Author’s response to reviews

Title: Anthropometric, Biochemical and Clinical Assessment of Malnutrition among Egyptian Children with Chronic Liver Diseases: A Single Institutional Cross-sectional Study

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Author’s response to reviews:

Dear Editor and Reviewers,

I am pleased to resubmit for publication of the revised version of BMGE-D-18-00788, entitled “Anthropometric, Biochemical and Clinical Assessment of Malnutrition among Egyptian Children with Chronic Liver Diseases: A Single Institutional Cross-sectional Study”. I would like to express our gratitude to you and the reviewers for the extremely helpful comments and for your guidance in the revision. In the revised manuscript we followed the BMC Gastroenterology journal style. I hope that our efforts have succeeded in allaying your and the reviewers’ concerns.

I have addressed each of their concerns as outlined below.

Comments to the Author

Alfredo Larrosa-Haro, M:D., D.Sc. (Reviewer 1)

1. This work proposes to evaluate the nutritional status of children with CLD and make anthropometric associations and with some biochemical indicators; the number of cases studied is one of the relevant aspects.
Regarding the design, an analytical cross-sectional study is proposed and a control group is included, which does not seem correct since the group with CLD seemed to correspond to its universe and the control group is selected. The evaluation of the nutritional status with z-score was already made against a parameter, so the use of a control group is debatable.

Thank you for your comments. The following figure gives an overview of the different study types in medical research.1

Based on the study objectives, method of collection and data evaluation, the current research was classified as cross-sectional analytic study.

Our study aimed to assess the nutritional status among chronic liver diseased children and estimate its prevalence. Malnutrition, represented in the high prevalence of stunting, increasing rates of underweight, and simultaneously increasing rates of obesity remains high in Egypt especially in young children under five years of age 2 as follows:

• Stunting remains a significant public health concern in Egypt, affecting 1 in 5 children
• Wasting has increased significantly since 2000, and the trend is significantly higher among girls
• Wasting and underweight stand at 8 and 6 percent, respectively
• The incidence of anemia is high, standing at 27 percent 2

Therefore, it was essential to assign a comparative group to identify the nutritional status of study cases compared to age and sex matched controls who are expected to have or at risk of being malnourished.

References


https://www.unicef.org/egypt/media/2686/file

2. The z values of the control group are on the positive side of the distribution curve and in almost all cases when observing the SD they exceed + 2SD which makes it questionable if it can be considered as a nutritionally "healthy" group.
Another aspect related to the control group are ethical aspects in particular with blood samples which would at least require a particular mention.

Thank you for your comments. As mentioned in the previous comment, Malnutrition, represented in the high prevalence of stunting, increasing rates of underweight, and simultaneously increasing rates of obesity remain high in Egypt especially in young children under five years of age 1 as follows:

- Stunting remains a significant public health concern in Egypt, affecting 1 in 5 children
- Wasting has increased significantly since 2000, and the trend is significantly higher among girls
- Wasting and underweight stand at 8 and 6 percent, respectively
- The incidence of anemia is high, standing at 27 percent

In our study, all potential participants including case and control groups, were assured that participation is absolutely voluntary and that he or she will be free to withdraw their participation. Potential benefits of the current research findings to participants and society were comprehensively described in the consent form and informed consent process. A description of benefits to the subject or to others, which may reasonably be expected from participating in the research were explained to the entire study groups prior to commence the study.

Based on assent guidelines for children by age, those who aged 0 to 6 years old (the study participants) require no assent form with accepted separate parental permission form (Child Assent and Permission by Parents or Guardians, AARRPP Elements: I.1.G, II.3.F, II.4.A). Ethical statement is provided in the manuscript, Methodology section, Page 8, Lines (4 - 6).

References


3. There is no justification for the evaluation of 2 biomarkers and it seems that the authors taken them because they had availability more than for being part of the research question.

Thank you for these observations. Although, Egypt is low-income country in which the limited resources for health care aren’t adequate to meet the health care needs, however, these didn’t influence our decision making in choosing the current study biomarkers.
Vitamin D is crucial for skeletal development and its deficiency is the major cause of hepatic osteodystrophy. As a result, children with CLD are prone to have not only low bone mass, fractures and short stature, but also rickets and spine abnormalities. Therefore, one of the study objectives was 1st to investigate the prevalence of vitamin D deficiency among CLD patients, 2nd adjust the dose of vitamin D supplementations for all CLD patients regularly attend the hepatology clinic based on the study results.

