

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 62721

**Title:** Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis

**Reviewer's code:** 05077656

**Position:** Editorial Board

**Academic degree:** MBChB, MD, MSc, PhD

**Professional title:** Doctor, Lecturer

**Reviewer's Country/Territory:** Germany

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2021-01-16

**Reviewer chosen by:** Jin-Lei Wang

**Reviewer accepted review:** 2021-01-28 09:59

**Reviewer performed review:** 2021-01-28 11:09

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
<https://www.wjgnet.com>

#### **SPECIFIC COMMENTS TO AUTHORS**

The study is important, prospective and highlighting good issues. However, I would recommend re-writing of the abstract. It is so long and showing many results.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 62721

**Title:** Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis

**Reviewer's code:** 05727079

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Italy

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2021-01-16

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-01-22 15:10

**Reviewer performed review:** 2021-01-28 12:48

**Review time:** 5 Days and 21 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

#### **SPECIFIC COMMENTS TO AUTHORS**

Intersting study that opens the route of an accurate understanding of gut microbioma. I think it is necessary, as you said in the conclusions, to increase the number of the persons involved.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 62721

**Title:** Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis

**Reviewer's code:** 03580207

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Associate Chief Physician

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2021-01-16

**Reviewer chosen by:** Jin-Lei Wang

**Reviewer accepted review:** 2021-01-17 06:25

**Reviewer performed review:** 2021-01-30 01:16

**Review time:** 12 Days and 18 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
<https://www.wjgnet.com>

#### **SPECIFIC COMMENTS TO AUTHORS**

This is an interesting study about gut dysbiosis and prognosis in cirrhosis. Main problems: The results of stool microbiome assessed by 16S rRNA gene sequencing should be displayed in objective images by analysis software.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 62721

**Title:** Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis

**Reviewer's code:** 03075520

**Position:** Peer Reviewer

**Academic degree:** MD, MSc

**Professional title:** Chief Doctor, Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2021-01-16

**Reviewer chosen by:** Jin-Lei Wang

**Reviewer accepted review:** 2021-01-17 14:01

**Reviewer performed review:** 2021-01-31 11:45

**Review time:** 13 Days and 21 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

Reviewers' comments Manuscript ID:: 62721 Title:

Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis Gut dysbiosis and prognosis in cirrhosis Comments: Gut dysbiosis is common in cirrhosis. To study how gut dysbiosis affects the prognosis of patients with cirrhosis. The case-control study included 48 in-patient cirrhotics and 21 healthy controls. Stool microbiome was assessed using 16S rRNA gene sequencing. The authors used to assess dysbiosis modified dysbiosis ratio (MDR):  $[\text{Bacilli}(\%) + \text{Proteobacteria}(\%)] / [\text{Clostridia}(\%) + \text{Bacteroidetes}(\%)]$ . Patients with MDR more its median made up the group with severe dysbiosis, others did the group with non-severe dysbiosis. The follow-up period was 4 years. The results showed that the mortality rate of patients with severe dysbiosis was significantly higher than that of patients with non-severe dysbiosis (54.2% vs. 12.5%;  $p=0.001$ ). The presence of severe dysbiosis was independent risk factors for death (HR = 8.6[1.9-38.0];  $p = 0.005$ ). The abundance of Enterobacteriaceae ( $p=0.002$ ), Proteobacteria ( $p=0.002$ ), and Lactobacillaceae ( $p=0.025$ ) was increased and the abundance of Firmicutes ( $p=0.025$ ) and Clostridia ( $p=0.045$ ) was decreased in the gut microbiome in the deceased patients compared with survivors. The abundance of Bacilli ( $p=0.017$ ), Enterococcaceae ( $p=0.005$ ) and Lactobacillaceae ( $p=0.021$ ) was higher and the abundance of Clostridia ( $p=0.047$ ) was lower in those who died during the first year of follow-up compared with those who survived this year. The abundance of Enterobacteriaceae ( $p=0.009$ ) and Proteobacteria ( $p=0.010$ ) was higher in those who died in 2nd-4th years of follow-up compared with survivors. The deceased patients had a higher MDR value than the survivors (0.131[0.069-0.234 vs. 0.034[0.009-0.096];  $p=0.004$ ). If we took an MDR value of 0.05 as the cutoff point, it predicted patient death within the next 4 years with a sensitivity of 65.2% and a specificity of 81.3%. If we used 0.11, then the sensitivity was 81.3% and the specificity was 62.5% (AUC = 0.755[0.611-0.899]). If we applied an MDR



