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Psychological, Cognitive, and Laboratory Characteristics of End-Stage Liver Disease Patients

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Abstract

Background: End-Stage Liver Disease (ESLD) causes several clinical and psychological comorbidities. Some accompanying psychiatric disturbances have significant effects on the patients' quality of life.

Objectives: Thus, we aimed to evaluate some psychological characteristics of ESLD patients.

Methods: A cross-sectional study was conducted on 91 ESLD patients aged 18 - 70 years. We assessed the patients using the California Verbal Learning Test (CVLT), Fatigue Severity Scale, Epworth Sleepiness Scale, and Hospital Anxiety and Depression Scale. Also, we measured the demographic and some laboratory data of the participants. The data were analyzed by SPSS version 21 software, and P values of less than 0.05 were considered significant.

Results: The study included 68 men and 23 women with a mean age of 41.9 $\pm$ 13.72 years (range 19 - 68). The mean scores of fatigue (40.6 $\pm$ 14.8) and anxiety (12.98 $\pm$ 2.76) were more than the normal range. The most significant association was seen between age and CVLT items (attention (P = 0.01), immediate memory (P < 0.001), short delay free recall (0.01), and short delay cued recall (0.03).

Conclusions: End-stage liver disease patients had anxiety, fatigue, and memory disorders in addition to their poor clinical conditions. Although the main treatment of ESLD is liver transplantation but the psychological and cognitive problems before transplantation in these patients are prognostic factors for post-operation compliance and follow up.

Keywords: End-Stage Liver Disease, Psychological, Characteristics, Memory, Depression, Anxiety

1. Background

End-Stage Liver Disease (ESLD) is the terminal and irreversible stage of liver disease, which is a common cause of mortality and morbidity in the world. In 2010, about one million deaths were recorded worldwide due to ESLD (1-3). End-stage liver disease is a progressive disease that contributes to several mortal complications. The majority of these complications include variceal bleeding, hepatic encephalopathy, massive ascites, spontaneous bacterial peritonitis, electrolyte imbalance, and hepatorenal syndrome. Most of these complications occur at working ages and confront patients with several financial, psychological, and social problems (4, 5).

Liver transplant is the only valid treatment, and the patients hope to receive the organ before mortal complications get started. On the other hand, the chronicity and progressive cycle of the disease create a boring condition for ESLD patients. The confrontation with these hopeful and hopeless states can cause some physical, cognitive, and emotional disturbances. Several studies reported depression, anxiety, cognitive deficit, and sleep disorders among chronic liver disease patients (6-10). Also, fatigue defined as malaise, exhaustion, lethargy, and loss of motivation is prevalent among ESLD patients (11).

Additionally, memory deficit is common in chronic liver diseases, especially ESLD (7, 12-15). All of these disorders, accompanied by the deterioration of clinical conditions, can significantly reduce the quality of life and cause poor compliance with treatment. Thus, ESLD patients progress into poor conditions and finally die.

2. Objectives

Therefore, we aimed to evaluate some psychometric parameters, including memory performance, anxiety, de-

pression, daytime sleepiness, and fatigue as cognitive and mood conditions of ESLD patients. Also, we evaluated the laboratory and demographic data in cirrhosis and investigated their relationships with the psychometric parameters.

3. Methods

A cross-sectional study was conducted in the Namazi Educational Hospital of Shiraz University of Medical Sciences, Fars province. It is a referral center for transplantation in the south of Iran. Among 112 patients enrolled during six months, finally, 91 ESLD patients with transplant team confirmation according to clinical manifestations, laboratory findings, and imaging studies cooperated with the study. All the participants were aged between 18 and 70 years and could write and read. Patients who had known severe psychiatric and mental problems were excluded. Data collection started after approval of the study by the Ethics Committee of Shiraz University of Medical Sciences and obtaining written informed consent from patients. The demographic data included age, sex, weight, marital status, job status, education level, and illness duration. The laboratory data included prothrombin time (PT), international normalized ratio (INR), aspartate amino transferase (AST), alanine amino transferase (ALT), direct bilirubin (DB), total bilirubin (TB), albumin, sodium (Na), potassium (K), blood urea nitrogen (BUN), creatinine (Cr), platelets (PLT), model for end-stage liver disease (MELD) score, Child-Pugh score, and tumor marker CA 125 and CA 19-9, which were collected from the patient profiles. Besides, all participants were assessed using California verbal learning test (CVLT) (16), hospital anxiety and depression scale (HADS) (17), fatigue severity scale (18), and the Epworth sleepiness scale (19).

