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Malnutrition and Nutrition-related Complaints in Liver-transplant Candidates in Iran

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ABSTRACT

Introduction: This study aimed to evaluate the prevalence of nutrition-related complaints and malnutrition among liver transplant candidates in Iran.

Methods: This cross-sectional study was conducted in two hospitals in Iran from May to October 2021. The nutritional status of patients was evaluated by subjective global assessment (SGA), and the food intake of patients was assessed by a 3-day food record. In addition, anthropometric indices, including weight and body mass index (BMI), were measured.

Results: A total of 43 patients were evaluated. Men accounted for 58% of patients, and mean BMI and age were 24.5±5 kg/m^2, and 48±14 years, respectively. The total prevalence of malnutrition before liver transplantation was 83.7%. Nausea in patients with malnutrition was significantly higher ($P<0.05$). Low Energy intake was observed in 90.7%, while low protein intake was reported in 69.8% of patients before liver transplantation.

Conclusion: Malnutrition, low-calorie, and low protein intake were prevalent among patients before liver transplantation.

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Introduction

Studies have shown that the number of patients on the waiting list for liver transplantation has increased from 2006 to 2016 in Iran (1). Cirrhotic patients are exposed to malnutrition for various reasons before transplantation, including inflammation, decreased energy and protein consumption, malabsorption, changes in nutrient metabolism, hypermetabolism, hormonal disorders, and external factors such as alcohol consumption. In addition, fasting periods affect malnutrition (2). Decreased energy and protein intake lead to protein-energy malnutrition (PEM), the commonest cause of malnutrition in cirrhotic patients. The range of patients with insufficient energy intake varies from 9.2 to 100% based on the evaluation methods in different studies (3-5). Protein-Energy malnutrition is associated with increased short- and long-term mortality in patients with end-stage liver disease (ESLD), including liver transplant candidates (6). Malnutrition before liver transplantation could be associated with increased length of stay (LOS) and high mortality rates (7, 8).

Considering the necessity of evaluating the nutritional status of liver transplant patients, the lack of related studies in Iran on the nutritional status of liver transplant patients, and malnutrition in liver transplant, this study evaluated the nutritional status and food intake of patients before liver transplantation.

Material and Methods

The data of this present cross-sectional study were collected from a cohort study in two hospitals in Iran, Montaseriyeh Hospital, Mashhad, and Firoozgar Hospital, Tehran. Details of the method, including inclusion and exclusion criteria, are provided elsewhere (9). The inclusion criteria were patients above 18 years on the waiting list for liver transplantation from May to October 2021 and those with consent for participation in the study. The exclusion criteria were refusal to participate in the study or patient death. The sample size determined 33 patients based on a Lim et al. (10) study, which reported

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the malnutrition rate before transplantation as 84.8% based on subjective global assessment (SGA). An alpha error of 0.05 and d=0.126 was considered, using the formula for estimating a qualitative variable in a population. The final sample size was increased to 43 patients considering a 30% dropout rate. The research protocol was approved by the School of Medicine, Mashhad University of Medical Sciences, Biomedical Research Ethics Committee (IR.MUMS.MEDICAL.REC.1399.815). All patients signed the consent form before entering into the study.

Demographics and laboratory values

Characteristics such as age, gender, weight, height, smoking status, and comorbidities were extracted from medical charts. Fasting venous blood samples were collected from all patients during hospitalization to determine Albumin, Total Protein, Fasting blood sugar (FBS), Cell blood count (CBC), Bilirubin, International normalized ratio (INR), and Prothrombin Time (PT), Blood urea nitrogen (BUN), Creatinine, Iron, Zinc, Sodium, Potassium, Triglyceride, Total Cholesterol, Low-density lipoprotein (LDL), High-density lipoprotein (HDL), Liver enzymes including Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Gama-glutamyl Transferase (GGT) and Lactate dehydrogenase (LDH), to evaluate nutritional status, inflammatory response, and cirrhosis severity.

Child-Pugh scoring system includes three categories to express the severity of liver cirrhosis (11): five to six points: for good hepatic function (A), seven to nine points: for moderately impaired hepatic function (B), and ten to 15 points: advanced hepatic dysfunction (C).

The model for End-Stage Liver Disease (MELD) score is a prognostic scoring system based on laboratory parameters that predict 3-month mortality due to liver disease. MELD scores range from six to 40 and are defined as (12):

9.57 * loge (creatinine) + 3.78 * loge (total bilirubin) + 11.2 * loge (INR) + 6.43.

