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Dear Editors

We thank to the reviewers for the insightful comments. We answered all the comments, and the modifications are tracked in the text.

We hope this meets the reviewer's expectations in regards to the questions, and appreciate your time in reading the document again.

Sincerely, the authors

Reviewer #1:

1. In the Abstract-methods, Methods section and Discussion section it is stated that this is a prospective cohort study. Yet in the Informed Consent Statement file it is written that „This is a retrospective cohort chart review". Hence please clarify by showing the original ethics approval of your institution what type of study this is and if the primary outcome parameter was already defined by March 2005.

Answer: This study was part of a larger study that evaluated many other data, some were retrospective and other not, motivating some publications (Appel-da-Silva MC, Miozzo SA, Dossin IA, Tovo CV, Branco F, de Mattos AA. Incidence of hepatocellular carcinoma in outpatients with cirrhosis in Brazil: A 10-year retrospective cohort study.WJG 2016 Dec 14;22:10219-10225; and John JA, de Mattos AA, da Silva Miozzo SA, Comerlato PH, Porto M, Contiero P, da Silva RR. Survival and risk factors related to death in outpatients with cirrhosis treated in a clinic in Southern Brazil. Eur J Gastroenterol Hepatol 2015;27:1372-70), and when the epidemiologist was consulted, he understood this was a prospective cohort. The fact that we evaluate a sample of patients from the use of PPI to the occurrence of the SBP outcome allows for the analysis of the Hazard

Ratio, that is, a comparison of the incidence of SBP among users and non-users of PPI, unlike most studies already published starting from the SBP outcome and evaluating which patients were using PPI, expressing their results from the relative risk of this association. The study of Terg R. et al (J Hepatol. 2015;62:1056-60) has a similar design, and was considered prospective. However, we undestand the point of view of the reviewer, and in agreement with the statistician we considered it to be an historical cohort, and modified in the text (lines 51, 83 and 126).

2. Did you perform a power calculation based on previous literature; since "PPI/SBP" is a debated topic and the observable differences might need big cohorts?

Answer: It was not performed a power calculation. This is a historical cohort, and when compared with other cohorts of the literature, it is possible to show that the "n" of the present study was representative. In the recent metanalysis of Khan et al (2015), from the 14 studies included, most included less than 300 patients.

- „For patients with SBP, survival at 60 months was 55.1%, vs. 61.7% in patients without SBP (p=0.34)." - this is in contrast to previous literature. Please discuss appropriately.

Answer: In fact, because this is an outpatient cohort, infections when present were community-based, resulting in a lower mortality, since in this population the percentage of multiresistant bacteria is low. In this regard, we have published a study demonstrating the importance of multiresistant bacteria in hospitalized patients (Costabeber AM, Mattos AA, Sukiennik TC. Prevalence of bacterial resistance in hospitalized cirrhotic patients in Southern Brazil: a new challenge. Rev Inst Med Trop Sao Paulo. 2016;58:36.), now cited in the Discussion (lines 292-298).

3. Statistical analysis: „p=0.05" - the letter p is not shown properly in the word file.

Answer: The change was accepted and modified as suggested (line 168).

4. Did PMN count or serum sodium also emerged as risk factors for SBP development as shown in Liver Int. 2015 35(9):2121-8. or Korean J Intern Med. 2009 Jun;24(2):106-12.

Answer: The diagnosis of SBP was reviewed from the charts, and many times the diagnosis was made only if ≥ 250PMN/mm^3. Therefore, the PMN count is not available for all the patients with SBP. With regard to serum sodium, the present study did not established "a priori" an intention to study this variable. So, the data on serum sodium are available in the databank, and sometimes not from the period in which the patients presented SBP. Therefore, we prefer not to evaluate these data.

5. - How many patients in the group of no PPI user had peptic ulcer, GERD or dyspepsia?

Answer: This information is on line 204: 19 patients had a diagnosis of peptic ulcer (12.6%), 20 presented gastric esophageal reflux (13.1%), and 17 used PPI to treat dyspepsia (11.3%).

6. - What were the numbers of patients taking other reflux-therapeutics in both groups (e.g. H2 blocker; antacid)?

