

The Effect of Nutritional Status on Outcome of Hospitalization in Paediatric Liver Disease Patients

YASMEEN MANSI¹, SHEREEN ABDEL GHAFFAR², SHAYMAA SAYED³, HANAA EL-KARAKSY⁴

ABSTRACT

Introduction: Liver is an important organ for metabolism. It has a major role in integrating the various biochemical pathways of metabolism. Thus, children with chronic liver disease are at high risk for developing undernutrition, with important prognostic implications.

Aim: To evaluate the nutritional status of hospitalized paediatric liver disease patients and its effect on outcome.

Materials and Methods: We prospectively analysed the nutritional status of 59 consecutive patients during their first 24 hours of admission, at the Hepatology Unit, using the following indices: weight/age, height/age, weight/height, Body Mass Index (BMI), arm circumference and triceps skinfold, subcapular skinfold, and mid upper arm circumference.

Results: According to the measurements: 35.6% were under-weight, 49% were stunted, 10% were wasted by weight for

length/height percentile and 5% were wasted by body mass index, 49% had percentage of ideal body weight below normal, 27% had head circumference below 3rd percentile, 59.4% had triceps skinfold thickness below 5th percentile, 66% had subscapular skinfold thickness below 5th percentile; 56% had arm circumference below 5th percentile. There was no correlation between these growth parameters and mortality. However, we found a positive correlation between decreased triceps skinfold thickness and prolonged hospital stay. Malnourished patients, according to triceps skinfold thickness, were significantly younger and they were the ones who suffered from cholestatic disorders of infancy.

Conclusion: Only triceps skinfold thickness was found to be a useful predictor for a prolonged hospital stay. Serial measurements may be more effective.

Keywords: Hospitalized children with liver disease, Nutritional assessment, Skin fold thickness

INTRODUCTION

Paediatric patients with chronic liver disease have a high prevalence of impaired growth and malnutrition. Malnutrition has many mechanisms including low caloric intake, anorexia, dietary restrictions, impaired digestion, impaired absorption, defective hepatic synthesis, storage and metabolic functions. In addition, patients with liver disease have increased nutritional demands and abnormal nutrient loss [1,2].

Nutritional status and liver disease affect each other [3]. Chronic liver disease leads to malnutrition and liver functions can be impaired by malnutrition [4]. Both will lead to higher risk of infections and lower survival rate after liver transplantation [5,6].

Assessing the nutritional state of children at the time of admission to hospital is an important part of their clinical evaluation [7,8]. This includes the collection of anthropometric and biochemical data as well as a clinical, dietary assessment and body composition analysis [9,10]. Good long term outcome can be achieved by appropriate assessment and well-timed nutritional interventions [11,12].

Many parameters have been proposed to assess under-nutrition in patients with liver diseases including the presence of ascites, decreased protein synthesis and impaired renal function [13,14].

Regarding high prevalence of malnutrition associated liver disease in Egypt; this study was performed in order to assess the nutritional status of hospitalized paediatric patients with liver disease, on admission, to document its effect on their outcome.

MATERIALS AND METHODS

In this descriptive prospective study, we included all infants and children with liver disease admitted to the inpatient ward of the Paediatric Hepatology Unit, at Cairo University Paediatric Hospital, over a six-month period from the beginning of November 2013 to the end of April 2014. The study protocol was approved by the Institutional Review Board and Ethical Committee. All cases were

enrolled after consent was obtained from the parent/guardian.

All patients underwent nutritional evaluation on admission to the ward, including:

Nutritional history: Including the presence of nutritional risk by history as having feeding intolerance, recurrent attacks of vomiting and/or diarrhea, anorexia and limited financial resources.

Examination for signs of malnutrition, vitamins or minerals deficiency.

Laboratory work up: including complete blood count, liver function tests and serum albumin, kidney function tests, as well as serum sodium, potassium, calcium, phosphorous and iron.

Anthropometric measurements (S1): We performed anthropometric measurements for 62 patients, during their first 24 hours after admission. Only cases with sufficient data were included.

Body weight (W) was measured in kilograms (kg) and reported to the nearest 0.1kg. It was plotted on Egyptian growth curves [15] and the patient was considered underweight if the percentile was below 3rd percentile [16].