Nutritional Assessment

A trained nurse measured the patients' weight in a standard position with minimal clothing and no shoes. A scale with an accuracy of 100g was used to measure the weight, and a stadiometer was used to determine the height of the patients. The patient was asked about their usual weight in the previous six months to calculate the weight loss percentage of the patients in the last one and six months. Weight loss percentage defined as 100* (usual weight of one or six months ago - measured weight)/typical weight of one or six months ago). The body mass index (BMI) was computed as estimated body weight (kg) divided by height (m) squared. BMI <18.5 kg/m^2 and BMI 18.5 to 24.9 kg/m^2 were considered underweight and normal weight, respectively. Patients with a BMI of 25 to 29.9 kg/m^2 and a BMI ≥ 30 kg/m^2 were considered overweight and obese, respectively (13). In the case of mild to moderate ascites, 5% of the weight and 15% in refractory ascites were reduced to overcome the effect of ascites on BMI(14). Malnutrition was diagnosed and reported based on the subjective global assessment (SGA) tool and protein-energy intake.

Subjective Global Assessment

The nutritional data of the SGA questionnaire include 1) current weight and weight change in the past two weeks, one and six months; 2) nutritional history (diet intake, appetite), gastrointestinal problems (nausea, vomiting, diarrhea), physical evaluation (signs of fat loss and muscle wasting, edema, and ascites) and functional physical capacity (15). Patients were classified in one of three kinds of stages:1) well-nourished (SGA-A), 2) moderately malnourished (SGA-B), or 3) severely malnourished (SGA-C) based on the SGA tool.

Dietary intake and Protein-Energy Malnutrition

A 3-day nonconsecutive food record assessed the patient's food intake. Through a direct interview, we completed food intake records on one weekend and two regular days. Nutritionist IV software calculated the mean of 3-day energy and nutrient intake.

Each patient's energy and protein requirements were calculated based on the ESPEN guideline (16) and compared with the energy and protein intake of the patient. Protein-energy malnutrition was defined as the intake of protein and energy less than the individual needs.

Bioelectrical Impedance Analysis (BIA)

Bioelectrical Impedance Analysis (BIA) has applications for cirrhotic patients with or without ascites (17, 18). A multi-frequency bioelectrical impedance analyzer, InBody S10 (Biospace Co., Ltd., Korea), was used based on the manufacturer's guidelines. Patients were asked

to remove watches, glasses, jewelry, and other metal objects. Patients had a supine position with legs apart and arms parallel with the body but not touching the body or all impedance measurements. The BIA test was not performed if a patient had a fever or was in shock. The total body water (TBW), fat mass (FM), fat-free mass (FFM), basal metabolic rate (BMR), waist circumference (WC), and arm muscle circumference (AMC) data were measured by BIA for all patients.

Statistical Analysis

SPSS software version 26.0 was used for analyzing the data. The Kolmogorov-Smirnov test checked the normality of the distribution of quantitative variables. The chi-square test evaluated the relationship between qualitative variables and nutritional status. One-way ANOVA and Kruskal-Wallis tests were implemented to compare quantitative variables between groups. All tests were two-sided, and the significance level was 0.05 in all tests.

Table 1. Baseline characteristics of the candidate patients for liver transplantation

characteristics	Group n = 43
Weight (kg)	68.2±16
BMI (kg/m^2)	24.5±5
WC (cm)	71.1±11
AMC (cm)	21±3
FFM (kg)	50.2±13
FM (kg)	18.9±10
TBW (L)	36.9±9
Total protein (g/dl)	6.5±1
Albumin (g/dl)	3±0.6
Ferritin (ng/ml)	333.6 (101-676)
FBS (mg/dl)	100 (89-120)
Hematocrit (%)	34.7±6
Platelet	108 (66-201)
Hemoglobin (g/dl)	11.6±2
Creatinine (mg/dl)	1.2±0.6
BUN (mg/dl)	24.6±15
Cholesterol (mg/dl)	123.5 (105.5-170.5)
LDL (mg/dl)	68.5 (50-83)
HDL (mg/dl)	35.5±16
TG (mg/dl)	104.5 (73-140)
T.Bili (mg/dl)	4.7 (2.9-9.6)
D.Bili (mg/dl)	2 (1.2-5.8)
PT	17±5
INR	1.4 (1.1-1.8)
AST (UL/l)	81.8±56
ALT (UL/l)	47 (32-92)
ALP (UL/l)	508±354
LDH (UL/l)	479.5 (380-562)
GGT (UL/l)	127.3 (56-219)
Iron (ug/dl)	99.5±62
TIBC	273±64
Zinc (ug/l)	59±27
Sodium (mEq/L)	137 (135-140)
Potassium (mEq/L)	4.1 (3.7-4.6)
BMR (kcal)	1456±273
SBP (mmHg)	116 (105.5-120)
DBP (mmHg)	70 (67.5-80)
Child-Pugh stage	
A	5
B	19
C	19
Etiology	
Cryptogenic	11
HBV/HCV	9
PSC/PBC	6
AIH	4
Other	13