Insulin Growth Factor family (IGF) is considered the most anabolic hormones inducing anabolic metabolism, stimulation of DNA synthesis, cell proliferation, and meiotic division. Circulating levels of IGF-1 decrease sharply in patients with CLD as the liver synthesizes most of the circulating IGF-1. Subsequently, low IGF-1 levels lead to bone loss and other metabolic changes in patients with cirrhosis. In addition, circulating IGF-1 has been found to correlate with the status of liver disease, histologic grade of fibrosis, and liver reserve scores such as CTP and MELD, which is used to predict 3-month mortality risk to determine liver organ allocation priorities. Recent studies showed that the baseline plasma IGF-1 level was statistically significantly associated with patients' survival and synthetic function of the liver.2 Better recognition and understanding of this system can contribute to discovery of new and improved versions of current preventive and therapeutic actions in CLD. Also, these results help to outline the clinical benefits of controlling serum IGF-1 levels in children with chronic liver diseases in Egypt

References


4. A table of correlation of anthropometric indices with a number of significant correlations is presented. It is not clear what is the reason for including this large number of anthropometric indicators, which makes it difficult to explain what these significant relationships mean and makes this large amount of data on one hand difficult to interpret and on the other does not establish which of them responds to the objective raised. It is a known fact that when studying sample of healthy or malnourished pediatric subjects these significant correlations are observed in what it has been called "anthropometric harmony".

We would like to thank the reviewer for his valuable comments and careful review of the manuscript. According to the latest WHO data published in 2017, liver disease deaths in Egypt reached 53,687 or 10.45% of total deaths. The age adjusted Death Rate is 84.71 per 100,000 of population ranks Egypt #1 in the world. In this context, the study findings definitely bear
significant clinical implications. In the revised version of manuscript, Table 4 displays the biochemical and hematological parameters that only significantly correlated with anthropometric indicators in chronic liver disease patients. We highlighted the significant results, removed parameters that showed no significant correlations. Now, it became clear and well-organized to speed up the comprehension and interpretation of the study’s findings with a larger amount of information in a shorter time span. Results section, Table 4.

5. It is known that the presence of edema associated with hypoalbuminemia - which frequently occurs in this type of patients- introduces an important bias in the interpretation of indicators that include weight as a variable as it suebestimates deficit. The authors do not report the presence of edema or the albumin values; only correlation coefficients and value of $p$ are presented. Albumin is a difficult marker to interpret since on the one hand it can express liver failure in the synthesis of proteins and on the other hand malnutrition.

Thank you for your comments. Nutritional evaluation of children with CLD is essential, but it has several challenges. The presence of visceromegaly, ascites, and peripheral edema can limit the use of weight, the most common index for nutritional evaluation. Therefore, a meticulous physical exam, several anthropometric measures, and individualized complementary tests are indispensable for a reliable nutritional evaluation of these patients. TST, AC and other upper limb measures are more reliable, as these parameters do not consider the weight or affected by edema and could be extremely important in clinical practice, allowing for an early diagnosis of nutritional deficits. Malnutrition was only detected when the evaluation was not restricted to weight and height measures 1. This was adopted in the current study. In addition, we excluded all patients who had marked edema extending to upper extremities or tense ascites.

Albumin was utilized in many studies for nutritional assessment in. Liver has a large reserve and unless most of it is damaged, the synthesis of albumin is not impaired markedly. 2 In previous Egyptian study carried out on CLD pediatric patients, mean values of serum albumin were within normal limits in patients with chronic hepatitis, which indicate these patients, have relatively preserved liver function. The corresponding values were deranged in large proportion of patients with cirrhosis indicating hepatic failure. The difference for values of albumin between these two groups was statistically significant. The values also revealed significant differences ($p<0.05$) among Child-Pugh class A, B and C with marked deterioration of the parameters in class C compared with Class A and B. 3

References


In summary, this is a valuable series due to the number of patients and the large amount of related data that, although it is proposed as an analytical study, does not propose a hypothesis and stays in the descriptive field despite carrying out statistical tests of the relational level.

