

Determining the frequency and severity of malnutrition and correlating it with the severity of liver cirrhosis

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Background/aims: Malnutrition is a significant problem in cirrhosis of the liver worldwide. Inadequate data is available on the nutritional status of Pakistani patients. This study aimed to determine the frequency and severity of malnutrition in patients having cirrhosis of the liver and to compare the degree of malnutrition with the severity of liver disease. **Materials and Methods:** Two hundred ninety-eight patients with liver cirrhosis were included in the study. Nutritional status was assessed using the Royal Free Hospital Global Assessment scheme for cirrhotics. The patients were categorized into well-nourished, and mild to moderately and severely malnourished. Various degrees of malnutrition were compared with severity of disease according to Child-Pugh staging. **Results:** In the 298 patients with liver cirrhosis, hepatitis C (54,36%) and B (35,90%) were the commonest aetiologies, followed by autoimmune hepatitis (3,35%), primary biliary cirrhosis (2,34%), Wilson's disease (1,34%), haemochromatosis (1,0%), cryptogenic cirrhosis (1,0%), and alcohol being the rare cause (0,67%). 14,42% patients were well-nourished, (54,02%) were mild to moderately malnourished and (31,54%) were severely malnourished. Malnutrition is more frequent in virus-related cirrhosis, and the degree of malnutrition increases with increasing clinical severity as assessed by Child- Pugh stages with statistically significant p-value of 0.001. **Conclusion:** Moderate to severe malnutrition among diverse aetiologies of cirrhosis is quite common in Pakistan. The degree of malnutrition increases with increasing clinical severity of cirrhosis of liver.

Key words: Mid-arm muscle circumference, triceps skinfold thickness, body mass index, anthropometry

Malnütrisyonun sıklığı ve ciddiyetinin değerlendirilmesi ve sirozun ciddiyetiyle ilişkisinin saptanması

Giriş ve Amaç: Malnütrisyon karaciğer sirozunda dünya çapında bir problemdir. Pakistan'lı hastaların beslenme durumları ile ilgili veriler de yetersizdir. Bu çalışmada karaciğer sirozlu hastalarda malnütrisyonun sıklık ve ciddiyetinin değerlendirilmesi ve karaciğer hastalığının ciddiyetiyle malnütrisyon derecesinin karşılaştırılması amaçlanmıştır. **Gereç ve Yöntem:** Karaciğer sirozlu 298 hasta çalışmaya alındı. Beslenme durumları, sirozlular için Royal Free Hospital Global Assessment şeması kullanılarak değerlendirildi. Hastalar, iyi beslenmiş, hafif, orta ve ciddi malnütrisyon olarak kategorize edildi. Malnütrisyon dereceleri ile Child Pugh evrelemesine göre hastalık dereceleri karşılaştırıldı. **Bulgular:** Karaciğer sirozlu 298 hastanın etyolojileri değerlendirildiğinde; hepatit C (%54,36) ve B (%35,90) en sık nedenlerdi, bunu takiben otoimmün hepatit (%3,35), primer biliyer siroz (%2,34), Wilson hastalığı (%1,34), hemokromatoz (%1,0), kriptojenik siroz (%1,0) ve alkol en nadir nedendi (%0,67). Hastaların %14,42'si iyi beslenmiş, %54,02'si hafif veya orta malnütrisyon ve %31,54'ü ciddi malnütrisyon idi. **Sonuç:** Pakistanda sirozun geniş etyolojik spektrumunda orta ve ciddi malnütrisyon gayet sık görülmektedir. Sirozun klinik ciddiyeti arttıkça malnütrisyonun derecesi de artmaktadır.

Anahtar kelimeler: Orta kol kası çevresi, triseps deri kıvrım kalınlığı, beden kitle indeksi, antropometri

INTRODUCTION

Protein-calorie malnutrition (PCM) has increasingly been recognized as an important and most ignored prognostic factor which can influence the clinical outcome of patients suffering from cirrhosis of liver. PCM has been described in 60 to 100 percent of patients with decompensated cirrhosis and at least 20 percent with compensated cirrhosis (1-2). Malnutrition is associated with increased morbidity and mortality rates in patients with cirrhosis of the liver. Malnourished patients with liver cirrhosis have a higher rate of hepatic encephalopathy, infections, and variceal bleeding and are also twice as likely to have refractory ascites (3-5).

