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Research Article

Association between Nutrition Assessment Tools and Long-Term Survival in Cirrhosis Patients Undergoing Liver Transplant Assessment

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Keywords

- Cirrhosis
- Malnutrition
- Nutrition assessment tools
- long-term survival

Abstract

Background: This study aimed to explore longitudinal relationships between bedside nutrition assessment tools (NAT): hand grip strength (HGS), mid upper arm circumference (MAC), and subjective global assessment (SGA), and clinical outcomes including: liver related hospitalizations, and liver transplant-free survival (LTFS) in patients undergoing liver transplantation assessment.

Methods: Cirrhosis patients, referred to a cirrhosis focused malnutrition clinic, (N=41) completed NAT during the baseline visit and received one follow-up visit with NAT reassessment and were then followed up 24-months post assessment (median 23.0 months (IQR: 10.5 -29.1)). Log rank Kaplan-Meier and Cox proportional-hazard regression models were used to assess associations between demographic, clinical characteristics and NAT with outcomes.

Results: Neither baseline NAT assessment or improvements affected the risk of hospitalizations in our cohort. In univariate analyses, improvement of SGA status (Hazard ratio [HR]: 0.28, 95% confidence interval [CI] 0.09-0.88, p=0.03) HGS (HR: 0.91, 95%CI 0.83-1.00, p=0.05) and MAC (HR 0.85, 95% 0.72.1.00, p=0.05) were associated with LTFS. However, NAT did not independently predict LTFS in adjusted multivariate analyses.

Conclusions: Prospective larger cohorts are needed to further evaluate the impact of temporal improvement of NAT on LTFS and hospitalizations.]

ABBREVIATIONS

NAT: Nutritional Assessment Tools; **SGA**: Subjective Global Assessment; **HGS:** Hand Grip Strength; **MAC:** Mid-Arm Circumference; **BMI:** Body Mass Index; **RD:** Registered Dietitian; **EMR:** Electronic Medical Record; **LTFS:** Liver Transplant-Free Survival; **GI:** Gastrointestinal.

INTRODUCTION

Liver cirrhosis contributes significantly to mortality globally, and its incidence is projected to increase given rising rates of obesity [1]. Malnutrition in cirrhosis is diagnosed in 5-99% of patients depending on the nutrition assessment tool used[2]. Identifying malnourished patients with cirrhosis is critical, as malnutrition may lead to adverse clinical outcomes including hepatic encephalopathy (HE), infections, spontaneous bacterial peritonitis, ascites, gastrointestinal (GI) bleeding, hepatorenal syndrome and increased mortality [3] . Malnutrition in patients admitted to hospital has implications for healthcare resources, as malnourished patients incur greater costs while hospitalized and experience prolonged duration of hospitalization compared to well-nourished patients[4]. Malnutrition in cirrhosis arises from complex pathophysiological mechanisms that include decreased oral intake, decreased absorption, and altered metabolism[5]. Studies in malnourished cirrhosis patients have reported varying results for the effectiveness of nutrition interventions to improve clinical outcomes[6] .

Nutrition assessment tools (NAT) are used to identify malnourished patients who may benefit from nutrition intervention. These NAT include simple bedside tools such as subjective global assessment (SGA), and objective anthropometric measurements (e.g., handgrip strength [HGS] and mid upper arm circumference [MAC]), and objective comprehensive tools that

include body composition (e.g., dual X-ray absorptiometry) and cross-sectional measures of skeletal muscle (e.g., CT/magnetic resonance imaging).

While objective comprehensive measures of body composition can be a surrogate marker of malnutrition in the presence of sarcopenia and predict poor outcomes, they are expensive and not readily accessible. Bedside measures of nutrition status are readily available and require minimal resources to execute. Previous studies in cirrhotic patients with malnutrition have explored the efficacy of NAT to predict outcomes(7-10). While relationships between HGS, SGA class and clinical outcomes have been established, few of the reviewed studies evaluated whether changes in HGS, SGA or MAC were significantly related to clinical outcomes. Bedside measures that help identify those at risk for malnutrition who may benefit from timely referrals for nutritional interventions, would be beneficial additions to routine clinical assessment.

In this pilot study, we aimed to explore temporal associations between improvement of bedside NAT (HGS, MAC and SGA) and clinical outcomes, including liver-free transplant survival (LFTS), and hospitalization rates in cirrhotic patients undergoing liver transplant assessment who attended a cirrhosis focused malnutrition clinic.]

