

CLINICAL STUDIES

Nutritional status: its influence on the outcome of patients undergoing liver transplantation

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Abstract

Background: Malnutrition is frequently present in case of end-stage liver diseases, and in cirrhotic patients, a poor nutritional status is considered to be one of the predictive factors for increased morbidity and mortality rates after surgery. The impact of the recipients' malnutrition on the outcome of liver transplantation (LT) is still under debate and recent studies have shown controversial results. **Patients and methods:** We prospectively analysed the nutritional status of 38 consecutive patients undergoing LT in our University Hospital. Subjective global nutritional assessments (SGA) and anthropometry were used for the evaluation of the nutritional status. Energy expenditure, dietary intake and energy balance were also evaluated. After LT, multiple short-term outcomes that could be influenced by the nutritional status, such as number of episodes of infections (bacterial, viral and fungal) until discharge from hospital, length of stay in intensive care unit (ICU), length of hospital stay and in-hospital graft and patient's survival, were recorded. **Results:** Malnutrition was identified in 53% of cases according to the SGA. Pretransplant nutritional status, haemoglobin levels and disease severity were independently associated with the number of infection episodes during the hospital stay. The presence of malnutrition was the only independent risk factor for the length of stay in the ICU and the total number of days spent in hospital. **Conclusion:** The present data suggest that recipients' malnutrition should be taken into account as a factor that increases complications and costs after LT.

Malnutrition is frequently associated with chronic liver disease and has been proved to have important prognostic implications (1, 2). Its prevalence may range from 20 to 80% depending on the methods used for the nutritional assessment and the severity of liver disease; those patients with a more advanced liver insufficiency are in fact known to have more severe protein/calorie malnutrition (3–5). The pathogenesis of malnutrition in chronic liver diseases is multifactorial and includes a reduction in nutrient and calorie intake because of anorexia and dietary restrictions, impaired intestinal absorption, abnormalities of carbohydrate, lipid and protein metabolism and increased proinflammatory cytokine levels resulting in a hypermetabolic state that may occur in advanced liver disease stages. Multiple techniques have been proposed to detect malnutrition in patients with liver disease (6–13); it is, however, a well-known fact that some common nutritional parameters can be misleading in advanced liver disease because of

water retention and ascites (6), compromised protein synthesis (7) and coexisting alterations in the renal function (8). Although there is no gold standard for the assessment of malnutrition in patients with liver disease, anthropometric measurements, such as arm muscle circumference and triceps skinfold, were utilized in large groups of cirrhotic patients and proved to be able to identify muscle and fat depletion (1, 2). The subjective global nutritional assessment (SGA), which is based both on physical signs of malnutrition and nutritional history, has also been utilized to evaluate the nutritional status in patients with chronic liver disease and, in particular, in those awaiting liver transplantation (LT) (14, 15). As malnutrition is known to be associated with a greater risk of post-operative complications and mortality rates in patients with liver disease (16, 17), this correlation was also suggested in cirrhotic patients undergoing LT (18). Recipients' malnutrition was found to be associated with increased operative blood loss, length of stay in the

intensive care unit (ICU), mortality and total hospital charges after LT by some authors (15, 18, 19), but not by others (14, 20, 21). Whether the presence of a compromised nutritional status plays a role as an independent risk factor in the outcome of LT is therefore still under debate even if the current opinion is that malnutrition should not be considered as a contraindication to the procedure (11). In this study, we prospectively analysed the nutritional status in a group of patients undergoing LT and its relationship with their short-term clinical outcome.

Patients and methods

All consecutive patients awaiting elective LT for end-stage liver diseases at the Transplant Centre of the 'Sapienza,' University of Rome, were considered for a prospective study between July 2006 and January 2008. Patients requiring LT for fulminant hepatic failure (three patients) or those (eight patients) who did not consent to participate in this study (mainly because, living beyond the region, they would not be able to attend all the programmed visits) were excluded. The selection criteria for being enlisted for elective adult LT in our centre were an end-stage liver disease with a model for end-stage liver disease (MELD) score >10 (22, 23) or liver cirrhosis with hepatocellular carcinoma (HCC) (staged as T2) (24). The allocation of organs to waiting list recipients was based on the severity of the MELD score; patients with a diagnosis of T2-HCC received additional points to obtain a minimum MELD score of 22. This study was approved by the Ethical Committee of the Policlinico Umberto I, and written informed consent was obtained from all the participants.