The pathogenesis of malnutrition in cirrhosis of the liver is multifactorial. Protein, carbohydrate, and lipid metabolism are all affected by liver disease. Contributing factors include inadequate dietary intake, impaired digestion and absorption, and altered metabolism. Anorexia, nausea, encephalopathy, gastropathy, ascites, and concurrent alcohol consumption can all contribute to a reduction in dietary intake (6). Malabsorption and maldigestion of nutrients can also result from bile salts deficiency, altered intestinal motility, bacterial overgrowth, mucosal injury, portal hypertensive changes to the intestine, and increased intestinal permeability (7-9). Apart from the above-mentioned established factors, myths and fads about diet related to liver diseases in countries like Pakistan further contributes to the problem.

Despite of a correlation between poor nutritional status and a decreased survival rate, there still goes a debate as whether the increased mortality rate is caused by malnutrition or by the advanced liver disease itself. Alberino *et al.* (10) identified malnutrition as an independent predictor of mortality in cirrhotics. Regardless of the fact that nutritional status was replaced by prothrombin time in the modified Child–Pugh classification, its presence should alert the clinicians similar to other complications such as ascites and hepatic encephalopathy.

There is no gold standard test for the assessment of nutritional status in patients with cirrhosis of the liver. It is impractical to attempt detailed nutritional assessment in all patients. Assessment of malnutrition in everyday clinical practice is therefore quite difficult and challenging because of the objectivity of the methods used and the tendency of fluid retention (ascites) in cirrhosis of liver

which may alter the results (2). Therefore, different parameters like phase angle or body mass cell measurement by bioelectric impedance analysis (BIA) to assess the nutritional status have been used and evaluated where some of them are quite useful and easy to perform and do not require high expertise (6, 11).

The European Society for Clinical Nutrition and Metabolism (ESPEN) recently recommended the most sensitive, convenient, technically less demanding and simple bedside method that is subjective global assessment (SGA) or anthropometry to identify patients at high risk of undernutrition (11).

Malnourished patients with cirrhosis of the liver have a higher rate of complications and an overall increased mortality. Pakistan has a high burden of liver cirrhosis and the data available on nutritional status in these patients are limited.

The objectives of the study were:

1. To determine the frequency and severity of malnutrition in our population by using the Royal Free Hospital Global assessment scheme (RFH-GA).
2. To compare the degree of malnutrition with the clinical severity of cirrhosis.

MATERIALS and METHODS

Patients

Local institutional ethics committee approval was sought before commencing the study. This hospital-based, non-interventional, descriptive study was performed on patients admitted with the diagnosis of cirrhosis of the liver at Civil Hospital Karachi from June 2009 to May 2010. All 298 cirrhotic patients were screened from medical outpatient departments. Histories with detailed examination were recorded through specially designed proforma along with Royal Free Hospital Global Assessment (12) data collection form (RFH-GA) for assessment of malnutrition in cirrhosis of the liver. Informed consent was obtained from all patients.

Inclusion criteria

1. All adult patients with cirrhosis with different etiologies.
2. Aged 18 years and above.

Exclusion criteria

1. Patients with underlying malignancy

2. Patients with any chronic debilitating illness like tuberculosis (TB) and diabetes mellitus (DM).

Study protocol

The research instruments used in the study were RFH-GA Scheme, clinical evaluation and biochemical assessment. Cirrhosis of the liver was confirmed on clinical, biochemical, radiological (trans-abdominal ultrasound or computerized tomography had to demonstrate a small shrunken liver with or without splenomegaly and intra-abdominal varices) and histopathological grounds, wherever required.

Nutritional assessment

Nutritional assessment was based on newly devised validated RFH-GA scheme for cirrhotics (Figure-1). All measurements were taken by the same single investigator, to avoid any inter- or intra-observer variation.