MATERIALS AND METHODS

Study Design and Recruitment

This is a real-world prospective single-centre study completed from 2014 to 2017 at the Foothills Medical Center malnutrition clinic in Calgary, Alberta, Canada. All adult patients with decompensated cirrhosis without hepatocellular carcinoma who were undergoing liver transplant assessment were referred to the malnutrition clinic for detailed nutrition assessment and management as a part of routine clinical care, and were invited to participate in this study. Participants received a comprehensive nutrition assessment, including counselling by a registered dietitian (RD) with expertise in malnutrition and cirrhosis, and an appointment with a nutrition-focused gastroenterologist at baseline (n=69). Patients were offered a follow-up visit in the malnutrition clinic 3-6 months after the baseline visit, however only 41 patients presented for follow-up (Figure 1). The study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB15-0106) and all patients provided written informed consent.

NUTRITION ASSESSMENT TOOLS

Subjective Global Assessment

The SGA is a validated NAT that combines patient history and physical examination into three categories: A (well-nourished), B (moderately malnourished), and C (severely malnourished) [11]. SGA classification was performed by both the cirrhosis malnutrition clinic RD and gastroenterologist individually, with a final rating achieved by consensus.

Body Mass Index

To calculate BMI each patient had their measured height and weight recorded at the initial clinic visit using the same scale and stadiometer.

Dry Weight

The estimation of dry body weight is a common challenge in patients with cirrhosis, with few validated methods to accurately describe this. Using previously described methods, 5% of the patient's measured weight was subtracted in the presence of mild ascites, 10% with moderate ascites and 15% with severe

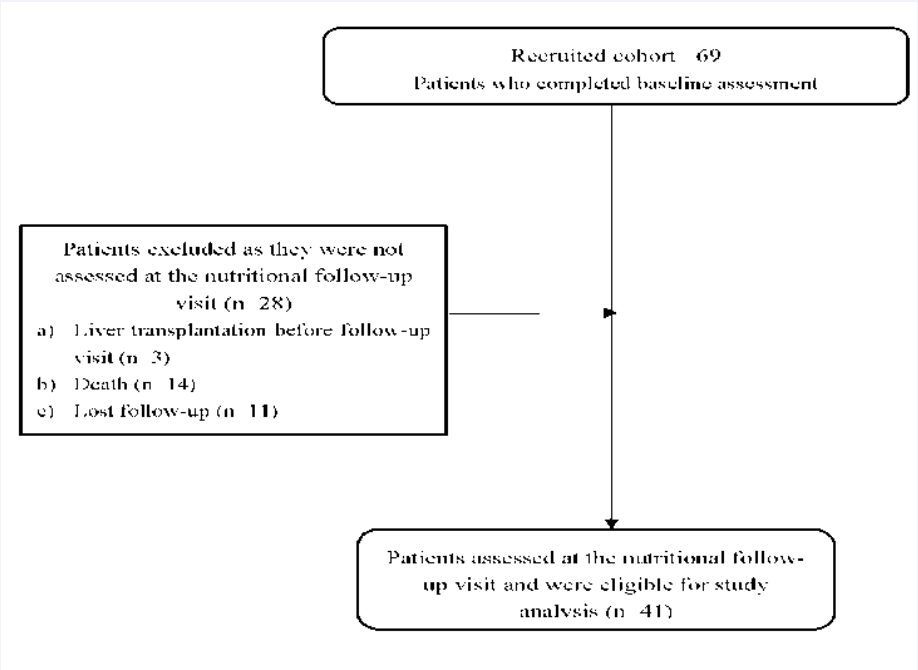

Figure 1 Study flowchart.

ascites. The severity of ascites was determined sonographically. An additional 5% was subtracted if bilateral pedal edema was present[12].

Mid Upper Arm Circumference and Hand-grip Strength

MAC was obtained by measuring the circumference of the upper arm at a point halfway between the olecranon and the humoral head in the non-dominant arm in all patients. MAC was dichotomized (low <28.2 cm and high ≥28.2 cm) to reflect muscle adequacy[13]. HGS was also measured in the non-dominant hand using a calibrated Jamar dynamometer. Patients were seated in a chair with both feet on the ground, and the hand was placed on an armrest at a 90-degree angle. HGS was tested using three consecutive measurements with a one-minute recovery between attempts. The single best measurement was recorded. HGS was divided into a binary variable (low and high) using HGS of <26kg (low) for men and <16 kg (low) for women[14]. BMI, MAC and HGS were completed by one of three trained clinic nurses at baseline and follow-up.

