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Background

End-stage liver disease (ESLD) not only causes severe physical deterioration, but it can also lead to psychological issues [1]. The development of orthotopic liver transplantation (OLT) has improved long-term survival and the quality of life of recipients [2], and the 1-, 10-, and 18-year survival rates associated with adult OLT have reached 83% to 88%, 68% to 72%, and 48% to 56%, respectively [3]. However, due to the gap between supply and demand, candidates are placed on waiting lists and may have to wait for a long time before receiving the transplant. During this time, patients face multiple stressors: declining physical health; constant worry about whether the procedure will take place on time and, more importantly, in time [4]; the financial cost; and so forth.

The combination of these stressors can contribute to psychological disorders such as anxiety and depression. The prevalence rates for anxiety and depression have been estimated to be 14% to 52% and 17% to 60%, respectively [4]. Pretransplant depression and anxiety affect posttransplant health-related quality of life (HRQOL) [5]. Furthermore, pretransplant depression also affects posttransplant psychiatric morbidity [6], while anxiety can negatively affect the course of the disease by impairing adherence to treatment [7].

Sleep disturbance, including compromised sleep quality, has been reported among liver transplantation candidates on a waiting list [8]. Furthermore, sleep disturbance has a prevalence of 48% to 81% in patients with liver cirrhosis, which is much higher than in the general population [9]. Therefore, sleep disturbance appears to be a particular problem in waiting list candidates.

Deficits in activities of daily living are common in patients with ESLD. Functional decline, polypharmacy, and cognitive impairment, which is often seen in elderly patients, may contribute to the high risk of physical disability. These deficits can be a predictor of mortality and, more importantly, they could determine posttransplant disability reversion for candidates on a waiting list [10].

These considerations indicate a need to improve the mental and sleep status of patients. Thus, it is important to identify the predictors of disability and the factors related to psychological disorders and sleep disturbance that could be recapitulated in the patients' psychosocial factors. Such predictors and factors should be used as the basis for developing diagnostic and therapeutic interventions because they could help prevent the worsening of candidates' symptoms and the negative consequences.

The model for end-stage liver disease (MELD) score was initially created to predict the survival of transjugular intrahepatic

portosystemic shunts but then applied as a standard metric to reflect the severity of liver diseases [11]. The MELD score has been statistically proved to predict 3-month mortality and to indicate the severity of ESLD. Thus, it is used as a determining factor for the OLT waiting list in accord with the idea of "the sickest first" [12]. Patients with a MELD score \geq 15 are considered eligible to be placed on the waiting list. However, an exception exists for several diseases, whereby severity is not indicated by a higher MELD score [13]. A national study of the US liver transplant database revealed that a higher survival benefit was found in patients with a higher MELD score. A pretransplant MELD score of 31 to 34 predicted a 43 times greater relative life expectancy, while a MELD score of 35 to 40 had a 128 times higher expectation [14]. In addition to its ability to predict physiological outcomes, the MELD score also exhibits the potential to simultaneously reveal psychological outcomes in terms of health-related quality of life (HRQOL). Higher posttransplant HRQOL was found in patients with a higher pretransplant MELD score [13,15,16]. However, more research should be done to verify the correlation between MELD scores and psychological issues. Furthermore, the association between MELD score and sleep disturbance and daily living abilities remains unclear.

Thus, this study aimed to assess the affective status, sleep quality, and daily living abilities of candidates on the OLT waiting list at a single center in China and to identify the association between these factors and disease severity as represented by the MELD score.

Material and Methods

Study design

This cross-sectional, single-center study included 53 pretransplant patients for whom surgery was indicated were recruited from the ward of the liver transplantation center of Renji Hospital, Shanghai, China, from May to December 2019. This study was approved by the Ethics Committee of Renji Hospital (No. [2017] 164).

