Xanthi, August 13, 2023

Dear Editor,

We kindly express our gratitude for the quick and concise review you and the two reviewers have conducted. All comments received are of substantial value for ameliorating the quality of the manuscript. As a matter of fact, we have put all our effort to resolve every single issue raised throughout the review process in a point-to-point detailed answer following.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The author(s) had put great effort and hard work in this manuscript. The present manuscript is a meta-analysis of the value/utility of QTc interval prolongation in patients with liver cirrhosis. The subject is not original and is well known, however, to my knowledge no meta-analysis studied this issue.

We thank the reviewer for the encouraging comment.

It should be mentioned that the QTc interval is known to be affected by many factors some of them are characteristically present in cirrhosis: the presence or absence of hyperdynamic circulation (which is the case in most patients with cirrhosis specially Child B and C), the intake of drugs such as B blockers, recent attack of bleeding OV, electrolyte imbalance due to diuretic treatment (very common in Child B and C). All the above factors should be put in mind when conducting a research like that and when drawing a conclusion.

We thank the reviewer for the insightful comments.

We have designated the prominent role that the hyperdynamic circulation might play in QTc prolongation by adding a small paragraph discussing the

association between the severity of cirrhosis and QTc ("High certainty of evidence has been also demonstrated that QTc prolongation in cirrhosis is more pronounced in severe forms of the disease, revealing a dose-response gradient effect of Child-Pugh score on QTc. It has been shown that patients with cirrhosis with QTc > 440 msec had higher MELD scores when compared with patients with QTc ≤ 440 msec. The correlation between the severity of cirrhosis and QTc prolongation might reflect the key role that aggravating hyperdynamic circulation leading to cirrhotic cardiomyopathy plays in the pathophysiology of the disease as well as the electrolyte imbalance superimposed by diuretic administration[80]").

We have emphasized on the potential effect of various regimens by adding the phrases "This phenomenon could be partly attributed to the redefinition of QTc-affecting drugs, such as beta-blockers and diuretics" and "diuretics, anti-rejection regimens such as tacrolimus" in the "Discussion" section.

Aiming to explicitly investigate the potential effect of β-blockers in cirrhotics, we have properly revised the last paragraph of the "Introduction" section, as well as the "Study selection" and "Data extraction" paragraphs of the "Materials and Methods" section. As a result, we have added a relevant paragraph in the "Results" section ("The effect of β-blockers on QTc was investigated using data from three relevant studies, Patients with cirrhosis who were treated with β-blockers presented shorter QTc than those who were not (SMD: -0.540; 95%CI: -0.836 to -0.243; $P < 0.001$); I^2 was 0.0% (95%CI: 0.0-92.1%; $P = 0.653$)"), as well as **Figure Supplementary 3**. This finding is further discussed in the "Discussion" section of the revised manuscript ("Of note, other factors such as β-blockers, electrolyte imbalance due to diuretic treatment, and a recent episode of gastrointestinal bleeding might affect QTc. Similar to previous studies, we have demonstrated that β-blockers exert a negative effect on QTc[31,88,95].").

As far as the effect of acute gastrointestinal bleeding is referred, we have properly revised the last paragraph of the "Introduction" section, as well as

the "Study selection" and "Data extraction" paragraphs of the "Materials and Methods" section. As a result, we have added a relevant paragraph in the "Results" section ("QTc was prolonged during acute gastrointestinal bleeding, as deduced from two studies providing paired data (SMD: 1.800; 95%CI: 0.287-3.313; P = 0.020); I^2 was 96.7% (95%CI: 91.1-98.8%; P < 0.001) (Supplementary Figure 4). Moreover, QTc was restored among survivors after an episode of gastrointestinal bleeding (SMD: 0.183; 95%CI: -0.051-0.417; P = 0.124); I^2 was 0.0% (95%CI: 0.0-0.0%; P = 0.770) (Supplementary Figure 5)."), as well as **Figure Supplementary 4 and Figure Supplementary 5**. Moreover, we further discussed this finding in the "Discussion" section of the revised manuscript ("Moreover, we have shown that QTc is prolonged during acute gastrointestinal bleeding and is restored among survivors. This finding is also similar to recent studies[40,72]").

To increase the impact of this work it should have been including studies in cirrhosis patients at first diagnosis and/or non hospitalized cirrhosis patients and should state the absence of any comorbid condition that might affect the QTc interval.