Nutrition Intervention

Patients were required to complete a 3-day food diary prior to attending the baseline clinic appointment. The food diary was completed over two weekdays and one weekend day to ensure accuracy of intake. The RD subsequently completed a 24-hour food recall to confirm food record accuracy. Patients were provided personalized nutrition counselling based on recommendations from recently published guidelines and patient preferences[15]. Specifically, energy and protein recommendations were provided based on estimated dry-BMI in non-obese subjects and estimated adjusted dry-BMI in patients with obesity (dry BMI>30 kg/m^2) [12]. In malnourished patients, (SGA B or C), optimal energy and protein recommendations were based on providing 30-35kcal/kg/day, and 1.2-1.5g/kg/day respectively, whereas in SGA A patients, optimal energy and protein recommendations were for 25-30kcal/kg/day and 1.0-1.2g/kg/day. All patients were encouraged to consume multiple, frequent meals and snacks, and include a late-night snack with a mixed source of carbohydrate and protein to minimize the deleterious effects of prolonged fasting during sleep in cirrhotics.

Clinical Outcomes Data

The primary study outcome was survival time to liver transplantation or death event (LTFS) after a follow up visit to our clinic, and the secondary outcome was hospitalization related to hepatic decompensation, including variceal bleeding, hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis. We followed our cohort up to December 31, 2019 (Figure 1).

STATISTICAL ANALYSIS

To describe the data, continuous variables are reported as medians with the Inter-Quartile Range (IQR), and categorical varia bles are reported as counts and percentages. To evaluate the association between SGA classes at baseline and demographics, clinical variables and NAT, Kruskal-Wallis and Chi-square tests were used for continuous and categorical variables respectively. To identify predictors of liver related hospitalization and LTFS, Log rank Kaplan-Meier tests and Cox proportional hazard regression models were used to evaluate the effect of covariates including our NAT variables at time of the dietary intervention follow-up visit on liver related hospitalization and LTFS. Estimates were reported as hazard ratios (HRs) with accompanying 95% confidence intervals (CIs). To assess changes in NAT after implementing the nutritional intervention, we created categorical variables to measure changes between follow-up and baseline for SGA, HGS and MAC. Categorical variables were classified into three groups: a) worsened status (e.g., decline from SGA A to B or B to C, decline of HGS or MAC from a high to low group); b) stable status (patient maintained stable classification in SGA, HGS and MAC groups); and c) improved status (e.g., progress from SGA B to A or C to A, improvement of HGS or MAC from low to high group). We evaluated the categorical change variable for each NAT as well as crude change in continuous variables for HGS and MAC in our Cox proportional regression models. Similarly, we assessed changes in MELD-Na score from baseline to follow-up as categorical and continuous variables. Categories of MELD-Na were defined as stable, improved or worse (to be defined as worse or improved, MELD-Na score had to change by at least 1 point from baseline to follow-up). In the univariate analysis for liver related hospitalization and LTFS, inclusion criterion for the multivariate models was set a priori for each exposure variable with p<0.10. We adjusted for age and sex in our multivariate models. Analyses were conducted using Stata Statistical Software, version 16.1 (College Station, Texas).]

RESULTS AND DISCUSSION

Patient Characteristics

We recruited 69 cirrhosis patients, all of whom were offered a follow-up visit after 3-6 months of baseline assessment. Out of that cohort, 41 (59.4%) patients presented for and completed the follow-up nutritional assessment. Patients who completed the follow-up assessment had similar demographic, clinical characteristics, NAT baseline assessments similar to those who were lost to follow up, Table 1. The median follow-up duration between baseline assessment and the follow-up visit was 9.3 months (IQR: 6.2-11.7). For our cohort who attended the nutritional follow-up visit (n=41), the median clinical outcomes follow-up duration till December 2019 was 23.0 months (IQR: 10.5-29.1). In our study, 26.8% (n=11) had liver transplant in our follow up cohort compared to 10.7% (n=3) in those who were lost to follow up (p=0.10), while mortality was 31.7% (n=13) among follow-up patients compared to 20.3% (n=14) in those who were lost to follow-up (p=0.13). Patients who had a nutritional assessment follow-up visit had lower liver related hospitalization likelihood compared to those who were lost to follow-up (39.0% [n=16] vs. 64.3% [n=18]), p=0.04.