Thank you so much for these comments that have helped a lot in focusing and sharpening the paper’s basic arguments and propositions. We would like to express our gratitude to you for helping us to do much better work.

Claudia Mandato (Reviewer 2):

The manuscript entitled "Anthropometric, Biochemical and Clinical Assessment of Malnutrition among Egyptian Children with Chronic Liver Diseases: A Single Institutional Cross-sectional Study" analyzes the nutritional status of children affected by chronic liver dysfunction and its relations to markers of disease severity. This is a crucial topic as malnutrition has been related to a worse prognosis in this population of children.

I have some concern regarding the manuscript:

1. Introduction and discussion section does not refer to the most recent publications in this field: Nutritional Needs and Support for Children with Chronic Liver Disease, Nutrients 2017, 9, 1127; doi:10.3390/nu9101127 ; EASL Clinical Practice Guidelines on nutrition in chronic liver disease, Journal of Hepatology 2019 vol. 70 j 172-193; Nutrition and Liver Disease, Nutrients 2018, 10, 9; doi:10.3390/nu10010009. In particular, authors should refer to sarcopenia and discuss on the newer tools for nutritional assessment such as handgrip strength (a simple, inexpensive, and effective method to detect malnutrition in cirrhotic patients) , DEXA or Tetrapolar bioelectrical impedance analysis (BIA). Please add these references and comments

Thank you for comments. Following the reviewer’s recommendations, in the revised copy of manuscript, a new paragraph was added describing the new modalities and recent publications.
Introduction section, Page 4, Lines (10-13, 16-18) and References, Ref 5, 9.

2. Authors did not report dietary regimen of the malnourished and healthy children, which could have influenced the biochemical parameters, including IGF-1

Thank you for your comments. The overall aim of the study was to assess the anthropometric nutritional status of CLD children based on direct (conventional) and indirect arm measurements and correlate these parameters with the severity of liver disease, liver functions and other biomarkers. Dietary regimen wasn’t reported as; 1st, assessment of dietary intake requires a quantitative methodology to estimate the nutritional adequacy of certain group through
evaluating the mean group usual energy and nutrient intakes. The 24 h recall method is usually employed to assess the type of food and the quantities consumed in the last 24 h. Food Frequency Questionnaire (FFQ) is another method in the form of a questionnaire used to obtain frequency, food and beverage consumption over a specified period of time, typically the past month or year. Among the well-recognized methodological challenges associated with both methods is the issue of reliability, defined as the extent to which repeated recalls estimate usual dietary intake without error. Low reliability is due to both recall and social desirability bias. Presumably, this goes beyond the aim of the study. 2nd, the data collected in the context of the current research are already varied and generous.

The biomarkers including IGF-1 and vitamin D are expected to be lower in CLD patients compared to the healthy population. Those 2 biomarkers were utilized in many studies dealing with the same topic. Thus, these markers were mainly measured to be correlated with the severity of the liver cirrhosis in addition to the assessment of nutritional status.

References


3. Please report that Prealbumin is a more sensitive marker of malnutrition compared to albumin, as it has a shorter half-life.

Thank you for your comment. In the revised manuscript, this information was added. Now it reads “Although, serum albumin has low specificity and sensitivity as a nutritional index compared to pre-albumin, particularly in patients with CLD…..etc”, Discussion section, Page 13, Line 10-11.

4. Authors concluded with the sentence: Our results identified anthropometric arm indicators and MUAC/A measurement as the most effective applied methods for assessing nutritional status in CLD children. I believe study result are insufficiently to support this sentence which should be change in: “Our results identified anthropometric arm indicators and MUAC/A measurement as an effective applied methods for assessing nutritional status in CLD children”.

We would like to thank the reviewer for her support and observation. In the revised copy of the manuscript, this phrase was replaced based on your recommendations. Now, it reads (Our results identified anthropometric arm indicators and MUAC/A measurement as an effective applied

Thank you again for your support and great insightful comments that have certainly helped again in achieving much better work. We sincerely hope that you like the changes we have made to the manuscript.

