CLINICAL IMPLICATION OF MUSCLE WASTING IN CIRRHOSIS

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Malnutrition is a risk factor for morbidity and mortality in cirrhotics. Sarcopenia, a manifestation of malnutrition can be measured by computed tomography (CT)scan using the lumbar muscle at L3 level.

Aim: Recently, a lower reference value for Skeletal Muscle Index (SMI) or Skeletal Muscle Area (SMA/height sq) claims to predict 6 months mortality . Using this value, we aimed to assess the prevalence of sarcopenia in cirrhotics and evaluate correlation between muscle wasting, liver impairment and mortality.

Patients and Methods . The SMI of 72 patients with cirrhosis was measured by CT. Clinical and laboratory characterisitics were correlated with SMI using pearsons r. Kaplan Meier with log rank was used to determine the survival probability of sarcopenia.

Results: Seventy two patients with cirrhosis were included. Sarcopenia was diagnosed in 26% of the patients. Results showed that only age (p=<.001), BMI (p=.005) and creatinine are significantly related to SMI. Study revealed that patient with sarcopenia has 24 weeks survival at 37.9 % versus 72.3 % for those without, and 48 weeks survival of 37 % and 68.5% for patients with and without sarcopenia (p=0.038).Univariate analysis showed that lower serum albumin (p=0.015), higher serum creatinine (p=0.05) presence of ascites (p=0.025) or encephalopathy (p=0.004) and lower SMI were associated with poorer survival . However, only SMI was found to be an independent predictor (OR 0.981, 95% CI 0.964-0.968 ; p=0.029)of survival on multivariate cox regression analysis.

Conclusion: Muscle wasting in cirrhosis can predict poor survival.

Introduction

Prognostic assessment of patients with liver cirrhosis remains a difficult task. Clinical outcome of these patients may be variable and mortality may be due to hepatic decompensation and its ensuing complications such as ascites, variceal bleeding , susceptibility to infection , kidney dysfunction, hepatic encephalopathy and hepatocellular carcinoma.

Presently, Child Pugh score and Model for End-Stage Liver Disease (MELD) scores are our present tool for predicting mortality in cirrhotics. The Child Pugh Score which was originally develop to predict mortality in surgery is widely used and has been useful in determining prognosis and treatment response[1] . However it is limited by the subjective evaluation of ascites and encephalopathy. Meanwhile, the MELD score has the advantage of avoiding the use of subjective variable by using serum bilirubin, INR and serum creatinine and has been proven to predict the risk of short term mortality of at least three months in end stage liver disease (ESLD) in various etiologies and severity. [2-3]. Similar to the Child Pugh score , the MELD score failed to evaluate the nutritional and functional status of cirrhotic patients.

The importance of nutritional assessment in cirrhotic is frequently overlooked despite the importance of nutrition status in the overall prognosis of cirrhotic patient. . Sarcopenia , a term denoting a reduced quantity of skeletal muscle is usually associated with aging but it can also be present in chronic disease and malignancy. Unknown to many, muscle wasting or sarcopenia is a common but hidden complication of liver cirrhosis which significantly contributes to the overall survival, mortality, quality of life and resistance to stressors (surgery and infection) of a cirrhotic patient.

There are various mechanisms that can contribute to the development of sarcopenia in cirrhosis. The metabolic disturbance brought about by the liver disease such as increase energy expenditure [4], insulin resistance [5] and impaired glycogen stores may aggravate muscle protein loss. Cirrhotics can easily go to gluconeogenesis with long interval between meals which can cause muscle mass breakdown to provide amino acids for glucose formation. Loss of appetite due to distorted taste sensation brought by zinc and magnesium deficiency [6] and early satiety due to small bowel dysmotilitity, gastro paresis and ascites may contribute. Patients need frequent meals to protect muscle mass but food may not always be provided or is unpalatable due to sodium restriction . Muscle wasting is further aggravated by lack of physical activity among these patients. Furthermore, the chronic inflammatory state [7], recurrent infection [8] and sympathetic hyperactivity[9] contributes to the elevated resting expenditure characteristic of cirrhotics.

Several methods are available to evaluate the nutrition status of the cirrhotic patients however, most are limited by the lack of objectivity, reproducibility and prognostic discrimination. In these regard, muscle mass quantification with cross sectional imaging studies constitute an attractive index of nutritional status in cirrhosis [10,11,12,). Computed tomography (CT) imaging of lean tissue is not affected by the presence of fluid overload and reflects a chronic detriment in the general physical condition rather than acute severity of the liver disease[13).

