Answering Reviewers

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The article by Zi-jin Liu et al. is a meta-analysis of published work concerning the outcome of patients with cirrhosis and type 2 diabetes mellitus (T2DM) compared to patients with cirrhosis alone. The authors make a remarkable effort to collect all papers concerning their subject and to select among them the ones complying to preset strict criteria. The subject is clinically interesting, but apparently the literature was not ripe enough to help the authors in their task. The number of relevant articles was small and quite heterogenous in order to end-up with robust results. The authors conclude that T2DM patients with cirrhosis have higher mortality and propensity for hepatocellular carcinoma compared to patients with cirrhosis alone. Differences in episodes of secondary bacterial peritonitis, development of ascites, variceal bleeding and hepatic encephalopathy did not reach statistical significance. The article is short, well written, but leaves several questions unanswered as expressed bellow.

A. General Comments: English language needs further improvement.

Answer: We will let translation company or native speaker further polish our English language.

B. Major Comments:

1. (Page 6, line 2): I suppose that at baseline both T2DM and noT2DM patients would have been in a compensated cirrhosis state and without past events related to complications of cirrhosis.

Answer: Table 1 showed the compensated or decompensated state of liver cirrhosis enrolled in our meta-analysis. You can see most of the studies enrolled not only compensated liver cirrhosis, but also decompensated state of liver cirrhosis. The majority of the original articles not clearly distinguished these two states of liver cirrhosis, because they hypothesized that type2 diabetes not only led to the transferring from compensated to decompensated state by increasing decompensated event like ascites or varies bleeding, but also worsening the decompensated liver cirrhosis by increasing the frequency of decompensated event happening. Due to the relatively small amount of the original article, it's quite hard for us to clearly distinguished the Compensated or decompensated state of liver cirrhosis and made subcategory analysis.

Author	Year	Patients number	Country	Compensated/decompensated liver cirrhosis
Bianchi	1994	382	Italy	Compensated and decompensated
Quintana	2011	110	Mexico	Compensated
Sang	2020	8631	Australia	

				Compensated and decompensated
Wlazlo	2013	226	Netherlands	Compensated and decompensated
Holstein	2002	52	Germany	Compensated and decompensated
Elkrief	2014	342	France	Compensated and decompensated
Veldt	2008	541	Netherlands	Compensated and decompensated
Yin	2019	436	China	Decompensated
Liu	2016	72731	USA	Compensated
Ioannou	2007	2120	USA	Compensated and decompensated
N'kontchou	2006	771	France	Compensated
Wang	2020	207	China	Compensated and decompensated
Nishida	2006	56	Japan	Compensated and decompensated
Yang	2016	739	USA	Compensated and decompensated
Labenz	2020	240	German	Compensated and decompensated
Torisu	2007	47	Japan	Compensated and decompensated
Braia	2016	2556	Romania	Compensated and decompensated

Table 1 Compensated/ Decompensated state of liver cirrhosis.

2. (Page 8, line 3): In order to compare the outcome of cirrhotic patients with or without diabetes type 2, one should verify that both groups were similar at baseline. That means that the authors must pay attention to the following items:

i. Was the state of glucose regulation of diabetic patients similar in all articles used in this meta-analysis? The HbA1c% in all studies must appear in the text and table 1. This note refers especially for the SBP comparisons.

Answer: We have added glucose regulation of DM in table 1 in our manuscript. Nishida's research showed that the prognosis of patients with liver cirrhosis and DM was worse than patients with liver cirrhosis accompanied with normal glucose tolerance

group/ impaired glucose intolerance group[1]. However, as far as we know, seldom research found that the level of blood glucose controlled or HbA1c% might increase the mortality or other liver decompensated events on liver cirrhosis accompanied DM patients. That's probably the reason that most of the original articles didn't make further stratified analysis. Although we realized that blood glucose-controlled level might influence the prognosis of liver cirrhosis, the different standard of blood glucose-controlled level in the original article limited us to make further analysis. (Table 2)