We express our gratitude to the reviewer for the insightful comment. We have additionally carried out a sensitivity analysis to investigate the potential effect of hospitalization, comorbidities or treatments with known effect on QT; limited our search to studies having enrolled outpatients with cirrhosis in the absence of any other co-morbid condition or treatment with known effect of QT. A relevant phrase has been added in the "Statistical analysis" paragraph of the "Materials and Methods" section ("A subgroup analysis was performed to investigate the potential effect of hospitalization, comorbidities, and treatments affecting QT."). Moreover, a relevant paragraph has been added in the "Results" section ("A subgroup analysis was carried to investigate the potential effect of hospitalization, comorbidities, and treatments affecting QT. Thus, when non-hospitalized patients with corrhosis without any other co-morbid condition or treatment with known effect of QT were considered (n =

1448), the QTc combined mean was 444.0 msec (95%CI: 437.8–450.1) with an I^2 of 92.4% (95%CI: 89.6-94.5%; P < 0.001). When patients with cirrhosis who either might have been hospitalized or presented other comorbidities or were treated with regimens affecting QT were considered (n = 6267), the QTc combined mean was 445.3 msec (95%CI: 439.6–450.6) with an I^2 of 98.1% (95%CI: 97.9-98.4%; P < 0.001). These two groups of studies yielded comparable results (P=0.823)"), accompanied by **Figure Supplementary 1and Figure supplementary 2**. Finally, a relevant phrase has been added to the "Discussion" section ("However, the overall effect of treatments affecting QT, hospitalization for acute illness, and comorbidities on QTc prolongation in patients with cirrhosis is debatable if not negligible as suggested by the relevant sensitivity analysis carried out in the present study.").

COMMENTS: The abstract is too long and contains many unneeded details for an abstract. Should be summarized.

We thank the reviewer for the comment. We have omitted most SMD and 95% CI values. Moreover, we have removed every unnecessary detail. As a consequence, the abstract has been curtailed from 532 to 478 words (~10%).

The aim: What exactly is the aim of this work. Is it: assessing if QTc is prolonged in liver cirrhosis(compared to control subjects), OR OR defining a cutoff value of QTc predicting disease severity OR studying its utility in assessing severity of cirrhosis (CTP and MELD scores)? I think the study is totally concerned with last question (and that what was also written PROSPERO). So, the aim should be clearly stated. Also in the aim of work: studying the "Factors" mean all the factors including the effect of drugs, the presence or absence of bleeding, hospitalization, other comorbid conditions....etc. The present manuscript only studied the effect of age, sex, and severity of liver disease as predicted from CTP and MELD scores. So, the aim should be corrected.

We thank the reviewer for the crucial comment. We apologize for not being clear enough. Indeed, our aim is to: i) determine the mean QTc in cirrhotics, ii)

assess if QTc is prolonged in cirrhotics, and iii) investigate whether QTc is affected by factors such as sex, age, severity, etiology, regimens such as β-blockers, acute illness such as gastrointestinal bleeding, and liver transplantation. The thouroughly revised, analytical information has been embedded in the "Aim" paragraph of the "Abstract" ("To determine the mean QTc in cirrhotics, assess whether QTc is prolonged in patients with corrhosis, and investigate whether QTc is affected by factors such as sex, age, severity, etiology, treatment, acute illness, and liver transplantation (Tx)").

Methods: Google scholars are not a usual source or search database included in meta-analysis, sometimes it contains unpublished data. A meta-analysis and systematic review should include only published peer reviewed studies. Why including those few studies from Google scholar?

We thank the reviewer for the comment. Permit us to respectfully explain our approach as follows.

As stated in Cochrane Handbook, "failure to identify trials reported in conference proceedings and other grey literature might affect the results of a systematic review (https://handbook-5-1.cochrane.org/chapter_6/6_2_1_8_grey_literature_databases.htm)".
Moreover, it has been suggested that gray literature does not necessarily have lower quality than studies published in peer-reviewed journals (**Conn VS**, Valentine JC, Cooper HM, Rantz MJ. Grey literature in meta-analyses. *Nurs Res* 2003;**52**:256-61PMID: 12867783 DOI: 10.1097/00006199-200307000-00008). Therefore, we have chosen to search Google Scholar especially for conference proceedings and other grey literature, despite that publication bias has not been detected. Of note, no unpublished data of interest were detected, as stated in the "Study selection" paragraph of the "Results" section.

We apologize for being unclear regarding this issue. Thus, we have appropriately amend the relevant phrase for "We also utilized the Google Scholar database to retrieve any additional published or unpublished data,

such as conference proceedings and other grey literature" in the "Literature search" paragraph of the "Materials and Methods" section.

There is a contradiction between PROPSERO data and the manuscript. In PROSPER; the publication date were from Jan 2003, while in the manuscript says it is since 1998! should be revised and should be as mentioned in POSPERO.

We thank the reviewer for the watchful comment. Indeed, we have appropriately revised the PROSPERO data; a relevant phrase has been added in the "Literature search" paragraph of the "Materials and Methods" section ("PROSPERO data were revised on August 8, 2023").