In this retrospective study we aim to determine the prevalence of sarcopenia in patients with liver cirrhosis who underwent a CT scan of the abdomen, to determine the clinical and laboratory factors that influence the prevalence of sarcopenia, and to determine the effects of sarcopenia on mortality of patients with cirrhosis ..

Methodology

Study Population

In this retrospective study, we reviewed 558 abdominal CT scan reports done from January 2010 to December 2014. Medical records of 178 patients who had CT scan findings of liver cirrhosis portal hypertension or fatty infiltration were reviewed for clinical and biochemical evidence of chronic liver disease [15]. Patients who had an active malignant disease or hepatocellular carcinoma were excluded. Seventy two patients fulfilled the inclusion criteria.

Clinical and Laboratory Assessment

Data obtained from the medical charts included gender, weight, height, body mass index (BMI), presence of ascites and hepatic encephalopathy, liver biochemistries, serum albumin, serum creatinine, INR, MELD scores and Child Pugh Scores . Biochemical examination results should have been determined 2 weeks before or after the abdominal CT scan was taken. All markers were measured by established laboratory methods. Patients who were alive at the last follow up were contacted to determine their latest status.

Sarcopenia Assessment

The cross-sectional area of the skeletal muscles (cm^2) was measured on CT imaging at the caudal end at the level of the third lumbar (L3) vertebra. The L3-level skeletal muscle area provides a significant estimate of the total body skeletal muscle mass from a single abdominal cross-sectional image[16]. The skeletal muscles at this L3 level were manually outlined and consist of the psoas, erector spinae, quadratus lumborum,transversus abdominis, internal oblique, external oblique, and rectus abdominis.

The area was calculated on plain or with contrast CT imaging using GE Advantage Workstation Voxtool 3.0 .64m which enables measurement of specific tissue demarcation by the Hounsfield unit from +29 to +150. The L3 skeletal muscle area was then normalized by the height squared (m^2) to give the skeletal muscle index (SMI) (cm^2/m^2) .The L3 skeletal muscle index was expressed as cross sectional muscle area / height-

squared and cutoffs for sarcopenia will be based on SMI: <42 cm^2/m^2 for women and <50 cm^2/ m^2 for men [17]. All images were analyzed by the investigator and concurred by another observer (CC) within the Section of CT Scan, Department of Radiology at Chinese General Hospital and Medical Center.).

Statistical Analysis

Descriptive statistics such as frequency and percentage were used for categorical data while mean and standard deviation were utilized for continuous variables and were analysed using the Fisher's exact test and the independent t-test respectively.

Clinical and laboratory characteristics were correlated with SMI using Pearson's r. Kaplan Meier with Log Rank was also used to determine whether patients with sarcopenia has significantly lower survival probability as compared to those without sarcopenia.. Data processing and statistical analyses were performed using SPSS.

Statistical Software version 11.

Results and Discussions

Table 1. Baseline Characteristics

The baseline characteristics and the laboratory data of the 72 patients are shown in Table 1.The mean age of patients with sarcopenia are older (73.9±11.0 vs. 63.6 ± 11.9; p= 0.012)). Eight of the 41 in our male study group had sarcopenia ,19.5% while 2 out of 31 females had sarcopenia, 6.4% (p= 0.113) The results show that the BMI of patients with sarcopenia was significantly lower (22.1±4.8) as compared to those without , whose average BMI is 24.9 (p=0.051). The results also showed that patients with sarcopenia and without sarcopenia has the same characteristic albumin (p=.372), bilirubin (p=.358), ALT (p=.783), creatinine (p=.313) and sodium (p=.748). Likewise, table shows that there is no significant difference in Child Pugh classification (p=.781) and MELD score (p=.564) between patients with sarcopenia and those without. Lastly,

considering the BMI classification, results show that patients with sarcopenia are more likely to be underweight, while patients without sarcopenia are more likely to be normal, overweight or obese.