Author	Year	Patients number	Country	Glucose regulation of DM
Bianchi	1994	382	Italy	Not described
Quintana	2011	110	Mexico	Not described
Sang	2020	8631	Australia	Not described
Wlazlo	2013	226	Netherlands	Median non-fasting glucose of 9.8 mmol/l
Holstein	2002	52	Germany	Basal C-peptide of 1.66 ± 0.85 nmol/L
Elkrief	2014	342	France	Not described
Veldt	2008	541	Netherlands	Not described
Yin	2019	436	China	Not described
Liu	2016	72731	USA	Not described
Ioannou	2007	2120	USA	Not described
N'kontchou	2006	771	France	Not described
Wang	2020	207	China	Not described
Nishida	2006	56	Japan	HbA1c (%) of 5.6 ± 1.6%
Yang	2016	739	USA	HOMA2-IR2: 8.3±4.9
Labenz	2020	240	German	HbA1c (%) of 5.1(4.6,5.5)
Torisu	2007	47	Japan	Not described
Braia	2016	2556	Romania	Not described

Table 2 Glucose regulation of diabetic patients.

ii. Was the gravity of cirrhosis similar in the tested (DM) and the control (non-DM) group? The Child-Pugh class and/or the MELD score must appear in the text and analyzed accordingly.

Answer: We have added Child-Pugh class and/or the MELD score of DM in table 1 in our manuscript. As you can see, in most of the studies, the liver function between DM and the non-DM were comparable. However, a few 'real worlds' studies didn't describe

the liver function because they enrolled large number of patients from digital medical systems and they couldn't evaluate patients' liver function one by one. (Table 3)

Author	Year	Patients number	Country	MELD score/Child-Pugh score (Non-DM vs DM)
Bianchi	1994	382	Italy	Child-Pugh score: 7.31±2.28 vs 7.35± 2.20 (p>0.05)
Quintana	2011	110	Mexico	MELD score:10.3 ± 3.7 vs 11.9 ± 4.7 (p=0.07)
Sang	2020	8631	Australia	Not described
Wlazlo	2013	226	Netherlands	MELD score: 12.2±7.5 vs 11.8 ±7.3(p=0.681)
Holstein	2002	52	Germany	Child-Pugh score:44% of patients had stage A cirrhosis, 37% had stage B and 19% had stage C
Elkrief	2014	342	France	Median MELD score of 10
Veldt	2008	541	Netherlands	Not described
Yin	2019	436	China	MELD score: 9.1±2.1 vs 9.2 ±1.9(p=0.537)
Liu	2016	72731	USA	Not described
Ioannou	2007	2120	USA	Not described
N'kontchou	2006	771	France	Not described
Wang	2020	207	China	MELD score:7.22±3.98 vs 8.29±2.35 (p=0.141)
Nishida	2006	56	Japan	Child-pugh score:6.8 ± 2.4 vs 6.9 ± 2.3 (p>0.05)
Yang	2016	739	USA	MELD score: 12.4±5.7 vs 11.6 ±5.1(p=0.04)
Labenz	2020	240	German	MELD score:10(8,15) vs 9(7,13) (p=0.043); Child-Pugh B/C:42.3% vs 36.9% (p=0.453)
Torisu	2007	47	Japan	Not described
Braia	2016	2556	Romania	Not described

Table 3 Liver functions of patients enrolled in meta-analysis

iii. Please make sure and mention it in the text that mortality was liver-related and not overall mortality. It is already well known that cirrhotic patients with T2DM die mainly of cardiovascular complications.

Answer: In 1999, Marchesini first described that cirrhotic patients, even in the presence of overt diabetes, were at low risk of cardiovascular disease. They assumed that low prevalence might be related to shorter duration of diabetic disease, also in relation to reduced life expectancy, as well as to liver disease-induced abnormalities protecting the cardiovascular system from atherosclerosis[2]. Wlazlo and Nishida also found that the majority of the liver cirrhosis accompanied T2DM patient's death were liver-related, and very few were caused by T2DM complications[1,3]. In this meta-analysis, we focused on the all-cause mortality of T2DM and Non-T2DM patients with cirrhosis.

iv. What was the underlying cause of chronic liver disease? In order to have sound results both groups must have had similar etiology of liver disease. Otherwise, groups are not comparable

Answer： The underlying cause of chronic liver disease was described below. In most of the original articles, the etiologies were comparable between T2DM and Non-T2DM groups.