Assessment of nutritional status

The nutritional assessment was performed during a dedicated outpatient examination before LT and repeated every 3 months until the procedure. For each patient, the following data were considered: anthropometric measurements, SGA, measurement of basal energy expenditure (BEE), estimation of calorie intake and total energy expenditure and laboratory tests.

Anthropometric measurements

Body mass index (BMI) was computed as body weight (kg)/height (m²). Body weight was measured after treatment of ascites and/or water retention, if present. In a few patients, dry weight was calculated by deducting an estimated weight for ascites and/or oedema.

Mid-arm circumference (MAC, cm) was measured at the midpoint between the tip of the acromion and the olecranon process on the non-dominant side of the body using a flexible tape measure.

Skinfold measurements were determined at four sites: triceps, biceps, sub-scapular and supriliac areas (mm), according to Durnin and Womersley (25). All the mea-

surements were taken on the non-dominant side of the body, with the patients standing in a relaxed position, using a Harpender skinfold caliper (John Bull British Indicators Ltd., St Albans, UK) with a pressure of 10 g/mm³ applied to the surface area. The average of three consecutive readings was recorded. To reduce measurement errors, all the readings were carried out by the same operator.

Mid-arm muscle circumference (MAMC) was calculated by the formula: MAMC = MAC - [π triceps skinfold thickness (TSF)]. Mid-arm muscle area (MAMA) and mid-arm fat area (MAFA) were calculated using the MAC and TSF according to the following equations:

$$\text{MAMA (cm}^2\text{)} = [\text{MAC} - (\pi \text{TSF})]^2 / 4\pi$$

$$\text{MAFA (cm}^2\text{)} = (\text{MAC} \times \text{TSF}) / 2 - \pi(\text{TSF})^2 / 4$$

Patients with MAMA and/or an MAFA value below the 5th percentile of the standard for an age- and gender-matched population were recorded (26).

Subjective global nutritional assessment

The SGA was carried out according to Detsky *et al.* (27) and based on the nutritional history (weight loss, dietary intake and gastrointestinal symptoms) and clinical examination (physical signs of malnutrition, such as depletion of subcutaneous fat and muscle mass) of the patients. Patients were classified as those with no malnutrition (SGA-A) and those with malnutrition (SGA-B or -C).

Indirect calorimetry

Basal energy expenditure and patterns of oxidized substrates – starting from the measurement of oxygen consumption (VO₂), the production of carbon dioxide (VCO₂) and the urinary excretion of nitrogen – were measured by indirect calorimetry with a canopy mode (Deltatrac Metabolic Monitor; Datex Instruments, Helsinki, Finland). All the measurements were carried out in a room with a controlled temperature (24 °C), between 08:00 and 09:00 hours; the patients were asked to fast during the last 12 h. The airflow through the canopy was adjusted to maintain a constant fraction of exhaled CO₂; O₂ and CO₂ consumption values were printed every minute. Measurements were continued until they reached stable values (5% minor variations) maintained for at least 10 min; VO₂, VCO₂ BEE were calculated by a dedicated software.

Dietary intake

Daily calorie and macronutrient intakes were evaluated through dietary interviews referring to the last month before the nutritional assessment. To provide a more accurate estimate of food intake, dietary interviews were carried out with the aid of a computer software [WINFOOD; Medimatica, Colonnella (TE), Italy] equipped with visual images of food portions. The same software was used to quantify the average daily calorie intake and the

percentages of carbohydrates, lipids and proteins. The total energy intake (TEI) was expressed in kcal/day.

Daily energy expenditure

Daily energy expenditure was calculated by the factorial method in the 24-h period when the dietary evaluation took place. Each patient's physical activity was assessed by a specific questionnaire aimed at evaluating the hours spent by the patients sleeping, lying awake in bed, sitting, walking, training, etc. To calculate the energy cost of each activity, BEE was multiplied by an activity factor for a reference Italian population (28). Daily energy expenditure was obtained by the sum of the energy cost of each activity performed by each patient during the 24 h. In this calculation, the dietary-induced thermogenesis – proved to be equivalent to 10% of daily energy intake – was not considered.