value of 0.14 as the cutoff point, then it predicted patient death within the next year with a sensitivity of 71.4% and a specificity of 82.9% (AUC = 0.767[0.559-0.974]). MDR was higher in patients with cirrhosis than in health controls (0.064[0.017-0.131] vs. 0.005[0.002-0.007];  $p < 0.001$ ), and in patients with decompensated cirrhosis than in patients with compensated cirrhosis (0.106[0.023-0.211] vs. 0.033[0.012-0.074];  $p = 0.031$ ). When taken as the cut-off point MDR value 0.01, it makes it possible to distinguish patients with cirrhosis from healthy individuals with a sensitivity of 81.3% and a specificity of 90.5% (AUC=0.884[0.806-0.962]). MDR correlated negatively with prothrombin ( $r = -0.295$ ;  $p = 0.042$ ), cholinesterase ( $r = -0.466$ ;  $p = 0.014$ ) and serum albumin ( $r = -0.449$ ;  $p = 0.001$ ) level and positively with Child-Turcotte-Pugh scale value ( $r = 0.360$ ;  $p = 0.012$ ). The data above suggest gut dysbiosis is associated with a poor long-term prognosis in cirrhosis. It is a topic of interest to the researchers in the related areas, but the paper needs some improvements before acceptance for publication. My detailed comments are as follows: 1. the introduction, materials and methods in the paper work well, especially the severity of liver disease was determined using the Child-Turcotte-Pugh (CTP) scoring system, Gut microbiome analysis using a Qubit 2.0 fluorimeter (London, UK) and quantitative PCR, amplicon sequences was classified with the Ribosomal Database Project (RDP) classifier and RDP database and Follow-up 2. Results are good and the resolutions of the are high, but the part of discussion is not well discussed combined with results and references and should make some modifications. 3. The language is not fluent, suggesting that it should be edited by an English native editor. 4. The references are not up-to-date, references of the last 10 years should be cited, please cite last 10 years references, especially references for the last 5 years. 5. The conclusion should be concise and only summarize the most important contribution of the research. 6. The format of tables are not formal, they should be revised as the format of three-line table, please revise them. Please make some revisions, especially in the

part of results,discussion ,references and language-editing. After making some revisions,the paper may be considered for publication.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 62721

**Title:** Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis

**Reviewer's code:** 03580207

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Associate Chief Physician

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Russia

**Manuscript submission date:** 2021-01-16

**Reviewer chosen by:** Le Zhang

**Reviewer accepted review:** 2021-03-01 07:43

**Reviewer performed review:** 2021-03-01 07:53

**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

The manuscript has been essentially improved. I have no further questions or



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

suggestions.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Hepatology

**Manuscript NO:** 62721

**Title:** Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis

**Reviewer's code:** 03075520

**Position:** Peer Reviewer

**Academic degree:** MD, MSc

**Professional title:** Chief Doctor, Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Russia

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**Reviewer chosen by:** Le Zhang

**Reviewer accepted review:** 2021-03-01 09:42

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**Review time:** 1 Hour

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

World Journal of Hepatology

REVIEWER' COMMENTS

Manuscript NO: 6272 Manuscript Title: Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis

REVIEWER' COMMENTS: To study the influence of gut dysbiosis on prognosis in cirrhosis, the case-control study included 48 in-patients with cirrhosis and 21 healthy controls. Stool microbiome was assessed using 16S rRNA gene sequencing. We used modified dysbiosis ratio (MDR):  $[\text{Bacilli}(\%) + \text{Proteobacteria}(\%)] / [\text{Clostridia}(\%) + \text{Bacteroidetes}(\%)]$ . Patients with MDR more the median made up the group with severe dysbiosis, others did the group with non-severe dysbiosis. The follow-up period was 4 years. The results showed the mortality rate of patients with severe dysbiosis was significantly higher than that of patients with non-severe dysbiosis (54.2% vs. 12.5%;  $P = 0.001$ ). The presence of severe dysbiosis was independent risk factors for death ( $\text{HR} = 8.6[1.9-38.0]$ ;  $P = 0.005$ ). The abundance of Enterobacteriaceae ( $P = 0.002$ ), Proteobacteria ( $P = 0.002$ ), and Lactobacillaceae ( $P = 0.025$ ) was increased and the abundance of Firmicutes ( $P = 0.025$ ) and Clostridia ( $P = 0.045$ ) was decreased in the deceased patients compared with the survivors. The deceased patients had a higher MDR value than the survivors ( $0.131[0.069-0.234]$  vs.  $0.034[0.009-0.096]$ ;  $P = 0.004$ ). If we applied an MDR value of 0.14 as the cutoff point, then it predicted patient death within the next year with a sensitivity of 71.4% and a specificity of 82.9% ( $\text{AUC} = 0.767[0.559-0.974]$ ). MDR was higher in patients with cirrhosis than in health controls ( $0.064[0.017-0.131]$  vs.  $0.005[0.002-0.007]$ ;  $p < 0.001$ ), and in patients with decompensated cirrhosis than in patients with compensated cirrhosis ( $0.106[0.023-0.211]$  vs.  $0.033[0.012-0.074]$ ;  $P = 0.031$ ). MDR correlated negatively with prothrombin ( $r = -0.295$ ;  $P = 0.042$ ), cholinesterase ( $r = -0.466$ ;  $P = 0.014$ ) and serum albumin ( $r = -0.449$ ;  $P = 0.001$ ) level and positively with Child-Turcotte-Pugh scale value ( $r = 0.360$ ;  $P = 0.012$ ). The data suggest that gut dysbiosis is associated with a poorer long-term prognosis in cirrhosis. It is a topic of interest to the researchers in the related areas, my detailed comments are as follows: 1. the introduction, materials and methods in the paper work very

well ,especially Theoretical substantiation of the modified dysbiosis ratio,the Child-Turcotte-Pugh (CTP) scoring system,.Gut microbiome analysis and Follow-up.  
2.Results are good,and the figures are clear 3.The language is fluent 4.The references are almost up-to-data,except reference8,11,15,17,references of the last 10 years should be cited. Pelase make minor revisions, espically in the parts of references. After making minor revisions,the paper may be considered for publication.