Claudio Augusto Marroni (Reviewer 3):

1. The aim of this study was to evaluate nutritional changes in children with chronic hepatopathy from 6 months to 6 years. There is great dispersion in the age group, which may hinder the homogeneity of the evaluation.

Thank you for your comments. 5-year interval age classification is usually adopted in Egypt Health Demographic and Health Survey (https://egypt.unfpa.org/sites/default/files/pub-pdf/0e0409a0-7af6-46d5-a346-7a7d9aeb12c6.pdf). Based on this classification, we included 2 age groups with no obvious great dispersion.

When a study population is identified, selection bias occurs when the criteria used to recruit and enroll patients into separate study cohorts are inherently different. This can be a particular problem with case-control and retrospective cohort studies where exposure and outcome have already occurred at the time individuals are selected for study inclusion. Prospective studies where the outcome is unknown at time of enrollment are less prone to selection bias.

Reference


2. Compares two groups: the sick group with normal group.

The exclusion criteria are rigid, trying to achieve greater uniformity of the sick group.

Thank you for the comment. Inclusion and exclusion criteria define who can be included or excluded from the study sample. The exclusion criteria include factors or characteristics that make the recruited population ineligible for the study.* For example, patients with liver disease were excluded if they had associated comorbidities e.g. renal and cardiac insufficiency, received a liver transplant and who were very ill e.g. tense ascites and massive edema. These factors may be confounders for the outcome parameter.

Reference
3. In the clinical evaluation there is an adequate distribution of cases regarding gravity (CTP A, B and C). They emphasize the importance of nutritional evaluation and its diagnosis in the prognosis of chronic hepatic disease. They point out the lack of a golden standard in the nutritional evaluation of cirrhotics. The evaluation should be broad and varied, contemplating a set of different methods, with different parameters, which complement each other, including the participation of laboratory results, which improves the evaluation as a whole.

Thank you for this comment. In the original manuscript, this is already mentioned in the conclusion section “Integrating comprehensive clinical assessment, anthropometric measurements and objective biochemical analyses……..”, Conclusion section, Page 16, Lines 3-6.

4. The anthropometric parameters used, which provide us the Z score, pediatric peculiarity, give very different reports between the two groups, valuing measures assessed in the upper limbs (fat and muscle area), with a score Z -3 to -2. There is a statistical correlation between the anthropometric parameters and the laboratory tests, obviously, due to the present disease, which is aggravated in the clinical comparison (CTP C), emphasizing sarcopenia indirectly, but very importantly.

Thank you for the comment. In the revised copy of manuscript, this is added to the Discussion section, Page 13, Lines 5, 6. It now reads “These findings indirectly reflect sarcopenia that worsens with progression of the liver disease”. Sarcopenia was also mentioned in the revised copy, Introduction, Page 4, Line 10.

5. Anthropometric measures, even though they are not the most accurate, and evaluating a segment and not the global one, present advantages because they are simple, easy, fast, inexpensive, fast interpretation, acceptable, can have greater population coverage, and are replicable.

Thank you for this observation. Although screening for nutritional status has been found to be a cost-effective strategy, and is recommended by the Joint Commission for the Accreditation of Health Care Organizations, research indicates that many patients may never be screened and up to 50% of malnourished individuals are never identified. Given that Egypt, being a low income country, has limited resources, researchers are challenged to use high quality diagnostic tools in the least expensive way at different clinical settings. The same concept we adopted in the current study.

6. Methods such as EBI could be more scientific, however, in young children, there is a lack of standardization, and probably why it was not used.

Thank you for this observation. Measurements of Electrical Bioimpedance (EBI) are being used for cardiovascular monitoring, body composition assessment and other monitoring applications
that could benefit significantly from smart textile technology. However, no solid ground research conducted in pediatric age group. *

In the revised copy of manuscript, new diagnostic tools including EBI were mentioned in Introduction section, Page 4, Lines 16-18.

Reference


7. This is an unpublished study that diagnoses malnutrition in children with chronic hepatopathy and can thus serve as a parameter for supplementary and complementary therapeutic intervention aiming at a better quality of life and preparation for liver transplantation.

We recommend publishing the paper

We thank the reviewer for thoughtful review of our work and kind words, as these comments led us to an improvement of the work. We have thoroughly re-reviewed the manuscript and corrected any errors we came across.