We thank the editor and reviewers for the opportunity to submit our revised manuscript **(Manuscript NO: 39293)** entitled: "**Favorable Clinical Outcome of Non-Alcoholic Liver Cirrhosis Patients with Coronary Artery Disease: A Population-Based Study**." The manuscript has been corrected in accordance with the reviewer's comments. ***All of the reviewers' and editors' comments were included and responded point-by-point.*** The below responses were colored, and the changes made in the text and the tables are **highlighted in red**.

Response to Reviewer #1 (Reviewer's ID:03832930) :

I read with interest the original research by Tsai MC et al. The study is of interest since it examines the controversial role of coronary artery disease in the favorable outcome of non-alcoholic liver cirrhosis patients, in a population-based study. The manuscript is well written in a comprehensive way. However, in my opinion, there still are several things need to be clarified.

1. In the abstract, it is not clear if the inclusion period of the newly diagnosed non-alcoholic LC patient was during 2006 or from 2006 until 2011. They did not mention the mean ± SD or median [IC 95% range] of the follow-up period. They should clarify this in the abstract and also give this information in the materials and methods section. The should clearly specified the inclusion date of the first and last subjects included in the analysis

- The inclusion period of the newly diagnosed non-alcoholic LC cohort was from 2006 until 2011. The mean follow-up period for the newly diagnosed non-alcoholic LC cohort (3409 patients) was 1,152±633 days with a median of 1,169 days, maximum of

2,920 days, and a minimum of 7 days. We add the information in the abstract, materials and methods section. Thanks for the suggestion.

2. The authors mentioned that CAD and hyperlipidemia were less prevalent in the control group, however they did not give the prevalence and p values in the abstract. Also, the data regarding CAD prevalence is missing in table 1. The authors should include this information in the abstract and in table 1.

- The prevalence and p values of CAD and hyperlipidemia are added to the abstract and table 1. Thanks for the suggestion.

3. Considering that Taiwan is an endemic area of viral hepatitis, the authors mentioned that this minimized the confounding effects for alcohol consumption in this non-alcoholic liver cirrhosis cohort. However, they do no give any information regarding the treatment for viral infection (hepatitis B and C); was the proportion of treated patient similar in both groups of patients this information should be given in table 2, in the results section and should be discuss the possible influence of the treatment on the results. Moreover, the statistical analyses should be adjusted for the vital treatment.

- Thank you for the suggestion. In Taiwan, under the National Health Insurance (NHI) program, reimbursement for nucleoside analogues for HBV cirrhotic patients meeting the criteria (liver cirrhosis with splenomegaly and HBV DNA ≥ 2,000 IU/mL) began on 1, July 2010 (our inclusion period 2006 – 2011). On the other hand, the proportion of interferon plus ribavirin treatment for HCV infected patient with liver cirrhosis was very low in Taiwan. The proportions of both

hepatitis B and hepatitis C treatment were very low in the inclusion period. Therefore, we did not analyze the influence of treatment.

4. In materials and methods, instead of given de ICD-9-CM codes for the comorbidities (this information could be given in supplemental material) the authors should clearly describe the criteria of diagnosis of how each comorbidity was defined, with special emphasis on the definition of CAD, which is the end point measurement.

- In materials and methods section, we summary the ICD-9-CM codes in a new supplementary table (table appendix 1). We add the criteria of diagnosis of comorbidities which was defined as having 3 times of outpatient visits or one time of admission. We also emphasize the definition of newly diagnosed CAD (1 inpatient or 3 outpatient codes) as the first-time of the CAD. Thanks for the suggestion.

5. Did the authors calculate the sample size to be able to observed a significant association between non-alcoholic LC with CAD? Considering the conflicting results so far published, it is desirable to calculate the statistical power of the cox regression model.

- The sample size needed is 133 cases for 95% confidence levels, estimated by using hypothesized 10 % frequency of outcome factor in the study cohort 3409 cases. The cases of non-alcoholic LC with CAD are 170 which are larger than 133 in the study. In addition, the power of this study is 100% for 95% confidence levels, estimated by 3236 patients risked in CAD disease (5.1%)

in the study group and 16180 patients risked in CAD disease (17.4%) in the control group. Thank you for the suggestion.

6. Family history of CAD is a very important coronary risk factor, was this information recorded in the 3236 patients and in the 16180 controls? Could this information have any influence in the prevalence of CAD in each group? This issue should be discussed in the discussion section.

- The family history was not recorded in the Taiwanese National Health Insurance research database. We add this critical limitation in the discussion section.

7. The authors should briefly explain what does hyperlipidemia means, is TC>200mg/dl, LDL-C, >160 mg/dL, TG>150mg/dl a combination of two or more???