3.1. California Verbal Learning Test

The CVLT evaluates cognitive functions by measuring repetition learning, intrusions, semantic organization, proactive interference, serial position effects, and both memory recall and recognition of word lists during immediate and delayed stages (20, 21). The CVLT performance includes attention, short delay free recall, short delay cued recall, long delay free recall, long delay cued recall, immediate memory, and long delay recognition. We used a valid and reliable Persian version of CVLT (22). The test was performed as follows. A physician read list A words for patients and they were asked to recall as many words as they could and repeat this trial four times. This process was to measure immediate memory. Then, the examiner read list B words and again asked the patients to recall as many words as they could from list B. Instantly, the examiner asked the patients to recall as many words as they could from list A to measure short delay free recall. During the recall process, the patients were cued to remember the groups to which the words belonged (i.e. animal, transportation, vegetable, and furniture groups) to measure short delay cued recall. Next, the patients were required to complete the remaining parts of the questionnaire within 20 min. Then, they were asked to recall as many words as they could from list A to measure long delay free recall. They were also provided with the cue categories to measure long delay cued recall. In the end, the patients were asked to put each word in its list A or B to test their recognition. The patients obtained one point score for recalling each correct word and the highest score was 16.

3.2. Hospital Anxiety Depression Scale (HADS)

This reliable and self-administered questionnaire is used to evaluate anxiety and depression status (19). The HADS is divided into two subscales including HADS-A with seven items on a four-point Likert scale between 0 and 3 for anxiety and HADS-D with seven items on a four-point Likert scale between 0 and 3 for depressive symptoms. The score of each subscale is between 0 and 21. A score of < 8 is non-case, 8 - 10 is borderline, and > 11 indicates significant levels of anxiety and depressive symptoms. We used the Persian version of HADS with α Cranach of 0.86 for depression and 0.78 for anxiety (23).

3.3. Fatigue Severity Scale

This self-administered questionnaire has nine items. The patients were asked to pick a number from 1 to 7 that best described their degree of agreement with each statement on the scale, with 1 indicating strong disagreement and 7 indicating strong agreement. The total score is between 9 and 63 and a score of > 36 shows severely fatigue patients that need to undergo more evaluations.

3.4. Epworth Sleepiness Scale

This self-administered questionnaire with eight items evaluates the level of daytime sleepiness. The range of the score is between 0 and 24. The patients were asked to rate each item on a scale from 0 to 3, based on the likeliness of falling asleep in eight life situations given in each statement. A score of 0 - 9 is normal, and the patients with a score of > 10 should undergo more evaluations.

3.5. Statistics

Statistical analyses were performed with SPSS software (SPSS version 21, IBM corporation, Armonk, NY, USA). Descriptive data were reported as mean ± standard deviation (SD). The independent sample *t*-test was used as a parametric test after confirming the normality of data and the equality of variances. The chi-square test was used to make comparisons for the categorical data. Person correlation was used for continuous data with normal distribution to assess the correlation between psychological parameters. A P value of < 0.05 was set as the significance level.