Height (H)/length (L) was measured in centimeters (cm) and reported to the nearest 0.1cm. It was plotted on Egyptian growth curves [15] and the patient was considered stunted if the percentile was below the 3rd percentile [16].

Using the data for W and H or L, we obtained the following indices: weight/height (W/H) or weight/length (W/L).

Head circumference was applied for patients 3 years of age or younger. The value was reported to the nearest 0.1 cm and plotted on Egyptian growth curves [15]. The head circumference was considered normal if it was in between 3rd and 97th percentile [16].

Body mass index (BMI) was applied for patients with age of 2 years or older. It was calculated using the following equation: BMI= body weight (in kg)/ height (in meters)². Assessment of percentiles was

done using Egyptian growth curves [15]. The patient was considered wasted if the percentile was below 3rd percentile [16].

Percentage of Ideal Body Weight (PIBW) is the weight at admission/ideal body weight for age [17].

Ideal body weight = (height cm² x 1.76) / 1000 [18].

Nutritional status was classified as follows: within normal range if PIBW was 90–100% and below normal if PIBW < 89% [19].

Triceps Skinfold (TSF) thickness was applied for patients 2 months and older. It was measured in millimeters using Slim Guide Plastic Skinfold Caliper [20,21]. The diagnosis of malnutrition was based on diminished values of TSF below the 5th percentile [22].

Subscapular Skinfold (SSF) thickness was applied to patients 2 months and older. It was measured in millimeters using Slim Guide Plastic Skinfold Caliper [21].

Mid Upper Arm Circumference (MUAC) was measured in millimeters and the reading was taken to the nearest millimeter and plotted on Egyptian growth curves [15].

Upper Arm Muscle Area (UAMA) by height: It was applied to patients with height between 84-182cm for males and 84-173cm for females. It was calculated based on measurements of MUAC and TSF, assuming that the upper arm and its constituents are cylindrical, using the following equation [23]:

$$\text{MUAC} - \text{TSF} \times p$$

$$\text{UAMA} =$$

$$4p$$

Outcome: The outcome of the patient at the end of hospital stay was recorded with special stress on complications, and patients were classified into those with favourable or unfavourable outcomes according to mortality or occurrence of complications namely: Paediatric Intensive Care Unit (PICU) admission, prolonged hospital stay (more than 14 days), re-admission to hospital within one month after discharge, development of hepatic encephalopathy and/or bleeding after admission.

STATISTICAL METHODS

Quantitative variables were presented by mean and Standard Deviation (SD) if normally distributed data and analysed by student t-test. They were presented by median and Interquartile Range (IQR) if not normally distributed and analysed by Mann-Whitney U test.

RESULTS

The present study included 62 cases who were admitted to the inpatient ward of the Paediatric Hepatology Unit, Cairo University Paediatric Hospital, Cairo, Egypt. Two cases had insufficient data and the mother of the third case refused to participate, so they were excluded from the study. Out of the remaining 59 cases: 30 were females (50.8%) and 29 (49.2%) were males. The median age of the patients was 8.5 months with Interquartile Range (IQR: 44.5).

The most common diagnosis of these patients was cholestatic disorders of infancy (69.5%) including cases with cholangitis following Kasai porto-enterostomy, biliary atresia, progressive familial intrahepatic cholestasis and Alagille syndrome. The remaining 18 patients (30.5%) had other hepatic disorders including Wilson disease, Caroli disease, congenital hepatic fibrosis, sclerosing cholangitis, glycogen storage disease, Neimann Pick disease, cryptogenic cirrhosis and auto-immune hepatitis.

Patients with cholestatic disorders of infancy were significantly younger than patients with other diagnoses ($p < 0.0001$). Nutritional risk by history was present in 28 patients (47.5%): anorexia in 18 patients (64%), 6 patients (21%) suffered from recurrent attacks of vomiting and 4 patients (15%) had limited financial resources.

As for the predominant signs and symptoms in our patients: pallor was present in 76.3%, jaundice in 61%, and fever in 25%.