Answer: In our country these are not currently used medications, since the Public Health System only provides omeprazole for free.So, none were on these medications. These data were included in the Discussion (line 263-265).

Reviewer #2:

1.The study has grammatical and spelling errors which should be corrected.

Answer: The grammar was revised, and we hope you will appreciate to read the manuscript again. Some confusing paragraphs were modified.

2.The authors have rightly pointed out that previous meta-analyses on this topic have been inconclusive at best. They have cited two such analysis. I would recommend to cite a meta-analysis by Khan et al. This is the only analysis which used the GRADE framework and results are consistent with what authors found in this study.

Answer: We accepted the recommendation and the meta-analysis of Khan et al (2015) was included in the text (line 275-282).

3. Previously only two prospective studies exist on this topic and both did not show any association. It is important to realize that associations found with retrospective studies are more consistent with confounding rather than true associations. Therefore, the authors should describe these prospective studies and meta-analysis by Khan et al in greater detail in the discussion section to support their own results.

Answer: We accepted the recommendation and the meta-analysis of Khan et al (2015) was included in the text (line 275-282).

4. How can we be sure that non-users were not taking over the counter PPI?

Answer: The information was based on patient and family information, being systematically questioned in the consultations, as it could cause a bias in the evaluation. We would like to emphasize that this is a poor population and that the Public Health System only dispenses medicines through a medical prescription from the hospital where the patient is referred.

Reviewer #3:

1.This study compared the incidence of SBP in patients with cirrhosis with or without PPI use. The design of the study was mentioned as a prospective study. It is an observational study where authors performed looks like a retrospective analysis of this cohort.

Answer: There is some disagreement between the nomenclature used by different authors. The fact that we evaluate a sample of patients from the use of PPI to the occurrence of the SBP outcome allows for the analysis of the Hazard Ratio, that is, a comparison of the incidence of SBP among users and non-users of PPI, unlike most studies already published starting from the SBP outcome and evaluating which patients were using PPI, expressing their results from the relative risk of this association. Anyway, we take the reviewer's suggestion and consider this to be an historical cohort study (lines 51,83 and 126).

2.How did you arrive at the sample size, also mention the power of the study.

Answer: It was not performed a power calculation. This is a historical cohort, and when compared with other cohorts of the literature, it is possible to show that the "n" of the present study was representative. In the recent metanalysis of Khan et al (2015), from the 14 studies included, most included less than 300 patients.

3.All high risk patients were excluded and mainly Child A and B patients were included. Also elaborate the PPI use, were the PPI use present at enrollment?, also compare the dose, type and duration of PPI use.

Answer: The number of patients Child C is limited because it is an outpatient cohort, which in no way detracts the study, since we are evaluating patients with ascites. Despite the lower number of Child C patients, an association between the degree of liver dysfunction and the incidence of SBP was observed. Specifically in patients with MELD > 15 (n=78), a reasonable number of high risk patients, we observed that 19 (33.3%) developed events (Table 2).

PPI was being used at the time of inclusion in the study. Being this one hospital of the public health system, the medication available free of charge is omeprazole 20 mg qd. Therefore, this comparison was not made. This information has now been included in the lines 183-184.

4.One patient flow diagram with patient enrolled, excluded, included, follow up and outcomes can be included.

Answer: The flow diagram was included (Figure 1 – line 181)

5.Please include the range of follow along with median follow up time.

Answer: The medium follow-up period between the non PPI users was 32.2 (7 to 60) months, and 27.1 (3 to 60) months between the PPI users (included in the text, line 181-182)

6.Ascitic fluid analysis with cultures in patient with SBP should be included.

Answer: By definition, all patients with diagnosis of SBP had equal or higher 250 PMN, regardless of the presence of culture, according to criteria established by the EASL and AASLD (line 151). In what way, it has already been demonstrated in our environment, the low performance of the cultural examination (de Mattos AA, Costabeber AM, Lionço LC, Tovo CV. Multi-resistant bacteria in spontaneous bacterial peritonitis: a new step in management? WJG 2014;20:14079-86 and Coral G, de Mattos AA, Damo DF, Viégas AC. Prevalence and prognosis of spontaneous bacterial peritonitis. Experience in patients from a general hospital in Porto Alegre, RS, Brazil (1991-2000)]. Arq Gastroenterol 2002;39:158-62).