4. Results

This study enrolled 91 patients (68 men and 23 women) with a mean age of 41.9 ± 13.72 (19 - 68) years. Besides, 69 (75.8%) patients were married and 54 (59.3%) were employed. Most of the participants (n = 68, 68.1%) had high school educational status. Also, 12 (13.2%) patients had diabetes mellitus. The most common diseases among the patients were hepatitis 41 (45.1%), cryptogenic 17 (18.7%), and cholestatic 14 (15.4%). Besides, 72 (79.1%) patients had undergone liver transplantation, 15 (16.5%) patients were in the transplant list, and the remaining four patients (4.4%) expired. Table 1 shows other descriptive data.

Most of the patients (n = 78) with moderate to severe anxiety were more than 45-years-old (n = 38), had hepatitis (n = 39), had high school educational status (n = 60), were in CHILD class 2 (n = 51), and had a MELD score of more than 20 (n = 40). The relationships between anxiety and platelets (P = 0.02), CA 125 (P = 0.02), and CA 19 - 9 (P = 0.02) were significant. Also, most of the participants with moderate to severe depression were more than 45-years-old (n = 40) with a diagnosis of hepatitis (n = 41). The educational level of this group was high school (n = 61) and 53 patients were employed; 51 patients were in CHILD class 2 and 41 patients had a MELD score of more than 20. Depression had a significant relationship with DM (n = 12, P = 0.03). Besides, 34 (34.7%) patients had severe fatigue and 40 (44%) patients had a sleepiness score of greater than 10. The descriptive results of CVLT, depression, anxiety, sleepiness, and fatigue are shown in Table 2. Four items of CVLT had relationships with age, including short delay free recall (P = 0.01), short delay cued recall (P = 0.03), immediate memory (P < 0.001), and attention (P = 0.01). Other correlations between CVLT items and laboratory data and sleepiness, fatigue, anxiety, and depression are shown in Table 3.

5. Discussion

Our study aimed to evaluate demographic data, laboratory results, and some psychological characteristics of patients with liver cirrhosis. There was no significant relationship between the laboratory data and demographic parameters. The MELD score of our study was almost 20; this score shows that the risk of mortality among our patients was 19.6% (24). There was no significant relationship between the MELD score, as a predictive tool for survival, and psychometric parameters. Some other studies found no correlation between the MELD score and psychological parameters as the health-related quality of life among patients before orthotopic liver transplantation (25-28). On the other hand, Togashi et al. found that a high MELD score in the pre-transplant group had a relationship with the low quality of life (29). Also, Santos et al. reported that a lower MELD score had a relationship with a high anxiety score (30). There were controversies in this relationship in pre-transplant patients, so more prospective studies and using other psychometric tools for the evaluation of life expectancy are recommended. In the HADS, only anxiety had a significant relationship with platelets, CA 125, and CA19-9. A parallel interaction exists between platelets and brain cognitive functions. There is a hypothesis about the importance of platelets in the noradrenergic and serotoninergic systems in the pathophysiology of anxiety disorders (31). Nakamura et al. reported that peripheral-type benzodiazepine receptors (PBRs) on platelets have a relationship with anxiety and the density of platelets PBR is highly associated with anxiety tolerance (32). We found this relationship in ESLD patients and due to the platelet count and function disorders in these patients, being anxious could be reasonable with this hypothesis. The relationship between CA 125 and anxiety may be due to the awareness of patients about CA 125 as a tumor marker and knowledge of surveillance. In the Reid study, there was a moderate association between a high level of CA 125 and anxiety, but the association was not statistically significant (33). As a tumor marker, CA 19-9 had a relationship with anxiety in our study. Also, a case report concluded that a high level of CA 19-9 is not necessarily associated with ovarian malignancy and may be due to patients' anxiety (34). Overall, tumor markers such as CA 125 and CA 19-9 can elevate in various non-malignant processes, including liver diseases. Besides, False positive rising of CA-125 among ESLD patients with ascites and esophageal varices can cause anxiety and stress in these patients. Therefore, if any tumor markers are elevated in these patients after negative malignancy workup, we should assure the patients about no neoplastic events to reduce their stress and anxiety.