The inclusion criteria required study participants to (1) meet the indications for liver transplantation in Renji Hospital; (2) be age 18 or older; (3) agree to participate in the study in person; and (4) sign informed consent. The exclusion criteria were (1) having schizophrenia, bipolar disorder, or any other severe mental disorder; and (2) having significant diseases, other than hepatic diseases, such as cardiovascular, respiratory, renal, endocrine, and immune diseases.

Informed consent was obtained from all participants. Afterward, they provided their personal information, including sex, highest

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education, occupation, economic status, marital status, and alcohol and tobacco use. They then received the scales described below from a qualified medical worker, who completed 2 clinician-rated scales and helped collect the self-rated scales from participants after they finished these instruments on their own in their wards. Four medical workers participated in the data collection and the assessment of clinician-rated instruments. They were all well trained to use a standard procedure and to avoid bias. Participants' MELD scores were calculated from the latest blood test results. Their medical records were reviewed to obtain liver disease type, duration of illness, time on the waiting list, mental disorder history, and corresponding medication.

Rating scales

Scales were used to assess participants' depression, anxiety, sleep quality, and activities of daily living.

To assess depression and anxiety, we used the Hamilton Rating Scale for Depression (HAMD-17) [17] and the Hamilton Anxiety Rating Scale (HAM-A) [18], 2 clinician-rated scales. For sleep quality, we used the Pittsburgh Sleep Quality Index (PSQI) [19]. For assessing daily living ability, we used the Activity of Daily Living Scale (ADL) [20]. These instruments have been widely used in China and all have been translated into Chinese, including adaptation to culture and idiom.

HAMD-17 and HAM-A

HAMD-17 is a clinician-rated scale designed to rate the severity of major depressive disorder (MDD) symptoms. It contains 17 items that relate to the symptoms observed in MDD, such as depressed mood; feelings of guilt; suicidal ideation insomnia; lack of interest in work and activities; thought retardation; agitation; psychic anxiety; somatic anxiety; somatic symptoms; loss of libido; hypochondria; weight loss; and lack of insight. HAMD-17 is evaluated by a gualified clinician interviewing patients while observing their symptoms; items are rated on scales of 0 to 4, 0 to 2, or 0 to 3 points (based on different item sets). The higher the points, the more severe the symptoms are, with a maximum score of 52. A normal total score is 0 to 7; a total score of 8 to 16 indicates probability of depression disorder; a total score between 17 and 24 is considered to indicate moderate MDD severity; and a total score of 25 or above signals severe depression [17,21,22].

Similar to HAMD-17, HAM-A is also clinician rated, but it is designed to rate anxiety symptoms based on 14 items, such as anxious mood; tension; fears; insomnia; intellectual ability; depressed mood; somatic, sensory, cardiovascular, respiratory, gastrointestinal, genitourinary, and autonomic symptoms; and observed behavior during the interview. Each item is scored from 0 (not present) to 4 (severe), and the maximum total score is 56. A total score of 0 to 7 is normal; 8 to 16 indicates probable anxiety; 17 to 24 indicates mild anxiety; 25 to 30 indicates moderate to severe anxiety; and 30 or above indicates severe [17,23].

HAMD-17 and HAM-A have been translated into Chinese, incorporating Chinese idioms and culture, and these scales have good reliability and validity [23]. Fourteen facilities in China cooperated in studying the reliability and validity of HAMD-17, which was found to have a reliability coefficient of 0.88 to 0.99 (P<0.01). For assessing depressive disorder, the authenticity coefficient was 0.92. In a study with 19 patients with anxiety disorder, the reliability coefficient was 0.93 (P<0.01) [24]. Another study, which included 36 patients with anxiety, showed that the validity coefficient was 0.36 (P<0.05) [25].