Hepatomegaly was present in 81.4% of cases, splenomegaly in 55.9%, ascites in 39% and lower limb oedema in 8 patients (13.6%). The basal anthropometric measurements of the study population are shown in [Table/Fig-1].

Parameter	Below normal percentile N (%)	Within normal percentile N (%)	Above normal percentile N (%)	Not applicable N (%)
Body weight	21 (35.6)	38 (64.4)	-	-
Length/height	29 (49.2)	30 (50.8)	-	-
Weight for length/height	6 (10.2)	42 (71.2)	8 (13.6)	3 (5)
BMI	3 (5)	13 (22.1)	4 (6.7)	39 (66.1)
Percentage of ideal body weight	30 (51)	29 (49)	-	-
Head circumference	16 (27.2)	31 (52.5)	-	12 (20.3)
Triceps skin fold	35 (59.4)	18 (30.5)	-	6 (10.1)
Subscapular skin fold	39 (66.1)	14 (23.3)	-	6 (10.1)
Mid upper arm circumference	33 (56)	26 (44)	-	-
Upper arm muscle area by height	12 (20.4)	3 (5)	-	44 (74.6)

[Table/Fig-1]: Basal anthropometric measurements of the study group (n=59)
BMI - Body Mass Index.

The outcome of the patients enrolled in our study showed that 25 patients had an unfavourable outcome: 3 patients (5%) were admitted to PICU, 16 patients (27%) had a prolonged hospital stay, 12 patients (17%) were readmitted to hospital within 1 month of their discharge, 7 patients (11.8%) developed hepatic encephalopathy, 5 patients (8.4%) developed bleeding and 7 patients (11.8%) died.

[Table/Fig-2] shows a comparison of the anthropometric measurements between the groups with favourable and unfavourable outcome. We did not find a statistically significant difference between both groups regarding the anthropometric measurements.

Serum calcium and serum potassium were significantly lower in the unfavourable outcome group. Serum phosphorous was lower, as well, but the difference did not reach statistical significance. Moreover, the group with the unfavourable outcome had statistically significant higher levels of total and direct serum bilirubin, lower total serum proteins and serum albumin and more impaired coagulation [Table/Fig-3].

We chose to classify our patients into malnourished and non-malnourished groups according to parameters involving the arm, to avoid misinterpretation of other parameters that might be affected by organomegaly, ascites or peripheral oedema. We classified our patients according to TSF, SSF or MUAC into malnourished and non-malnourished groups. Both groups were compared with each other regarding the complications whether morbidity or mortality. According to TSF, we found a significantly longer duration of hospital stay in malnourished versus non-malnourished patients (31.4% vs.11.1%) ($p < 0.01$) [Table/Fig-4]. Although malnourished patients had higher mortality rate, more ICU admissions and more development of encephalopathy and bleeding after admission, however, the difference did not reach statistical significance [Table/Fig-4]. On the other hand, according to either SSF or MUAC, no statistically significant difference was found between malnourished and non-malnourished groups as regards mortality or morbidity [Table/Fig-4].

According to the TSF, malnourished infants were statistically significantly younger than infants in the non-malnourished group ($p = 0.008$) and suffered predominantly from cholestatic disorders of infancy [Table/Fig-5].

DISCUSSION

We used a combination of body weight, length/height and skinfold thickness measurements for nutritional assessment for our

Parameter	Favourable outcome, N=34, (%)				Unfavourable outcome N=25, (%)				p-value
	Below normal percentile N (%)	Within normal percentile N (%)	Above normal percentile N (%)	N/A N (%)	Below normal percentile N (%)	Within normal percentile N (%)	Above normal percentile N (%)	N/A N (%)	
Body weight	14 (41.2)	20 (58.8)	-	-	7 (28)	18 (72)	-	-	0.296
Length/height	17 (50)	17 (50)	-	-	12(48)	13 (52)	-	-	0.879
Weight for length/height	4 (11.8)	22 (64.7)	5 (14.7)	3 (8.8)	2 (8)	20 (80)	3 (12)	0 (0)	0.398
BMI	1 (2.9)	6 (17.6)	3 (8.8)	24 (70.6)	2 (8)	7 (28)	1 (4)	15 (60)	0.539
Percent of ideal body weight	17 (50)	17 (50)	-	-	12 (48)	13 (52)	-	-	0.879
Head circumference	8 (23.5)	18 (52.9)	-	-	4 (16)	13 (52)	-	-	0.675
Triceps skin fold	19 (61.3)	12 (38.7)	-	-	16 (72.7)	6 (27.3)	-	-	0.386
Subscapular skin fold	22 (71)	9 (29)	-	-	17 (77.3)	5 (22.7)	-	-	0.608
Mid upper arm circumference	19 (55.9)	15 (44.1)	-	-	14 (56)	11 (44)	-	-	0.993
Upper arm muscle area by height	6 (17.6)	2 (5.9)	-	26 (76.5)	6 (24)	1 (4)	-	18 (72)	0.809

