Does protein energy malnutrition affect the outcome in Tunisian cirrhotic patients ?

La dénutrition a-t-elle un retentissement sur le pronostic du cirrhotique Tunisien ?

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RÉSUMÉ

Prérequis : La dénutrition protéino-calorique est fréquente au cours de la cirrhose. Son diagnostic est difficile en raison des différentes méthodes d'évaluation nutritionnelle qui sont mises à défaut en présence d'une insuffisance hépatique. Elle constitue un facteur de mauvais pronostic.

Objectif : Déterminer la prévalence et les facteurs de risque de survenue de dénutrition chez le cirrhotique et évaluer son retentissement sur le pronostic.

Méthodes : Etude prospective menée de Juin 2011 à Mai 2013. Les caractéristiques générales des patients et de la cirrhose ont été précisées. L'état nutritionnel a été évalué par les paramètres anthropométriques [indice de masse corporelle sec (IMC), pli cutané tricipital (PCT), circonférence musculaire brachiale (CMB)]et le subjective global assessment (SGA). Les facteurs de risque associés ont été recherchés et l'influence de la dénutrition sur l'évolution de la maladie et sur la survie a été étudiée.

Résultats : Nous avons inclus 104 cirrhotiques : 54 femmes (51,9%) ; âge moyen de 57 ans. La cirrhose était principalement d'origine virale. Le score de Child-Pugh était : B dans 35,6% et C dans 33,6% des cas et le score de Meld moyen de 16 (extrêmes : 6-37). La prévalence de la dénutrition était de 16,3% en utilisant l'IMC sec, 32,7% en utilisant le PCT, 39,4% en utilisant la CMB et 62,5% en utilisant le SGA. Les facteurs de risque de dénutrition retrouvés en analyse multivariée étaient: le Child Pugh C (par la CMB et le PC [p=0,027, OR 3,6 et p=0,047, OR 3,5 respectivement]), les antécédents d'encéphalopathie hépatique (par le SGA: p=0,018, OR 6,9), la cholestase chronique (par l'IMC sec: p=0,028, OR 4,6). La survie sans complications était réduite chez les cirrhotiques dénutris avec une différence significative en utilisant l'IMC sec (p=0,001). En analyse multivariée, le seul paramètre nutritionnel indépendant associé à une diminution de la survie sans complications était l'IMC sec <18,5 kg/m2 (p<0,001, RR 3,2) et particulièrement l'encéphalopathie (p=0,038, RR 2,66). En analyse univariée, la survie globale était réduite chez les cirrhotiques dénutris (par l'IMC sec, le SGA et le PC [p=0,03, p=0,014 et p=0,015 respectivement]). Mais cette différence n'a pas été retrouvée en analyse multivariée.

Conclusion : La prévalence de la dénutrition dans notre étude variait de 16,3 à 62,5% en fonction des paramètres nutritionnels utilisés. La sévérité de la cirrhose était un facteur de risque indépendant de dénutrition. La dénutrition était un facteur prédictif indépendant de survenue de complications de la cirrhose. En revanche, si celle-ci réduisait significativement la survie globale, l'association n'était pas indépendante, mais liée à la sévérité de la cirrhose.

Mots-clés
Cirrhose- Dénutrition-Anthropométrie- Pronostic

SUMMARY

Background: Malnutrition is commonly seen in cirrhotic patients and has been shown to adversely affect outcome. However, it remains associated with the severity of cirrhosis. Therefore, its role as an independent prognostic factor is still under debate. The aims of our study were to determine the prevalence of malnutrition in cirrhotic patients and determine whether this condition was an independent prognostic factor.

Patients and methods: We prospectively analyzed the nutritional status of 104 consecutive patients with cirrhosis Subjective global nutritional assessment (SGA) and anthropometry [dry body mass index (BMI), triceps skinfold (TSF), arm muscle circumference (AMC)] were used for the evaluation of the nutritional status. Complications of cirrhosis during follow-up and patient's survival were recorded. Global survival and survival without complications was studied by Kaplan Meier method and using Log Rank test.

Results: Prevalence of malnutrition ranged from 16.3 and 62.5% according to the method of nutritional assessment used. Survival without complications was reduced in malnourished patients. This difference was significant when assessing malnutrition by dry BMI (p=0.001). In multivariate analysis, malnutrition defined by dry BMI<18.5 kg/m2 was an independent predictor of complications (p<0.001; RR 3.2) especially hepatic encephalopathy (p=0.001; RR 2.66). In univariate analysis, global survival was worse in malnourished patients (by BMI and SGA; p=0.03 and p=0.0014 respectively), but this trend was lost in multivariate analysis.