Conclusion: Should be the same in the abstract as in the end of the manuscript. It should just answer the question in the aim of work (and in PROSPERO). At the end, due to the many factors affecting the QTc interval (as mentioned above); the manuscript should not draw a final solid conclusion like (Therefore, QTc is an easy-to-perform, inexpensive, and efficient tool for assessing liver cirrhosis)!

We thank the reviewer for the watchful comment. We have appropriately revised the "Conclusion" paragraph by avoiding any exaggerations; the revised version placed in the end of the manuscript is identical with the one included in "Abstract" ("QTc is prolonged in cirrhosis independently of sex, age, and etiology but is correlated with severity and affected by β-blockers and acute gastrointestinal bleeding. QTc is improved after liver Tx").

Research background/motivation/perspectives and objectives should be modified according to the above comments.

We thank the reviewer for the watchful comment. The research background, motivation, objectives, and perspectives have been properly modified.

Exclusion: again there were a contradiction between PROSPERO data and the manuscript. Were studies published as abstracts included or excluded? Kindly revise the PROSPERO, the study selection section and fig.1

We thank the reviewer for the watchful comment. We have added the phrase "(3) studies published only as abstracts" in the "Study selection" paragraph of the "Materials and Methods" section so as to clarify exclusion criteria. Moreover, we have properly revised the relevant PROSPERO data. Last, Figure 1 was revised to also include the revised search protocol proposed by Reviewer #2.

Discussion: Kindly explain the sentence (Therefore, this compensatory mechanism might be compromised in patients with cirrhosis of alcohol etiology in case that decline from alcohol abstinence occurs).

We thank the reviewer for the comment. We apologize for the vague syntax. The sentence "decline from alcohol abstinence occurs" was amended for "alcohol consumption persists".

Also, what is meant by (inextricably intertwined).

"Inextricably intertwined" means "cannot be considered separately".

Limitations should be mentioned under a separate subtitle, and should be clearly explained. The last paragraph of the last section (limitations) is not understood, may be the sentence was too long! Should be revised. Again, limitations are many as mentioned before. Explaining the limitations and not underscoring them is important for the integrity of any research. This part is the one that other researchers/readers will improve in further studies to add more and more to our knowledge.

We thank the reviewer for the comment. The "Limitations" paragraph has been subtitled separately. The content of the paragraph, as well as the related references, have been properly revised incorporating all alterations performed according to the reviewer's valuable suggestions/corrections.

Forest plot figures are not clearly showing data. May it is Zoomed in more than needed, the part of the legend "with and against" is not properly put in its exact place.

We apologize for the inconvenience that forest plots may have caused. We have revised all forest plots so as to have properly zoomed and symmetrical x-axis as well as to demonstrate the "with and against" information properly centered in its exact place.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors have developed an interesting and novel work in the context of liver cirrhosis. A systematic review and meta-analysis of the relationship between QT interval and disease status has been designed for the first time in the literature. The manuscript is coherent, and the structure is adequate. The risk of bias analysis includes different correct studies.

We thank the reviewer for the encouraging comments.

However, to improve the quality of the manuscript, I propose the following suggestions and comments: Material and methods: How many authors conducted the systematic review? Please indicate the initials of the names.

We thank the reviewer for the watchful comment. Both authors have conducted literature research, study selection, and data extraction. Regarding literature search, the initials of the authors' names have been clearly stated in the revised text by addition of the phrase "The literature search was performed by both authors (VP and KM)".

In addition, the literature review is usually performed by 2 or 3 authors, and a different coauthor is included to resolve discrepancies once the results have been agreed upon. I suggest that this be included as a methodological limitation in the discussion.

We thank the reviewer for the valuable comment. The phrase "First, the literature review has been conducted by only two authors; while no different

coauthor was available to resolve any discrepancies, the most experienced author (KM) undertook the latter task. ” has been added to the “Limitations” paragraph.

The phrase "KM was responsible for resolving any discordance" is duplicated.

We thank the reviewer for the comment. We have omitted the first report of the duplicated phrase.

The search strategy only contemplates the term "QTc", but terms such as "QT interval, QT-interval, Q-T syndrome or QT syndrome" can be found in the literature. Please confirm that the strategy includes all available scholarly articles or, if not, add the missing ones.