[Table/Fig-2]: Comparison between anthropometric measurements in favourable and unfavourable outcome groups (n=59).

N/A: Not applicable.

BMI - Body Mass Index

Profile	Favourable outcome N=34		Unfavourable outcome N=25		p-value
	Mean	SD	Mean	SD	
Hemoglobin (g/dl)	9.46	2.1	9.28	1.72	0.727
Hematocrit	29.06	6.37	27.96	5.1	0.480
AST (U/L)	182.56	163.07	272.88	292.40	0.136
ALT (U/L)	102.32	82.37	141.96	155.79	0.211
Total bilirubin (mg/dl)	8.15	8.69	15.25	11.45	0.013*
Direct bilirubin (md/dl)	3.93	4.72	6.46	4.58	0.043*
Total protein (g/dl)	5.93	1.08	5.08	1.35	0.013*
Albumin (g/dl)	2.99	0.60	2.54	.63	0.007*
GGT (U/L)	290.82	391.81	220.64	287.27	0.452
ALP (U/L)	527.18	317.15	456.17	465.90	0.492
INR	1.36	0.71	2.05	1.07	0.005*
Blood urea nitrogen level (mg/dl)	10.15	9.81	11.12	16.54	0.779
Serum creatinine level (mg/dl)	0.43	0.32	0.50	0.82	0.644
Serum sodium level (mmol/L)	137.09	7.03	134.44	5.51	0.124
Serum potassium level (mmol/L)	4.84	0.87	4.27	0.86	0.016*
Serum calcium level (mg/dl)	9.03	0.91	8.52	0.83	0.032*
Corrected calcium	9.87	0.71	9.65	0.59	0.217
Serum phosphorus level (mg/dl)	4.06	1.39	3.34	1.62	0.076
Serum iron (mcg/dl)	79.91	55.77	66.00	50.05	0.327

[Table/Fig-3]: Comparison between laboratory findings in favourable and unfavourable outcome groups (n = 59)

paediatric hepatic patients upon admission. These methods are available; they have fast application and low cost and they can be incorporated into the routine of the nutritional assessment of these patients, especially in developing countries.

The anthropometric measures, which depend on body weight and/or length/height: revealed that the degree of malnutrition varied widely, ranging from 5% of patients according to BMI to 49% of patients according to their PIBW. In addition to the discrepancy in the degree of malnutrition between these measurements, there are some limitation to their use. Body weight in patients with liver disease may be misleading. It is affected by the presence of ascites, peripheral oedema and organomegaly [24]. In our study, 48 patients (81.4%) had hepatomegaly, 33 patients (55.9%) had splenomegaly, 23 patients (39%) had ascites and 8 patients (13.6%) had bilateral