In our baseline cohort (n=69), 19 patients (27.5%) were categorized as SGA class A, 28 patients (40.6%) SGA class B, while 22 patients (31.9%) were SGA class C. Patients with different SGA classes at baseline were similar in sex, age, measured BMI, energy and protein intake, and etiology of liver disease, Table 2. However, patients with SGA class C had higher rates of ascites compared to SGA B or A (81.8%, 50.0%, and 21.1%, p<0.01, respectively). Similarly, SGA C had higher MELD-Na compared to

Table 1: Demographics, clinical variables and outcomes according to completion of the nutritional intervention.

Variable	Patients at baseline* (n=69)	Patients completed intervention* (n=41)	Patients lost follow up (n=28)	P value
Male sex, n (%)	39 (56.5)	23 (56.1)	16 (57.1)	0.93
Age in years, median (IQR)	56 (50-62)	54 (45-61)	57 (52-63)	0.27
Measured BMI kg/m^2, median (IQR)	23.4 (21.2-26.4)	23.1 (21.3-25.8)	24.3 (20.7-27.5)	0.64
Dry BMI kg/m^2, median (IQR)	22.4 (20.2-25.3)	22.4 (20.3-25.2)	22.3 (19.0-25.3)	0.74
Alcohol related Etiology n (%)	32 (46.4)	15 (36.6)	17 (60.7)	0.05
Ascites, n (%)	36 (52.2)	18 (43.9)	18 (64.3)	0.10
MAC cm, median (IQR)	26 (23-29)	27 (24-28)	26 (23-32)	0.82
MAC Group – High, n (%)	22 (31.9)	13 (31.7)	9 (32.1)	0.97
HGS kg, median (IQR)	22 (17-28)	22 (18-28)	22 (16-28)	0.90
HGS Group – High, n (%)	41 (59.4)	25 (61.0)	16 (57.1)	0.75
SGA				0.78
SGA A, n (%)	19 (27.5)	11 (26.8)	8 (28.6)	
SGA B, n (%)	28 (40.6)	18 (43.9)	10 (35.7)	
SGA C, n (%)	22 (31.9)	12 (29.3)	10 (35.7)	
MELD-Na, median (IQR)	15 (9-18)	16 (11-19)	14 (9-18)	0.52
Liver transplantation, n (%)	14 (20.3)	11 (26.8)	3 (10.7)	0.10
Mortality, n (%)	27 (39.1)	13 (31.7)	14 (50.0)	0.13
Liver related hospitalization, n (%)	34 (49.3)	16 (39.0)	18 (64.3)	0.04
Energy intake per Kcal/Kg / dry weight, median (IQR)	27.1 (21.5-35.1)	27.1 (20.0-35.1)	27.3 (21.5-57.8)	0.58
Protein intake in gram /Kg / dry weight, median (IQR)	1.2 (0.8-1.8)	1.2 (0.7-1.8)	1.2 (1.1-2.3)	0.38

* Assessment values for all presented variables were collected at the first assessment of study inclusion

SGA A (median: 17 [IQR: 14-20] vs. 9 [7-15], $p<0.01$). MAC was associated with SGA class, as SGA class A had a median MAC of 29 cm (IQR: 26-33) compared to SGA class C who had a median MAC of 25 cm (IQR: 22-27, $p<0.01$). However, median HGS was not different across SGA classes (median 21 kg in SGA C vs. 28 kg in SGA A, $p=0.07$), Table 2.

Predictors of LTFS and Liver related Hospitalizations

Among patients who completed the nutritional intervention (n=41), measured BMI (adjusted HR 1.11 [1.00-1.23]) was the only independent predictor of LTFS, Table 3. Although HGS was eligible to be included in our multivariate model, it was not an independent predictor (HR 0.97 [0.92-1.02]) for LTFS in our adjusted model, Table 3. MELD-Na was the only independent predictor of liver related hospitalizations in our cohort (adjusted HR: 1.29 [1.07-1.55]), Table 4. None of the baseline NATs were associated with longitudinal risk of liver related hospitalizations.