7.Please discuss the strengths and limitations of the study in one paragraph.

Answer: The strenght of the present study was included in line 212-215 and 230-232, and the limitations in line 307-309.

8.Correct minor spelling mistakes.

Answer: The grammar was revised, and we hope you will appreciate to read the manuscript again. Some confusing paragraphs were modified.

Reviewer #4:

1.There is lack of certain important information such as dose and type of PPI.

Answer: The present study was performed in a great hospital of the public health system, and the medication available free of charge for patients is omeprazole 20 mg qd. This information has now been included in the lines 183-184 and 263-265.

2. I would like to know how many patients from the non-PPI group were started on a PPI during follow up, and vice versa.

Answer: There was no record of initiation of PPI during follow-up in the non-PPI group, and 27 patients used PPI for a period of less than 3 months.

3.Some of the data were obtained from reviewing the chart, thus it suggests part of the data was collected retrospectively, which is important to remark thus we are aware of the potential biases.

Answer: This is a possible limitation of the study and was included in the text (lines 307-309).

4.Another known risk factor for SBP development, protein concentration in ascitic fluid, has not been reported. How many patients in each group had indication for primary prophylaxis and how many were receiving it?

Answer: Patients who were in use of secondary prophylaxis were excluded from the study, as refused on line 179.As a rule, the patients were not subjected to primary prophylaxis because the majority had no signs of severity when they had low protein levels and the few who had the proteins in the ascites liquid were not lower than 1.5 g / dl (Fernández J et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology. 2007;133:818-24).

5.Minor language polish is also needed.

Answer: The grammar was revised, and we hope you will appreciate to read the manuscript again. Some confusing paragraphs were modified.

Reviewer #5:

1. It must be a common practice for authors to number pages sequentially.

Answer: We agree and the pages numbering was added.

2. Throughout the text (including Abstract) there are several grammatical, syntax, and spelling errors. You should seek a copyediting service provided by professional English language editing company. 3. Several paragraphs from all sections of the manuscript are rather confusing, difficult to be followed by the readers, and should be rewritten.

Answer: The grammar was revised, and we hope you will appreciate to read the manuscript again. Some confusing paragraphs were modified.

4. ABSTRACT:

a) Aim: last 2 lines: please, make the aim more clear.

b) Method: first line "without patients with.." please, make corrections. It is difficult to understand if your study was a prospective one-while "Patients charts were reviewed to collect information..."! Please, make correction to "MELD "scored" etc. My advice is to rewrite the entire Methods text.

c) Results: are confusing. -How many of 738 enrolled cirrhosis have been followed-up 60 months? -How many of PPI users and nonusers have been followed-up 60 months?

