplantation have depression and anxiety symptoms and, if so, to determine the relationship of these symptoms with the stage of the liver disease and other conditions.

Methods. Ninety patients with liver cirrhosis and 31 who underwent liver transplantation for liver cirrhosis were included in the study. Patients were divided into 4 groups. Patients with Child−Pugh A cirrhosis were group 1, patients with Child−Pugh B cirrhosis were group 2, patients with Child−Pugh C cirrhosis were group 3, and transplanted patients were group 4. All patient groups answered Beck Depression Inventory and Beck Anxiety Inventory questionnaires.

Results. Depression and anxiety scores were similar in patients who underwent liver transplantation and in the Child−Pugh A and Child−Pugh B groups. The lowest depression score was observed in the Child−Pugh A group. This was not statistically different from the patients in the liver transplantation group (3.19 ± 3.487, 7.13 ± 7.822, $P > .05$). Depression and anxiety scores were statistically higher in the Child−Pugh C group (25.55 ± 8.878, 21.66 ± 11.053, and 25.55 ± 8.878, respectively; $P < .001$), and depression and anxiety scores increased as the cirrhosis stage increased.

Conclusions. In patients with Child−Pugh C liver cirrhosis, evaluation for symptoms of anxiety and depression is strongly recommended.

LIVER cirrhosis is a clinical condition that develops after a long period of inflammation resulting in the replacement of healthy liver parenchyma with fibrotic tissue and regenerative nodules. In cirrhosis, the disease changes from an asymptomatic phase (compensated cirrhosis) to a symptomatic phase (decompensated cirrhosis), with complications often associated with hospitalization, impaired quality of life, and high mortality. Treatment of liver cirrhosis is determined by the causes and complications, and in some cases, liver transplantation may be required [1]. Timely identification of possible psychiatric symptoms such as depression and anxiety in liver cirrhosis and liver transplant patients is essential. To our knowledge, there is little data on the psychological effects of the disease and their relationships with liver function. However, such mental health problems may have negative consequences, increasing the risks for both morbidity and mortality before and after transplantation [2].

Depression and anxiety-related conditions are risk factors for morbidity and mortality in community-based and non-transplant chronic disease populations. However, it is unclear whether such relationships occur in the context of transplantation. However, despite such protocols, prevalence rates of clinically significant depression and anxiety in transplant recipients remain significantly higher than rates in the general population. They are equal to or greater than rates in other chronic disease cohorts [3]. This study aims to determine whether patients with both liver cirrhosis and liver transplantation have psychiatric symptoms such as depression and anxiety, and if so, to

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determine the relationship of these symptoms with the stage of the disease and other conditions.

MATERIALS AND METHODS

Ninety patients on the transplant list due to liver cirrhosis and 31 patients who underwent liver transplantation due to liver cirrhosis were prospectively included in the study. Informed consent was obtained from all patients. Of the donors, 22 were alive and generally close relatives of the patient; other donors were cadavers. Prisoners were not used in this study, and participants were neither pressured nor paid. The study was carried out by the Helsinki Congress and the Istanbul Declaration. Patients with mental retardation, degenerative neurologic diseases, Alzheimer's, or dementia were excluded.

Patients who developed hepatic encephalopathy due to liver cirrhosis and refused to complete the questionnaire were also excluded. The causes of cirrhosis were recorded. Patients were divided into 4 groups. Patients with Child−Pugh A cirrhosis were group 1, patients with Child−Pugh B cirrhosis were group 2, patients with Child−Pugh C cirrhosis were group 3, and transplanted patients were group 4. Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) questionnaires were answered by all patients. A specialist psychiatrist grouped patients according to the scale results as those with mild, moderate, and severe depression and anxiety symptoms.

Beck Depression Inventory

The BDI evaluates the emotional, somatic, mental, and motivational symptoms of depression. It consists of 21 items. Each item has a rating between 0 and 3. An increased total score is interpreted as increased severity or level of depression.

The standardized cutoff values are as follows:

- Minimal depression symptoms: scores between 0 and 9
- Mild depression symptoms: scores between 10 and 16
- Moderate depression symptoms: scores between 17 and 29
- Severe Depression Symptoms: scores between 30 and 63

Beck Anxiety Inventory

The BAI questionnaire scans and evaluates the severity of anxiety symptoms rather than diagnosing an anxiety disorder. The individual answers the multiple-choice questions considering the previous week. According to the severity of symptoms, choices include "any, mild, moderate, or severe." The answers are scored 0 to 3 accordingly, and a calculated higher total score indicates more severe anxiety symptoms.