The daily energy expenditure was listed as total energy expenditure (TEE) and expressed in kcal/day. The total energy balance (TEB; kcal/day) was calculated as $TEB = TEI - TEE$.

Laboratory values

Laboratory data [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ -glutamyltransferase, total bilirubin, protein, albumin, international normalized ratio (INR), blood urea nitrogen, creatinine, serum sodium, lymphocyte count, haemoglobin, serum cholesterol and serum triglycerides] were measured by established standard laboratory methods.

The severity of cirrhosis was classified according to the Child–Pugh (29) and the MELD (23) scores. The MELD score presented in the text and tables was always derived from laboratory parameters, without further corrections.

Donor risk index

To evaluate the possible influence of the quality of the graft on the transplantation outcome, we utilized the donor risk index proposed by Feng *et al.* (30). This score takes into account parameters such as donor's age, race, donation after cardiac death, partial or split, height and cold time. We arbitrarily chose a donor risk index > 1.5 to identify those patients with a higher risk of graft failure after transplantation.

Outcomes

All outcomes were evaluated during the hospital stay until discharge. Patients were initially in a dedicated intensive care unit (ICU) and then in the Department of Transplant Surgery. Out-patient follow-up was not included in this analysis. The following parameters were recorded:

- (a) Blood products' usage (red blood cells and plasma);
- (b) Episodes of infection during hospitalization. The diagnosis of infection – classified as bacterial, viral or fungal – was confirmed when one or more microorgan-

isms requiring a systemic pharmacological therapy were identified;

- (c) Delayed wound healing;
- (d) Acute organ rejection;
- (e) Length of stay in the ICU;
- (f) Total length of stay in the hospital;
- (g) In-hospital graft-failure and
- (h) In-hospital mortality.

Statistical analysis

All data resulting from continuous variables are presented as mean \pm standard deviation and/or median \pm range; the data resulting from categorical variables are expressed as percentages or counts. We computed Pearson's correlation coefficients between numerical variables and assess their significance. We used non-parametric rank-based tests for comparing continuous variables across groups. In particular, differences between malnourished patients and those without malnutrition were determined using the Mann–Whitney test, and the Kruskal–Wallis test was used when there were more than two groups. We investigated the relationship between categorical variables using the χ^2 -test. Clinical parameters of liver disease severity (Child–Pugh and MELD scores) and nutritional status (SGA, BMI, MAC, MAMC, TSE, TEE, TEB, etc.) were analysed as possible predictors of three outcomes (number of infections, days spent in the ICU and in the hospital) after LT.

For the number of infections, a generalized linear model with a natural logarithmic link and Poisson family (31) was used. For the days spent in the ICU and in the hospital, comparisons between groups induced by categorical variables were performed using log-rank tests, and relationships with numerical variables were estimated using univariate Cox models. Multivariate models were also built for prediction of the three outcomes. The Cox model was used for the 'length of stay' variables. In all cases, the predictors included in the model were chosen minimizing the Akaike information criterion (32) and retain the significant covariates in the model. A value of $P < 0.05$ was considered as statistically significant. Where appropriate, the Bonferroni method was used as correction for multiplicity of testing. The P -values reported are already adjusted for multiplicity. The software used for the analyses was R (R Development Core Team, version 2.6, Vienna, Austria) (33).

Results

Population characteristics

Among the 52 patients enrolled in this study, six died while in the waiting list; one was excluded because of the enlargement of his liver tumour above the Milan criteria. Seven patients were still awaiting LT when the study was closed. The present results, therefore, refer to the 38 patients who received a previous nutritional assessment and underwent LT during the observation period.

Table 1. Demographical and clinical characteristic of the 38 patients undergoing liver transplantation according to their nutritional status (no malnutrition subjective global nutritional assessment-A, malnutrition subjective global nutritional assessment-B, -C)