Baseline Characteristics	Sarcopenia (+) (n=10)	Sarcopenia (-) (n=62)	p value	Total
Age (mean ± sd)	73.9±11.0	63.6±11.9	0.012	65.0±12.2
Gender, n, %				
Male	8 (19.5)	33 (80.5)	0.113	41 (100.0)
Female	2 (6.5)	29 (93.5)		31 (100.0)
BMI	22.1±4.8	24.9±4.2	0.059	24.5±4.4
BMI Category, n, %				
Underweight	3 (50.0)	3 (50.0)	0.051	6 (100.0)
Normal	4 (11.4)	31 (88.6)		35 (100.0)
Overweight	3 (12.0)	22 (88.0)		25 (100.0)
Obese	0 (0.0)	6 (100.0)		6 (100.0)
Albumin (g/L) n=63	26.2±8.4	28.6±7.6	0.372	28.2±7.7
Bilirubin (umol/L) n=51	17.8±5.5	29.1±34.1	0.358	27.3±31.6
ALT (U/L) n=48	42.5±28.6	45.3±25.4	0.783	44.8±25.6
Creatinine (umo/L) n=66	143.8±133.2	98.3±52.6	0.313	105.2±71.2
Sodium (mmo/L) n=55	131.9±8.8	132.9±6.3	0.748	132.7±6.8
INR n=63	1.3±0.3	1.3±0.3	0.696	1.3±0.3
MELD Score n=50	12.9±5.6	11.8±4.8	0.564	11.9±4.9
Child-Pugh classification, n, % (n=50)				
A (n=16)	2 (12.5)	14 (87.5)	0.781	16 (100.0)
B (n=26)	5 (19.2)	21 (80.8)		26 (100.0)
C (n=8)	1 (12.5)	7 (87.5)		8 (100.0)

Table 2. Correlation between SMI and other variables

Results showed that only few variables are significantly correlated with SMI. Specifically, results show that only age (p<.001) ,BMI (p=.005) and creatinine are significantly related to SMI. Moreover, the resulting Pearson r of -0.439 indicates that the older a patient the more likely to have a lower SMI. On the other hand, the resulting pearson r of 0.326 denotes that a higher BMI value will more likely have a higher SMI. Lastly, the resulting pearson r of -0.205 means that a higher creatinine will more likely result to a lower SMI.

Variables	Pearson r	p value
Age	-0.439	0.000
BMI	0.326	0.005
Albumin (g/L)	0.196	0.124
Bilirubin (umol/L)	0.096	0.504
ALT (U/L)	0.143	0.332
AST (U/L)	-0.121	0.541
Creatinine (mmol/L)	-0.205	0.099
Sodium (mmol/L)	0.053	0.703
INR	-0.124	0.331
Meld Score	-0.195	0.174
Child–Pugh in points	-0.095	0.507

Figure 1. Kaplan Meier Curve

After a median follow up period of 18.9 weeks, a total of 9 patients died, with the most common cause of death being sepsis (30%) followed by hepatorenal syndrome and renal failure (20%), hepatic encephalopathy (5%) and others (cardiac arrest, extrahepatic malignancy ,trauma).

Kaplan Meier analysis of survival revealed that patients with sarcopenia had significantly poorer survival compared to patients without sarcopenia. Twenty four week survival of those with sarcopenia is at 37.9 % versus 72.3 % for those without, while the 48 weeks survival of those with sarcopenia is 37% and 68.5% for patients without sarcopenia. (p=0.038)

Univariate analysis showed that lower serum albumin (p=0.015), higher serum creatinine (p=0.05), presence of ascites (p=0.025 or encephalopathy (p=0.004) and lower SMI (p=0.011) were associated with poorer survival. However, only SMI was found to be an independent predictor (OR 0.981, 95% CI 0.964-0.968; p=0.029) of survival on multivariate cox regression analysis.

Figure 1. Survival of patients (in weeks) with and without sarcopenia

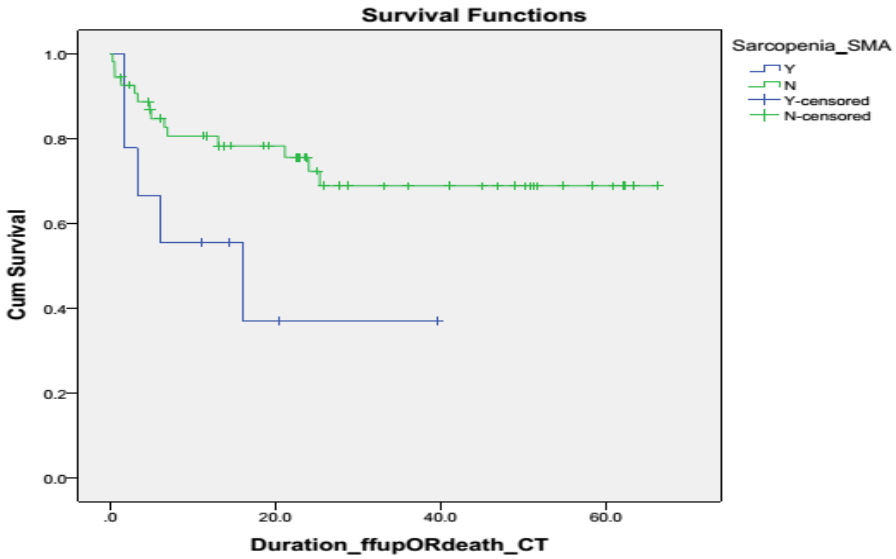

Image A. 63 yo with sarcopenia .
Image B. 64 yo male with normal SMI.

