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Adipopenia is the Rapid Screening Tool that Best Predicts Mortality in Patients with Decompensated Cirrhosis: Results of a Prospective Study

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ABSTRACT

Background & Aims: Patients with liver cirrhosis (LC) often have malnutrition (MN), which can be associated with decompensation, infection, and death. The aims were to determine: the prevalence of MN in patients with LC and ascites, its impact on mortality, and the relationship between MN and spontaneous bacterial peritonitis (SBP).

Methods: Nutritional status (NS) was analysed in cirrhotic patients, experiencing their first episode of ascites, who were consecutively admitted at two clinical liver centres between November 2014 and October 2016. The participants underwent diagnostic paracentesis and were followed up to assess their outcomes.

Results: 110 participants underwent NS assessment in addition to routine clinical procedures. The prevalence of MN was 30.9% according to corrected body mass index, 67.3% according to upper mid-arm muscle area (UMA) and 40% according to upper mid-arm fat area (UFA). The percentages of the participants remaining alive were 68.1% at 3 months, 59.3% at 6 months, 45.1% at 12 months and 24.2% at the end of the study. Univariate analysis showed that SBP, model for end-stage liver disease (MELD), UFA, UMA and age were significantly associated with mortality. Multivariate analysis showed that only SBP, MELD and UFA (hazard ratio 2.2) were independently associated with mortality. There was a correlation between adipopenia, but not sarcopenia, and SBP.

Conclusions: Adipopenia, as assessed by UFA, was present in 40% of the cirrhotic patients, and it was independently associated with mortality.

Key words: malnutrition – adipopenia – sarcopenia – liver cirrhosis – ascites - spontaneous bacterial peritonitis – prognosis.

Abbreviations: BMI: body mass index; cBMI: correct body mass index; CI: confidence interval; CTP: Child Turcotte Pugh; DEXA: dual-energy x-ray absorptiometry; HVPG: hepatic venous pressure gradient; LC: liver cirrhosis; HBV: hepatitis B virus; HCV: hepatitis C virus; MAC: mid-arm circumference; MELD: model for end stage liver disease; MN: malnutrition; N: nourished; NASH: non-alcoholic steato hepatitis; NS: nutritional status; OLT: orthotopic liver transplantation; SBP: spontaneous bacterial peritonitis; SD: standard deviation; TSF: triceps skin fold; UFA: upper mid-arm fat area; UMA: upper mid-arm muscle area; U: undernourished.

INTRODUCTION

Malnutrition (MN) affects more than 50% of patients with liver cirrhosis (LC) and is more prevalent in the advanced stages of liver disease [1-4]. It is an important predictor of morbidity and mortality, especially in patients with decompensated disease. Moreover, MN is an important issue if liver transplantation is required; however, the prognostic tool that is universally used for the prioritization of transplantation, the model for end-stage liver disease (MELD), does not quantify this.

Malnutrition in LC has a multifactorial origin, and is not only related to alterations in nutritional intake, but also to changes in the liver itself, in the muscle, and in the gastrointestinal tract. Patients with LC, especially those with an alcohol-related aetiology [5] and those with ascites, show anorexia because of nausea or the effect of ascites to compress the stomach, causing early satiety, and resulting in asthenia [6, 7]. Moreover, high circulating bound leptin concentration has been identified in cirrhosis patients, and this correlates positively with energy expenditure and is often associated

with MN [8, 9]. Furthermore, unnecessary dietary restriction, as frequently prescribed by physicians, such as a substantial sodium and/or protein restriction, make the diet less palatable, which can further compromise nutrition in cirrhotic patients [10].

Several methods have been used to assess nutritional status (NS), including clinical and laboratory parameters, physical assessments, anthropometric measurements, and image analysis [11-13]. Some of these are easy to perform and inexpensive (anthropometric parameters [14], hand grip strength [15] and electrical bioimpedance testing [16]), while other tools, for example analysis of cross-sectional images of muscle, are precise, but expensive and impossible to do at bedside [17]. Thus, there is no current simple standard method for the assessment of NS in this type of patient [18].

In LC, MN can be complex, manifesting a number of features simultaneously, although it is principally characterized by sarcopenia and adipopenia [19-22]. In fact, sarcopenia is present in 40-70% of cirrhotic patients [23], while fat mass (assessed using a triceps skin-fold measurement) is low in 30-40% of patients [4], and both worsen alongside the progression of the liver disease [24].

