

Author's response to reviews

Title: Anthropometric and clinical assessment of malnutrition in Malaysian patients with advanced cirrhosis

Authors:

Mei-Ling Sharon Tai (sharon@ummc.edu.my)
Khean-lee Goh (klgoh56@streamyx.com)
Siti Hawa Mohd Taib (msitihawa@yahoo.com)
Sanjay Rampal (rampal.s@gmail.com)
Sanjiv Mahadeva (sanjiv@ummc.edu.my)

Version: 2 **Date:** 29 March 2010

Author's response to reviews: see over

The Editor
Nutrition Journal

Dear Sir/ Madam

Re: Anthropometric, biochemical and clinical assessment of malnutrition in Malaysian patients with advanced cirrhosis

On behalf of the authors, I would like to thank the reviewers for their helpful criticisms that have enabled us to improve the quality of our manuscript. Our response to the reviewers, in point-by-point format is as follows:

Reviewer No. 1

Major comments

1) the authors claim that in Asia the number of people developing cirrhosis is large however the number of patients enrolled in this study is rather small and this is an important limitation for the relevance of the results. It is unclear if exclusion criteria were utilized for the selection of patients as, formally, inclusion and exclusion criteria were not reported

Response:

The total number of patients with cirrhosis in Asia is large. However, the patients in this study was a specialized group – they were hospitalized patients, from a single centre, with decompensated (advanced) cirrhosis - & hence the small number. We acknowledge the small number as one of the limitations of the relevance of this study.

The inclusion criteria were “ all patients with decompensated liver cirrhosis, above the age of 18, who were hospitalized during the period of study”. The exclusion criteria were as follows:

- (a)hepatocellular carcinoma
- (b)hepatic encephalopathy grades 3-4

These selection criteria have been specified in the “METHODS” section.

2) information about how many patients presented an active alcohol intake is lacking

Response:

Seven patients (58.3% of the patients with alcoholic cirrhosis) had active alcohol intake during the period of study. This information has been added to the manuscript.

3) *in section Methods it would be better to include a definition of the criteria used in the study for the diagnosis of malnutrition. Some times the authors have used anthropometry (< 5th or < 25th percentile MAC or MAMC) and some times SGA with different results*

Response:

Malnutrition was defined as “< 5th percentile MAMC” & this has been added in the METHODS section in the revised manuscript.

4) *The authors made no attempt to define the patients dry weight which can be estimated after total Paracentesis has been performed. As 41.7% of patients had ascites at admission considering a wrong body weight caused an overestimation of BMI but also an underestimation of the calorie intake expressed as Kcal/kg. This pitfall was not considered.*

Response:

The patients’ dry weight was not available. We acknowledge this limitation in our study. This statement has been added in the discussion section.

5) *The authors failed to consider the gender difference of anthropometric parameters therefore the mean values reported in Tables for TST, MAC, MAMC are often meaningful. 1/3 of patients were females and females are known to have higher fat mass and lower muscle mass vs males. The proposed normal range/expected values shown in Table 2 for MAC, TST, and MAMC are those for males or females? Normal referenced values should be different for males and females. To avoid the creation of further sub groups (Child Pugh B or C, males or females...) I suggest the authors to present the results as % of those below the cut off (< 5th percentile).*

Response:

We are grateful to the reviewer for highlighting this issue. We have presented the data in Table 2 in the format suggested, while incorporating suggestions from Reviewer No. 2.

6) *It is unclear if the dietary interview is referred to the home diet or to the in-hospital diet. The protein content of the diet is not reported.*

Response:

The dietary interview refers to the in-hospital diet – this has been clarified in the manuscript. The protein content of the diet was not reported because there is a lack of local data on protein content in the Malaysian local diet.

Minor comments

1) *bio-impedance evaluation is cited in the abstract but is not reported in the results*

Response:

This was an error on our part, as Bio-impedance was not measured. We have now removed the sentence on Bio-impedance evaluation.

2) *prealbumin is cited in methods but is not reported in the Results*

Response:

This was an error on our part, as pre-albumin was not measured. We have now removed this.