- We add this definition in the materials and methods section. Hyperlipidemia was defined as having any one of the elevated lipid profile (total cholesterol (TC) ≥200 mg/dl, low-density lipoprotein cholesterol (LDL-C), ≥160 mg/dL, or triglyceride (TG) ≥150 mg/dl. Thank you for the suggestion.

8. On page 11, at the end of the second paragraph the authors should include the data of the adjusted model instead of the unadjusted model, and if so, the hepatic encephalopathy is no longer the comorbidity with the highest HR, this should be corrected.

- "Ascites or peritonitis" had the highest AHR 2.34 (95% CI, 2.06-2.65) is corrected as suggested. Thanks for the suggestion.

9. On page 11, in the third paragraph the authors should include the word respectively, after the 95%CI values are given

- We correct the error. Thank you for the suggestion.

10. The authors recognized that the severity of CAD was not recorder. The authors should discuss the potential impact of this important information on the results they have shown.

- We add the important information in the discussion section. A case-control study reported that nonobstructive CAD was more prevalent in cirrhotic patients than matched control subjects (30.6% versus 23.4%, P=0.001) (An, J. et al. *Circulation* 2014) This may contribute to the better survival rates for LC patients with CAD. Thank you for the suggestion.

Response to Reviewer #2 (Reviewer's ID:00060494):

A nationwide retrospective longitudinal Cohort population-based cohort study based on the Taiwanese National Health Insurance research database (NHIRD).

1. In your study, the co-morbidities are different between the study and control group. Therefore, a propensity score based grouping may be considered.

- In the study, the control subjects were matched with the patients in the study cohort in the ratio of five to one (5 control subjects per case-patient) in terms of sex, age (40-49, 50-59, 60-69, and >69 years), residence, and entry year. We were afraid that we were unable to compare the difference of the co-morbidities between study and control cohort if we use propensity score to match the co-morbidities. Thank you for the suggestion.

2. In study group, there are more CAD risk factors (eg, DM, HTN, CKD) but there is less probability to CAD occurrence. Please give an explanation to this issue

- Thank you for the point of view. An, J. et al. reported a case-control study focused on the CAD prevalence of CAD in liver cirrhosis (An, J. et al. *Circulation* 2014). They analyzed asymptomatic liver cirrhosis patients or cirrhotic patients without CAD history and matched controls using computerized coronary angiography. They found nonobstructive CAD (luminal obstruction < 50%) was more prevalent in the matched cirrhotic cases (30.6% versus 23.4%, P=0.001) but obstructive CAD did not differ significantly between the cirrhotic and control groups (7.2% versus 7.9%, P=0.646). The severity of CAD in liver cirrhosis patients was less severe than controls. They also found that DM and HTN were higher in liver cirrhosis patients which were consistent with our study. We believe that liver cirrhosis per se has a protective effect against atherosclerotic events by the favorable cardiovascular risk profiles such as thrombocytopenia, coagulopathy, and low blood pressure.

3. Please supply the data of mean F/U years of these patients. I think that relative less F/U period of such a disease (CAD) may be impact on the Hazard ratios of mortality in non-alcoholic LC patients. It may be a limitation of this study.

- This is an important limitation of this study. We add the follow-up data in the material and methods section and discuss this limitation in the discussion section. The mean follow-up period for the newly diagnosed non-alcoholic LC cohort (3409 patients) was 1,152±633 days with a median of 1,169 days, maximum of 2,920 days, and a minimum of 7 days. Thanks for the suggestion.

Response to Reviewer #3 (Reviewer's ID:02520738) :

To: Editorial Board World Journal of Gastroenterology Title: "Favorable Clinical Outcome of Non-Alcoholic Liver Cirrhosis Patients with Coronary Artery Disease: A Population-Based Study" Dear Editor, I read this manuscript and I think that: -

1. More numerical data should be added to the results section of the abstract. Please provide.

➢ We add more numerical data in the abstract section. Thanks for the suggestion.

2. Inclusion and exclusion criteria should be better described. Please provide. - A flow chart of the study should be added.

➢ Thank you for the suggestions. We redraw the flow chart of the study design (figure 1).

3. The use of ICD9 could also be considered as a limitation of the study design. –

➢ We discuss this important limitation in the discussion section. Thanks for the suggestion.

4. NALC can influence endothelial function and increase cardiovascular risk of individuals. Please discuss such a point in relation to the paper from Ciccone MM et al. J Cardiovasc Med (Hagerstown). 2015 Jan;16(1):11-21.

- Thank you for the suggestion. We add the discuss and the citation of the reference in the discussion section. HBV and HCV hepatitis can influence the vessel function causing endothelial dysfunction has been demonstrated in previous studies. We believe that liver cirrhosis per se has a more powerful protective effect against atherosclerotic events by the favorable cardiovascular risk profiles such as thrombocytopenia, coagulopathy, and low blood pressure.