Cirrhotic patients who are malnourished more frequently develop complications related to liver disease, such as ascites and infections, and in particular, spontaneous bacterial peritonitis (SBP). Indeed, MN is significantly associated with the development of SBP [25]. Spontaneous bacterial peritonitis is the most common type of bacterial infection in cirrhotic patients [25, 26]. The incidence of SBP has been estimated to be 3.5% per year in outpatients with decompensated cirrhosis and 7-30% in hospitalized patients with cirrhosis and ascites [26-28]. Furthermore, the survival rate of such patients with SBP is only 40% one year after the first episode [29].

There are a number of challenges in discussing MN in patients with LC. First, NS is not routinely assessed in all cirrhotic patients, and secondly, a range of methods have been used to assess and define MN in the literature, and consequently there is no universally accepted definition. The paradox is that the calculated prevalence of MN in cirrhotic patients, especially in those with ascites, varies according to the method used to analyse NS, with the risk that the prevalence of MN may be underestimated and it may be misdiagnosed.

The aims of the present study were to determine the prevalence of MN in cirrhotic patients with ascites, the impact of MN on the mortality rate in these patients and the relationship between MN and SBP.

METHODS

In total, 110 consecutive patients were enrolled in this prospective study in two institutions specialized in the treatment of liver disease between November 2014 and October 2016. The study ended in September 2019. All the adult patients with LC of any aetiology who were admitted to the two units because of a first episode of ascites were initially included. Patients with other types of decompensation and/or complications of cirrhosis (acute gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome or hepatocellular carcinoma), or with severe comorbidities (neoplastic disease, neurological disease, heart failure, or chronic renal failure), were excluded. Patients with alcohol-related liver disease were only enrolled if they had been abstinent for at least 6 months upon admission.

An independent Ethics Committee (AORN Cardarelli/Santobono-Pausilipon; Protocollo N.659, delibera N.25, 18.11.2014), approved the study and the anonymous use of the data. The study was conducted in accordance with the Declaration of Helsinki.Written informed consent was obtained from each patient enrolled in the study.

Demographic, clinical, biochemical, and imaging data were collected and recorded in a specially prepared database. Alcohol-related liver disease was diagnosed if the maximum daily alcohol intake of 30 g/day for men and 20 g/day for women had been exceeded over a period of more than five years [30]. All the participants were assessed for the presence of SBP and their NS. Spontaneous bacterial peritonitis was diagnosed on the basis of the results of paracentesis: a neutrophil count of more than 250/mm^3 was considered to be positive for SBP [31] and antibiotic therapy was immediately started. Nutritional status was assessed using anthropometric parameters. The Child-Turcotte-Pugh (CTP) class and the MELD score were used to assess the severity of liver disease.

The anthropometric assessment included the measurement of height, body weight, body mass index (BMI), triceps skin-fold thickness (TSF), mid-arm circumference (MAC) and the derived measures of upper mid-arm muscle area (UMA) and upper mid-arm fat area (UFA). BMI was calculated as body mass (kg)/height (m)^2. Body mass was measured before the treatment of ascites. The BMI cut-off values used, were calculated using the Campillo method, on the basis of the severity of the ascites: a BMI value of ≤23 kg/m^2 was deemed to be pathological in patients with mild ascites, and a cut-off value of ≤25 kg/m^2 was used in patients with moderate-to-severe ascites. These values are referred to as corrected BMI (cBMI) [32].

The two principal anthropometric measures made in the upper arm were the TSF and the MAC. To minimize intra-operator variability, the mean value of three consecutive measurements was recorded, and to reduce measurement errors all readings were performed by the same experienced operator at each centre. The inter-operator variability during the training period was acceptable (k index=0.85, confidence interval [CI] 0.78–0.92). The TSF (cm) was measured using Harpenden Skinfold Calipers (HaB International Ltd., Southam, UK) at the mid-point between the acromion and the olecranon of the non-dominant arm. The measurement was made with the participant standing upright, with their arms hanging down loosely. The skin fold was pulled away from the muscle and measured using the calipers, with a measurement being made 4 seconds after the calipers were released. Mid-arm circumference (cm) was also measured at the mid-point between the acromion tip and the olecranon process on the non-dominant side of the body, using a flexible meter.