Conclusion: In our study, malnutrition was an independent predictor of complications in cirrhosis. However, it did not appear as an independent prognostic factor for global survival. These results raise again difficulties to clarify whether malnutrition influence itself the prognosis of cirrhosis or if it is only related to the severity of cirrhosis.

Key-words
Cirrhosis-Malnutrition-Anthropometry-Prognosis

Malnutrition frequently occurs in end stage liver disease. It has been described in several studies as a factor of poor prognosis with decreased survival and increased risk of complications (1). Its prevalence range from 20% to 60% depending of the methods used for nutritional assessment and the severity of liver disease (2,3).
The pathogenesis of malnutrition in cirrhosis is multifactorial and includes a reduction of nutritional intake, malabsorption, abnormality of carbohydrate, lipid and protein metabolism and hypermetabolic states (4).
The assessment of nutritional status in cirrhotic patients is challenging: common nutritional parameters can be misleading in advanced liver disease because of water retentionand the alteration of hepatic function. Other parameters must be used in the evaluation of these patients (2,4).
Recommended method in this situation is anthropometry: arm muscle circumference (AMC), triceps skinfold (TSF) and dry body mass index (BMI) (3).Subjective global nutritional assessments (SGA) which is based both on physical signs of malnutrition and nutritional history has also be used as method of evaluation of nutritional status in patients with cirrhosis (3).
In several studies, malnutrition has been described to have negative impact on prognosis. It was found to be associated with an increased risk of complications of cirrhosis and a high rate of mortality (1,5,6). However it remains closely related to the severity of cirrhosis. Therefore, its role as an independent prognostic factor is still under debate.In this study we prospectively analyzed the nutritional status in a group of cirrhotic patients and its relationship with their clinical outcome during follow up.

METHODS

Prospective study conducted between June 2011 and May 2013 including all consecutive cirrhotic patients followed in our department.The diagnosis of cirrhosis was based on clinical, laboratory and ultrasonographic findings or histologically confirmed. Were excluded: patients aged less than 18 years, type I hepatorenal syndrome and patients with disease causing malabsorption. Characteristics of patients and cirrhosis were studied.

Assessment of nutritional status

The nutritional assessment was performed at baseline by the anthropometric measurements and the SGA.

Anthropometric measurements

Body Mass Index (BMI) was calculated using the formula based on weight (in kilograms) divided by squared height (in meters): BMI = weight/height^2. For the dry BMI calculation, dry weight was calculated by deducting an estimated weight for ascites and /or oedemaas follows (7):
- according to the ascites intensity: mild ascites: - 2 kg; moderate ascites: - 6 kg; severe ascites: - 14 kg
- according to oedema intensity: mild oedema: - 1 kg; moderate oedema: - 5 kg; severe edema: - 10 kg

Mid arm circumference (MAC) was measured at the midpoint between the tip of the acromion and the olecrane process on the non dominant side of the body using a flexible tape measure.
Triceps skin-fold thickness (TSF) was measured to the nearest millimeter at the right arm using a skinfold caliper (8).Arm muscle circumference (AMC) was calculated by the formula: AMC = MAC - (3.14 x PCT).
Patient with dry BMI < 18.5 kg/m^2, PCT and /or AMC < 5th percentile of the standard for age and gender matched population were considered as malnourished (9-11).

Subjective global nutritional assessment (SGA) was 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 (12).Patients with malnutrition were classified SGA-B or -C.

Outcomes

Complications of cirrhosis such as hepatic encephalopathy, ascites, hepato-renal syndrome type I or II, refractory ascites, variceal bleeding, spontaneous bacterial peritonitis and other infections were noted during follow up. Patient's survival was also recorded.

Statistical analysis

All data resulting from continuous variables are presented as mean±standard deviation and/or median±range; the data resulting from categorical variables are expressed as percentages or counts. Cirrhotics with malnutrition were compared to those without malnutrition. The influence of malnutrition on the outcome was studied from survival without complications and global survival in univariate and multivariate analysis. This datawas evaluated by Kaplan Meier method and using Log Rank test.A value of $p<0.05$ was considered as statistically significant.

RESULTS

Population characteristics

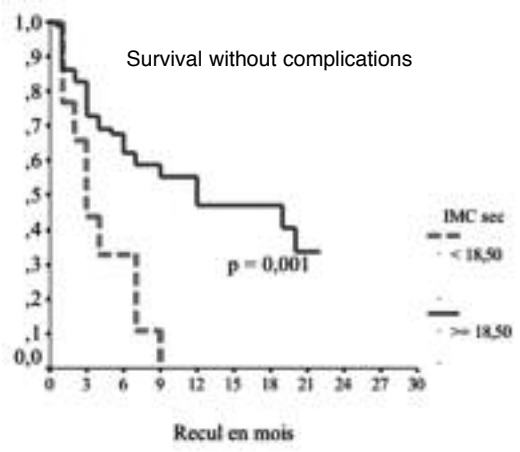
One hundred and four patients with cirrhosis were included (54 females =51.9%); mean age of 57 years. Main etiologies of cirrhosis were: viral B in 14.4% and C in 36.5%; auto-immune in 11.5%, cryptogenetic in 13.5%, alcoholic in 3.8% and nonalcoholic steato-hepatitis in 3.8%.Child-Pugh score was B in 35.6% and C in 33.6% while mean Meld score was 15.5 (extremes: 6-37).