Change in NAT Over time

We evaluated the impact of change in nutritional outcome measurements using NAT (SGA, HGS, MAC) as well as MELD-Na in patients who completed the follow-up assessment (n=41). Seven patients had worsening SGA (e.g. SGA class A to B or C), 19 patients had stable SGA class and 15 patients had improvement of SGA class. As for HGS, 2 patients had worsening HGS measurements (from high HGS group to low HGS group), 33 maintained HGS status, and 6 patients had improved HGS measurements (from low HGS group to high HGS group). Similarly, 3 patients had worsening MAC measurements, 35 patients had stable MAC measurements (having same group: low to low or high to high), and 3 patients had improved MAC measurements. Only 9 patients had stable MELD-Na score during the study time, while 18 patients had higher MELD-Na and 14 patients had lower MELD-Na after follow-up assessment. Intake of energy and protein at follow-up compared to baseline was not significantly different (median 27.1 kcal/kg [IQR: 20.0-35.1] vs. 25.8 kcal/kg [20.5-32.8], $p=0.52$; Protein: 1.19 g/kg [0.73-1.76] vs. 1.16 g/kg [0.69-1.43], $p=0.10$).

Longitudinal Association between Improvement in NAT and LTFS

In the univariate analyses SGA improvement predicted LTFS (HR: 0.28 [95%CI: 0.09-0.88], $p=0.03$), Table 5. Similarly, improvement of HGS and MAC were associated with better survival (HGS HR: 0.91, 95% CI 0.83-1.00, $p=0.05$; and MAC HR: 0.85, 95% CI 0.72-1.00, $p=0.05$). However, in the age and sex adjusted multivariate analysis none of these predictors were significant independent predictors of LTFS.

Table 2: Patient characteristics based on SGA before the nutritional intervention.

Variables	SGA A (n = 19)	SGA B (n = 28)	SGA C (n = 22)	*p*-value
Gender – Male, n (%)	12 (63.2)	12 (42.9)	15 (68.2)	0.16
Age in years, median (IQR)	55 (40-59)	57 (50-62)	57 (51-63)	0.14
Measured BMI kg/m^2, median (IQR)	25.0 (22.3-28.6)	23.9 (21.0-28.8)	22.1 (21.3-23.6)	0.09
Dry BMI kg/m^2, median (IQR)	24.7 (20.1-28.6)	22.8 (20.2-25.7)	20.8 (18.9-22.7)	0.02
Alcohol related etiology, n (%)	9 (47.4)	11 (39.3)	12 (54.6)	0.56
Ascites, n (%)	4 (21.1)	14 (50.0)	18 (81.8)	<0.01
MAC cm, median (IQR)	29 (26-33)	27 (24-29)	25 (22-27)	<0.01
MAC Group – High, n (%)	11 (57.9)	9 (32.1)	2 (9.1)	<0.01
HGS kg, median (IQR)	28 (18-34)	22 (17-28)	21 (16-25)	0.07
HGS Group – High, n (%)	16 (84.2)	18 (64.3)	7 (31.8)	<0.01
MELD-Na, median (IQR)	9 (7-15)	16 (11-20)	17 (14-20)	<0.01
Energy per Kcal/Kg / dry weight, median (IQR)	26.7 (20.7-36.5)	26.5 (20.3-33.2)	26.9 (21.0-35.0)	0.93
Protein in gram /Kg / dry weight, median (IQR)	1.3 (0.7-1.6)	1.2 (0.6-1.4)	1.1 (0.8-1.3)	0.84

Table 3: Baseline predictors of liver transplantation free survival.

Predictor	Univariate analysis Hazard Ratio [HR] (95% Confidence interval [CI])	*P*	Multivariate analysis Adjusted HR (95%CI)	*P*
Age	1.01 (0.97-1.04)	0.72	1.03 (0.98-1.08)	0.26
Male sex	0.84 (0.37-1.88)	0.67	0.53 (0.20-1.40)	0.20
Alcohol related etiology	0.50 (0.20-1.27)	0.15		
Having ascites	1.76 (0.79-3.94)	0.17		
MELD-Na	1.03 (0.95-1.13)	0.47		
Measured BMI	1.09 (0.98-1.20)	0.10	1.11 (1.00-1.23)	0.04
Dry BMI	1.08 (0.98-1.20)	0.13		
SGA				
A	Ref			
B	0.82 (0.28-2.36)	0.70		
C	2.03 (0.80-5.12)	0.13		
HGS, continuous variable	0.96 (0.91-1.01)	0.10	0.97 (0.92-1.02)	0.28
HGS, categorical variable				
Low group	Ref			
High group	0.52 (0.23-1.19)	0.12		
MAC, continuous variable	1.01 (0.91-1.13)	0.83		
MAC, categorical variable				
Low group	Ref			
High group	1.42 (0.62-3.25)	0.41		

Longitudinal Association between Improvement in NAT and Liver related Hospitalizations

Improvement among NATs was not associated with liver related hospitalizations, Table 6. Improvement in energy intake approached significance in both univariate and multivariate analysis (adjusted HR: 1.06 [0.99-1.14]).