Scoring is as follows:

- Mild anxiety symptoms: scores between 8 and 15
- Moderate anxiety symptoms: scores between 16 and 25
- Severe anxiety symptoms: scores between 26 and 63

This study was approved by the Ataturk University Ethics Committee before the study began; the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Statistical analysis

SPSS version 20 (IBM SPSS, Inc) was used for data analysis. The statistical analysis used mean ± SD for continuous variables, and frequency and percentage for categorical variables were defined. The groups' general and demographic characteristics were determined by the frequency (descriptive analysis: frequency analysis for a single variable) analysis. Because the data findings did not show normal distribution according to the Kolmogorov−Smirnov test, nonparametric tests were applied. The Kruskal−Wallis test was used for mean comparisons of multiple independent groups. Post hoc Tamhane's T2 analysis was used for multiple comparisons. The χ^2 test was used to determine the relationship between categorical variables. A binary logistic regression model was applied to jointly model anxiety and depression as binary dependent variables: age, sex, patient groups, smoking, presence of diabetes mellitus (DM) and hypertension (HTN), and disease duration as independent variables. Adjusted odds ratio and 95% CIs are presented for the association of independent variables affected by depression and anxiety. In all models, individuals without depression and anxiety were taken as reference categories. $P \leq .05$ was considered statistically significant.

RESULTS

Of the patients with cirrhosis included in the study, 34 developed the condition secondary to hepatitis B virus, 2 to hepatitis C virus, 7 to autoimmune hepatitis, 9 to alcoholic hepatitis, 7 to portal vein thrombosis, 3 to alveolar hydatid cyst, 1 to Wilson's disease, 1 to Budd-Chiari syndrome, 1 to primary biliary cirrhosis, and the remaining patients had cryptogenic liver cirrhosis. Of the 31 patients in the Child−Pugh A group, 11 were women. In the Child−Pugh B group, 13 of the 30 patients were women. Of the 29 patients in the Child−Pugh C group, 10 were women. In the liver transplantation group, 19 of the 31 patients were women. No statistical difference was observed between the groups (Table 1; $P = .124$).

When evaluated according to age in our study, the patients in group 3 were statistically older than those in the other groups (Table 1; $P < .001$). Regarding disease duration, the disease duration of the patients in group 1 was significantly shorter than the other groups (Table 1; $P < .001$). Depression and anxiety scores were statistically higher in group 3 (25.55 ± 8.878, 21.66 ± 11.053, and 25.55 ± 8.878, respectively; Table 1; $P < .001$), and depression and anxiety scores increased as the cirrhosis stage increased.

Depression and anxiety scores were similar in patients who underwent liver transplantation and in groups 1 and 2 (Table 1). The lowest depression score was observed in the Child−Pugh A group (group 1). This was not statistically different from the patients in the liver transplantation group (3.19 ± 3.487,7.13 ± 7.822, $P > .05$; Table 1).

When we divided the scores according to BDI as minimal, mild, moderate, and severe, 30 (97%) of the patients in group 1 had minimal scores, whereas in group 2, 18 (60%) were in the minimal, 9 (30%) mild, 2 (7%) moderate, and 1 (3%) severe group. In Child−Pugh C patients, 4 (14%) were mild, 16 (55%) moderate, and 9 (31%) severe. In the liver transplant group, 22 (71%) patients were in the minimal, 7 (23%) in the mild, 1 (3%) in the moderate, and 1 (3%) in the severe categories (Table 1).