Author	Year	Patients number	Country	Etiology of the patients
Bianchi	1994	382	Italy	Alcohol, HBV, PBC, autoimmune and cryptogenic
Quintana	2011	110	Mexico	Alcohol, HBV, HCV, autoimmunity, and cryptogenic
Sang	2020	8631	Australia	Alcohol, cryptogenic, NAFLD, HBV, metabolic liver disease, autoimmune liver disease, inflammatory liver disease and unspecified
Wlazlo	2013	226	Netherlands	Alcoholic, NASH, viral, autoimmune and others
Holstein	2002	52	Germany	Alcohol, hepatitis C, hepatitis B, cryptogenic, primary biliary cirrhosis, hemosiderosis and hemochromatosis
Elkrief	2014	342	France	HCV
Veldt	2008	541	Netherlands	HCV
Yin	2019	436	China	Alcoholic, virus, AIH and others

Liu	2016	72731	USA	Alcoholic, nonalcoholic and biliary
Ioannou	2007	2120	USA	HBV, HCV, alcohol and others
N'kontchou	2006	771	France	HCV and alcoholic cirrhosis
Wang	2020	207	China	Not described
Nishida	2006	56	Japan	HBV, HCV, alcohol and unknown
Yang	2016	739	USA	HCV
Labenz	2020	240	German	Alcohol, viral hepatitis, NAFLD, autoimmune and cryptogenic
Torisu	2007	47	Japan	Alcoholic
Braia	2016	2556	Romania	Not described

Table 4 Etiology of patients enrolled in meta-analysis

C. Minor Comments:

1. (Page 3, line 2): The word "Therefore" is inappropriate. The sentence which follows is not a consequence of the previous sentence. Consider change.

Answer: We have changed the sentence.

2. (Page 6, lines 15-16): What kind of etiology? Do you mean "etiology of underlying liver disease"? Please clarify.

Answer: 'Etiology' meant the cause of cirrhosis. We have revised it in our manuscript to avoid misunderstanding.

Reference

1.Tsutomu Nishida, M.D., Shingo Tsuji, M.D., Ph.D., Masahiko Tsujii, M.D., Ph.D.,et al, Oral Glucose Tolerance Test Predicts Prognosis of Patients with Liver Cirrhosis, American Journal of Gastroenterology, 2006;101:70–75.

2. Giulio Marchesini, Michela Ronchi, Gabriele Forlani, et al, Cardiovascular Disease in Cirrhosis. A Point-Prevalence Study in Relation to Glucose Tolerance, Am J Gastroenterol 1999;94(3):655–622.

3. Nick Wlazlo, Marleen Greevenbroek, Joyce Curvers, et al, Diabetes mellitus at the time of diagnosis of cirrhosis is associated with higher incidence of spontaneous bacterial peritonitis, but not with increased mortalityClinical Science (2013) 125, 341–348.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Authors conducted a systematic review and meta-analysis of T2DM and liver cirrhosis complications. The manuscript is well-written, with good English. I recommend publishing the article.

My only suggestion is that the paragraph of "Quality of Studies" should be merged with the previous one, one-sentence paragraphs should be avoided.
Answer: We have merged it with the former paragraph in our manuscript.

Science editor: 1 Scientific quality: The manuscript describes a meta-analysis of the type 2 diabetes mellitus increases liver transplant-free mortality in patients with cirrhosis. The topic is within the scope of the WJG. (1) Classification: Grade C and Grade D; (2) Summary of the Peer-Review Report: The authors conducted a systematic review and meta-analysis of T2DM and liver cirrhosis complications. It is well-written and interesting. However, the questions raised by the reviewers should be answered; and (3) Format: There are 2 tables and 7 figures. (4) References: A total of 37 references are cited, including 5 references published in the last 3 years; (5) Self-cited references: There are no self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B and Grade B. A language editing certificate issued by AJE was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, and the PRISMA 2009 Checklist. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by 2 grants. The topic has not previously been published in the WJG.

5 Issues raised:
(1) The "Author Contributions" section is missing. Please provide the author contributions;
Answer: The 'Author Contributions' section is on the first page of our manuscript.

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)
Answer: Since our former funding were suspended, this research was not funded.

(3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;
Answer: We have uploaded the PPT of figures.

(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text;
Answer: We have added 'Article Highlights' parts in our manuscript.

(5) The scientific quality can't meet the requirement of WJG. 6 Recommendation: Transferring to the World Journal of Meta-Analysis.