DISCUSSION

This real-world pilot study in patients undergoing assessment for liver transplantation is one of the first studies to characterize the longitudinal relationship between change in nutrition status over time using SGA, HGS and MAC and assess their relationship with long-term LTFS (median ~ 2-years) and hospitalization. While we observed a trend between improvement in SGA, HGS and MAC and longer LTFS in univariate analyses, these associations were not statistically significant in multivariate analyses. We did not identify any significant association between change in SGA, HGS and MAC with liver related hospitalizations, however, greater hospitalizations were observed in patients who had an improvement in SGA. Additionally, we confirm the high prevalence of malnutrition (>70%, SGA B and C) in patients

Table 4: Baseline predictors of hospitalization.

Predictor	Univariate analysis	*P*	Multivariate analysis	*P*
Age	0.99 (0.94-1.06)	0.96	1.01 (0.94-1.09)	0.78
Male sex	1.11 (0.26-4.63)	0.89	1.06 (0.24-4.60)	0.94
Alcohol related etiology	0.45 (0.09-2.26)	0.33		
Having ascites	2.18 (0.52-9.11)	0.29		
MELD-Na	1.28 (1.07-1.53)	0.007	1.29 (1.07-1.55)	0.007
BMI	1.03 (0.90-1.17)	0.70		
Dry BMI	0.94 (0.80-1.12)	0.50		
SGA				
A	Ref			
B	1.76 (0.85-4.52	0.24		
C	2.00 (0.92-5.11)	0.53		
HGS, continuous variable	1.00 (0.921-1.08)	0.98		
HGS, categorical variable				
Low group	Ref			
High group	1.66 (0.34-8.23)	0.54		
MAC, continuous variable	0.95 (0.81-1.12)	0.54		
MAC, categorical variable				
Low group	Ref			
High group	0.87 (0.18-4.32)	0.87		

Table 5: Impact of changes in SGA, HGS and MAC on liver transplant free survival.

Predictor	n	Univariate analysis Hazard Ratio (95% CI)	*P*	Multivariate† Adjusted Hazard Ratio (95%CI) (adjusted for age and sex)	*P*
SGA					
Declined	7	Ref		Ref	
Stable	19	0.61 (0.23-1.63)	0.32	1.40 (0.39-5.02)	0.60
Improved	15	0.28 (0.09-0.88)	0.03	0.59 (0.15-2.41)	0.47
HGS*					
Declined	2	Ref			
Stable	33	0.30 (0.07-1.33)	0.11		
Improved	6	0.52 (0.09-2.91)	0.46		
HGSᶠ	41	0.91 (0.83-1.00)	0.05	0.92 (0.84-1.01)	0.09
MAC*					
Declined	3	Ref			
Stable	35	0.69 (0.16-2.97)	0.62		
Improved	3	1.38 (0.19-9.91)	0.75		
MACᶠ	41	0.85 (0.72-1.00)	0.05	0.86 (0.70-1.06)	0.17
MELD-Na					
Declined	18	Ref			
Stable	9	0.87 (0.27-2.78)	0.82		
Improved	14	1.63 (0.68-3.96)	0.27		
MELD-Naᶠ	41	1.05 (0.95-1.17)	0.33		
Change in measured BMI ᶠ	41	1.05 (0.85-1.29)	0.10	1.12 (0.87-1.43)	0.38
Change in dry BMI ᶠ	41	1.04 (0.85-1.27)	0.72		
Change in energy intake ᶠ	41	1.00 (0.98-1.02)	0.98		
Change in protein intake ᶠ	41	0.82 (0.48-1.48)	0.55		

*Changes with HGS and MAC were evaluated on HGS and MAC categorical variables respectively.
ᶠHGS, MAC, MELD, measured BMI, dry BMI, energy and protein intake were presented as continuous variables and HR for each 1-point improvement between baseline and follow up assessment
†Variables with *p*-value <0.1 in univariate analysis were included in the multivariate analysis
**Energy difference (kcal/kg) and protein difference (g/kg) were calculated as change from baseline to follow-up.

referred for liver transplant assessment. We did not identify any association between baseline SGA, HGS, MAC and LTFS, either in univariate or multivariate analyses, in contrast to reports from other groups, however unexpectedly, measured baseline BMI was significantly associated with LTFS in both univariate and multivariate models.