When we categorized symptom classes as absent, mild, moderate, and severe according to BAI, 29 (94%) of those in the

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Table 1. Demographic Characteristics, Depression, and Anxiety Status of the Groups

			Child−Pugh A (n = 31)	Child−Pugh (n = 30)	Child−Pugh (n = 29)	Transplant (n = 31)	*P* value
Age	Mean ± SD		51.16 ± 13.424[‡,§]	55.07 ± 10.945[‡]	63.76 ± 9.657[†]	41.58 ± 16.998[§]	< .001*
Sex	Women	n (%)	11 (36)	13 (43)	10 (35)	19 (61)	.124
	Men	n (%)	20 (65)	17 (57)	19 (66)	12 (39)	
Smoke	No	n (%)	16 (52)	14 (47)	12 (41)	20 (65)	.312
	Yes	n (%)	15 (48)	16 (53)	17 (59)	11 (36)	
DM	No	n (%)	25 (81)	22 (73)	14 (48)	29 (94)	.001*
	Yes	n (%)	6 (19)	8 (27)	15 (52)	2 (7)	
HTN	No	n (%)	28 (90)	23 (77)	20 (69)	27 (87)	.133
	Yes	n (%)	3 (10)	7 (23)	9 (31)	4 (13)	
Duration of disease	Mean ± SD		2.55 ± 1.338[§]	3.97 ± 1.721[‡]	5.62 ± 2.484[†]	4.94 ± 2.081[†,‡]	< .001*
Depression score	Mean ± SD		3.19 ± 3.487[‡]	9.40 ± 7.605[§]	25.55 ± 8.878[†]	7.13 ± 7.822[‡c]	< .001*
Depression	Minimal	n (%)	30 (97)	18 (60)	0 (0)	22 (71)	< .001*
	Mild	n (%)	0 (0,0)	9 (30,0)	4 (13,8)	7 (22,6)	
	Moderate	n (%)	1 (3,2)	2 (6,7)	16 (55,2)	1 (3,2)	
	Severe	n (%)	0 (0)	1 (3)	9 (31)	1 (3)	
Depression case	Not case	n (%)	30 (97)	27 (90)	4 (14)	29 (94)	< .001*
	Case	n (%)	1 (3)	3 (10)	25 (86)	2 (7)	
Anxiety score	Mean ± SD		3.10 ± 2.737[‡]	7.43 ± 5.418[§]	21.66 ± 11.053[†]	8.58 ± 11.372[‡c]	< .001*
Anxiety	None	n (%)	29 (94)	20 (67)	1 (3)	20 (65)	< .001*
	Mild	n (%)	2 (7)	7 (23)	7 (24)	6 (19)	
	Moderate	n (%)	0 (0)	2 (7)	13 (45)	3 (10)	
	Severe	n (%)	0 (0)	1 (3)	8 (28)	2 (7)	
Anxiety Case	Not case	n (%)	31 (100)	27 (90)	8 (28)	26 (84)	< .001*
	Case	n (%)	0 (0)	3 (10)	21 (72)	5 (16)	

Groups without a common letter are different from each other.
DM, diabetes mellitus; HTN, hypertension.
† Indicate the same columns are different from each other ($P < .05$).
‡ Indicate the same columns are different from each other ($P < .05$).
§ Indicate the same columns are different from each other ($P < .05$).

Child−Pugh A group were in the absent symptom class. For Child−Pugh B, 20 (67%) had no symptoms, 7 (23%) were in the mild, 2 (7%) in the moderate, and 1 (3%) in the severe class. In Child−Pugh C patients, 7 (24%) were mild, 13 (45%) moderate, and 8 (28%) severe. In the liver transplantation group, 20 (65%) had no symptoms, 6 (19%) were in the mild, 3 (10%) in the moderate, and 2 (7%) in the severe class (Table 1).

We categorized the depression groups as those with minimal and mild symptoms and not cases with moderate to severe symptoms. We performed a binary logistic regression model analysis of the factors affecting case status. None of the factors such as age, sex, Child−Pugh A, B, smoking, presence of DM, presence of HTN, and disease duration significantly affected depression. However, Child−Pugh C had a statistically

Table 2. Binary Logistic Regression Model Analysis of Factors Affecting Depression Case Status

	Regression Coefficient	Standard Error	Wald	*P* Value	Odds Ratio	95% CI
Constant	−1.382	1.581	0.764	.382	0.251	
Age	−0.019	0.030	0.398	.528	0.982	0.926−1.040
Sex* women	−0.664	0.943	0.495	.482	0.515	0.081−3.272
Child−Pugh A	−0.531	1.361	0.152	.697	0.588	0.041−8.471
Child−Pugh B	0.803	1.068	0.566	.452	2.233	0.275−18.095
Child−Pugh C	5.225	1.272	16,880	< .001*	185.860	15.371−2,247
Smoking	−0.601	0.946	0.404	.525	0.548	0.086−3.502
DM presence	−0.531	0.928	0.327	.568	0.588	0.095−3.630
HTN presence	0.142	0.942	0.023	.880	1.153	0.182−7.298
Duration of disease	0.009	0.157	0.003	.956	1.009	0.742−1.371