Results

This study included 43 patients with a mean age of 48±14 and a mean MELD score of 16.8 ±6. The patients were predominantly males (58%) with a normal body mass index (46.5%). The most common etiology that led to liver transplantation was cryptogenic (11 patients) (Table 1). The most prevalent nutritional complaints were anorexia (61.5%) and nausea (59%), based on SGA. Eight patients were in the category well-nourished (A), 16 patients were in the category moderate malnutrition (B), and 19 patients were in the category severe malnutrition (C) based on the SGA classification.

The main demographical, clinical, and biochemical characteristics of the patients classified based on their nutritional status are reported in Table 2. Patients with severe malnutrition presented lower BMI and Phase angle, higher total bilirubin and direct bilirubin, and higher MELD and Child-Pugh scores.

Table 3 shows the frequency distribution of nutritional complaints in the three groups of well-nourished, moderate, and severe malnutrition. Nausea was significantly higher in the cirrhotic patients with malnutrition.

Table 2. Demographical and clinical characteristics of the 43 patients undergoing liver transplantation according to their nutritional status

	Well-nourished (8)	Moderate Malnutrition (16)	Severe Malnutrition (19)	P-Value
Age(years)	45.4±15	53.5±12	45±14	0.17
Gender (M/F) (n)	5/3	10/6	10/9	0.85
Etiology				
Cryptogenic	4 (36.4)	3 (27.3)	4 (36.4)	0.247
HBV/HCV	1 (11.1)	5 (55.6)	3 (33.3)	0.543
PSC/PBC	1 (16.7)	2 (33.3)	3 (50)	0.99
AIH	0	3 (75)	1 (25)	0.383
Others	2 (15.4)	3 (23.1)	8 (61.5)	0.354
Anthropometrics				
BMI (kg/m^2)	25±5	27.3±5	21.8±4[b]	0.006*
Overweight or Obesity, n (%)	4 (22.2)	9 (50)	5 (27.8)	0.204
Normal BMI, n (%)	3 (15)	7 (35)	10 (50)	0.783
Low BMI, n (%)	1 (20)	0	4 (80)	0.146
Weight loss (%)	7 (19.4)	14 (38.9)	15 (41.7)	0.865
Weight loss > 5%, n (%)	1 (20)	2 (40)	2 (40)	0.99
Weight loss > 10%, n (%)	2 (9.1)	9 (40.9)	11 (50)	0.296
Biological markers				
Total protein (g/dl)	7.2±0.5	6.7±0.9	6.1±1.2	0.054
Albumin (g/dl)	3.3±0.6	3.2±0.7	2.8±0.5	0.13
Albumin < 3.5 g/dl, n(%)	5 (14.7)	11 (32.4)	18 (52.9)	0.05*
Albumin < 3 g/dl, n(%)	2 (9.5)	8 (38.1)	11 (52.4)	0.322
Hb (g/dl)	12.5±0.8	12±2.2	10.9±2.7	0.2
HCT (%)	36±3	36±6	33±7	0.35
Cr (mg/dl)	1.18±0.5	1.17±0.5	1.24±0.8	0.9
BUN (mg/dl)	20±6	22±9	28.6±22	0.34
T.Bili (mg/dl)	3.7 (3.3-5.8)	2.9 (1.3-6)	8.5 (5.3-16)[ab]	0.002*
D.Bili (mg/dl)	1.9 (1.3-2.3)	1.2 (0.5-3.2)	4.6 (1.5-11.4)[b]	0.007*
AST (UL/l)	85.8±58	66.6±52	94±59	0.35
ALT (UL/l)	55 (25-63)	38 (25-65.5)	58 (33-108)	0.2
ALP (UL/l)	405±230	399±213	644±448	0.08
LDH (UL/l)	523 (415-529)	461 (356-543)	480 (358-665)	0.6
GGT (UL/l)	109 (44-271)	131 (81-164.5)	147 (52-261)	0.46
Cholesterol (mg/dl)	143 (122-160)	131 (114.5-177.5)	111 (97.5-186)	0.3
LDL (mg/dl)	61 (50-83)	71 (53.5-99.5)	56.5 (45-87)	0.7
HDL (mg/dl)	43.4±12	36±18	31±15	0.26
TG (mg/dl)	125 (80-206)	81 (62.5-125)	126.5 (74-270.5)	0.08
FBS (mg/dl)	91 (85-130)	100 (92-137)	100 (86-120)	0.64
MELD score	16.7±4	13.5±5	19.7±6[b]	0.007*
Child-Pugh score	8.5±1.4	8.4±2.2	9.9±1.4[b]	0.034*