3) *In section Methods the authors should only describe the methods which were utilized in the study. Other considerations (see all the paragraph regarding biochemical parameters) should be preferably be moved in the Discussion.*

Response:

In our revised manuscript, we have described only the methods which were utilized in the study. Description of other biochemical parameters not utilized in the study have been removed.

4) *I suggest to utilize MAMC as measure of muscle protein mass instead of MAC. In fact MAC includes both fat and muscle while MAMC is calculated by subtracting fat to MAC (pag 7 : Anthropometry)*

Response:

Thank you for this valuable suggestion. In the revised manuscript, MAMC is used as a measure of muscle protein mass instead of MAC. $MAMC = MAC - (3.1415 * TSF)$

5) *low albumin levels in liver cirrhosis are mainly influenced by the failure in liver capacity of protein synthesis. (this is evident in Table 3) but the authors seem to be always concerned about "inflammation" . The mechanism of reduced protein synthesis needs to be reported.*

Response:

Low albumin levels in liver cirrhosis which are mainly influenced by the failure in liver capacity of protein synthesis has been added in the discussion section in the manuscript.

6) *Results: I suggest to change as "reason for admission was tense ascites with need of paracentesis"*

Response:

“The reason for admission was tense ascites with need of paracentesis” was added in the results section of the manuscript.

Reviewer No. 2

Major revision

1. INTRODUCTION:

a) The objective of determining malnutrition in Asian liver cirrhosis patients is an important goal, but using different tools for assessing nutritional status without previous validation muddles the outcome due to the different results. Most studies using several factors like SGA have come up with consistent assessment results due to their sticking to one validated tool. In this case combining SGA with anthropometric measurements like MAC or MAMC would be acceptable if these were designed to reinforce each other, but correlating them with different forms of cirrhosis and trying to determine significance appears to be in cross purposes.

Response:

We thank the reviewer for highlighting this issue. As per his advice, we have decided to use the SGA as the major tool of nutritional assessment when comparing against severity and aetiology of liver cirrhosis.

b) What is needed in the introduction is clearness in the problem presented and in the goals. Is the study aimed at showing a profile of nutritional status in this group of liver cirrhosis and to compare this with the other groups? (e.g. Asian versus western). Or is the study aimed at showing differences in nutritional patterns in the different types of liver cirrhosis patients? Or are all of the above questions the goal of this study? All these have to be clearly stated in the introduction

Response:

The goals of this study have been clarified in the Introduction. Essentially, it is the following:

- a) to determine the prevalence of malnutrition in Malaysian patients with cirrhosis using standard nutritional assessment tools and
- b) to compare nutritional differences between various aetiologies.

2. METHODS:

a) For clearness and flow, suggest to include inclusion or exclusion criteria within the description of patient recruitment.

Response:

(a) Inclusion criterion was patients aged > 18 years with decompensated liver cirrhosis who were hospitalized between August 2006 and March 2007.

Exclusion criteria were:

- (i) hepatocellular carcinoma

(ii) hepatic encephalopathy grades 3-4

(b) Please be clear in delineating the criteria of diagnosis for liver cirrhosis that is: enumerate the criteria first, then discuss each point

Response:

Cirrhosis was diagnosed based on a combination of clinical features, blood profile and radiological imaging. Clinical features were of those of portal hypertension, i.e. ascites and/or gastrointestinal varices. Blood profile included evidence of thrombocytopenia and/ or coagulopathy. Radiological features, either with trans-abdominal ultrasound or computerized tomography, had to demonstrate a small shrunken liver with or without splenomegaly and intra-abdominal varices.

This statement has been added to the Methods section.

c) Please indicate how you arrived at the values of the MAMC (better still include the formula)

Response:

$MAMC = MAC - (3.1415 * TST)$

In the nutritional assessment section there is a need to separate the different nutritional assessment tools to determination of fat stores, muscle mass, and functional capacity in order to have a clear delineation of the levels of body composition values and effects. This is where there is also a need to qualify the use of SGA versus BMI since some studies have shown that SGA when compared with BMI came up with more malnourished patients (Norman K et al. The Subjective Global Assessment reliably identifies malnutrition-related muscle dysfunction. Clin Nutr 2005; 24(1): 143-50)

Response:

Separation of nutritional assessment tools to determine fat stores (TST), muscle mass (MAMC) and functional capacity (SGA, Handgrip strength) has been done in the nutritional assessment section in Methods.