Prevalence of malnutrition

The prevalence of malnutrition was 16.3% according to dry BMI<18.5kg/m^2, 32.7% according to the TSF<5th percentile of reference population, 39.4% according to the AMC<5th percentile and 62.5% according to SGA.

Influence of malnutrition on the outcome of cirrhotic patients. Mean follow up was 9 months (extremes: 1-23). Incidence of complications.
In univariate analysis, survival without complications was reduced in malnourished patients whatever the method of nutritional assessment used. In multivariate analysis, malnutrition by dry BMI was an independent predictor of complications (mean survival of 12 vs 4 months for those with BMI <18kg/m^2; p<0.001; RR 3.2).This correlation between dry BMI and survival without complications is showed in figure 1.

Figure 1: Curves of survival without complications in patients with different nutritional status according to dry BMI (body mass index).



When detailing the complications one by one, we found that:
Survival without hepatic encephalopathy, in univariate analysis, was reduced in malnourished patients with a statistical significance when we used dry BMI. In multivariate analysis, dry BMI<18.5 kg/m^2 was found as a parameter independently associated with occurrence of hepatic encephalopathy during follow up (21 vs 4 months; p=0.001; RR 2.66).
For all others complications, survival without ascitic decompensation, variceal bleeding, hepato-renalsyndrome, refractory ascites, spontaneous bacterial infection or without infection was reduced in malnourished patients in univariate analysis. The difference was significant for variceal bleeding and bacterial infection, and not significant for hepato-renal syndrome.
In multivariate analysis, any nutritional parameter was found as a parameter independently associated with increased risk of occurrence of complications during following up. Data from the univariate study (mean survival without complications) are summarized in Tables1-3.

Table 1: Mean survival without variceal bleeding according to the nutritional status

	Malnutrition	No Malnutrition	P
BMI	11.5 months (6.1-16.9)	20.4 months (18.7-22.1)	0.0002
TSF	17.3 months (13.7-20.9)	18.9 months (17-20.9)	NS
AMC	16.1 months (12.9-19.4)	20.3 months (18.3-22.3)	0.068
SGA	18.1 months (15.6-20.7)	19.5 months (17.2-21.8)	NS

BMI:body mass index;
TSF: triceps skin fold thikness,
AMC: arm muscle circumference,
SGA: Subjective global nutritional assessments
NS: no significant

Table 2 : Mean survival without hepato-renal syndrome according to the nutritional status

	Malnutrition	No malnutrition	P
BMI	18 months (13.4-22.7)	20.4 months (19.1-21.8)	NS
TSF	19 months (16-22)	20.5 months (19-21.9)	NS
AMC	18.7 months (15.7-21.7)	20.7 (19.2-22.1)	NS
SGA	17.7 months (15.5-20)	20.4 months (19.1-21.8)	0.024

BMI:body mass index;
TSF: triceps skin fold thikness,
AMC: arm muscle circumference,
SGA: Subjective global nutritional assessments
NS: no significant

Table 3: Mean survival without infections according to the nutritional status

	Malnutrition	No malnutrition	P
BMI	8.2 months (4.1-12.2)	16 months (14-18)	0.036
TSF	14.8 months (11.4-18.2)	15.9 months (13.6-18.2)	NS
AMC	14.3 months (1.8-10.4)	16.4 months (14.1-18.6)	0.068
SGA	13.4 months (10.8-15.9)	17.8 months (15.3-20.3)	0.042

BMI:body mass index;
TSF: triceps skin fold thikness,
AMC: arm muscle circumference,
SGA: Subjective global nutritional assessments
NS: no significant

Survival
In univariate analysis global survival was reduced in malnourished patients. This difference is statistically significant using dry BMI (15 vs 10 months, p=0.03)and SGA (17.7 vs 11.8 months, p=0.014).
These results are shown in figure 2 and 3.
When multivariate analysis was performed to test the independent value of nutritional parameters among other variables related to the underlying liver disease, the presence of malnutrition failed to show any influence on survival. Only ascites and hepatocellular carcinoma (HCC) were found to have an independent prognostic value.
The results of Cox multivariate proportional hazard analysis are shown in Table 4.