There was a significant relationship between depression and DM in our study. Several studies confirm this relationship. Glycemic control and life-style modification by regular training and diet balance can improve depression. However, comorbid diseases like ESLD can promote depres-

Table 1. Descriptive Variables of the Study

Variables	N	Mean	SD	Minimum - Maximum
Weight (kg)	88	70.97	15.18	40 - 128
Illness Duration (days)	87	60.21	61.72	1 - 240
MELD score	88	19.94	5.38	8 - 33
CHILD score	85	8.71	2.02	5 - 14
PT	82	17.79	4.05	12.2 - 32.3
INR	82	2.17	2.43	1 - 23
AST	83	82.88	60.14	16 - 380
ALT	83	57.96	45.42	10 - 240
DB	83	2.42	4.60	0.1 - 36.7
TB	83	4.98	5.59	0.4 - 34.2
Albumin	83	3.28	0.53	1.7 - 4.5
Na	75	137.83	4.23	120 - 148
K	75	4.21	0.62	2.9 - 6
BUN	81	14.91	7.27	5 - 52
Cr	83	0.9	0.33	0.1 - 2.5
Platelets	81	118608.64	108773.669	20000 - 673000
CA 125	15	421.27	574.21	7.1 - 1929
CA 19-9	15	75.18	138.66	0.6 - 546

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CA 125 and CA 19-9, Child-Pugh score and tumor markers; Cr, creatinine; DB, direct bilirubin; K, potassium; INR, international normalized ratio; MELD, model for end-stage liver disease score; Na, sodium; PLT, platelets; PT, prothrombin time; TB, total bilirubin

Table 2. Scores of CVLT, HADS, Fatigue Severity Scale, and Epworth Sleepiness Scale

Variables	N	Mean	SD	Minimum - Maximum
Short delay free recall	91	10.18	3.24	3 - 16
Short delay cued recall	91	10.85	2.9	3 - 16
Long delay free recall	91	10.25	3.57	0 - 16
Long delay cued recall	91	11	3.42	0 - 17
Long delay recognition	91	14.3	2.32	4 - 16
Immediate memory	91	48.23	12.76	16 - 103
Attention	91	6.75	5.68	1 - 55
Depression	90	8.07	2.16	2 - 13
Anxiety	89	12.98	2.76	4 - 18
Sleepiness	83	9.19	4.61	0 - 20
Fatigue	88	40.6	14.87	9 - 63

sion in DM patients. In this study, we focused on memory status as a cognitive function in ESLD patients. For this evaluation, we used CVLT with parameters including attention, immediate memory, short delay free recall, short delay cued recall, long delay free recall, long delay cued recall, and recognition. We found that the most significant relationship was between age and the four items of CVLT performance. There is a general agreement that age influences memory status. Some studies have reached the same results as our study that memory and learning performance may decline with advanced age (35, 36). Our participants were overall in the middle-aged group and we recommended the evaluation of memory function by age to distinguish the effect of clinical conditions and the normal

Table 3. Pearson Correlation Between CVLT Items and Laboratory Data and Depression, Anxiety, Fatigue, and Sleepiness[a]