Upper mid-arm muscle area and UFA were calculated using the MAC and TSF measurements.The equations used for the calculation of the UMA(cm^2) and the UFA(cm^2) were:UMA=$[MAC-(TSF\times3.14)]^2/12.56$ and UFA=$[(MAC^2)/12.56]$–UMA [32]. The UMA and/or UFA values were considered

pathological if they were lower than the fifth percentile of the standard for that population, according to age and gender, as reported in the Frisancho tables [33].

Malnutrition was defined as the presence of at least one pathological value among the cBMI, UFA and UMA, determined according to the criteria described above. Malnutrition was then classified as "absent" (no pathological value), "mild-to-moderate" (one or two pathological values) or "severe" (all three pathological values).

We did not perform a formal sample size calculation. We aimed to recruit at least 100 patients in the 24 months available for enrolment. Descriptive statistics were generated for all the studied parameters. The normality of continuous data was evaluated using the Shapiro-Wilk test [34]. Normally distributed data are reported as means and standard deviation (SDs) and non-normally distributed data are reported as medians and ranges. To compare continuous data between groups, Student's t-test or the Mann-Whitney test was used, as appropriate.

Categorical data are expressed as proportions and percentages, with 95%CIs (exact binomial confidence intervals). The frequencies were compared using the chi square (χ^2) or Fisher's exact test, as appropriate. For practical purposes, MELD score was categorised into three classes: class 1 (0–14), class 2 (14.1–20), and class 3 (>20). Cohen's kappa statistic was used to asses inter-operator reliability, to verify agreement between the two operators who performed the anthropometric measurements, which were evaluated as categorical variables.

The univariate analysis of survival was performed for biochemical parameters, age, gender, aetiology of cirrhosis, SBP, cBMI, UMA, UFA, MELD, and CTP using the Kaplan-Meier method, and the effects of each were compared using the log-rank test. Multivariate analysis was performed using multivariate backward stepwise Cox regression. Analyses were performed using SPSS statistics software, version 25 (IBM Inc., Armonk, NY, USA). Statistical significance was accepted when $p<0.05$.

RESULTS

The baseline characteristics of the study population are shown in Table I. The 110 participants were mostly male (69.1%) and had a median age of 61 years (range 26–85 years). The majority of patients had moderate-to-severe ascites (56.4%, 95%CI: 46.6–65.8%) and had CTP Class B (64.5%: 95%CI 54.9–73.4%). Their mean MELD score was 16.26 (±6.43). SBP was present in 27.3% (95%CI 19.2–36.6%) of the participants.

The calculated prevalence of MN varied according to the anthropometric parameter used for the assessment of NS. Most of the participants had pathological values of UMA (67.3%, 95%CI 57.7–75.9%), while 30.9% (95%CI 22.4–40.4%) had pathological values of cBMI and 40% (95%CI 30.8–49.8%) had an abnormal UFA. Across the whole sample, the majority of participants (87, 79.1%, 95%CI 70.3–86.3%) had at least one result that was indicative of MN. MN was classified as absent in 23 participants (20.9%, 95%CI 13.7–29.7%), mild-to-moderate in 61 (55.5%, 95%CI 45.7%-64.9%), and severe in 26 (23.6%, 95%CI 16.1-32.7%).

Table I. Patients' characteristics

	N=110	%
Gender male	76	69.1
Age >65 years	69	62.7
Etiology		
HCV	38	34.5
HBV†	18	16.4
HBV+HCV	3	2.7
Alcohol††	17	15.5
HBV+alcohol	3	2.7
HCV+alcohol	15	13.6
HBV+HCV+Alcohol	2	1.8
NASH	3	2.7
Other	11	10
Main origin of liver disease		
HCV (every occurrence)	58	52.7
HBV (every occurrence)	26	23.6
Alcohol (every occurrence)	37	33.6
Ascites		
Mild	48	43.6
Moderate to severe	62	56.4
Child-Turcotte-Pugh		
Class A	12	10.9
Class B	71	64.5
Class C	27	24.5
MELD		
Up to 14 points	48	43.6
From 14.1 to 20 points	37	33.6
Above 20	25	22.7
Laboratory parameters, median (range)		
Bilirubin, mg/dL	3.00	0.41-17.0
Albumin g/dL	3.10	1.70-5.10
INR	1.50	0.96-4.04
Creatinine mg/dL	1.00	0.40-3.62
Azothemia mg/dL	46.50	12-200
White cells (x10^9/L)	4.40	1.9-18
Plathelets (x10^9/L)	81.05	17-267