Parameter		Non-malnourished N, (%)	Malnourished N, (%)	p-value
Triceps skinfold thickness (n=53)	Prolonged hospital stay (> 14days)	2 (11.1)	11 (31.4)	<0.01*
	Re-admission within one month	4 (22.2)	8 (22.9)	1.0
	ICU admission	0 (0)	2 (5.7)	0.543
	Hepatic encephalopathy	1(5.6)	5 (14.3)	0.651
	Bleeding	0 (0)	5 (14.3)	0.153
	Mortality	1 (5.6)	5 (14.3)	0.651
Subscapular skinfold thickness (n=53)	Prolonged hospital stay (>14days)	2 (14.3)	11(28.2)	0.473
	Re-admission within one month	2 (14.3)	10 (25.6)	0.480
	ICU admission	1 (7.1)	1(2.6)	0.462
	Hepatic encephalopathy	2 (14.3)	4 (10.3)	0.649
	Bleeding	1 (7.1)	4 (10.3)	1.000
	Mortality	2(14.3)	4(10.3)	0.649
Mid upper arm circumference (n=59)	Prolonged hospital stay (>14days)	7 (26.9)	9 (27.3)	0.976
	Re-admission within one month	3 (11.5)	9 (27.3)	0.136
	ICU admission	2 (7.7)	1 (3.0)	0.578
	Hepatic encephalopathy	3 (11.5)	4(12.1)	1.000
	Bleeding	1(3.8)	4(12.1)	0.372
	Mortality	3(11.5)	4(12.1)	1.000

[Table/Fig-4]: Comparison of malnourished and non-malnourished children

according to nutritional status assessed by triceps skinfold thickness, subscapular skinfold thickness and mid upper arm circumference

Parameter		Non-malnourished (n=18) N, (%)	Malnourished (n=35) N, (%)	p-value
Sex	Female (N=27)	11 (61.1)	16 (45.7)	0.29
	Male (N=26)	7 (38.9)	19 (54.3)	
Age in months	Median (IQR)	45 (66.8)	7 (15)	0.008*
Diagnosis	Cholestatic disorders of infancy	7 (38.9%)	28 (80.0%)	0.01*
	Other hepatic disorders	11 (61.1%)	7 (20.0%)	

[Table/Fig-5]: Comparison of age, sex and diagnoses between malnourished and non-malnourished groups according to triceps skinfold thickness(n=53).

lower limb oedema. There are also limitation of BMI for body composition assessment. It is highly correlated with many different components of body weight as lean mass, skeletal muscle mass, fat mass, and bone mass; but, it cannot differentiate between them [25,26]. Consequently, the presence of ascites, peripheral oedema and/or hepatosplenomegaly which are common in patients with liver disease, makes arm anthropometrics an alternative tool in identifying malnutrition as it estimates muscle mass and fat stores [2].

We detected malnutrition in a larger number of patients, when we used skinfolds and mid upper arm circumference measurements: ranging from 56% by MUAC, 59.4% according to TSF and 66% by SSF. Skinfolds and MUAC measurements are considered useful parameters to assess subcutaneous fat and muscle mass [10]. Moreover, they are less likely to be affected by oedema because oedema is more readily accumulated in the lower body. They are considered to be more accurate measurements than height because variations in these parameters appear earlier than changes in height [27].

Following liver transplantation, children with chronic liver diseases experience significant degrees of undernutrition and the prevalence of malnutrition varies according to the index used [28]. According to Zamberlain and co-workers, there is a 2-fold increase in the detection of malnutrition by MUAC, and TSF versus W/H [29]. Similarly, we detected a 5 to 10 -fold increase in the detection of malnutrition by skin fold measurements versus W/H.

Despite the fact that, we found a significant number of malnourished patients by our single basal measurements on admission, this did not seem to affect the outcome of hospitalization of these patients, whether favourable or unfavourable. Analysing the patients data according to arm parameters, only below normal TSF was associated with prolongation of hospital stay >14 days.

This is similar to the results of a previous study revealing that the index which better reflected the nutritional risk in cirrhotic children was the triceps skinfold thickness [30].

In addition, these malnourished patients were younger significantly, and they were the ones who suffered from cholestatic disease of infancy. This can be attributed to the fact that infants with cholestatic disorders suffer from early onset of their disease, in addition to fat malabsorption and deficiency in fat soluble vitamins [31,32] which constitute a complex situation resulting in malnutrition. Patients with biliary atresia have more serious nutritional deficit [33].

TSF is used to estimate body fat and MUAC to estimate muscle mass. But, TSF thickness reflects peripheral fat as it is measured at an extremity site. So, we additionally measured SSF thickness which refers to central fat as it is measured on the trunk. That was done to analyse different patterns of fat distribution [34,35]. In patients with chronic hepatic insufficiency, fats are used as a metabolic substrate for energy production [7].