Pittsburg sleep quality index

PSQI is a scale that assesses sleep quality and disturbances within the past month. It contains 19 self-rated items and 5 items that are rated by partners. The 19th self-rated item and the 5 partner-rated items are not scored. The scored 18 items relate to 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component contains items that match the category, and each component is scored from 0 to 3 based on the total score of the items it contains. Each item is rated from 0 to 3, with the higher score indicating greater frequency of the problem. The maximum score is 21, and a total score of 5 or more is considered as indicating a sleep disorder [19]. The scored part (18 self-rated items) of PSQI was translated into Chinese in 1996 by Xianchen et al. [26], who also studied the reliability and validity of the scale. Their findings indicated that the Chinese version of PSQI had good internal consistency, test-retest reliability, and high concept and criterion-related validity, with a sensitivity of 98.3% and a specificity of 90.2%.

Activity of daily living scale

ADL was developed by Lawson and Brody in 1969 [20], and it comprises the Physical Self-Maintenance Scale (PSMS) and Instrumental Activities of Daily Living Scale (IADL). The PSMS and IADL scales were developed to assess ADL and IADL, and they include 6 ADL items (eating, dressing, grooming, walking, bathing, and toileting) and 8 IADL items (telephone use, shopping, food preparation, housekeeping, laundry, public transportation use, handle finances, and taking medicines). Each of the items is rated from 1 to 4 (1, can do; 2, can do with some difficulty; 3, need some help to do; and 4, cannot do independently), and the maximum score is 56. A total score of 22 or higher indicates significantly disability in ADL [20,27].

Grouping standard

The patients were divided into a high MELD score group (MELD score \geq 15) and a low MELD score group (MELD score <15) to identify the influence of severity of disease on depression, anxiety, sleep disturbance, and ADL. We chose the cutoff point of 15 because patients with a score \geq 15 are considered to be eligible to be on the waiting list and have significant survival benefit from OLT [13]. During our literature search, we found several studies using this standard [28,29].

Statistical analysis

First, the data were checked for normal distribution by the Kolmogorov-Smirnov test, and data were found to not be normally distributed. Therefore, the Spearman test for correlation was used to assay the correlation between variables. A nonparametric statistical test (the Mann-Whitney U-test) was used to verify the statistical differences between groups, with the significance being 5%. Microsoft Excel (Microsoft, Redmond, WA, USA) and SPSS 26.0 (IBM, Armonk, NY, USA) were used for data input and statistical analysis.

Results

Demographic information

Fifty-three candidates were included as participants in this study; 41 (77.4%) were men and 12 (22.6%) were women. The average age was 52.2±12.67 years (range, 21 to 84). For educational status, we considered the highest education received by each participant. Two (3.8%) had primary education; 22 (41.5%), lower secondary education; 12 (22.6%), upper secondary education; 9 (17%), short-cycle tertiary education; 6 (11.3%), bachelor's degree or equivalent; and 2 (3.8%), master's degree or equivalent. For monthly income, 19 (35.8%) had a monthly income below 430 USD; 10 (18.9%) had 430 to 717 USD; 7 (13.2%) had 717 to 1147 USD; 7 (13.2%) had 1147 to 1434 USD; 2 (3.8%) had 1434 to 2151 USD; 4 (7.5%) had 2151 to 2868 USD; and 4 (7.5%) had above 2868 USD. To provide context for the income status, we note that the minimum wage in China is around 140 to 360 USD, differing by province. The marriage status was as follows: 2 (3.8%) participants were not married, 48 (90.6%) were married, and 3 (5.7%) were divorced. The average duration of illness was 47.1±66.7 months, ranging from 0.25 to 240 months. The average time on the waiting list was 1.9±2.47 months, ranging from 0 to 12 months. The most common underlying disease was hepatitis B cirrhosis (30/53; Table 1).

The average MELD score was 14.2 ± 9.3 , ranging from 3.0 to 46.0. The low MELD score group (MELD <15) included 34 (64.2%) participants, the high MELD score group (MELD \geq 15) contained 18 (34.0%), and 1 participant's MELD score was not specified (Table 1). No statistical difference was found for highest education (*P*=0.507), marital status (*P*=0.749), monthly income (*P*=0.721), duration of illness (*P*=0.779), or time on the waiting list (*P*=0.555) between 2 groups.