	Age	Weight	Illness Duration	MELD score	CHILD score	PT	I.N.R	AST	ALT	DB	TB	Albumin	Na	K	BUN	Cr	marriage	education	occupation	Depression	Anxiety	Sleepiness	Fatigue
Short delay free recall	0.01 (-0.25, 91)[b]	0.02 (-.024, 88)	0.11 (0.17, 87)	0.73 (-0.03, 88)	0.35 (0.10, 85)	0.33 (-.010, 82)	0.58 (-0.06, 82)	0.20 (0.14, 83)	0.32 (0.10, 83)	0.45 (0.08, 83)	0.14 (0.16, 83)	0.91 (0.01, 83)	0.24 (0.13, 75)	0.04 (-.023, 75)	0.05 (-0.21, 81)	0.05 (-.021, 83)	0.10 (-.017, 89)	0.31 (0.10, 89)	0.12 (-0.17, 77)	0.48 (-0.07, 90)	0.45 (0.08, 89)	0.54 (-0.06, 83)	0.66 (0.04, 88)
Short delay cued recall	0.03 (-0.21, 91)	0.36 (-0.09, 88)	0.74 (0.03, 87)	0.47 (0.07, 88)	0.14 (0.16, 85)	0.56 (0.06, 82)	0.84 (0.02, 82)	0.55 (0.06, 83)	0.43 (0.08, 83)	0.91 (0.01, 83)	0.24 (0.13, 83)	0.96 (-0.005, 83)	0.76 (0.03, 75)	0.09 (-0.19, 75)	0.24 (-0.13, 81)	0.46 (-0.08, 83)	0.73 (-0.03, 89)	0.09 (0.18, 89)	0.14 (-0.16, 77)	0.53 (-0.06, 90)	0.20 (0.13, 89)	0.92 (-0.01, 83)	0.42 (0.03, 88)
Long delay free recall	0.09 (-0.27.91)	0.01 (-.25, 88)	0.10 (0.17, 87)	0.97 (-0.003, 88)	0.44 (0.08, 85)	0.57 (0.06, 82)	0.52 (0.07, 82)	0.66 (0.04, 83)	0.42 (0.08, 83)	0.67 (0.04, 83)	0.55 (0.06, 83)	0.80 (-0.02, 83)	0.33 (0.11, 75)	0.05 (-0.22, 75)	0.14 (-0.16, 81)	0.12 (-0.17, 83)	0.09 (-0.17, 89)	0.09 (0.18, 89)	0.01 (-0.27, 77)	0.99 (0.001, 90)	0.76 (0.03, 89)	0.85 (0.02, 83)	0.23 (0.12, 88)
Long delay cued recall	0.05 (-0.029, 91)	0.36 (-0.09, 88)	0.30 (0.11, 87)	0.75 (0.03, 88)	0.30 (0.11, 85)	0.54 (0.06, 82)	0.68 (0.04, 82)	0.50 (0.07, 83)	0.44 (0.08, 83)	0.98 (0.002, 83)	0.35 (0.10, 83)	0.96 (-.005, 83)	0.56 (0.06, 75)	0.04 (-0.23, 75)	0.07 (-0.19, 81)	0.27 (-0.12, 83)	0.17 (-0.14, 89)	0.10 (0.17, 89)	0.01 (-0.26, 77)	0.44 (-0.08, 90)	0.22 (0.13, 89)	0.78 (0.03, 83)	0.55 (0.06, 88)
Long delay recognition	0.06 (-0.19, 91)	0.22 (-0.13, 88)	0.16 (0.15, 87)	0.88 (0.01, 88)	0.81 (0.02, 85)	0.79 (-0.03, 82)	0.59 (0.05, 82)	0.68 (0.04, 83)	0.34 (0.10, 83)	0.64 (0.05, 83)	0.44 (0.03, 83)	0.61 (0.05, 83)	0.48 (-0.08, 75)	0.08 (-0.20, 75)	0.07 (-0.19, 81)	0.27 (-0.10, 83)	0.49 (-0.07, 89)	0.79 (0.02, 89)	0.16 (-0.16, 77)	0.40 (-0.08, 90)	0.28 (0.11, 89)	0.54 (0.06, 83)	0.39 (0.09, 88)
Immedia memory	<0.0001 (-0.35, 91)	0.24 (-0.12, 88)	0.42 (0.08, 87)	0.96 (0.005, 88)	0.19 (0.14, 85)	0.99 (0.000, 82)	0.72 (-0.04, 82)	0.97 (0.003, 83)	0.51 (0.07, 83)	0.59 (0.05, 83)	0.85 (0.02, 83)	0.49 (0.07, 83)	0.79 (0.03, 75)	0.23 (-0.13, 75)	0.04 (-0.22, 81)	0.07 (-0.19, 83)	0.04 (-0.21, 89)	0.34 (0.10, 89)	0.09 (-0.29, 77)	0.73 (-0.03, 90)	0.49 (0.07, 89)	0.32 (0.10, 83)	0.31 (0.10, 88)
Attention	0.01 (-0.25, 91)	0.52 (-0.06, 88)	0.81 (-0.02, 87)	0.90 (-0.01, 88)	0.81 (0.02, 85)	0.79 (0.02, 82)	0.71 (-0.04, 82)	0.56 (-0.06, 83)	0.84 (-0.02, 83)	0.61 (-0.05, 83)	0.45 (-0.08, 83)	0.33 (0.10, 83)	0.36 (0.10, 75)	0.67 (-0.04, 75)	0.15 (-0.15, 81)	0.41 (-0.09, 83)	0.05 (-0.20, 89)	0.02 (0.24, 89)	0.04 (-0.23, 77)	0.95 (-0.006, 90)	0.40 (0.08, 89)	0.17 (0.15, 83)	0.47 (-0.07, 88)

