Dear Editor-In-Chief and Reviewers of the manuscript: “Cirrhotic cardiomyopathy: isn´t stress evaluation always required for the diagnosis?” submitted to the World Journal of Hepatology.

We thank you for all the comments you made which we consider to be relevant.

You can find our answers below.

Reviewer 1:

This is an interesting manuscript, and especially interesting for the general gastroenterologists, hepatologists, cardiologists and the internist. Its form needs some changes to be in a position to be published. First – when were your study performed – from to which year – over how many months? You should also point out the reason why your inclusion criteria are rather strict. Furthermore could you give us a short overview regarding what therapy was withheld for 24 h prior to your investigation – in a table? It would be of interest to know some more details of the main reasons for exclusion of the 47 patient – maybe in a table. The description of the echocardiographic method could be rewritten and boiled down, include a description of strain-/strain rate imaging and or/speckle tracking if it where done. It would also be in place to make a comment of possible implications a prolonged QTc means – what is its clinical implication. What about the 10 (26) that did not have CCM – could you revel information about them – trends in any direction? You have several correlations in your result section – maybe consider presenting correlations graphically – it would probably be easier to comprehend results in such manner. You also need to make an abbreviation list and polish your language.

Answers to Reviewer 1:

Our study was performed during 2011 and 2012.

Inclusion criteria were strict in order to meet cirrhotic cardiomyopathy criteria, whose definition was discussed at the 2005 World Congress of Gastroenterology in Montreal and presented after the meeting. The diagnosis of cirrhotic cardiomyopathy can only be made in the absence of risk factors for and known cardiac disease, otherwise the cardiac dysfunction can not be attributed to the cirrhotic cardiomyopathy *per se*. Neverthless, our inclusion criteria were as strict as dictated by the definition proposed and it is similar to that described in other reports regarding cirrhotic cardiomyopathy (for instance: Alexopoulou A *et al*. Diastolic myocardial dysfunction does not affect survival in patients with cirrhosis. Transpl Int 2012; 25 (11): 1174-81; Karagiannakis D

et al. Frequency and severity of cirrhotic cardiomyopathy and its possible relationship with bacterial endotoxemia. Dig Dis Sci 2013; 58 (10): 3029-36).

The therapy that was withheld for 24 h prior to our investigation was all the therapy that could interfere with the cardiovascular system and, consequently, alter the examinations´results **(corrected in the manuscript)**.

Table - therapy withheld prior to our investigation:

Therapy	**Patients (n)**
propranolol	15
furosemide	7
spironolactone	12

Table - reasons for exclusion of the 47 patients:

reason for exclusion	**Patients (n)**
diabetes mellitus	24
hypertension	12
ischemic cardiac disease	4
arrhythmia	3
chronic kidney disease	2
hepatic transplant	1
hyperthyroidism	1

Regarding echocardiographic examination, we performed standard 2d-echocardiographic and tissue Doppler imaging evaluations. Strain evaluation by speckle tracking derived indices was not performed. It is a novel technique that is not yet incorporated in the diagnostic approach to CCM (Ruiz-Del-Árbor L, Serradilla R. Cirrhotic cardiomyopathy. World J Gastroenterol. 2015; 21 (41) 11502-21). However, it seems a promissing method as it can detect a subtle systo-diastolic dysfunction before left ventricular ejection fraction becomes impaired. In that way, it could even better define/define earlier the systo-diastolic cardiac dysfunction in cirrhotic patients (also

recently reviewed in Ruiz-del-Árbor L, Serradilla R. Cirrhotic cardiomyopathy. World J Gastroenterol. 2015; 21 (41) 11502-21). (**added on the manuscript - conclusion section**).

The clinical meaning of prolonged QTc interval is not completed understood. "The clinical relevance of long QT in cirrhosis is not fully understood, yet. It is postulated that this alteration is associated with a poorer survival rate in class A patients of Child-Pugh classification. Patients with cirrhosis and prolonged QTc interval are at risk of developing ventricular arrhythmias such as torsades de pointes. The risk of development of the latter is unknown but is thought to be rare." (in Ruiz-del-Árbor L, Serradilla R. Cirrhotic cardiomyopathy. World J Gastroenterol. 2015; 21 (41) 11502-21). The clinical meaning of prolonged QTc interval (disease prognosis and risk of arrhythmias) was already mentioned in the discussion section.