HCV: hepatitis C virus; HBV: hepatitis B virus; NASH: non alcoholic steatohepatitis; MELD: model for end-stage liver disease; †Three patients were coinfected with HDV; ††Patients with an alcoholic aetiology had all been abstinent for at least six months at the time of enrollment in the study

Table II shows the incidence of some relevant clinical events during the follow-up. The median duration of follow-up was 10 months (range 1–70 months). Nineteen participants (17.3%, 95%CI: 10.7–25.7%) were lost to follow-up soon after their first visit and were excluded from the survival analysis. Seven participants (6.4%, 95%CI: 2.6–12.7%) developed hepatocellular carcinoma and were excluded at that time. Four patients (3.6%, 95%CI: 1.0–9.0%) underwent orthotopic liver transplantation (OLT) and were considered to have died at that time. The patients remaining alive of the 91 followed up were 62 (68.1%, 95%CI: 57.5–77.5%) at 3 months, (59.3%, 95%CI:

48.5–69.5%) at 6 months, 41 (45.1%, 95%CI: 34.6–55.8%) at 12 months, and 22 (24.2%, 95%CI: 15.8–34.3%) at the end of the study. Thus, the majority of patients died during the study (69, 75.8%, 95%CI: 65.7–84.2%).

Table II. Clinical events occurrence during the follow up

	N (%)
SBP	30 (27.3)
HCC	7 (6.4)
OLT	4 (3.6)
Lost of follow up	19 (17.3)
Follow up on 91 patients	
Months of follow up, median (range)	10 (1-70)
Cumulative survival†	N (%)
At 3 months	62 (68.1)
At 6 months	54 (59.3)
At 12 months	41 (45.1)
At the end of follow up	22 (24.2)

SBP: spontaneous bacterial peritonitis; HCC: hepatocellular carcinoma; OLT: orthotopic liver transplantation; †Kaplan-Meier product-limit estimator

Table III shows the prevalence of MN according to the principal characteristics of the patients. cBMI below the threshold and UFA below the fifth percentile were more prevalent in patients with SBP (30 patients, 46.7%, 95%CI: 28.3-65.7% and 60%, 95%CI: 40.6-77.3%, respectively; p<0.05). UMA below the fifth percentile was found to be present in 80.3% of male participants (95%CI: 69.5-88.5%, p<0.001) and in 60.3% of the participants with a non-alcohol-related liver disease (95%CI: 48.1–71.5%, p<0.05). In the participants classified as not having MN using all three anthropometric tests, SBP was diagnosed in only one of 30 (3.3%, 95%CI: 0.1–17.2%, p<0.001).

Univariate analysis (Table IV) showed that SBP, MELD (in three classes), MN grade, UMA and UFA were associated with survival, but cBMI and CTP were not. However, multivariate analysis (Table V) showed that the only factors independently associated with mortality were MELD, SBP and UFA, with SBP being associated with the highest risk of mortality [hazard ratio (HR) 3.1, 95% CI: 1.76–5.45), followed by MELD classes 2 and 3 and UFA (HR 2.35, 2.89 and 2.22, respectively).

Table VI shows the relationships among sex, age, alcohol-related liver disease, nutritional parameters (cBMI, UMA and UFA), prognostic scores (CTP and MELD) and SBP (as the dependent variable). Only UFA below the fifth percentile (HR 2.25, 95%CI: 1.21-4.20), cBMI below the corrected threshold (HR1.96, 95%CI: 1.08–3.53) and age ≥65 years (HR 1.92, 95%CI: 1.05–3.52) were found to be associated with the presence of SBP (p=0.015, p=0.038 and p=0.033, respectively), albeit weakly (Cramer's V of 0.25, 0.21 and 0.20, respectively).