We thank the reviewer for the watchful comment. We have additionally performed a search for "{[QTc] OR [QT interval] OR[QT-interval] OR [Q-T syndrome]} AND {[cirrhosis] OR [Child-Pugh] OR [MELD]}.This was clearly stated in the revised text at both “Abstract” and “Materials and Methods” section. As a result, three additional publications were retrieved, one of which was eligible (New reference #82). Thus, **Figure 1** has been corrected. Of note, the overall effect of etiology of cirrhosis in QTc has been demonstrated to be non-significant, as stated in the relevant paragraph of the “Results” section (Patients with cirrhosis of alcoholic etiology exhibited comparable QTc with those of viral etiology (SMD: 0.095; 95%CI: -0.109-0.264; P = 0.418). Heterogeneity was moderate (I^2: 47.8%; 95%CI: 0.0%-74.8%; P = 0.045)“. Moreover, the PROSPERO database has been properly revised.

Results: I suggest including quantitative results in the figures to facilitate understanding of the manuscript.

We thank the reviewer for the comment. Permit us to respectfully explain that, given that all data are provided in detail in Table 2, we preferred to avoid data duplication in forest plots. Thus, we used MedCalc software as it is simple and clear as far as the visualization result. However, in case the reviewer or the editor insist on providing all numerical details, we have no

objection in repeating the whole analysis with the use of RevMan 5.3 or Comprehensive Meta-Analysis software which are suitable for this kind of visualization, though fall short of clarity in figure files.

How do you explain the high heterogeneity of the results described in Figure 3?

We thank the reviewer or the insightful comment. The present study has concluded that QTc heterogeneity among patients with cirrhosis can be at least partly attributed to i) the severity of the disease in terms of either Child-Pugh stage or MELD score, ii) the administration of β-blockers, and iii) the co-existence of acute gastrointestinal bleeding, all being summarized in Table 3. However, we agree that the high heterogeneity might be still considered a limitation, as clearly stated at the "Limitations paragraph" ("Second, high heterogeneity has been detected, which was not attributed to any specified potential confounder, such as publication bias, NOS scoring, study type, device used, year of publication, hospitalization for acute illness, comorbidities, and treatments affecting QT except β-blockers."

Why is the pre-specified upper normal limit for QTc different in the studies analyzed?

This analysis has been performed to reveal the divergence among researchers regarding the QTc upper normal limit and to suggest the most widely acceptable value (namely 440 msec).

Figure 11: Please develop the methodology of the regressions in the figure. Also, please include the line equation and the statistical significance level.

We thank the reviewer for the watchful comment. During the revision process, an error regarding the regression of age was detected and corrected. Moreover, a new regression concerning the oldness of the included studies was added, along with **Figure 11D**. The regression method, the line equations as well as the relevant statistical levels have been analytically presented in the revised **Figure 11**. Moreover, the relevant information has been embedded in

the text ("QTc improvement after Tx remained unaffected by age (P = 0.417) and was negatively correlated with female ratio (P = 0.002), alcoholic etiology of cirrhosis ratio (P < 0.001), and oldness of study (P = 0.019) (**Figure 11A-D**)").

Figure 12 only includes three studies, which could be considered a limitation. I suggest discussing

We thank the reviewer for the comment. A relevant phrase in the "Limitations" paragraph has been added ("Last, it might be claimed that performing meta-analysis with very few studies, as in the cases of the effect of β-blockers on QTc, acute gastrointestinal bleeding effect on QTc, and QTc prolongation effect on overall survival in cirrhosis, might be a limitation. However, and when the results are not inconclusive, a quantitative meta-analysis is an acceptable approach[100]"). Moreover, an appropriate reference has been inserted (reference #100).

We have additionally performed the following corrections/alterations:

1) The title has been changed to "**Corrected QT interval in cirrhosis: A systematic review and meta-analysis**" to avoid the QTc abbreviation.

2) Reference #9 was amended for "**Lehmann M**, Bruns T, Stallmach A. Risk factors for QT interval prolongation owing to acute gastrointestinal haemorrhage in patients with cirrhosis. *Liver Int* 2013;**33**:321 [PMID: 23121501 DOI: 10.1111/liv.12010. Epub 2012 Nov 1]" as it erroneously duplicated reference #40.

3) Reference #100 was omitted as it erroneously duplicated reference #74.

4) References after #82 have been renumbered throughout the text as a result of the addition of new reference #82 due to revised search protocol (**Cichoż-Lach H**, Tomaszewski M, Kowalik A, Lis E, Tomaszewski A, Lach T, Boczkowska S, Celiński K. QT Interval Prolongation and QRS Voltage Reduction in Patients with Liver Cirrhosis. *Adv Clin Exp Med* 2015;**24**:615-622 [PMID: 26469105 DOI: 10.17219/acem/28681]).

Hoping that we have fulfilled all your and the reviewer's expectations, please permit us to submit the revised version of our invited manuscript entitled **"Corrected QT interval in cirrhosis: A systematic review and meta-analysis"** to *World Journal of Hepatology* in order to be considered for publication.

Yours Sincerely,

Vasileios Papadopoulos, MD, PhD