The Royal Free Hospital Global Assessment

The RFH-GA is a newly devised validated scheme for nutritional assessment in patient with cirrhosis of the liver. This is a simple bedside evaluation

tool that includes both subjective and objective components for nutritional assessment. The subjective component allows physicians to incorporate clinical information, dietary intake and physical status, while the objective component provides anthropometric measures like body mass index (BMI), triceps skinfold thickness (TSF), and mid-arm muscle circumference (MAMC). The RFH-GA scheme with integration of subjective and objective components of nutritional assessment provides nutritional category of cirrhotic patients into (12) adequately nourished, moderately malnourished, and severely malnourished.

Anthropometry

The anthropometric measurements were done for all patients, including TSF, mid arm circumference (MAC), and MAMC. All measurements were done in non-dominant arm of the patient. TSF, an established measure of fat stores, was measured to the nearest millimeter by Harpenden skin fold caliper (Baty Ltd, British Indicators) in a standard manner at mid-position between acromion and olecranon process (13). MAC was measured to the nearest centimeter with a measuring tape. Three measurements were taken for both TSF and MAC

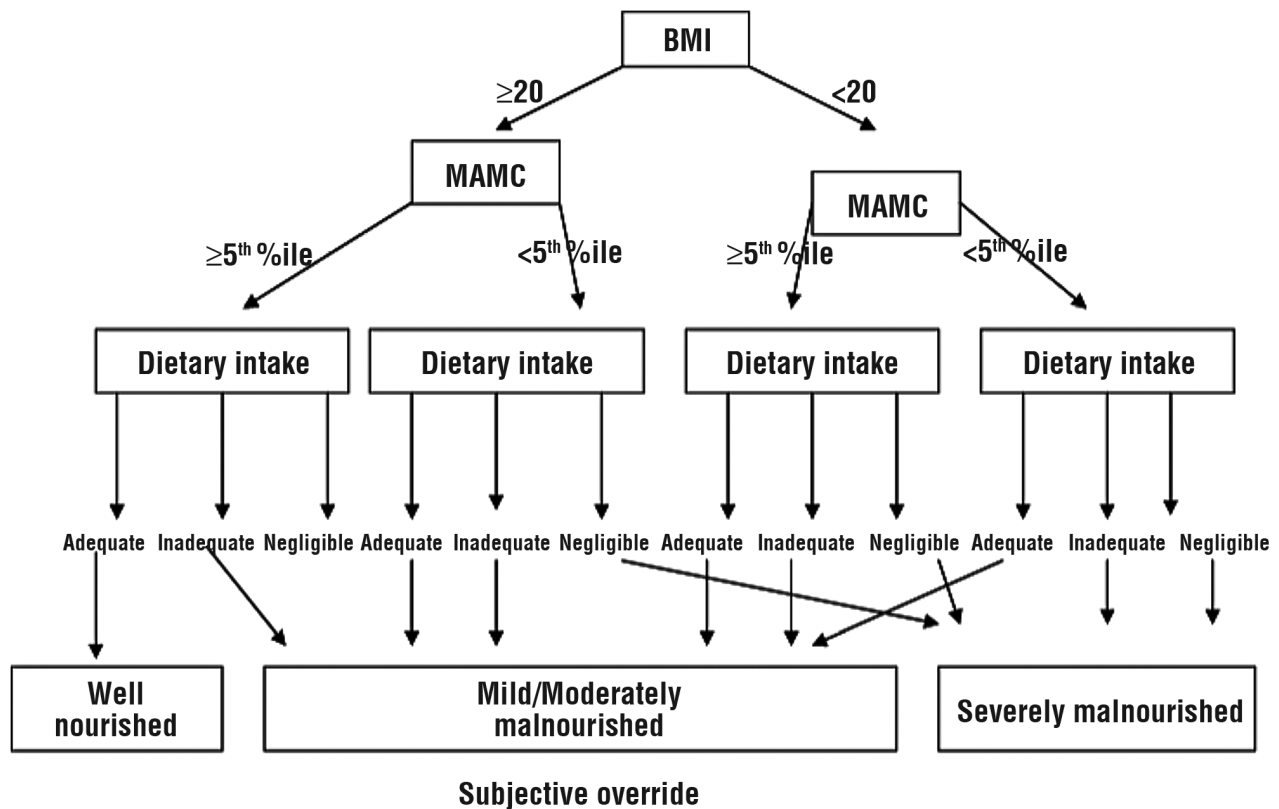


Figure 1. Royal Free Hospital Global Assessment Scheme (RFH-GA Scheme) Morgan et al. Hepatology, 2006 (12). BMI: Body mass index. MAMC: Mid-arm muscle circumference. %ile: Percentile.