Figure 2: Survival curves in patients with different nutritional status according to dry BMI.

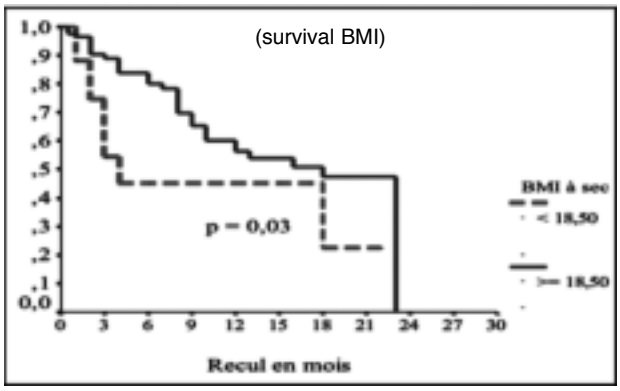


Figure 3 : Figure 3 Survival curves in patients with different nutritional status according to SGA.

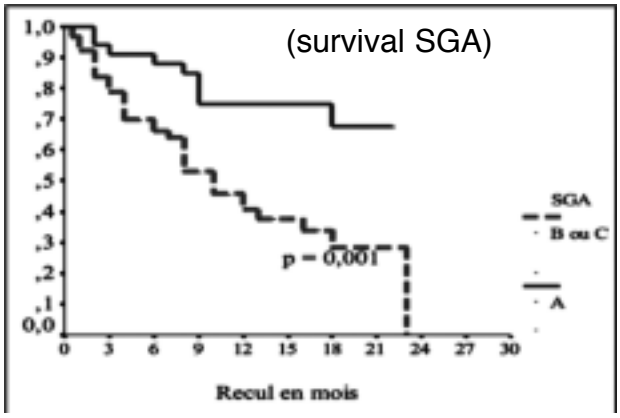


Table 4 : Factors associated with survival in cirrhotic patients (Data given as multivariate Cox proportional hazard analyses).

Variable	Relative Risk	95% confidence interval		P
		Lower	Upper	
Ascites	3.840	1.682	8.769	0.001
HCC	2.741	1.221	6.153	0.015
Refractory ascites	0.609	0.182	2.043	0.422
Hepatic encephalopaty	1.148	0.406	3.247	0.794
Infection	1.978	0.806	4.852	0.136
Dry BMI <18.5 kgm-2	0.987	0.363	2.683	0.979
AMC <5th percentile	1.212	0.523	2.809	0.653
SGA	1.563	0.527	4.632	0.421

DISCUSSION

This study has focused its attention on the prevalence of malnutrition in Tunisian cirrhotic patients and its role as an independent risk factor on the outcome (complications and survival). For the prevalence of malnutrition, our results are close to data from the literature. In fact, global prevalence of malnutrition in cirrhotic patients is 50% (all causes and all stages combined). Malnutrition affects 20% of patients with compensated cirrhosis and more than 60% of these patients with severe hepatic dysfunction (2,3).

Regarding the association of malnutrition with clinical course, previous reports showed that malnutrition negatively affects clinical outcome in terms of survival and complications (5,6). Huisman and al, found that malnutrition was an independent predictor of complications in cirrhosis (13).Singal and al, have shown that malnutrition among patients with cirrhosis correlates with poor quality of life, increased risk of infections, frequent hospitalizations, complications, mortality and patient survival after liver transplantation (14). Some studies have also shown that malnutrition was associated with the first bleeding episode, the presence of refractory ascites, occurrence of ascites and hepatic encephalopathy (8,15-18).

In the present study, the occurrence of ascitic decompensation, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, refractory ascites, spontaneous bacterial peritonitis and/or infections are higher in malnourished cirrhotic patients whatever the method of nutritional assessment used. Moreover in multivariate analysis, malnutrition by dry BMI<18.5 kg/m^2 was shown to be an independent predictor of complications especially hepatic encephalopathy.

Previous reports have focused their attention on the role of malnutrition as an independent risk factor of mortality; the results however, were controversial. In particular, two prospective series including 1000 and 85 cirrhotic patients have shown that malnutrition was not an independent factor associated with reducing survival (13,19).However numerous reports have appeared in the literature to support the fact that malnutrition was an independent risk factor of mortality in cirrhotic patients (14,20-24).In our study, survival was worse in malnourished patients, but this trend was lost in multivariate analysis.

In conclusion, we demonstrated that malnutrition was a frequent finding in cirrhotic patients and adversely affected the prognosis. Malnutrition was an independent predictor of complication in cirrhosis. However, it did not appear as an independent prognostic factor for global survival. These results raise again difficulties to clarify whether malnutrition influence itself the prognosis of cirrhosis or if it is only related to the severity of cirrhosis.

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