Table III. Prevalence of malnutrition according to age, gender, SBP, CTP, MELD and aetiology (N=110)

	cBMI	UMA	UFA	Malnutrition		
				Absent	Mild-Moderate	Severe
Whole population, N (%)	34 (30.9)	74 (67.3)	44 (40.0)	23 (20.9)	61 (55.5)	26 (23.6)
Gender, N(%)						
Male	21 (27.3)	61 (80.3)**	29 (38.2)	11 (14.5)	46 (60.5)	19 (25.0)
Female	13 (38.2)	13 (38.2)	15 (44.1)	12(35.3)	15 (44.1)	7 (20.6)
Age years, N(%)						
≤65	21 (30.4)	51 (73.9)	29 (42.0)	14 (20.3)	37 (53.6)	18 (26.1)
>65	13 (31.7)	23 (56.1)	15 (36.6)	9 (22)	24 (58.5)	8 (19.5)
SBP, N(%)						
Yes	14 (46.7)*	24 (80.0)	18 (60.0)*	1 (3.3)**	15 (50.0)	14 (46.7)
No	20 (25.0)	50 (62.5)	26 (32.5)	22 (27.5)	46 (57.5)	12 (15.0)
CTP, N(%)						
Class A	3 (25.0)	8 (66.7)	2 (16.7)	4 (33.3)	6 (50)	2 (16.7)
Class B	25 (35.2)	48 (67.6)	30 (42.3)	15 (21.1)	40 (56.3)	16 (22.5)
Class C	6 (22.2)	18 (66.7)	12 (44.4)	4 (14.8)	15 (55.6)	8 (29.6)
MELD, N(%)						
≤14	17 (35.4)	31 (64.6)	19 (39.6)	11 (22.9)	26 (54.2)	11 (22.9)
14.1-20	11 (29.7)	27 (73.0)	15 (40.5)	8 (21.6)	21 (56.8)	8 (2.60)
>20	6 (24.0)	16 (64.0)	10 (40.0)	4 (16.0)	14 (56.0)	7 (28.0)
Etiology, N(%)						
Non-alcohol related	22 (30.1)	44 (60.3)*	26 (35.6)	20 (27.4)	36 (49.3)	17 (23.3)
Alcohol related	12 (32.4)	30 (81.1)	18 (48.6)	3 (8.1)	25 (67.6)	9 (24.3)

SBP: spontaneous bacterial peritonitis; CTP: Child-Turcotte-Pugh; MELD: model for end-stage liver disease; cBMI: correct body mass index; UMA: upper mid-arm muscle area; UFA: upper mid-arm fat area; *p<0.05; **p<0.01

Table IV. Factors associated with survival (univariate analysis)†

	Median Survival (months)	95% CI	p
Gender			
Male	11	6.0-16.0	0.8
Female	8	1.0-17.0	
Age Classes, year			
<56	11	1.0-38.6	0.06
56-65	8	2.2-13.8	
>65	10	4.0-16.9	
SBP			
No	19	8.4-29.6	<0.001
Yes	3	1.7-4.3	
CTP Classes			
Class A	17	12.8-21.2	>0.05
Class B	12	5.5-18.5	
Class C	4	2.2-5.8	
MELD Classes			
<14.1	19	1.1-3.7	<0.05
14.1-20	5	1.0-11.1	
>20	4	1.0-8.5	
Malnutrition Classes			
Absent	29	9.3-48.7	<0.001
Mild-Moderate	12	5.4-18.6	
Severe	3	1-5.4	
cBMI			
Nourished	14	7.6-20.4	0.07
Undernourished	5	1.1-8.9	
UMA			
Nourished	19	3.9-34.2	<0.05
Undernourished	8	5.3-10.7	
UFA			
Nourished	19	7.6-30.4	<0.001
Undernourished	3	1.0-5.5	

For abbreviations see Table III. CI: confidence interval; †Kaplan-Meier product-limit estimator and log-rank test

Table V. Factors associated with mortality (multivariate analysis)†

	Hazard Ratio	95% CI	p
SBP	3.09	1.76-5.45	<0.001
MELD up to 14	reference category		
MELD above 20	2.89	1.58-5.31	0.001
MELD from 14.1 to 20	2.35	1.30-4.26	0.005
UFA <5th percentile	2.24	1.32-3.77	0.003

†Variables used in the Cox regression multivariable analysis: sex, age, alcohol-related aetiology, CTP, MELD, SBP, cBMI, UMA and UFA. For abbreviations see Table III. CI: confidence interval

Spontaneous bacterial peritonitis was associated with a very high risk of early mortality, and therefore we carried out a further analysis of the factors favouring survival, excluding the patients (n=30) who had SBP at admission. Fig. 1 shows Kaplan-Meyer cumulative survival curves and the log-rank test results for each variable. Among the nutritional parameters, cBMI did not affect survival, but UFA and UMA were strongly associated with mortality in undernourished cirrhotic patients.