[a] P value is significant at < 0.05.

[b] P value (Pearson correlation, number)

advance of age on learning and memory status.

We found that short and long delay free recall had an association with weight. Two other studies showed that BMI and obesity had a reverse correlation with immediate and delayed recall (37, 38). The recall memory and overeating can be related to each other. For example, healthy weight persons have a good memory to recall the last items that they ate at launch, causing reduced food intake later on (39). In our study, confounding factors such as obesity due to ascites could be effective in the overweight condition of patients, so obesity due to overeating, especially eating disorders, should be considered in further studies. The marital status could influence the attention of our participants. A study showed married people had better performance in recall and recognition (40). The other most significant correlation was between CVLT results and job status in our study. The CVLT performance of patients in three items (attention, long delay free recall, and long delay cued recall) had a reverse association with occupation so that having a job contributed to low long memory function. A study on Alzheimer's Disease (AD) showed that memory declines more rapidly in AD patients with higher occupational attainment (40). Our study showed no association between memory function and other psychological conditions such as depression, anxiety, fatigue, and sleepiness. The mean sleepiness score of the participants was below 10 and according to the standard scale, this score shows that most of our patients did not need any expert medical advice. Abdullah et al. reported that daytime sleepiness was high among cirrhotic patients, especially those who had hepatitis C (41). Fatigue was one of the other parameters we evaluated in ESLD patients. Although fatigue is the most common complaint of ESLD patients, the exact frequency of fatigue is variable (42-44). The mean score on the fatigue scale in our study was 40, and it was higher than the cutoff normal range, implying that the patients needed further evaluations. Most of the fatigue cases in ESLD patients were seen in Primary Biliary Cirrhosis (PBC) (45, 46). Treatment of fatigue with liver transplant is controversial. A study reported that fatigue decreased after transplantation (47), but another one showed that fatigue remained a persistent complaint after two years of transplantation (48).

In conclusion, we found some psychological problems in ESLD patients. Two factors could be effective in cognitive functions. Some demographic and anthropometric parameters had associations with the cognitive status of ESLD patients, independent of their clinical conditions, such as age, which is an inevitable factor. However, other items such as weight and laboratory data could be improved. We had some limitations such as the short duration of patients' evaluation and follow-up, missing data, and poor condition of some participants. Thus, we recom-

mend further evaluations about this topic on the separate groups of ESLD patients according to their culture, stage of the disease, and associated clinical conditions as exclusion criteria, and comparison with post-transplant patients. Although the main treatment of ESLD is liver transplantation but the psychological and cognitive problems before transplantation in these patients are prognostic factors for post-operation compliance and follow up.

Footnotes

Authors' Contribution: Study concept and design: M. B, M. Sh, and Z. A; analysis and interpretation of data: M. R and Z. A; drafting of the manuscript: M. Sh, M.B, and M. R; critical revision of the manuscript for important intellectual content: S. N, M. B, and M.R; statistical analysis: Z. A and S. Gh; administrative, technical, and material support: S. GH; study supervision: A.M and S. N

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