N = 121, R^2 = .45 (Cox-Snell), .67 (Nagelkerke). Model χ^2 (9) = 72.874, $P < .001$. Hosmer-Lemeshow goodness-of-fit test: $P = .839$; $P < .05$ value considered statistically significant.
DM, diabetes mellitus; HTN, hypertension.
* $P < .05$ value considered statistically significant.

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Table 3. Binary Logistic Regression Model Analysis of Factors Affecting Anxiety Case Status

	Regression Coefficient	Standard Error	Wald	*P* Value	Odds Ratio	95% CI
Constant	0.701	1.401	0.251	.617	2.016	
Age	−0.071	0.029	5.989	.014*	0.932	0.880−0.986
Sex* women	−0.732	0.870	0.709	.400	0.481	0.087−2.644
Child−Pugh A	−18,716	6706,796	0.000	.998	0.000	0.000−.0
Child−Pugh B	−0.099	1.006	0.010	.922	0.906	0.126−6.508
Child−Pugh C	3.658	1.079	11.493	.001*	38.781	4.679−321.405
Smoking	−1.791	1.022	3.075	.080	0.167	0.023−1.235
DM presence	2.117	0.881	5.781	.016*	8.309	1.479−46,675
HTN presence	1.858	0.901	4.253	.039*	6.409	1.097−37.458
Duration of disease	0.177	0.163	1.172	0.279	1.193	0.867−1.642

N = 121, R^2 = .42 (Cox-Snell), .63 (Nagelkerke). Model χ^2 (9) = 65,360, $P < .001$. Hosmer-Lemeshow goodness-of-fit test: $P = .966$; $P < .05$ value was considered statistically significant.

DM, diabetes mellitus; HTN, hypertension.

significant effect on the hazard ratio (HR 5.225; 95% CI, 15.371-2247.399; $P < .05$; Table 2).

We grouped the anxiety groups as no case, and the presence of mild symptoms as not case, the presence of moderate to severe symptoms as case, and performed a binary logistic regression model analysis of the factors affecting case status. Age negatively, having Child−Pugh C disease, DM, and HTN had a statistically significant effect on anxiety (respectively; HR, 0.071; 95% CI, 0.880-0.986; $P < .05$; HR, 3.658; 95% CI, 4.679-321.405; $P < .05$; HR, 2.117; 95% CI, 1.479-46.675; $P < .05$; HR, 1.858; 95% CI, 1.097-37.458; $P < .05$; Table 3).

DISCUSSION

To our knowledge, few studies have been conducted on the prevalence of depression and anxiety symptoms in patients with cirrhosis. In the study conducted by Hernaez et al [4], about 1 in 6 patients with cirrhosis had moderate to severe depression, and about half had moderate to severe anxiety. In the present study, both depression and anxiety symptoms were higher than these rates in all patients with cirrhosis. Therefore, patients with cirrhosis should be assessed for depression and anxiety symptoms, which can adversely affect their health and quality of life, and thus are essential to treat.

In a study conducted with patients with cancer, which can progress over time and cause death like cirrhosis, the frequency of depression/anxiety, which was 13% at the beginning of the disease, was found to increase to 30% in the final stages of the disease [5]. In the present study, we observed minimal/mild depression and anxiety symptoms in Child−Pugh A patients with cirrhosis. In contrast, depression and anxiety symptoms were exacerbated in end-stage liver disease (Child−Pugh C). This may be a symptom of the patient's hopelessness, feelings of being close to death, or related to the progressive disease affecting the brain through different mechanisms leading to increased susceptibility to depression and anxiety symptom severity. Indeed, the common mechanisms in both depression and chronic liver failure include changes in the microbiome, impaired intestinal permeability, and spread of toxins throughout the body, and the chronic effects of inflammation [6,7]. This also applies to anxiety symptoms, often associated with depression symptoms.