Table VI. Correlation among sex, age, alcohol-related aetiology, cBMI, UMA, UFA, CTP, MELD and SBP (N=110)

	SBP			Cramer's V†	P
	Yes	No	Total		
Gender, N (%)					
Male	24 (31.6)	52 (68.4)	76	0.15	0.17
Female	6 (17.6)	28 (82.4)	34		
Age, N (%)					
≤65	14 (20.3)	55 (79.7)	69	0.20	0.033
>65	16 (39.0)	25 (61.0)	41		
Alcohol, N (%)					
yes	12 (32.4)	25 (67.6)	37	0.08	0.5
no	18 (24.7)	55 (75.3)	73		
cBMI, N (%)					
Nourished	16 (21.1)	60 (78.9)	76	0.21	0.038
Undernourished	14 (41.2)	20 (58.8)	34		
UMA, N (%)					
Nourished	6 (16.7)	30 (83.3)	36	0.17	0.11
Undernourished	24 (32.4)	50 (67.6)	74		
UFA, N (%)					
Nourished	12 (18.2)	54 (81.8)	66	0.25	0.015
Undernourished	18 (40.9)	26 (59.1)	44		
CTP Classes, N (%)					
Class A	2 (16.7)	10 (83.3)	12	0.22	0.064
Class B	16 (22.5)	55 (77.5)	71		
Class C	12 (44.4)	15 (55.6)	27		
MELD Classes, N (%)					
up to 14	10 (20.8)	38 (79.2)	48	0.14	0.354
from 14.1 to 20	11 (29.7)	26 (70.3)	37		
above 20	9 (36.0)	16 (64.0)	25		

For abbreviations see Table III. CI: confidence interval. †Cramer's V is used to measure the strength of an association (0.10 small effect; 0.30 medium-sized effect; 0.50 large effect)

Table VII shows results of survival analysis (months of survival; median and 95%CI; log-rank test conducted for each categorical variable) using Kaplan-Meier curves. The only factors associated with mortality were MELD class >20 and UFA below the fifth percentile (p=0.011). Moreover, the multivariate analysis (Cox regression analysis) showed that these two factors were independently associated with mortality (HR 2.6, 95%CI: 1.2–5.7, p=0.013 and 2.6, 95%CI: 1.4-5.2, p=0.026, respectively).

DISCUSSION

The results of this study, despite all the methodological difficulties, show that UFA, a measure of adipopenia, was abnormal in 40% of the cirrhotic patients, and among the parameters related to MN that were assessed, it was the only one that was independently associated with mortality (HR 2.2).