In this study, SGA was used as the major tool of nutritional assessment. BMI was only used as a baseline comparison between cirrhotic patients and the local healthy population. The use of BMI was however limited by the lack of data on dry weight measurement in patients following paracentesis. We concur with the reviewer's suggestion that SGA was superior to BMI as a nutritional tool, as per the article identified. This fact has now been added to the "Discussion" section.

d) In the laboratory examinations the authors mentioned albumin and pre-albumin with the declaration that pre-albumin is better. The question is: why still use albumin in one of the tests? There is therefore need to further explain why albumin is included. There is also a need to explain further why correlation of albumin or pre-albumin with CRP is needed in this group of patients. Does the severity of the cirrhosis correlate with the results of these laboratory values?

Response:

The discussion on pre-albumin has now been removed from the methodology section, as we were unable to measure it in any case & including it in the earlier part of the manuscript was an error.

Despite its' limitations, serum albumin was used as it functioned as a surrogate marker of malnutrition and we were able to measure it as a routine test.

Both albumin and transferrin are negative acute phase proteins. To ensure that their low levels were not a result of inflammation, it was important to demonstrate that no inverse relationship existed with an inflammatory marker such as C-Reactive Protein.

Serum albumin and transferrin levels were demonstrated to be significantly lower in patients with Child-Pugh C liver cirrhosis compared to those with Child-Pugh B disease.

3. RESULTS

a) When reporting data comparison it is recommended that differences be quantified by statistical analysis thus when saying there is a difference, it means the statistical analysis was done and showed it. If there is none or no formal comparison using the mentioned statistical tools then mentioning such "differences" should be avoided. If there are differences it is also recommended to ALSO mention the p-value and the type of test used.

Response:

This point is noted. The statements have been altered accordingly.

b) This is the case in point in the Nutritional assessment section where differences were noted and not backed by statistics (or did the authors failed to mention them in table #2?). The same comment also applies in "clinical severity and nutritional parameters". The last section details the data comparing alcoholic versus non-alcoholic cirrhosis also makes comparisons with no significance. Suggest to reorganize and reformat the data presentation

Response:

As before, the statements regarding significance etc have been altered accordingly. Statistical comparisons have been inserted where appropriate. The data presentation has been reorganized and re-formatted – see new Table 2 & 3.

4. DISCUSSION:

a) Discussion on the differences of value from other groups (Asians and Caucasians) were mentioned, however there is a need to organize the discussion flow to the following areas:

a. What did this study show in the following areas?

i. Malnutrition incidence in the different types of cirrhosis

Response:

Malnutrition incidence in the different types of cirrhosis is presented below:

Alcoholic liver disease -	9/ 12 (75%) < 5 th percentile MAMC
Viral Hepatitis-	5/ 15 (33.3%) < 5 th percentile MAMC
Cryptogenic -	2/ 7 (28.6%) < 5 th percentile MAMC
Autoimmune -	1/ 2 (50%) < 5 th percentile MAMC

ii. Prevalence or percentage of malnutrition compared with other studies-

Response:

The prevalence of severe malnutrition in this Asian population of adults with cirrhosis was 50%, based on the definition of MAMC < 5th percentile. This level of malnutrition appears to be comparable to published data from Italy (34% of cirrhotics with MAMC < 5th percentile) and a more recent publication from Thailand (38% of cirrhotics with TSF < 10th percentile).

iii. Nutritional assessment tools-

Response:

SGA demonstrated a trend of correlating with clinical severity and cirrhosis aetiology. Higher rates of SGA grade C were observed in patients with Child-Pugh C (40%) compared to Child-Pugh B (25%) cirrhosis, and in alcohol-induced liver cirrhosis (41.7%) compared to nonalcohol related liver cirrhosis (29.2%). These differences were not statistically significant, probably as a result of the small sample size in this study.

Biochemical visceral proteins, such as serum albumin and transferrin levels, did correlate with severity of liver disease. However, this is most likely a result of liver synthetic dysfunction, rather than as a measure of malnutrition.

b. Did the etiologies have a role in the severity of the malnutrition? The authors discussed alcoholic versus non-alcoholic data – can they explain the differences? Why was this entity given much attention?