Regarding the sub-analysis of the 10 patients who were not diagnosed as having CCM, there are no trends to report.

List of abbreviations in order of appearance: CCM, cirrhotic cardiomyopathy; MELD, model for end-stage liver disease; pro-BNP, pro-Brain Natriuretic Peptide; QTc interval, corrected QT interval; TDI, tissue Doppler imaging; LV EDV, left ventricular end-diastolic volume; LV ESV, left ventricular end-systolic volume; LV EF, left ventricular ejection fraction; LV CR, left ventricular contractile reserve; DT, deceleration time; E/A ratio, early diastolic/atrial filling ratio; TIPS, transjugular intrahepatic portosystemic shunt. (**added on the manuscript - after the abstract**)

Reviewer 2:

Well written manuscript, very interesting topic, not totally original results, few important clinical correlations. Few tips to improve the quality of the manuscript as detailed in the list below. MAJOR POINTS: 1-The baseline characteristics of patients should be further detailed. In particular, authors should add the number and the kind of previous decompensations (e.g. ascites, variceal bleeding, hepatic encephalopathy etc.), the medical ongoing therapy (e.g. use of non-selective beta-blockers, carvedilol, diuretics), presence or not of comorbidities such as diabetes mellitus, cardiovascular disease, respiratory, renal diseases. All these aspects are of utmost importance to detect potential confounding factors for the prevalence of the cirrhotic cardiomyopathy (CCM) in this little series. 2-Authors should clarify if the collection of data was prospective or retrospective. 3-It would be interesting giving a clinical follow-up to the series compatible with the risk of worsening of cirrhosis. Due to the high number of Child A patients included, a follow-up of at least 4 years should be preferred. A survival analysis should consider the first decompensation event or a further decompensation that can occur after the basal evaluation of cardiac function, respectively, in compensated and decompensated patients at baseline. 4-Data show an association between QTc prolongation and the presence of varices but not ascites. First of all, it would be important to discriminate the grade of ascites. Second, this difference should deserve any comment in the discussion. MINOR POINTS: 1-The proportion of patients with alcoholic cirrhosis in the main text does not fit with that showed in Table 2-Mean MELD score in the main text should be expressed with decimals as in Table 1.

Answers to Reviewer 1:

MAJOR POINTS:

1 - We agree - **data added on table 1**, except the data regarding the comorbidities such as diabetes mellitus, cardiovascular disease, respiratory, renal diseases because they are part of the exclusion criteria of the study.

2 - Clinical data collection was retrospectively recorded **(added on the manuscript - material and methods section).**

3 - It would be a very interesting idea but the follow-up time is not still enough due to the high number of compensated patients.

4 - There was no relation between QTc interval prolongation or duration and the presence of ascites neither between QTc interval prolongation or duration and the degree of ascites (in that analysis, ascites was graded as absent, mild to moderate (diuretic responsive) and severe (diuretic refractory) - as this sub-analysis does not add any new info we have chosen not to present it - **a comment was added on the manuscript - discussion section**.

MINOR POINTS:

1 - **corrected on the manuscript**

2 - **corrected on the manuscript**

Reviewer 3:

Summary This is a clinical study performed in 26 patients with cirrhosis to examine the clinical features of cirrhotic cardiomyopathy (CCM). They found that the prevalence of CCM was 61.5%. At rest, only 2 (7.7%) patients had diastolic dysfunction and none of the patients had systolic dysfunction. Dobutamine stress echocardiography revealed the presence of diastolic dysfunction in more 6 (23.1%) patients and of systolic dysfunction in 10 (38.5%) patients. QTc interval prolongation was observed in 68.8% of the patients and increased pro-BNP levels in 31.2% of them. They concluded that CCM is a frequent complication of cirrhosis that is independent of liver impairment. Stress evaluation should always be performed, otherwise it will remain an underdiagnosed condition. General comments This is an interesting paper showing new topic. I have following observations. Specific comments Introduction The section is lengthy, particularly second half. Results “compensated (Child-Pugh class A)” Compensation and decompensation should be defined in the Method section. Page 11 ELECTROCARDIOGRAPHIC CHARACTERISTICS The paragraph needs to be organized. Discussion Small sample size should be stressed as a limitation of the study.