with average values calculated and recorded. MAMC, an established measure of muscle protein mass, was calculated from MAC and TSF using a standard formula: $MAMC = MAC - (3.1415 \times TSF)$ (13). The BMI was also calculated and recorded by formula (dry weight in Kg/height in m²). An estimated dry weight was determined by deducting a weight for ascites and/or edema from the measured weight. The deduction was based on clinical measurements; ascitic volume removed at paracentesis [estimated by subtracting paracentesis (total) volume, 1 L = 1 kg]. In cases where paracentesis was contraindicated or not possible, dry weight was assessed by adjusting ascites and edema according to Mendham (14) as shown in Table 1.

Dietary intake and assessment

The dietary intake assessment is an integral component of RFH-GA scheme for categorization of nutritional status of patients, thus the assessment of individual patient's oral intake was determined retrospectively by the three-day dietary recall method by the patients themselves or their attendants. Calculation of calories of food and drinks intake (composition of the diet) was calculated by the help of nutrition tables based on local reference data (15). Estimated requirements of intake were calculated by Schofield modified Harris-Benedict equation. Intakes were categorized as adequate if they met estimated requirements, inadequate if they failed to meet estimated requirements but exceeded 500 kcal/day, or negligible if they provided <500 kcal.

Malnutrition

The final nutritional status was established by using the RFH-GA scheme (12) for cirrhotic patients. The parameters were defined as <5th percentile MAMC for purposes of standardization with the literature. The patients are categorized into well, mild/moderately and severely malnourished.

Laboratory investigations

Serum albumin concentration is the most frequently used laboratory measure of nutritional status. Although non-specific, it has been used for assessing changes in nutritional status and stratifying risk of malnutrition (16). Apart from serum albumin, all other biochemical investigations related to liver cirrhosis were also carried out to establish severity of cirrhosis. Severity of liver disease was calculated according to the Child-Pugh score with grades A (mild) to C (severe) indicating the degree of hepatic reserve and function (17).

Statistical analysis

The data of the study was entered into Statistical Packages for the Social Sciences (SPSS) version 15.0 (SPSS Inc, Chicago, IL, USA) for statistical analysis. Mean and standard deviations were calculated for continuous variables, while percentages and proportions were applied for discrete variables. Chi-square test was used to compare the degree of malnutrition among patients with cirrhosis with clinical severity of disease by keeping p-value of < 0.05 as statistically significant.

RESULTS

A total of 298 patients with cirrhosis of the liver were recruited during the study period. The basic demography and patients' profile are highlighted in Table 2. The mean age of the patients was 44,20±SD 13 years. Out of 298 patients, 182 (61,07%) were male and 116 (38,92%) were female. Chronic viral hepatitis C (n =162, 54,36%) and B (n=107, 35,90%) were the most common aetiologies

Table 1. Guidelines for estimating fluid weight in patients with peripheral oedema and Ascites Mendhall 1992

	Oedema	Ascites
Minimal	1,0 Kg	2,2 Kg
Moderate	5,0 Kg	6,0 Kg
Severe	10 Kg	14,0 Kg

Table 2. Basic demography and patients' profile

Patient profile	Patients with cirrhosis n=298
Age	44,20±SD 13,6 years
Gender (Male:Female)	1: 0,64
Child-Pugh grade	
A	n=57 (19,12%)
B	n=147 (49,32%)
C	n=94 (31,54%)
Aetiology	
Hepatitis C	n=162 (54,36%)
Hepatitis B	n=107 (35,90%)
Autoimmune hepatitis	n=10 (3,35%)
Primary billiary cirrhosis	n=7 (2,34%)
Wilson's disease	n=4 (1,34%)
Haemochromatosis	n=3 (1,0%)
Cryptogenic cirrhosis	n=3 (1,0%)
Alcoholic cirrhosis	n=2 (0,67%)
Height (meter)	1,62±0,105
Weight (kilogram)	53±12
BMI (kg/m ²)	20,05±3,72