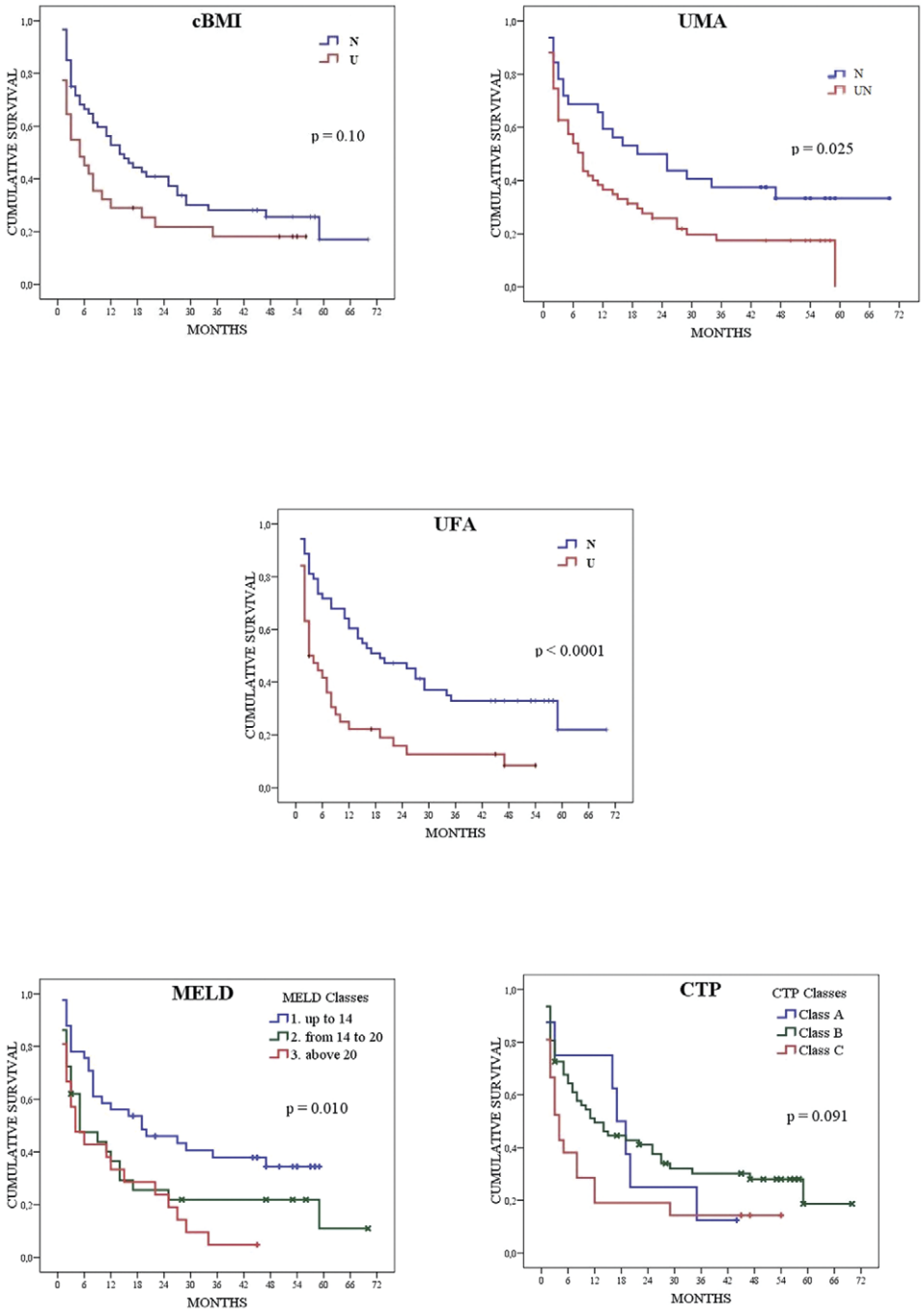

Fig. 1.Kaplan-Meier curves of the duration of follow up, stratified according to the results of anthropometric tests: A) cBMI, B) UMA, C) UFA, and prognostic scores D) MELD and E) CTP. For abbreviations see Table III.

Previous studies on MN in cirrhotic patients have all been focused on determining whether this variable, and sarcopenia in particular, influences the course of the disease and affects the risk not only of decompensation, but also of mortality [35, 36]. However, reports of studies with a sufficient sample size and an adequate duration of follow-up are rare in the literature. Furthermore, there is a clear dichotomy between research and clinical practice regarding MN, because despite an ever-increasing number of publications on the subject, very little use of the findings has been made in clinical practice.

The biggest challenge is to define MN because there are numerous methods for identifying its presence [37]. Some of these methods are impractical, economically and ethically questionable, such as the use of computed tomography to quantify the loss of muscle tissue [38] or the use of dual X-ray absorptiometry (DEXA), which exposes patients to potential harm and is expensive [39, 40].

Another general consideration is that depending on the method used, the percentage of cirrhotic patients that are judged to be malnourished in a sample varies. This is evident

Table VII. Survival analysis on patients without SBP (N=63)