Additionally, although it is known that mental stress is significant in the etiology of depression and anxiety symptoms, adverse effects of stress on liver functions have been reported, and this relationship is probably bidirectional [8]. The liver transplantation group's depression and anxiety levels were similar to the Child−Pugh A and B groups, but not in the level of no anxiety and depression. This might be due to liver transplantation not being sufficient to reverse all the medical conditions or similar to being fully healthy and having no liver disease. Also, these findings might contribute to the burden of chronic disease, compulsory hospital follow-ups, and taking too many medications after transplantation. Depression is a widespread community disease with a prevalence of 10% to 20% over one's lifetime [3], so without any diseases, including cirrhosis, it may well be seen in the study's patient group. Also, the duration after transplantation in the transplantation group changed. After transplantation, it may take some time for the patient to adapt to a new—after transplant—life and to overcome the cirrhosis and fear of death (possibly leading to or exacerbating the symptoms of depression and anxiety) and feel better than before, so the depression and anxiety level of the transplant group was similar to that of Child−Pugh A and B groups and was not in the level of symptom-free within depression and anxiety.

In a study conducted by Bianchi et al [9] in Italian patients with cirrhosis, BDI scores were indicative of a depressed mood in >50% of the patients with the presence of clinical symptoms. In other words, as in the present study, depression symptoms increased as the Child−Pugh score increased. This may be related to the deterioration of the patient's liver function, in terms of physical appearances, such as icterus and ascites, and in terms of deterioration of brain function after detoxification disorder. Additionally, the reason for the frequent occurrence of anxiety and depression symptoms in end-stage liver cirrhosis in the present study may be adverse living conditions such as frequent hospitalizations, malnutrition, sarcopenia, decreased working capacity, and inability to fulfill social and familial roles [10−13].

In a study by Hames et al [14], moderate to severe anxiety and depression symptoms were detected in approximately 25% of 40 patients who underwent transplantation, like our study, and this rate was reported to be higher than the normal population.

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Although the beneficial physical effects of liver transplantation on patients with end-stage liver disease have been well described, changes in the mental status of patients after liver transplantation have not been adequately investigated and are poorly understood. In a study by Benzing et al [15], transplant patients had significantly higher levels of depression and anxiety symptoms compared with the normal population before transplantation. In addition to the beneficial effects of orthotopic liver transplantation on liver function after transplantation, it was associated with significant improvements in depression and anxiety levels and a more optimistic view of the future in patients.

In a study conducted by Akbulut et al [16] with transplant patients, anxiety and depression rates were approximately 40%, like the findings of our study. As this rate was similar to our results in Child−Pugh A and B groups in our study, transplantation at this stage may not lead to significant psychological improvement. Patients who received transplants when they were probably in a worse physical and mental state have a post-transplant reduction in depression and anxiety symptoms, approaching those in Child−Pugh A and B. In the future, long-term follow-up studies on the duration of anxiety and depression symptoms in these patients, considering other confounding factors (life events, aging, effects of medications on mental status, etc.), may provide new data. With advances in medical practice, perioperative patient management, treatment of post-operative complications with minimally invasive methods, and the development of targeted treatment protocols with fewer side effects in liver transplant patients, mortality and morbidity rates have decreased significantly. Medical success after liver transplantation does not mean the individual is healthy; acceptable psychosocial well-being is the most important goal [17].

The present study had some limitations, including a limited number of participants, measuring the symptoms of depression and anxiety with self-rating scales, the absence of a proper psychiatric examination to diagnose the possible existence of depression and/or anxiety disorder, and the possible common physical and vegetative symptoms of depression and/or anxiety with cirrhosis itself such as fatigue, sleep, and appetite problems, body figure change, hand tremor, and nausea.

CONCLUSION

Anxiety and depression are common psychiatric disorders in cirrhosis and liver transplant patients. Although it is known that many factors may cause these disorders, based on the literature and our findings, we believe that the stage of the disease is a significant risk factor for anxiety and depression symptoms in cirrhosis patients. Especially in patients with Child−Pugh C liver cirrhosis, evaluation for anxiety and depression symptoms and diagnosis is recommended. Liver transplantation is not only a breakthrough in treating end-stage liver cirrhosis but also a treatment that can improve existing psychiatric symptoms and disorders such as depression and anxiety in patients.

DATA AVAILABILITY

Data will be made available on request.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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