HAMD-17 results

Among all participants, HAMD-17 scores ranged from 0 to 37, and 13 (24.5%) had scores \geq 7, indicating they had depression. In the high MELD score group, the average HAMD-17 score was 8.4±10.3, with 7 of 18 (38.9%) having a score \geq 7. The average score was 3.6±4.8, and 5 of 34 (14.7%) had a score \geq 7 in the low MELD score group (Table 2). No statistical difference was found in HAMD-17 scores between the 2 groups (*P*=0.063), but there was a tendency toward a higher score in the high MELD score group (Figure 1).

HAM-A results

HAM-A scores ranged from 0 to 38, and 13 (24.5%) participants had a score \geq 7 and were considered to have an anxiety disorder. The average score was 9.0±10.4 in the high MELD score group and 3.1±4.5 in the low MELD score group. In the high MELD score group, 7 of 18 (38.9%) had a score \geq 7, and 5 of 34 (14.7%) in the low MELD score group had a score \geq 7 (Table 2). The score was significantly higher in the high MELD score group than in the low MELD score group (*P*=0.024; Figure 1).

PSQI results

The minimum PSQI score was 0, while the maximum was 18. Thirty-two (59.5%) participants were considered to have a sleep disorder (total score >5): 13 of 18 (72.2%) in the high MELD score group, and 19 of 34 (55.9%) in low MELD score group. The average score was 9.5 ± 4.8 in the high MELD score group and 6.2 ± 4.2 in the low MELD score group (Table 2). The PSQI score was significantly higher in the high MELD score group (*P*=0.021; Figure 1).

ADL results

ADL scores ranged from 14 to 41, and 14 (26.4%) participants were considered significantly disabled (score \geq 22): 3 of 34 (8.8%) in the low MELD score group and 11 of 18 (61.1%) in the high MELD score group. The average score was 22.8±5.9 in the high MELD score group and 16.4±5.8 in the low MELD score group (Table 2). The ADL score was significantly higher in the high MELD score group (*P*=0.000; Figure 1).

Table 1. Demographic information on liver candidates divided by MELD score.

	MELD ≥15 n/percentage%		MELD <15 n/percentage%		
Gender					
Male	16	(88.9%)	24	(70.6%)	
Female	2	(11.1%)	10	(29.4%)	
Age (years)	51.78	3±13.077	51.9	01±12.571	
Highest education					
Primary education	1	(5.6%)	1	(2.9%)	
Lower secondary education	5	(27.8%)	16	(47.1%)	
Upper secondary education	6	(33.3%)	6	(17.6%)	
Short-cycle tertiary education	3	(16.7%)	6	(17.6%)	
Bachelor or equivalent	2	(11.1%)	4	(11.8%)	
Master or equivalent	1	(5.6%)	1	(2.9%)	
Monthly income (USD)					
Below 430	6	(33.3%)	13	(38.2%)	
430–717	6	(33.3%)	3	(8.8%)	
717–1147	2	(11.1%)	5	(14.7%)	
1147–1434	0	(0)	7	(20.6%)	
1434–2151	1	(5.6%)	1	(2.9%)	
2151–2868	1	(5.6%)	3	(8.8%)	
Above 2868	2	(11.1%)	2	(5.9)	
Marital status					
Single	1	(5.6%)	1	(2.9%)	
Married	16	(88.9%)	31	(91.2%)	
Divorced	1	(5.6%)	2	(5.9%)	
Underlying diseases					
Hepatitis B cirrhosis	11	(61.1%)	18	(52.9%)	
Liver carcinoma	1	(5.6%)	9	(26.5%)	
Alcoholic liver cirrhosis	2	(11.1%)	3	(8.8%)	
Autoimmune hepatitis	1	(5.6%)	3	(8.8%)	
Acute liver failure	2	(11.1%)	1	(8.8%)	
Liver retransplantation	1	(5.6%)	0	(0)	
Average duration of illness (months)	53.6	5±80.4	44	44.6±60.1	
Average time on the waiting list (months)	1.3	3±1.2	1	.9±2.3	

* There is 1 candidate with missing MELD SCORE.