BMI: Body mass index.

of chronic liver disease followed by autoimmune hepatitis (n=10, 3,35%), primary biliary cirrhosis (n=7, 2,34%), Wilson's disease (n=4, 1,34%), haemochromatosis (n=3, 1,0%), cryptogenic cirrhosis (n=3, 1,0%), and alcoholic liver disease as the rarest (n=2, 0,67%). Most of the patients had advanced liver disease with 147 (49,32%) cases of Child-Pugh B, 94 (31,54%) cases of Child-Pugh C cirrhosis, and 57 (19,12%) cases of Child-Pugh A stage.

Nutritional assessment

Out of 298 patients, 180 (60,04%) patients had BMI equal or greater than 20 kg/m² with 137 (45,97%) ≤5th percentile and 43 (14,42%) patients with MMAC values ≥ 5th percentile. BMI was equal or lesser than 20 kg/m² in 118 (39,56%) patients with 94 (31,54%) ≤5th percentile and (8,38%) ≥5th percentile. The anthropometric measurements (MMAC, TSF with BMI, daily caloric intake) and degree of malnutrition according to the RFH-GA scheme are highlighted in Table 3. Out of 298 patients, 43 (14,42%) were adequately nourished, 161 (54,02%) were mild to moderately malnourished, and 94 (31,54%) were severely malnourished. The frequency of malnutrition in virus-related

(hepatitis C and B) cirrhosis was higher than in the other aetiologies. The degree of malnutrition increases with increasing clinical severity as assessed by Child-Pugh stages with statistically significant p-value of 0,001 as shown in Table 4.

DISCUSSION

Malnutrition is commoner among hospitalized patients with cirrhosis of the liver than among the general diseased population. Among patients with cirrhosis and portal hypertension, malnutrition is associated with significantly higher in-hospital mortality and hospital resource utilization (18). Earlier studies of patients with cirrhosis reported rates of malnutrition as high as 65-90% (19-21). This study shows the mean age of presentation as 44,20±SD 13,61 years, while earlier study (22) from Pakistan has shown a bit higher age of 52,4±10,3 years. A study on Malaysian patients with cirrhosis of the liver has reported a mean age of 59,8±12,8 years (23). This study demonstrates 61,07% male and (38,92%) female patients similar to the earlier study, where 61,5% males and 38,5% female patients were reported (22).

Table 3. Anthropometric measurements (In accordance with the Royal Free Hospital - Global Assessment Scheme)

Anthropometric measurements	Gender	BMI ≥ 20 kg/m ² < 5 th %ile	BMI ≥ 20 kg/m ² > 5 th %ile	BMI ≤ 20 kg/m ² > 5 th %ile	BMI ≤ 20 kg/m ² < 5 th %ile
No of patients	Total	n=137, 45,97%	n=43, 14,42 %	n=24, 8,05 %	n=94, 31,54 %
	Males	n=87, 63,50 %	n=25, 58,13%	n=17, 70,83%	n=53, 56,38 %
	%Female	n=50, 36,49%	n=18, 41,86%	n=7, 29,16%	n=41, 43,61%
MAMC in cm	Male	Mean=16,2±SD 0,63	Mean=17,9±SD 0,66s	Mean=15,1±SD 0,10	Mean=13,6±SD 0,99
	Female	Mean=16,2±SD 0,62	Mean=18,5±SD 0,60	Mean=15,1±SD 0,13	Mean= 13,5±SD 0,99
TSF in mm	Male	Mean=11,7±SD 0,85	Mean=14,7±SD 1,07	Mean=10±SD 0,18	Mean=8,4±SD 1,13
	Female	Mean=11,5±SD 0,86	Mean=15±SD 0,84	Mean=10±SD 0,21	Mean=8.3±SD 1,02
Energy intake in KCal	Male	Mean=1201±SD 113,04	Mean=1812±SD 92,13	Mean=755±SD 92,46	Mean=491±SD 32,72
	Female	Mean=1190±SD 106,03	Mean=1836±SD 77,08	Mean=768±SD 132,21	Mean=490±SD 28,30
Global nutritional category					
Well- nourished		Nil	43	Nil	Nil
Mild/moderately malnourished		137	Nil	24	Nil
Severely malnourished		Nil	Nil	Nil	94

BMI: Body mass index. MAMC: Mid-arm muscle circumference. TSF: Triceps skinfold thickness.