	No malnutrition (18)	Malnutrition (20)	P
Age (years)	50 ± 11	54 ± 9	0.14
Gender (males/females) (n)	13/5	16/4	0.86
Origin of liver disease (alcoholic/viral/others) (n)	2/13/3	4/9/7	0.3
Diagnosis of HCC at least stage T2 (n)	11	3	0.004
Total bilirubin (mg/dl)	2.2 ± 1.8	6.9 ± 8.5	0.02
INR	1.30 ± 0.1	1.5 ± 0.3	0.02
Albumin (g/dl)	3.4 ± 0.6	2.8 ± 0.5	0.006
Ascites (previous or present) (n)	5	16	0.001
Hepatic encephalopathy (previous or present) (n)	4	12	0.04
Alanine aminotransferase (mU/ml)	61 ± 46	42 ± 30	0.1
Serum sodium (mEq/L)	138 ± 4.4	139 ± 7	0.88
Haemoglobin (g/dl)	12.9 ± 1.8	10.6 ± 1.7	0.001
MELD (physiological MELD score)	11.2 ± 4.1	19.1 ± 6.2	0.00005
Child–Pugh (score)	7.8 ± 2.0	9.7 ± 1.6	0.004
Donor risk index > 1.5 (n)	6	7	1.0

HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease.

Table 2. Anthropometric parameters and dietary intake of the 38 patients undergoing liver transplantation according to their nutritional status (no malnutrition subjective global nutritional assessment-A, malnutrition subjective global nutritional assessment-B, -C)

	No malnutrition (18)	Malnutrition (20)	P
BMI (kg/m ²)	26.8 ± 2.8	24.4 ± 3.5	0.02
MAMC (cm)	24.9 ± 2.9	23.4 ± 2.5	0.104
TSF (mm)	14.9 ± 5.8	10.4 ± 5.7	0.023
MAMA (mm ²)	49.3 ± 11.4	42.7 ± 8.0	0.096
MAMA < 5th (% patients)	17	85	0.000009
MAFA (mm ²)	20.2 ± 7.2	13.1 ± 8.5	0.0091
MAFA < 5th (% patients)	0	40	0.001
Lymphocyte count (n/mm ³)	1031 ± 425	1165 ± 962	0.508
Serum cholesterol (mg/dl)	133 ± 33	116 ± 65	0.147
Serum triglycerides (mg/dl)	95 ± 64	69 ± 33	0.247
TEI (kcal/day)	2240 ± 375	1796 ± 467	0.01
TEE (kcal/day)	2406 ± 289	2365 ± 448	0.586
TEB (kcal/day)	− 94.9 ± 289.5	− 564.8 ± 373	0.025
Protein intake (g/kg)	1.1 ± 0.3	1.1 ± 0.4	0.7

BEE, basal energy expenditure; BMI, body mass index; MAFA, mid arm fat area; MAMA, mid arm muscle area; MAMC, mid arm muscle circumference; SGA, subjective global nutritional assessment; TEB, total energy balance; TEE, total energy expenditure; TEI, total energy intake; TSF, triceps skin fold.

The main demographical, clinical and biochemical characteristics of the patients classified according to their nutritional status are reported in Table 1. Gender, age and origin of liver disease were comparable in the two groups. Malnourished patients presented with lower albumin and haemoglobin levels, a higher INR value, a higher prevalence of ascites and encephalopathy and higher MELD and Child–Pugh scores. Hepatocellular carcinoma T2 was the more frequent indication for LT in the well-nourished patients. The percentage of patients with a donor risk index > 1.5 was similar in the two groups. Anthropometric parameters (Table 2) were, as expected, significantly different in the two groups. This was evident for BMI ($P < 0.02$), TSF ($P < 0.03$) and MAFA ($P < 0.01$). The patients with MAMA and or MAFA < 5th percentile were also significantly different in the two groups. The TEE was not significantly different

in the two groups, while the TEI (kcal/day) was reduced in malnourished patients ($P < 0.01$); as a consequence, the TEB (kcal/day) was more negative in the latter group ($P < 0.001$).

Outcomes

Post-LT outcomes in recipients with and without malnutrition are shown in Table 3.

Blood usage

The nutritional status of the patients did not influence the request for blood products; the need for packed red blood cells or of fresh-frozen plasma was in fact comparable in the two groups.