Figure 1. These figures shows that based on two MELD groups, the high MELD group has significantly scores than low MELD score group for HAMA (P=0.024), PSQI (P=0.021) and PSMS and IADL scale (P=0.000). No statistically significant difference between these two groups found in HAMD-17 scores (P=0.063).

Table 2.	Results of HAMD-17. HAM-	A. PSOI and ADL b	ased on different MEL	D score groups.
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	Average score		Posi	tive	The Mann-Whitney-U-test
	MELD ≥15	MELD <15	MELD ≥15	MELD <15	Р
HAMD-17	8.4±10.3	3.6±4.8	7 (38.9%)	5 (14.7%)	0.063
HAM-A	9.0±10.4	3.1±4.5	7 (38.9%)	5 (14.7%)	0.024*
PSQI	9.4±4.8	6.2±4.2	13 (72.2%)	19 (55.9%)	0.021*
ADL	22.8±5.9	16.4±5.8	11 (61.1%)	3 (8.8%)	0.000*

* Statistically significant.

Table 3. Result of the Spearman test for correlation.

	Correlation coefficient				
	HAMD-17	HAM-A	PSQI	ADL	
MELD score	0.362**	0.430**	0.289*	0.585**	

* Correlation is significant at the 0.05 level (2-tailed); ** correlation is significant at the 0.01 level (2-tailed).

Relationship between MELD score and the scales

The results of the Spearman correlation test showed that the MELD score is positively correlated with HAMD-17 (r =0.362, P<0.01), HAM-A (r=0.430, P<0.01), PSQI (r=0.289, P<0.05), and ADL (r=0.585, P<0.01), which suggests that the higher the MELD score is, the more likely a transplant candidate on the waiting list had depression, anxiety, sleep disturbance, and daily living disability. No other variable included in the analyses (highest education, marriage status, economic status, age, duration of illness, and time on the waiting list) was correlated with the scores on these scales (Table 3).

Discussion

The present study found that the MELD score was positively correlated with levels of anxiety, depression, sleep disturbance, and ADL disability. OLT candidates on the waiting list with high MELD scores had more severe anxiety, sleep disturbance, and ADL disability than those with low MELD scores.

Pre-OLT depression and anxiety have been shown in several studies [7,30]. Only a few studies have examined the correlation between MELD score and depression and anxiety. Although a few of these studies recorded pre-OLT MELD scores, they did not assess whether a correlation existed and simply reported the mean scores [7,30]. However, a higher MELD score (\geq 13) after OLT has been shown to be associated with more severe depression; furthermore, depression was correlated with liver function [31]. These results generally coincide with our findings. They differed in that our assessments were conducted before OLT, and we found only a tendency toward higher HAMD-17 score in the high MELD score group rather than a statistical difference (P=0.063). To the best of our knowledge, the present study is the first to discover a statistical difference showing that a higher pre-OLT MELD score indicates a higher anxiety level. In contrast to our results, Cron et al. [32] found no correlation between depression and MELD score, while Benzing et al. [13] found no statistical difference between groups with high and low MELD scores with regard to depression and anxiety before transplantation. The cutoff point in the latter study was 10, rather than 15 as in the current study. The symptoms present in ESLD increase along with the severity of the disease, which represents a direct stressor to patients due to the physical distress and long disease duration. It is reasonable to believe that disease severity would affect the mood of patients, thus causing depression and anxiety to a corresponding degree with symptoms such as ascites, jaundice, and gastrointestinal hemorrhage. Annema et al. [4] found that the LDSI score, a subjective measurement of disease severity, is related to the trajectories of anxiety and depression. They emphasized the need to adequately manage the symptoms of ESLD, but they noted that further research was required on an objective measurement such as the MELD score. The results of this present study may imply that managing the physiological symptoms in ESLD could also help reduce psychological problems. But the relationship between cognitive appraisal of disease symptoms and the actual severity of the disease should be examined in future research. The core conflict between these 2 theories is the uncertainty of the biological basis of mood disorders. Since the MELD score is calculated by a formula incorporating 3 laboratory variables (international normalized ratio, serum creatinine, and serum bilirubin), our findings might be the starting point for future studies to focus on the relationship between biochemical markers and the severity of mood disorders as a comorbidity in chronic diseases.