Table 4. The Royal Free Hospital Global Assessment of malnutrition in varying severity of liver cirrhosis

Severity of cirrhosis	Well-nourished n (%)	Mild to moderately malnourished n (%)	Severely malnourished n (%)	p value #
Child- Pugh A (n=57)	43 (75,43)	14 (24,56)		
Child- Pugh B (n=147)		69 (49,38)	78 (53,06)	0,001
Child- Pugh C (n=94)		78 (82,97)	16 (17,02)	

Chi-square test

The frequency of chronic viral hepatitis correlates to their prevalence in Pakistan and Asia of nearly 60-70% of cirrhotics being anti-HCV positive (24-27) as recent studies suggest, where 50% cases of hepatocellular carcinoma in Pakistan are anti-HCV positive (28). Pakistan is in the intermediate HBV prevalence area with a carrier rate of 3-4% (29) also emphasizing HBV as an important cause of cirrhosis of the liver (22, 28). Alcohol has been proven to be the commonest reason of liver cirrhosis in the Western countries, while in our study, it was the rarest aetiology, probably due to religious prohibition of alcohol among Muslims.

The majority of the patients in this study had advanced cirrhosis of the liver (Child-Pugh C in 31,54% and Child-Pugh B in 49,32%) similar to earlier studies (22, 23). An earlier study (30) has contrasted to our study and showed less advanced chronic liver disease (Child-Pugh C in 15% and Child-Pugh B in 35%). More severe disease in this study as compared to Western studies is probably due to ineffective health care system, lack of education, poverty, and false believes about the disease.

There are various methods for the evaluation of malnutrition from simple weight changes, laboratory parameters (albumin, prealbumin), anthropometry, and Subjective Global Assessment (SGA) to highly sophisticated methods like bioelectrical impedance, depletion of body cell mass (BCM), isotope dilution and measurement of whole body potassium. An earlier study (31) found that weight changes and laboratory measurements are not reliable indicators of malnutrition, because the presence of ascites and edema will increase the measured weight, whereas the lean body mass may be reduced.

Similarly, concentrations of albumin and prealbumin could also be low because of reduced levels of synthesis rather than due to poor nutritional status. The assessments of muscle function measuring respiratory-muscle strength and hand-grip strength have also been used in nutritional evaluation; however, these measurements tend to be more useful when taken serially. An earlier study showed hand-grip strength as a highly sensitive test and might actually overestimate the prevalence of malnutrition (32).

Anthropometric measurements include TSF and MAC, which assess fat storage and skeletal muscle mass, respectively. The utility of anthropometric assessment was demonstrated in earlier studies and claimed not to be affected by the presence

of ascites and peripheral edema (11, 5). Another study contrasted the usefulness of anthropometric measurement as it can be affected by third spacing and may actually overestimate the data (33). Potential limitations of anthropometry include poor inter-observer reproducibility.

Depletion of body cell mass (BCM) is a useful estimation of nutritional status. (34) Decreased BCM before transplantation has been shown to correlate with a three-fold increase in post-transplant mortality rates (35-36). Although isotope dilution, measurement of whole body potassium, and in vivo neutron activation analysis are the most accurate methods currently available to assess body composition, these techniques are expensive, labor-intensive, and not even available everywhere so making them impractical for routine nutritional screening. Bioelectrical impedance is very useful for estimating BCM, but its accuracy can be affected by ascites (37).