Variable	Months of Survival median (95% CI)	Univariate p value	Adjusted HR (95% CI)	Multivariate p value
Overall	19 (8.4-29.6)			
Gender				
Male	22 (10.3-33.7)	0.313		0.151
Female	14 (0.1-29.7)		1.84 (0.80-4.25)	
Age, years				
≤65	27 (9.6-44.4)	0.09		0.389
>65	16 (11.5-20.5)		1.41 (0.68-2.94)	
Ethiology				
Alcohol	27 (9.8-44.2)	0.26		0.503
Other	16 (5.2-26.8)		0.70 (0.30-1.62)	
cBMI				
Normal value	25 (13.3-36.7)	0.33		0.465
Under Normal value	12 (0.1-27.4)		0.72 (0.29-1.76)	
UMA				
Normal value	25 (6.3-43.7)	0.09		0.191
Under Normal value	12 (6.3-23.7)		1.54 (0.81-2.97)	
UFA				
Normal value	27 (15.0-39.0)	0.011		0.026
Under Normal value	8 (2.4-13.6)		2.65 (1.37-5.15)	
CTP Classes†				
A	17 (13.4-20.6)	0.641	Reference category	
B	25 (12.7-37.3)		0.46 (0.15-1.42)	0.176
C	12 (2.6-21.04)		0.68 (0.19-2.48)	0.559
MELD Classes‡				
1 (≤14)	29 (9.8-48.3)	0.12	Reference category	
2 (14.1-20)	14 (7.2-20.8)		1.67 (0.80-3.52)	0.175
3 (>20)	15 (2.1-27.9)		2.65 (1.23-5.72)	0.013

For abbreviations see Table III. HR: hazard ratio; CI: confidence interval; †A vs B, p=0.552; A vs C, p=0.898; B vs C, p=0.419; ‡1 vs 2, p=0.356 ; 1 vs 3, p=0.036; 2 vs 3, p=0.314

in the majority of the published studies and, as in this study, the parameter used to define MN substantially affects the percentage of participants placed in this category [41, 42]. Indeed, the patients enrolled in the present study had a prevalence of MN of 79.1%, which was principally of mild-to-moderate severity (55.5%). However, when their BMIs were corrected for the presence of ascites, 30.9% of the patients were found to be malnourished, but 67.3% were sarcopenic and 40% were adipopenic. This difficulty with definitions has led to diametrically opposite conclusions being drawn in previous studies, but with MN being found to be an independent risk factor for mortality or a key factor in the progression of cirrhosis in some [43, 44].

Furthermore, even in the most thorough reviews, a dichotomy between the tools that are most appropriate for research and those that can be used most easily in clinical practice emerges [45]. Unfortunately, it is likely that until we can unify the methods and definitions, clinicians will continue to use the test that is most readily available in their institution. This will perpetuate the non-comparability of data and make it difficult to accurately determine the importance of MN in clinical practice.

Regarding the importance of the relationship between nutrition and the onset of infections, one of the evidence is provided by this study, where a low percentage (only 1 in 30) of SBP was found in well-nourished patients.These data once again underline that there is a high risk of developing a serious infection, such as SBP, in malnourished patients.

Furthermore, if the presence of SBP on admission was not taken into consideration, adipopenia had the same predictive value as a high MELD score. These data further reinforce the value of adipopenia as an important predictor of survival in cirrhotic patients. This finding is not new; in fact, recently it has been shown that the loss of fat tissue is associated with a higher mortality in women with cirrhosis [25]. From a clinical point of view, it has been shown that normal subcutaneous adipose tissue mass is associated with a survival benefit, especially in female with cirrhosis [25] and cancer patients [46].

In addition, a reduction in subcutaneous adipose tissue mass and an increase in myosteatosis are significantly

associated with decompensation of liver disease and death [25, 47]. In summary, taking all these findings together, both the skeletal muscle and adipose tissue compartments seem to play crucial roles in the prognosis of patients with cirrhosis.

The present study was limited by its relatively small sample size. However, the number of participants was determined by the selection of patients experiencing their first episode of decompensation (ascites) and the exclusion of those who had already developed major decompensation, or who had experienced multiple episodes of decompensation (or both).

CONCLUSIONS

This study highlighted the importance of adipopenia in cirrhotic patients, especially in relation to mortality in those decompensated. However, the findings of the present study should be validated in a larger sample, and most importantly, over a longer period of time. Furthermore, it will be necessary to standardise the methods used to define MN because, as discussed, this aspect decisively influences its diagnosis and classification.

Conflicts of interest: None to declare.

Authors' contributions: M.D.L. conceived and designed the study, analyses the daya and performed the statistical analyses. L.A., A.L., M.I., L.F., M.A., D.P. collected the data. G.G.D.C.analysez the data. A.A.analyzed the data and drafted the manuscript.All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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