In a previous study of 117 patients, baseline SGA demonstrated significant associations with short-term mortality (90 days) in a multivariate analysis that included preoperative ascites, jaundice, spontaneous bacterial peritonitis, functional activity, and intraoperative fresh frozen plasma[7]. Using different covariates in the multivariate models, and differences in mortality follow-up period between our study and the previous study may explain the divergent results observed between SGA and mortality[7]. Another study in 50 cirrhosis patients[10] identified associations between baseline HGS and poor clinical outcomes including ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome; although similar to our findings, a significant association with mortality was not observed within 1-year of follow up. A subsequent study in patients with alcohol related liver disease identified HGS was lower in patients who died during three months of follow-up (18.0 kg ± 4.8 in deceased versus 24.2 kg ± 5.9 in survivors, p=<0.01), however this finding was not significant when included in a logistic regression model with alcohol ingestion, Child Pugh score, and Maddrey's discriminant function[16]. Recently, Yao et al. demonstrated a different set of bedside NAT (mid-arm circumference, triceps skinfold thickness and BMI) were not independently associated with survival in decompensated patients with cirrhosis, in contrast to objective measurements of sarcopenia using CT derived lumbar vertebrae skeletal muscle mass index in 147 patients with 5-years of follow-up [17]. SGA assessment, MAC, BMI and triceps skinfold thickness all may be affected by ascites leading to reduced accuracy. In contrast, findings from another group identified in 100 patients, 6-month survival rates in all cirrhosis patients were predicted by HGS (HGS 25.1 kg ± 8.5 in deceased versus 30.6 kg ± 10.9 in survivors, p<0.05) and SGA[9]. Unexpectedly we identified baseline measured but not dry BMI was associated with LTFS. This was surprising as close to half of our sample had clinical ascites, which would increase overall weight, but not impact muscle mass. The reasons for measured but not dry BMI as a predictor of LTFS are not fully understood. It would appear that bedside NAT are imperfect predictive tools of mortality in patients with advanced cirrhosis, in contrast to the prognostic value of objective measures of sarcopenia which are indisputable[18]. Small sample sizes and lack of power may explain the variability in study findings.

We did not identify a significant relationship between baseline NAT and hospitalizations, however, we confirmed baseline MELD as a predictor of hospitalization. In a larger retrospective cohort analysis of 957 patients with hepatic cirrhosis, similar to our study findings, MELD score was associated with increased cirrhosis specific and all-cause hospitalizations[19]. A recent meta-analysis evaluated the association between various NAT and pre-transplant complications[20]. BMI did not predict cirrhosis related complications, while SGA yielded inconsistent results. To our knowledge, our study is the first to report the association between baseline NAT and hospitalization over a long duration of follow-up.

We demonstrated that in our study improvement in SGA status, and incremental improvement in both HGS and MAC from baseline, predicted LTFS in univariate analyses. Of note, we observed incremental improvements in both HGS and MAC appeared to predict LTFS more effectively than change in risk group. To our knowledge, these are novel findings as very few nutrition studies in patients undergoing assessment for liver transplantation have assessed temporal changes in SGA, HGS and MAC in a clinical setting. In the multivariate analyses, a trend towards significance was observed between improvement in NAT and LTFS in our study. We anticipate that improvements in SGA, HGS and MAC over time, would increase LTFS in larger, adequately powered studies. In contrast we did not identify significant associations between improvement in NAT and hospitalizations. In a larger study, one could hypothesize that patients with improved SGA may respond more favourably to clinical interventions leading to more aggressive therapies such as those offered through hospitalization, rather than palliation.