Destckhy in 1987 proposed a very useful scheme known as Subjective Global Assessment (SGA) for nutritional assessment. The technique uses clinical information collected during history taking and physical examination to determine nutritional status without resort to objective measurements like anthropometry (38,39). This method of assessment has been used successfully to assess nutritional status in general medical and surgical patients. SGA was also used to determine nutritional status in cirrhosis by some investigators with little success.

Hass et al. (40) used a modified SGA scheme for nutritional assessment of cirrhotic patients especially of pre-transplant candidates. This scheme had certain limitations like its reproducibility and predictive value which was only validated by the original workers themselves and its assessment values for nutrition were not in accordance to anthropometric measurements as challenged by Naevu et al. (41). The RFH-GA scheme devised by Morgan et al. (12) which included both subjective and objective components (anthropometry) had been externally validated with significant correlations (by accurate measurement of body composition like densitometer, deuterium dilution and DE-XA) and showed significant predictive value for nutritional status even after adjustment for the degree of hepatic impairment.

From the above discussion, it is evident that even highly sophisticated methods for nutritional as-

assessment in cirrhosis of the liver are not without limitations. Moreover, these techniques are not available in Pakistan so RFH-GA scheme was used in this study as a simple, practical bedside method for nutritional assessment as anthropometry and subjective assessment were also recommended by ESPEN (11) for nutritional assessment in cirrhosis of the liver.

In the present study, 14,42 % of patients were found to be well-nourished. Almost 54,02% of patients were mild to moderately malnourished, and severe malnourishment was present in 31,54% of patients.

An earlier (22) local study has shown that 82.6% of patients had mild to moderate degree of malnutrition, while 41,6% had moderate to severe malnutrition. The above study did not categorize the patients according to the RFH-GA modified scheme and showed overall BMI, MAMC and TSF in patients of liver cirrhosis. An earlier study showed that 42% of patients with cirrhosis of the liver were well-nourished, 40% were mildly or moderately malnourished, and 17% were severely malnourished according to the RFH-SGA (5). Earlier Italian and Thai studies demonstrated a higher incidence of malnutrition in alcoholic cirrhotics compared to other aetiologies of cirrhosis, and these patients had more complications of cirrhosis (19, 42). The above studies showed higher incidences of malnutrition but did not categorize the patients into well-nourished, mild to moderately and severely malnourished.

The high frequency of malnutrition in virus-related (hepatitis C and B) among other aetiologies as shown in Table 4 is in contrast to previous studies where alcoholic cirrhosis was the major cause (19, 42). This study also revealed that degree of malnutrition increases with increasing clinical severity as assessed by Child-Pugh stages with statistically significant p-value of 0,001.

All complications of portal hypertension were fo-

und in this study, but with higher frequency in severely malnourished group. Nevertheless, the above observation could be due to either portal hypertension itself or severe malnutrition or both. The earlier largest studies, the Veterans Affairs Cooperative studies in 1984 and 1993 (43,44) on prevalence and severity of malnutrition along with other studies (45-47), have demonstrated that the severity of malnutrition correlated with that of liver disease and the development of complications, including hepatic encephalopathy, ascites, hepatorenal syndrome, post-transplantation outcome, and mortality.

Our findings of a greater frequency of complications among malnourished patients with cirrhosis and portal hypertension are consistent with the above studies.

There are some limitations of our study that should be noted. Firstly, the RFH-GA contains a subjective measurement and its assessment, as with ascites and encephalopathy may differ amongst individual clinicians or centers. Secondly, the study did not follow the patients till death so malnutrition cannot be proved as an independent prognostic factor of mortality in cirrhosis of the liver.

Malnutrition of moderate to severe degree in cases of cirrhosis with various aetiologies is quite common in this part of the world. Anthropometry and RFH-GA scheme are practical and effective tools for assessment of the degree of malnutrition. The frequency of malnutrition in virus-related (hepatitis C and B) cirrhosis was higher than in other aetiologies. Nutritional assessment with the RFH-GA scheme established a tendency towards more malnutrition with increasing clinical severity as assessed by Child-Pugh stages. Complications related to liver cirrhosis like infections, ascites, and hepatorenal syndrome are more common in severe malnutrition. Early detection of malnutrition and its correction can reduce the already high morbidity and mortality in cirrhosis of the liver.

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