We observed that SSF diagnosed malnutrition in 39 patients (66.1%). Although, we did not find significant relationship with the prognosis but it was the anthropometric method that diagnosed malnutrition in largest number of patients in our study.

UAMA by height is a good anthropometric measure as it can be used in conjunction with the W/H to obtain a more complete evaluation of growth and nutritional status; especially when the age is not accurately known or is unreliable [36]. However, this tool was not applicable in 44 patients (74.6%), whose heights were below 84 cm.

The use of biochemical tests for nutritional assessment in individuals with liver disease is questioned, because it may represent liver dysfunction and does not necessarily represent changes in nutritional status. Although we found a positive association between the unfavourable outcome and the presence of hyperbilirubinemia and impaired synthetic liver functions; these tests do not reflect the degree of malnutrition. Our results comply with previous research

indicating that anthropometric measurements were a better indicator of the nutritional outcome compared to biochemical data [37].

We observed that, there was a significant association between hypokalaemia and unfavourable outcome. Hypokalaemia could be due to the use of diuretics, to manage ascites and peripheral oedema [38]. Other possible causes include excessive vomiting, diarrhea, eating disorders, laxative use in management of hepatic encephalopathy [39].

We found that 32 patients (54.2%) had hypophosphatemia and it was found to be correlated with malnutrition assessed by MUA circumference. Phosphorus as many other electrolytes can be deficient with chronic liver disease especially cholestasis due to malabsorption [40]. Also, it can be decreased by the use of diuretics and refeeding syndrome [41].

In our study, we found an impaired creatinine level in 11 patients (18.6%). One of them was post-liver transplantation and was on immunosuppressant medications. The others were dehydrated during the time of examination. Cyclosporin and tacrolimus which are immunosuppressant medications that are used following liver transplantation, can cause renal insufficiency and hyperkalaemia [7,41]. We also observed hyperkalaemia in 5 patients (8.5%) which may be related to the use of diuretics, to manage ascites and peripheral oedema, which can cause both loss of potassium and eventually contribute to kidney damage. Damaged kidneys are not as able to maintain the balance of potassium, so hyperkalaemia can occur [38].

Assessment of nutritional status in critically ill patients is important because different studies have reported that, malnutrition may lead to prolonged length of ICU/hospital stay and increased rate of morbidity and mortality between these patients [42,43].

To our knowledge, this is the first study examining the relationship between the nutritional assessment of hospitalized infants and children with liver disease and their outcome.

LIMITATION

Our study limitation is that measurements were taken at a single time point, on admission, and not followed up during the hospital stay. The young age of our patients was another limitation, as some of the anthropometric measurements could not be applied below a certain age and height and this may explain why undernutrition was evident in many parameters but comparisons of favourable and favourable outcome groups did not reach statistical significance.

CONCLUSION

Infants and children with liver diseases, especially the younger ones with cholestasis, have a significant degree of malnutrition. Anthropometric measurements, especially the skinfold thickness measurements, combined with some laboratory parameters may be useful in the evaluation of their nutritional status. A single measurement of TSF thickness predicted a prolonged hospital stay with possible higher costs and complications, especially for the younger, cholestatic infants.

We recommend a proactive approach consisting of screening anthropometry interpreted using appropriate growth references, recognition of clinical manifestations associated with micronutrient deficiency, and timely aggressive nutrition support to maximize anabolism and optimize outcomes in our paediatric patients with chronic diseases, especially hepatic ones.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Pediatrics, Cairo University, Cairo, Egypt.
2. Professor, Department of Pediatrics, Cairo University, Cairo, Egypt.
3. Assistant Lecturer, Department of Pediatrics, Cairo University, Cairo, Egypt.
4. Professor, Department of Pediatrics, Cairo University, Cairo, Egypt.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Yasmeen Mansi,
Department of Pediatric, Faculty of Medicine, Cairo University, Cairo, Egypt.
E-mail: y.mansi2016@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: Jun 04, 2016

Date of Peer Review: Jun 24, 2016

Date of Acceptance: Aug 29, 2016

Date of Publishing: Dec 01, 2016