Table 3. Outcome and nutritional status of the 38 patients undergoing liver transplantation according to their nutritional status (no malnutrition subjective global nutritional assessment-A, malnutrition subjective global nutritional assessment-B, -C)

	No malnutrition (18)	Malnutrition (20)	P
Packed red blood cells during surgery (U)	8 ± 6	20 ± 26	0.24
Fresh-frozen plasma usage during surgery (U)	26 ± 11	49 ± 44	0.11
Episodes of infection (total number)	11	85	0.000001
Episodes of infection (number/patient)	0.6 ± 0.9	4.5 ± 3.1	0.0001
Bacterial infection (% of patients)	18	80	0.003
Viral infection (% of patients)	22	75	0.002
Fungal infection (% of patients)	11	50	0.025
Delayed wound healing (% of patients)	5	25	0.08
Acute graft rejection (% of patients)	17	25	0.82
Length of stay in ICU (days)	5 ± 9	20 ± 15	0.0007
Total length of hospitalization (days)	18 ± 10	41 ± 19	0.00016
In-hospital graft failure (n patients)	0	2	0.1
In-hospital mortality (n patients)	0	2	0.1

ICU, intensive care unit.

Episodes of infection

Twenty-seven patients (73%) had one or more infective episodes (either of bacterial, viral or fungal origin). One or more bacterial infections occurred in 21 patients, viral infections in 19 (89% cytomegalovirus and 11% herpes virus) and fungal infections (100% superficial *Candida* spp. infections) in 15 patients. Both the total number of infective episodes and the number of infections per patient were significantly higher in malnourished patients as compared with patients with no-malnutrition ($P < 0.000001$ and $P < 0.0001$ respectively). Gram-negative bacteria (*E. coli*, *Klebsiella*, *Pseudomonas aeruginosa*) were the more frequently isolated pathogens. The multivariate analysis showed that the total number of infections was influenced by a higher MELD (coefficient 0.0614; $P: 0.0001$) a lower haemoglobin (coefficient -0.10219 ; $P: 0.00011$) and the presence of malnutrition (SGA-B, -C) (coefficient 1.3323; $P: 0.00001$). In particular, it can be seen that patients with malnutrition are expected to experience on average 1.33 additional infections with respect to patients without malnutrition, having adjusted for the other significant factors.

Delayed wound healing

Six patients (16%) had a delayed wound healing and five of them were malnourished, but this difference did not reach statistical significance.

Acute graft rejection

Eight patients (22%) had an acute cellular rejection. The incidence of rejection, however, was not influenced by the nutritional status.

Length of stay in the intensive care unit/hospital

The mean length of stay in ICU was 13 ± 12 days (range: 2–45), while the mean hospitalization was 30 ± 19 days

(range: 9–67). As shown in Table 3, malnourished patients showed significantly longer lengths of stay both in the ICU and in the hospital. The multivariate analysis showed that the total number of days in the ICU was influenced only by malnutrition (SGA-B, -C) [hazard ratio (HR): 0.18; $P: 0.0003$], while all the other possible predictors were not included in the model. The total number of days of hospitalization was also influenced only by malnutrition (HR: 0.20; $P: 0.0001$). An HR < 1 implies that the presence of malnutrition leads to a longer stay in ICU and a longer hospitalization. The number of days spent in the ICU or in the hospital by patients with malnutrition is then significantly expected to be about five times the number of days, respectively, spent in the ICU or in the hospital by patients without malnutrition.

In-hospital graft survival

Two patients, both malnourished, experienced a graft loss, both for hepatic artery thrombosis, one after 15 and one after 45 days. One patient underwent re-transplantation and is still alive.

In-hospital mortality

Two patients (5%) died in the short term: one because of hepatic artery thrombosis 45 days after LT and the other because of sepsis and multiorgan failure 31 days post-procedure. Before LT, both these patients were classified as malnourished.

Discussion

Previous reports have focused their attention on the role of malnutrition as an independent risk factor on the outcome of LT (14, 18–21); the results, however, were controversial. In particular, two prospective series of 53 and 61 LT candidates failed to show any association between the pre-operative nutritional parameter and the survival or the