We did not demonstrate improvements in total energy or protein intakes in patients who completed follow-up assessments; a 1-point improvement in these variables was also not predictive of improved survival. It is possible that energy and protein intake improvement may have been significant if the sample was larger, and this combined with improvements in physical activity and functional measures may lead to NAT improvements in patients. An older study by Le Cornu et al. elegantly demonstrated how oral nutrition supplementation in patients awaiting liver transplantation could potentially improve HGS and MAC[21]. Patients who received the oral supplement had a greater trend towards overall survival, p=0.08, but SGA was not assessed. Manguso et al. identified a prescribed oral controlled for energy and protein in patients with cirrhosis improved MAC and serum albumin levels, however mortality data were not reported [22]. A meta-analysis explored whether oral or enteral nutrition supplementation impacted clinical outcomes in patients with cirrhosis and concluded there was insufficient evidence that oral and/or enteral supplementation improved clinical outcomes[23]; although subgroup analyses in patients who were less sick that received oral compared to enteral supplements suggested a potential mortality reduction. Very few of these studies assessed changes in SGA, HGS and MAC serially, following nutrition supplementation, and follow-up in these studies was much shorter than 2-years, compared to our study. Therefore it is still unknown if improvements in caloric and/or protein intake improve LFTS.

Our study is the first to demonstrate temporal improvements in SGA, MAC and HGS may be associated with increased long-term survival (2-years) in patients undergoing liver transplant assessment in univariate analysis. We posit that change in NAT over time may be an outcome of greater interest rather than static measurements at a single time point. The clinical relevance of this study's results is of significance. Improvement in SGA, MAC and HGS may be associated with improved survival, and this finding requires confirmation in larger studies. We cannot confirm that nutrition intervention led to improvements in NAT, as changes in

Table 6: Impact of changes in SGA, HGS and MAC on hospitalization.

Predictor	n	Univariate analysis Hazard Ratio (95% CI)	*P*	Multivariate† Adjusted Hazard Ratio (95%CI) (adjusted for age and sex)	*P*
SGA					
Declined	7	Ref		Ref	
Stable	19	0.20 (0.03-1.18)	0.08	0.78 (0.11-5.56)	0.81
Improved	15	0.35 (0.07-1.75)	0.20	5.10 (0.79-32.83)	0.09
HGS*					
Declined	2	Ref			
Stable	33	0.30 (0.07-1.33)	0.11		
Improved	6	0.70 (0.14-3.48)	0.46		
HGSf	41	0.91 (0.77-1.07)	0.26		
MAC*					
Declined	3	Ref			
Stable	35	0.69 (0.16-2.97)	0.62		
Improved	3	0.64 (0.08-5.03)	0.67		
MACf	41	1.04 (0.78-1.39)	0.79		
MELD-Na					
Declined	18	Ref			
Stable	9	0.87 (0.27-2.78)	0.82		
Improved	14	2.16 (0.54-8.68)	0.28		
MELD-Naf	41	1.08 (0.89-1.31)	0.44		
Change in measured BMI f	41	1.24 (0.93-1.66)	0.14		
Change in dry BMI f	41	1.00 (0.72-1.39)	1.00		
Improvement in energy intake f	41	1.05 (0.99-1.11)	0.08	1.06 (0.99-1.14)	0.09
Improvement in protein intake f	41	1.02 (0.31-3.29)	0.98		

*Changes with HGS and MAC were evaluated on HGS and MAC categorical variables respectively.
fHGS, MAC, MELD, measured BMI, dry BMI, energy and protein intake were presented as continuous variables and HR for each 1-point improvement between baseline and follow up assessment
†Variables with *p*-value <0.1 in univariate analysis were included in the multivariate analysis
**Energy difference (kcal/kg) and protein difference (g/kg) were calculated as change from baseline to follow-up.

energy and protein intake were not significantly improved in this small pilot, however it appears patients slightly improved their calorie and protein intake. Nutrition and other interventions, such as physical activity programs that may improve SGA, MAC and HGS in larger samples deserve further study.

The main limitations of our study are the lack of a control group and the small sample size. As this study was practice-based, and patients were referred to the cirrhosis malnutrition clinic we did not feel it was ethical to withhold nutrition therapy, therefore a control group was not possible. While every study patient was offered a follow-up visit, frequent non-adherence to follow-up was observed. In future, adequately powered studies are required to confirm these findings using multivariate analyses. With a larger sample size, we hypothesize some relationships may become significant.]

CONCLUSION

Prospective larger cohorts are needed to further evaluate the impact of temporal improvement of NAT on LTFS and hospitalizations should be considered.

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