

Dear Sir,

Thank you for your e-mail on September and for the opportunity to revise our paper entitled "Liver cirrhosis-effect on QT interval and cardiac autonomic nervous system activity" for the World Journal of Gastrointestinal Pathophysiology. We also thank you and the reviewers for their comments and the constructive criticism regarding this work. We hope we have successfully addressed all their comments as follows:

Reviewer #1.

Comment 1. In the discussion, it is stated that "high values of dQT predict cardiovascular mortality in patients with diabetes or coronary artery disease" (pag.11, line 14). Have the Authors some data to establish if this is true also in cirrhotic patients?

Our response:

Thank you for your response. There are no literature data on the potential association between dQT and mortality in patients with liver cirrhosis. This is stated now in the discussion section (page 11, paragraph 4, lines 6-7) as follows: "In the literature, there are no data on the potential association between dQT and mortality in patients with liver cirrhosis."

Comment 2. Considering that this is a cross-sectional study that cannot establish a cause-effect relationship, are there any data in the literature that can better describe the pathogenesis of QT prolongation in cirrhosis? One hypothesis reported in the discussion involves the possible enhanced sympathoadrenal activity by increased circulating levels of noradrenalin with a "probable" downregulation of beta-adrenergic receptors. However, the use of propranolol reduces QT interval in patients with advanced liver cirrhosis. Are there studies that related the use of beta-blockers to cardiovascular mortality in cirrhotic patients?

Our response:

Thank you for this comment. Although it is known that the use of propranolol reduces the risk of gastrointestinal bleeding in patients with cirrhosis, there are no data on the potential effect of beta-blockers on cardiovascular mortality. One systematic review and meta-analysis reported that the use of non-selective beta-blockers was not associated with a significant increase in all-cause mortality in patients with cirrhosis and ascites or refractory ascites. This is stated now in the discussion section (page 12, paragraph 2, lines 12-18).

Reviewer #2:

Comment 1. The Child-Pugh grade includes determination of hepatic encephalopathy. Did any of these patients have covert/overt hepatic encephalopathy and did this influence QT interval/CAN? If so, this should be included in the results/discussion.

Our response:

Thank you for your comment. Hepatic encephalopathy was an exclusion criterion of the study because patients with encephalopathy cannot cooperate to perform the autonomic functions tests. This is stated now in the Material and Methods section, subheading: participants (page 6, paragraph 2, line 8).

Comment 2. In the last paragraph of the results, the authors mention that diabetes and diuretics significantly influence the QT interval. The number of patients with these should be included in Table 1. Were there equivalent numbers of these patients in both the control and cirrhosis groups? In addition, does the data generated by the authors demonstrate that cirrhosis + diabetes increases QT interval/CAN to a greater degree than cirrhosis or diabetes alone?

Our response:

Thank you for your response. The number of participants with diabetes and use of diuretics is included now in Table 1. The number of the participants with either diabetes or use of diuretics were significantly lower in the control group as compared to the patients with cirrhosis group. However, it should be mentioned that multivariate linear regression analysis was performed only in the patients with cirrhosis group and not in the total cohort of the participants (controls and patients with cirrhosis). This is stated now in the results section, page 11, paragraph 1, line 1.

In addition, mean QT interval duration was not different between patients having both cirrhosis and diabetes (n=7) and those having cirrhosis without diabetes (n=44): 395.7 ± 41.2 msec vs. 381.9 ± 38.0 msec, respectively ($P = 0.38$). Furthermore, the values of the autonomic function tests did not differ significantly between participants having both cirrhosis and diabetes and those having cirrhosis without diabetes; deep breathing test: 1.09 ± 0.05 vs. 1.14 ± 0.14 , respectively, $P = 0.29$; Valsalva test: 1.40 ± 0.25 vs. 1.32 ± 0.35 , respectively, $P = 0.48$; lying-to-standing test: 1.09 ± 0.08 vs. 1.08 ± 0.09 , respectively, $P = 0.86$; orthostatic hypotension: 12.85 ± 9.50 mm Hg vs. 11.52 ± 9.73 mm Hg, respectively, $P = 0.73$. Three patients (42.9%) who had both cirrhosis and diabetes had CAN as compared to 25 (56.8%) to those who had cirrhosis without diabetes ($P = 0.49$).

The above are stated in the results section, page 10, paragraph 2, lines 1-11. In addition, we include a sentence in the discussion section (page 14, paragraph 3, lines 1-6) as follows: "It is known that diabetes is associated with higher prevalence of CAN and with QT prolongation. In our study, we did not find significant differences in these between patients having both diabetes and cirrhosis than those having cirrhosis without diabetes. However, the number of the participants with diabetes was small in our study and we cannot conclude robustly if presence of diabetes burdens further CAN or QT interval in patients with cirrhosis".

Comment 3. Minor wording errors exist such as the first sentence of introduction which should read, "...including the cardiovascular and autonomic nervous systems (ANS)." The authors should proofread and edit manuscript as necessary to reduce these errors.

Our response:

Thank you for your response. A native speaking English person read the manuscript and made the necessary changes and corrections.

Reviewer #3:

Comment 1. In the result part, please list subheading and show related results in this part.

Our response:

Thank you for your response. The results part has now subheadings.

Reviewer #4:

Comment 1. Remove most of method section.

Our response:

We removed the text from the method section that is not required; however, we kept the parts that were necessary for the reader to understand the study.

Comment 2. Data presented in result section are mostly unnecessary, remove them all.

Our response:

Parts of the results that are repeated in the tables have been removed from the results section. However, we kept the results that are not shown in Tables.

Comment 3. Rewrite the discussion with new wording also more concise text.

Our response:

Thank you for your response. The discussion section was written again with new wording and more concise text.