[a] P<0.05 VS Well-nourished [b] P<0.05 VS Moderate Malnutrition

One-way ANOVA and Kruskal Wallis analysis and chi-square test were performed

* Significant difference

BMI, Body Mass Index; Hb, Hemoglobin; HCT, Hematocrit; Cr, Creatinine; BUN, Blood Urea Nitrogen; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; TG, Triacylglycerol; T.Bili, Total Bilirubin; D.Bili, Direct Bilirubin; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ALP, Alkaline Phosphatase; LDH, Lactate dehydrogenase; GGT, Gama-glutamyl Transferase; FBS, Fasting Blood Sugar.

Table 3. Nutritional complaints in three groups of patients

	Well-nourished (8)	Moderate Malnutrition (16)	Severe Malnutrition (19)	P-Value
Nutritional complaints				
Anorexia	3 (11.1)	9 (33.3)	15 (55.6)	0.108
Nausea	1 (4)	11 (44)	13 (52)	0.019*
Constipation	0	6 (50)	6 (50)	0.113
Dry mouth	2 (16.7)	5 (41.7)	5 (41.7)	0.99
Vomiting	0	4 (36.4)	7 (63.6)	0.145
Diarrhea	0	3 (27.3)	8 (72.7)	0.054
Dysgeusia	0	4 (50)	4 (50)	0.451
No complaints	4	0	0	0.001*

Chi-square test was performed
* Significant difference

The intake of energy, protein, and carbohydrates in patients with severe malnutrition was significantly lower than in the other two groups. In addition, energy balance was negative in all three nutritional groups based on the SGA (Table 4).

The energy balance was negative in 90.7%, and protein intake of less than 1.2 g/kg was observed in 69.8% of patients before liver transplantation. The prevalence of Protein-energy malnutrition was 69.8% and had no significant relationship with age, gender, and MELD score. Figure 1 shows the age distribution of men and women with and without protein-energy malnutrition.

Table 4. The intake of energy and macronutrients in three groups of patients

	Well-nourished (8)	Moderate Malnutrition (16)	Severe Malnutrition (19)	P-Value
Energy intake (kcal)	1317±279	1212±193	1023±180[ab]	0.003*
Protein intake (g)	59±16	55±10	46±14[ab]	0.037*
Lipid intake (g)	36±8	34.5±5	31±6	0.076
Carbohydrate intake (g)	191±44	172±39	143±28[ab]	0.007*
TEE (kcal)	1726±393	1637±250	1640±320	0.78
Energy Balance (kcal)	-409±480	-424±330	-617±323	0.2

[a] P<0.05 VS Well-nourished [b] P<0.05 VS Moderate Malnutrition
One-way ANOVA analysis test was performed
* Significant difference
TEE, Total Energy Expenditure.

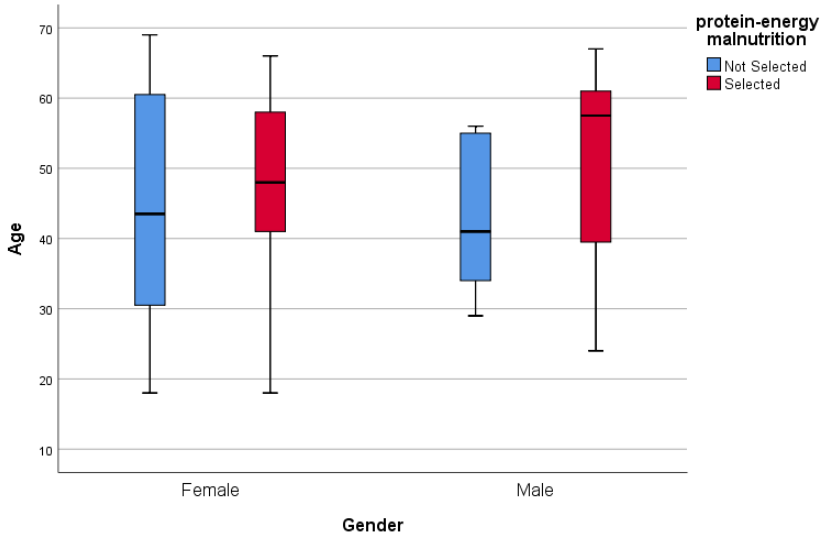

Figure 1. Age distribution in patients with and without protein-energy malnutrition

Discussion

The results showed that at the beginning of admission to the liver transplant department, 44.2% of the studied patients had severe malnutrition, of which 53% were women. Further, the most nutritional complaints of patients were anorexia (61.5%) and nausea (59%). Five people (12.8%) of the patients had a BMI lower than normal.