Response:

We have demonstrated that there was a trend towards more severe malnutrition in alcohol-related liver disease compared to other aetiologies –see above & new Table 3.

It is known that patients with alcohol-related liver disease suffer from malnutrition not only from their liver disease, but additionally from the poor oral intake & nutritional deficiency associated with alcoholism. Furthermore, several other studies in the West have alluded to this fact. Our data has supported this difference in nutritional status between various aetiologies of cirrhosis.

b) Mentioning CRP here without presenting data – is there data?

Response:

The mean CRP has been added in the Table 1.

c) Correlating degree of malnutrition with severity of liver cirrhosis needs some statistical analyses which need to be shown in the results and in the discussion

Response:

The statistical analyses has been done. We have discussed the lack of significance in the discussion, probably as a result of the small sample size.

5. CONCLUSIONS:

Please conclude only on data/information that were examined and analysed. There is also need to be more specific in the conclusion(s). Intake was mentioned but not dealt with in the results and discussion.

Response:

These points have been noted & the conclusion has been made more specific. The issue of intake has been added to the discussion section.

6. TABLES:

a) Table 1: Please modify the table to fit the following suggestions:

1. In the table title: suggest to change the title to something like “Patient Profile

Response:

The title of table 1 has been changed accordingly

2. In the etiology, suggest to qualify the severity of liver cirrhosis with the type of Cirrhosis

Response:

This has been performed in Table 1

c) Table 2: Please modify the table as follows:

1. Suggest to quantify the different based on the SGA status (2 columns) then placing the normal values in the third column.

Response:

The table has been modified as below:

	**SGA B	**SGA C	p value #	Normal values
Male patients with cirrhosis (n=23)				
BMI (kg/m ²)	26.3 ± 3.5	18.1 ± 1.6	< 0.0001	
*MAMC (cm) (% < 5 th percentile)	24.5 ± 3.6 (21.7)	19.4 ± 1.5 (39.1)	0.002	23.6 cm
*TST (mm) (% < 5 th percentile)	10.1 ± 3.1 0	5.9 ± 1.4 (4.3)	0.003	5 mm
Handgrip strength (kgF)	20.8 ± 7.9	16.1 ± 6.2	0.18	34.1 kgF
Albumin (g/l)	20.9 ± 7.4	23.0 ± 5.0	0.51	35-50 g/l
Transferrin (g/l)	1.7 ± 0.7	1.5 ± 0.8	0.68	1.8-2.7 g/l
Female patients with cirrhosis (n=13.)				
BMI (kg/m ²)	28.9 ± 4.3	19.4 ± 2.7	0.001	
MAMC (cm) (% < 5 th percentile)	28.1 ± 3.6 (0)	18.0 ± 0.9 (30.8)	<0.0001	18.5 cm
TST (mm) (% < 5 th percentile)	10.9 ± 4.2 (33.3)	8.6 ± 1.1 (33.3)	0.24	12 mm
Handgrip strength (kgF)	13.4 ± 5.2	9.1 ± 2.2	0.06	34.1 kgF

Albumin (g/l)	20.1 ± 4.4	17.2 ± 2.9	0.22	35-50 g/l
Transferrin (g/l)	1.9 ± 0.5	1.2 ± 0.4	0.03	1.8-2.7 g/l

2. What does kgF mean?

Response:

kgF means kilogram-force

d) Table 4: Suggest to remove this in as much as it focuses on the etiology due to alcohol and the values are not significant. Place the values/results instead in the Results section.

Response:

Table 4 has been removed. The data has been added into the “Results” text.

Minor essential revisions

1. Grammar corrections are needed and please remove comments that are not formal English like: “commonest” instead of most common.

Response:

Thank you for the comments on grammar. These have been corrected.

2. Some statistical tests were mentioned in the discussion or results which were not included in the methodology.

Response:

The Pearson statistical test used in the results section has been added in the statistical analysis section.

3. Table 3: please indicate the type of statistical analysis used in the comparison together with the notation whether the result is significant or not.

Response:

This has been made in Table 3. Statistical significance had been defined in the “Methods” section