Answers to Reviewer 3:

Compensated disease refers to Child-Pugh class A and decompensated disease includes Child-Pugh class B or C patients - **added on the manuscript - methods section**.

We agree - small sample size was stressed as a limitation of the study - **added on the manuscript - discussion and conclusion section.**

Reviewer 4:

Authors report their study on cirrhotic cardiomyopathy from a group of 26 patients. The topic is interesting, but there are some concerns that need to be addressed. 1. The vast majority (89%) of the group had alcoholic cirrhosis (perhaps more as some were listed as mixed cirrhosis). Authors state that alcoholic cardiomyopathy is different from CCM, which should be described here to support their statement. From their discussion it appears that there is much uncertainty about the definition of CCM, so this is a key matter to clarify. 2. The work has a major limitation as the patient sample is indeed small and this should be acknowledged and discussed. Some do not endorse using percentages for less than 100 cases, but at least they should not describe 'prevalence' for this small sample (rather call it proportion or fraction). Also, statistical power for some of their negative results (type II errors) may be explained by this fact. 3. As a result of the above, it appears that there is indeed no clear predictor of CCM in their experience: it just happens independent of etiology/severity of cirrhosis and its major laboratory parameters (creatinine, albumin, and even pro-BNP). Would authors speculate on when to consider CCM in advanced liver disease? This may be important as there are many other settings in which it is not alcoholic but viral or obesity-associated cirrhosis that dominates the picture. 4. Also because of the study size and since no regression analysis could be done, it seems quite premature to state that QTc prolongation is an independent marker of severe liver disease.

Answers to Reviewer 4:

1 - Cirrhotic cardiomyopathy is different from alcoholic cirrhosis. Some years ago, the cardiac dysfunction present in cirrhosis was attributed to the effects of alcohol toxicity on the heart. Subsequent investigations clearly demonstrated that the dysfunction at rest and the blunted cardiac response to stress was associated with cirrhosis *per se* rather than being an adverse effect of alcohol.

- This was extensively discussed by Lee RF in Lee RF Glenn TK, Lee SS. Cardiac dysfunction in cirrhosis. Best Pract Res Clin Gastroenterol 2007;21:125-140.

- Also, other important and recent articles address this item, for instance:

A) Zardi EM, Abbate A, Zardi DM, Dobrina A, Margiotta D, Van Tassell BW, Afeltra A, Sanyal AJ. Cirrhotic cardiomyopathy. J Am Coll Cardiol 2010;10:539-549 - "This syndrome is formally described as cirrhotic cardiomyopathy, which is defined as chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease and irrespective of the causes of cirrhosis, although some etiologies (e.g., iron overload and alcohol consumption) further impact on myocardial structure and function;

B) Ruiz-Del-Árbor L, Serradilla R. Cirrhotic cardiomyopathy. World J Gastroenterol. 2015; 21 (41) 11502-21 - "Initially the impaired left ventricular (LV) performance in cirrhotic patients was thought to be due to the direct toxic effect of alcohol. However, data from investigations performed since 1980s show that the blunted cardiac responses to diverse stimuli is not the result of alcohol. These findings support the concept of a specific heart disease termed "cirrhotic cardiomyopathy". Therefore, CCM is an entity clinically and pathophysiologically different from an alcoholic cardiomyopathy."

In our study, the main etiology for cirrhosis is alcohol, as in other studies reported in the literature: 77.0% have "pure" alcoholic cirrhosis and 11.5% (the ones that are reported as mixed (viral + alcohol)) have alcohol as a co factor of their disease. Indeed, 89% have alcohol as an etiologic factor, but no more than 89%!

2 - We agree - prevalence was replaced by proportion and small sample size was stressed as a limitation of the study - **alteration done on the manuscript.**

3 - As it was explained above in item 1, cirrhotic cardiomyopathy should be considered in every patient with advanced liver disease - cirrhosis, in "all settings/etiologies".

4 - We agree - the word "independent" should be removed - **alteration done on the manuscript.**