Subjective Global Assessment

The results indicated that based on the SGA questionnaire, the prevalence of malnutrition in patients before liver transplantation was 83.7%, and severe malnutrition was 44.2%. The prevalence of malnutrition was similar to most studies, but severe malnutrition was higher (10, 19-22).

Anthropometric and Biochemical Measurements

In this study, the body mass index, AMC, and FFM were lower in the severely malnourished group, but this difference was only significant for BMI. Like most studies, BMI was significantly lower in the malnourished group (23). The total bilirubin and direct bilirubin, MELD, and Child-Pugh scores were significantly higher among the laboratory measurements in the severe malnutrition group. In Merli (23), total bilirubin, MELD, and Child-Pugh scores were more elevated, and albumin was lower in the malnourished group. This study showed that serum albumin < 3.5 was significantly higher in patients with severe malnutrition. This phenomenon is explained due to more severe cirrhosis in these patients because the liver plays an essential role in the production of albumin (24). Topan found that lower serum albumin levels were associated with malnutrition in patients with cirrhosis (25).

Nutritional Complaints

The most nutritional complaints in patients waiting for a liver transplant were anorexia, nausea, and constipation. Nausea was significantly higher in malnourished patients. Studies have shown that anorexia is a significant symptom associated with liver cirrhosis and is vital because of presenting severe malnutrition and organ failure (26). Anorexia contributes up to 80% to the prevalence of disease-related malnutrition (DRM) in patients with decompensated liver cirrhosis (27). Anorexia may be caused by an imbalance between orexigenic and anorexigenic hormones, portal hypertension, chronic elevation of circulating pro-inflammatory cytokines, zinc and vitamin A deficiency, and delayed gastric emptying (28, 29).

Food Intake

Nutritional complaints such as nausea reduce the food intake of cirrhotic patients (30). In addition, dietary restrictions and recommendations for lower sodium and protein intake in cirrhotic patients contribute to less palatable diets, which are appropriate in the case of sodium restriction, but often inappropriate in the case of protein restriction (31). The low-sodium diet is recommended for cirrhotic patients with irreversible ascites (32). Low-sodium diets, however, are often difficult to follow due to their bland taste, resulting in a low energy intake. Morando et al. showed that cirrhotic patients with a low-sodium diet had a 20% reduction in mean daily energy intake compared to patients who did not follow the diet (33). In Merli (23), energy intake was lower in the malnourished group, but unlike our study, protein intake was not significantly different in the two groups. Patients with liver cirrhosis face nutritional challenges due to their lower energy and protein intake. The European Society for Clinical Nutrition (ESPEN) recommended that patients with liver cirrhosis have 25 to 30 kcal/kg of body weight energy intake and 1.2 to 1.5 g/kg of body weight protein intake (16). Before transplantation, 90.7% of patients consumed less energy, and 69.8% consumed less protein than recommended. Reviewing other studies revealed that some showed a higher energy intake rate in patients with liver cirrhosis than in our study. In Merli and Costa (23, 34), which evaluated patients' food intake using a 24-hour recall, patients received an average of 2000 kcal per day before transplantation. On the other hand, in Ferreira and Ribeiro (20, 35), similar to the results of our study, 90.7 and 71.4% of patients received less than their energy needs before transplantation, respectively. In addition, in Viana (36), the protein intake of 56.8% of liver transplant candidate patients was lower than the recommended amount. In Oey (37), 64.7% of patients waiting for a liver transplant received less than 1.2g of protein per kilogram of body weight.

Strengths and limitations

There were many limitations in implementing liver transplant surgery because of the outbreak of COVID-19, and more patients could not be collected. This study is multi-centered and conducted for the first time in Iran.

Conclusion

Malnutrition, low energy, and low protein intake were prevalent among liver transplant candidates. Most patients had nutrition-related complaints; nausea was more commonplace in malnourished patients.

Conflict of Interest

The authors have no conflict of interest

Authors' Contributions

Study concept and design: H. B., and M. N.; analysis and interpretation of data: M. A. and A. N.; drafting of the manuscript: H. B.; critical revision of the manuscript for important intellectual content: M. N.; statistical analysis: H. B.

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