global resource utilization (14, 20). In the present study, the total number of infections, the number of infections per patient and the percentage of patients who had a bacterial or a viral infection episode after LT were significantly higher in malnourished recipients. By applying a multivariate analysis, the severity of liver failure (higher MELD score), haemoglobin levels and a compromised nutritional status (SGA-B, -C) were shown to be predictors of the number of infection episodes per patient. The length of stay in the ICU and the total number of days of hospitalization were also significantly increased in those patients with a nutritional impairment. The severity of malnutrition (SGA-B, -C) was found to be the only independent predictor of the days spent in the ICU and of the total length of hospital stay. Previous studies have proposed that malnutrition may affect LT outcomes. Some of them, however, were rather old – as evidenced by their high mortality rate (18) – and others were retrospective studies (15, 18). As severe malnutrition is particularly evident in those patients with more severe liver dysfunction, the role of pre-operative malnutrition as an independent predictor of peri-operative mortality could never be clearly demonstrated. Selberg *et al.* (12) found that those patients with a better nutritional status at transplantation had improved survival rates after LT; in this study, however, the survival rate was evaluated by considering a rather long follow-up, and it is well known that many different factors may affect the long-term survival after transplantation (illness recurrence, acute rejection, renal failure, etc.), not necessarily influenced by the patients' nutritional status at the time of surgery. Harrison *et al.* (19), in a series of cirrhotic patients with a prevalence of cholestatic liver disease, showed that malnourished cases were at a higher risk for post-operative complications; however, the time spent in the ICU and the total time spent in the hospital were not different in well-nourished and in malnourished patients.

Other studies have failed to show a correlation between nutrition and post-LT outcomes (14, 20); in one of these reports, however, the proportion of patients with severe malnutrition was difficult to be deduced (20) and in the other study, mild to severe malnutrition was generalized (87%) and equally distributed among patients with different outcomes (14). In a recent Spanish study, all the patients waiting for LT were found in a normal nutritional status (21).

Despite these controversial results, the belief that malnutrition may increase the risk of patients undergoing LT, as for other surgical procedures in cirrhotic patients (16), has led to active protocols to improve the recipients' nutritional status before LT. The only randomized study in this field (34), however, could not demonstrate that intensive pre-operative nutrition is able to improve the patients' outcome. Although severe malnutrition is not considered a contraindication to LT (11), the need for nutritional counselling and support for this kind of patients has been recognized nowadays to reduce the severity of the nutritional impairment. According to

our experience, dietary counselling may only lead to a certain improvement in clinically stable patients who are followed for an adequate period of time while in the waiting list. However, because the allocation of organs is based on the severity of the MELD score, more severe patients are rapidly driven to transplantation, thus making it more difficult to deal with their nutritional problems. This prospective analysis is therefore aimed at reevaluating the independent contribution of nutrition on the outcomes of LT in patients who underwent transplantation in recent years.

Severe malnutrition was identified in more than half of our patients (53%) at transplantation. Unlike other studies (12), we did not find patients with a hypermetabolic state. As the REE was not increased and the daily physical activity was low, the TEE was not increased in our series; the mean TEB was, however, negative in malnourished cirrhotic patients, because their dietary intake was frequently lower than that recommended (11, 13). Peri-operative mortality was low in our series; no correlation could therefore be proven between malnutrition and mortality. Episodes of infections, the period spent in ICU and the total days spent in hospital were all strongly influenced by the recipients' nutritional status. The main shortcoming of our study was the relatively small number of patients, which may thus be subject to an inadvertent selection bias. The low number of events regarding graft or patient survival could have obscured the role of nutritional status on these parameters. Larger studies are required to examine the relationship between nutrition and short-term survival after LT as the outcome of LT depends on a number of factors, sometimes unpredictable (such as technical difficulties). We chose to enrol the patients prospectively in a relatively short time and to perform a complete nutritional assessment, including those parameters that have not been always reported in other studies (such as dietary intake and energy balance).

All the individual parameters of nutritional status (SGA, BMI, MAC, MAMC, TSF, TEE, TEB, etc.) were analysed as possible predictors of three outcomes (number of infections, days spent in the ICU and in the hospital), and SGA was the stronger independent predictor for the outcomes examined as continuous variables. The cause of this finding is probably because of the fact that SGA evaluation takes multiple information into account, information that also derives from the knowledge of single parameters such as muscle and fat loss, inadequate dietary intake and functional capacity. A correct and detailed nutritional assessment has probably improved our diagnostic capacity in detecting malnutrition and assessing a correct SGA.

In conclusion, we demonstrated that malnutrition may independently increase the resource utilization and the patients' post-LT risks. This suggests that particular attention should be focused on these patients, by evaluating their nutritional status and by planning possible nutritional corrections.

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