DISCUSSION

Our study indicates that muscle wasting or sarcopenia is present in about 20% of patients with cirrhosis. Majority of them tend to be older and male .Expectedly,patients who are underweight are more likely to be sarcopenic. However it should also be noted that patients who had normal BMI and overweight had a more than 10% probability of having sarcopenia, emphasizing the fact that BMI is not a very accurate measure of nutrition in patients with cirrhosis. Furthermore, our study indicates that biochemical parameters such as albumin, bilirubin, ALT, INR , the CPC and MELD score has no correlation with sarcopenia while serum creatinine is positively correlated with muscle wasting.

Muscle wasting in cirrhotics aggravates the other complications of cirrhosis including encephalopathy ,ascites and portal hypertension. Importantly, the presence of sarcopenia in cirrhotics were associated with worse survival compared to cirrhotics with no muscular abnormalities. In fact our study indicates that having sarcopenia increase the risk of death within 24 and 48 weeks by about 30 to 40 % as compared with patients who do not have muscle wasting .Our result is complimentary to the findings by Montano-Loza et al stating that a lower L3 SMI cut off in cirrhotics have relatively good discrimination capacity to distinguish cirrhotic patients with higher risk of dying within 6 months. [17]

Sarcopenia is originally defined as a muscle mass index less than 2 standard deviation below the mean of a young reference population. The Scientific Registry on Transplant Recipients (SRTR) reports in 2009 that (OPTN / SRTR 2009 Annual Data Report. HHS/HRSA/ HSB/DOT [18] patients 50 years or more are the most rapidly increasing population of cirrhotics. The underlying mechanisms for the development of sarcopenia

in cirrhosis such as inactivity, reduction of nutrient intake , oxidative stress of chronic low grade inflammation, ectopic adipose tissue deposition, changes in microcirculation and decline in hormonal and growth factors[19] may be augmented by the physiologic decline in metabolism of aging.

Patients with liver cirrhosis has a muted metabolic milieu that affects their muscles subsistence and formation. Mimicking a state of accelerated starvation, the dysregulated fatty acid oxidation and ketogenesis, amplified gluconeogenesis from amino acids, precocious glycogenolysis, and selective utilization of aromatic amino acids in the liver and branched chain amino acids of the skeletal muscle contribute to the development of sarcopenia .

Creatinine is excreted mostly by the kidney. It is derived mainly from muscle metabolism and proportional to the muscle mass.. As such, sarcopenics is foreseen to have reduced creatinine level. In patients with chronic liver disease, renal function is a wellrecognized predictor of survival [20].Increase in serum creatinine among cirrhotics may be due to hypovolemia, administration of nephrotoxic drugs, intrinsic renal disease particularly glomerulonephritis from hepatitis B or C and sepsis, one the most common cause of mortality in these patients. Septic shock maybe difficult to detect in the initial stage in cirrhotic patients because of absence of symptoms of bacterial infections in some of them or may sometimes be falsely attributed to the systemic vasodilation of advance cirrhosis. Because of the vague presentation of infection in these patients, it is recommended that infection should be looked into all cirrhotic patients presenting with sudden elevation of serum creatinine.

Muscularity assessment as a nutritional status index became an attractive option in recent years as it is not affected by fluid retention, subjective observation and interobserver variability. Various means of assessing the muscularity using CT has been studied. Measuring the psoas muscle area at L3- L4 level, the psoas muscle index at the umbilical level or the cross sectional area of lumbar muscle normalized by stature at the L3 level referred to as SMI has been used.. Our group measured the SMI as this is the single area

that best correlates with the whole body muscle volume as observed by Shen et al and was used by other studies. e.g.Mourtzaki et al and Montano –Loza et al(15,16,17).

One limitation of our study is that we used a definition of sarcopenia based on the study validated in a different population. Moreover, effect on survival from reversal of sarcopenia was not included as well.
In summary, nutrition and metabolic intervention among cirrhotic patients with sarcopenia has an impact with their over all survival. The altered metabolism of cirrhosis should be taken into consideration in nutrition planning .

Since liver transplantation is not available or necessary for the majority of cirrhotics, nontransplant options are required. We recommend that maintenance of muscle mass thru proper nutrition and regular exercise among patients with cirrhosis. . Inclusion of SMI measurement in abdominal CT of patients with cirrhosis may help in prognostication and guide a timely nutritional intervention in these patients.

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