Sleep disturbance is closely related to hepatic encephalopathy (HE), one of the clinical manifestations seen in ESLD and reported to affect 32% of patients with liver cirrhosis [9]. Several studies have focused on factors affecting sleep quality in ESLD, but only a few have examined the correlation between MELD score and sleep disturbance. Bruyneel et al. [33] found that sleep quality improved along with a significant decrease in HE severity after medical treatment. In an animal study, Felipo et al. [34] found that HE-model rats awoke more during sleep and took more naps during inactive phases than controls. In contrast, Gencdal et al. [35] found no correlation between MELD score and sleep quality. MELD score has not been found to depict the severity of HE in ESLD, and we were not able to obtain the HE status of all participants in this study. Thus, further research could focus on this particular problem to elucidate the relationship more precisely.

Few studies have examined the association between MELD score and ADL disability. Samoylova et al. [10] found that a higher MELD score was a predictor of new or increasing IADL disability, and they speculated that patients whose MELD scores are <12 have a much lower ADLs/IADLs disability rate since they only recruited patients with a MELD score \geq 12. In

our study, we proved their hypothesis by finding that a high MELD score group was significantly more disabled than a low MELD score group based on P=0.000. ESLD causes problems such as sarcopenia, functional decline, and malnutrition that contribute to disability, and it is reasonable to expect that the severity of the physiological condition deteriorates ADL similar to many other chronic diseases.

To our knowledge, the present study was the first to discover the correlation of MELD score with depression, anxiety, sleep disturbance, and ADL disability simultaneously. It also suggested the possibility that the MELD score reflects the severity of candidates' psychosocial problems, which is a more comprehensive role than the current one of only measuring the physiological severity of disease. The MELD score could accord with the biopsychosocial model of diseases, which would help clinicians consider not only the physiological and medical aspects of ESLD, but also the psychological and social factors.

The results shed light on the expanded clinical usage of MELD score in OLT. Most liver surgeons lack psychiatric expertise, but the MELD score is a value they commonly use in everyday practice. Given their familiarity with MELD scoring, they would be able to identify patients with potential psychological problems and could refer them to psychiatrists for evaluation of the affective status, sleep status, and ADL disability. Moreover, the MELD score could provide a reference for pretransplant and posttransplant intervention because it can

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also predict post-OLT HRQOL [13,15,16]. However, due to the limited amount of studies and contradictory findings, further research should be done to verify the validity of our findings.

Our study has its limitations. It is a single-center, cross-sectional study with a relatively small sample size. A future study should have a longitudinal design, focus on changes in MELD score over time, and include a larger sample size to test our findings. Future studies could also focus on the association between depression, anxiety, sleep disturbance, and disability to discover whether and how these problems affect each other.

Conclusions

In summary, MELD scores are correlated with anxiety, depression, sleep disturbance, and ADL disability, and a higher MELD score indicates more severe problems. The MELD score could be a more comprehensive indicator in OLT to quickly detect biopsychosocial problems associated with ESLD. Also, it could provide a reference for both medical and psychosocial intervention before and after OLT. Future longitudinal studies could determine the decline of MELD score caused by interventions to treat the psychological problems mentioned in our study.

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