Answer: All the Abstract was modified as suggested

5. Core-tip: Please, rewrite the first and last sentences.

Answer: The Core-Tip was modified as suggested

6. Introduction: too long. -First paragraph: please, make it clear. -Please, delete the last 2 lines from 4th paragraph.

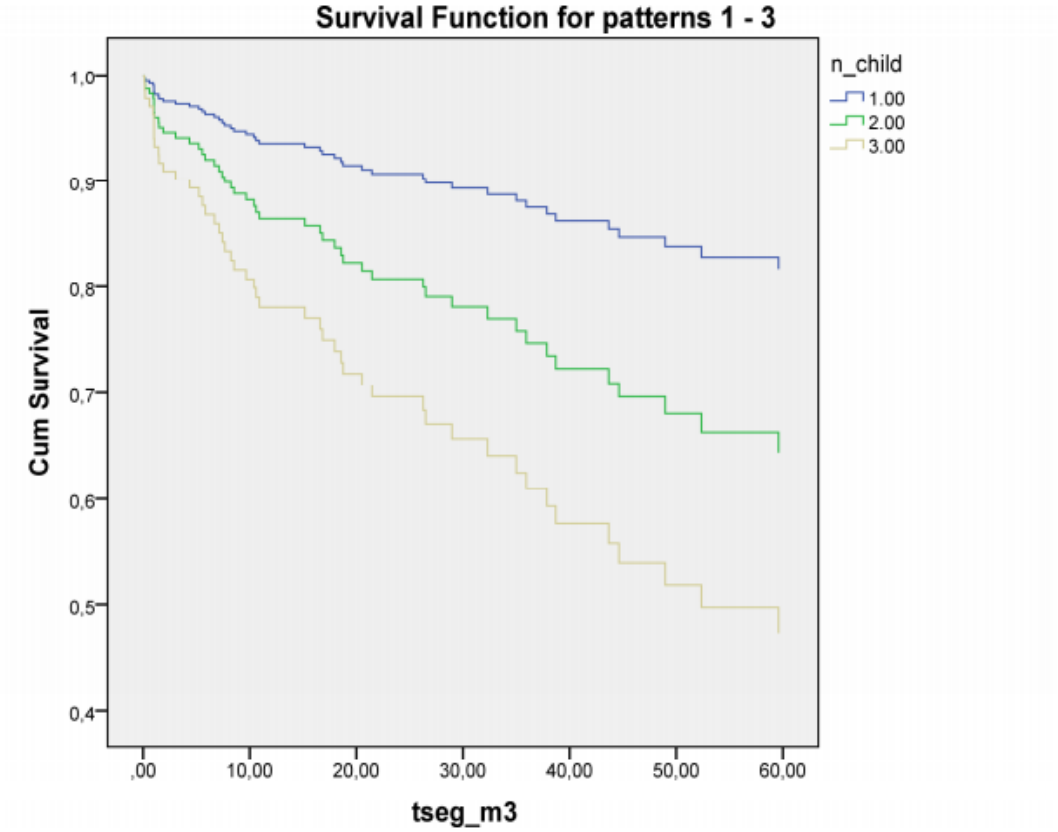
Answer: The Introduction was modified as suggested

7. METHODS:-again , is your study prospective? -did you have a statisticians?

Answer: The fact that we evaluate a sample of patients from the use of PPI to the occurrence of the SBP outcome allows for the analysis of the Hazard Ratio, that is, a comparison of the incidence of SBP among users and non-users of PPI, unlike most studies already published starting from the SBP outcome and evaluating which patients were using PPI, expressing their results from the relative risk of this association. But we understand the point view of the reviewer, and in agreement with the statistician we consider this an historical cohort study (lines 51 ,83 and 126).

8. RESULTS:-please, make more clear association of SBP with CHILD score (3rd paragraph) and survival at 60 months.

Answer: Using the COX model (Figure bellow), the events occurred in Child A 18.2%; Child B 35.6%; and Child C 52.7%; p<0.001.Throughout the follow-up period, the Child C patients presented a higher mortality (lines 197-199 and 297-298).



9. DISCUSSION: please, make comments to your results; do they show any additional data compared with similar reported studies? Please, mentioned the strengths and limitations of your study.

Answer: Thank you for your suggestion. The strength of the present study was included in line 212-215 and 230-232 , and the limitations in line 307-309.

10. CONCLUSION should be drawn more precisely, and refer to the aim of your study. The last sentence should be deleted. I regret that I cannot recommend your manuscript to be published until a major revision dealing with all the above comments is made.

Answer: We thank the reviewer for the suggestions. All of them were followed and highlighted in the text.

Reviewer #6:

The study includes only a limited number of patients with child C (MELD >15) or advanced cirrhosis. The prevalence of SBO is higher in this population. The study should be restricted to only this patient population, and should have a adequate power to reach a reasonable conclusion.

Answer: Indeed, the number of patients Child C is limited because it is an outpatient cohort, which in no way detracts the study, since we are evaluating patients with ascites. Despite the lower number of Child C patients, an association between the degree of liver dysfunction and the incidence of SBP was observed. Using the COX model, the events occurred in Child A 18.2%; Child B 35.6%; and Child C 52.7%; p<0.001. Throughout the follow-up period, the Child C patients presented a higher mortality (lines 197-199 and 297-298). Specifically in patients with MELD > 15 (n=78) we observed that 19 (33.3%) developed events (Table 2).