Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: Reviewers' comments Manuscript ID: 84675 Title:Sarcopenia in cirrhosis: prospects for therapy targeted to gut microbiota Comments : muscle mass and function, also known as sarcopenia, is common in patients with cirrhosis and is associated with a poor prognosis. Although the pathogenesis of this disorder has not been fully elucidated, a disordered gut-muscle axis probably plays an important role. Decreased barrier function of the gut and liver, gut dysbiosis, and small intestinal bacterial overgrowth (SIBO) can lead to increased blood levels of ammonia, lipopolysaccharides, pro-inflammatory mediators, and myostatin. These factors have complex negative effects on muscle mass and function. Drug interventions that target the gut microbiota (long-term use of rifaximin, lactulose, lactitol, or probiotics) positively affect most links of the compromised gut-muscle axis in patients with cirrhosis by decreasing the levels of hyperammonemia, bacterial translocation, and systemic inflammation and correcting gut dysbiosis and SIBO. However, although these drugs are promising, they have not yet been investigated in randomized controlled trials specifically for the treatment and prevention of sarcopenia in patients with cirrhosis. No data exist on the effects of fecal transplantation on most links of gut-muscle axis in cirrhosis; however, the results of animal experimental studies are promising. It is a topic of interest to the researchers in the related areas , but the paper needs large improvements before acceptance for publication.My detailed comments are as follows: 1.In this review, GUT-MUSCLE AXIS IN CIRRHOSIS and PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS are discussed along with Treating gut microbiota in cirrhosis: fecal transplantation. 2. The authors aimed to review the advances in GUT-MUSCLE AXIS IN CIRRHOSIS and PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS . But the parts of GUT-MUSCLE AXIS IN CIRRHOSIS is long ,should be abbreviated to 800 words in total ,the parts of PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS Are verbose ,it should be shorten to 1500 words totally.

Authors' response.

Dear Reviewer. Thank you for your suggestion, we have shortened the text as much as possible so as not to lose the meaning that we put in this review

3. There are too many references, they should be shorten to 80 references at most.In addition.The some of 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.

Authors' response.

Dear reviewer. Thank you very much for your suggestion. We have edited the reference list. It contains more than 85% of references to articles published within the last 10 years, and the rest cannot be replaced by newer ones.

4.The conclusion should be concise and only summarize the most important contribution of the research. Pelase make large revisions of the parts of GUT-MUSCLE AXIS IN CIRRHOSIS and PROSPECTS FOR GUT-MUSCLE AXIS THERAPY IN CIRRHOSIS, references, and conclusion.After making large revisions,the paper may be considered for publication.

Authors' response.

Dear Reviewer. Thank you for your suggestion, we have shortened the text as much as possible so as not to lose the meaning that we put in it.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This study analyzed the relationship between intestinal flora and sarcopenia in cirrhosis from several aspects, including imbalance of gut microbiota, excessive growth of gut bacteria, relationship between gut microbiota and gut muscle axis, and therapeutic prospects of gut microbiota regulating gut muscle axis. This study summarizes current relevant animal studies and mechanisms, and the summary is comprehensive. This problem is of great significance in clinical practice. However, there are still some issues to be addressed in this article: 1. It is suggested to supplement the clinical research related to intestinal microbial imbalance and cirrhosis of sarcopenia;

Authors' response.

Dear Reviewer. Thank you for your suggestion, we added this data:

"Patients with sarcopenia had higher serum levels of CRP, TNF-alpha, interleukin 1-beta, 2 and 6, granulocyte-macrophage-colony-stimulating factor, fibroblast growth factor, and C-X-C motif chemokine ligand 10 than patients without it[73]. Although serum LPS and myostatin levels in this study were higher in patients with sarcopenia than in those without, this increase did not reach the limit of significance[73]. There was no significant difference in zonilin and other cytokines levels and reported manifestations of cirrhosis between patients with and without sarcopenia[73]. Patients with sarcopenia were more likely to have ascites, higher Child-Pugh scores[76], and lower albumin levels[75] than patients with normal muscle mass. No other significant associations were reported in these studies on associations between gut microbiota and muscle mass in cirrhosis."

2. It is recommended to supplement the studies on the dominant intestinal flora and sarcopenia of cirrhosis in patients with cirrhosis;

Authors' response.

Dear Reviewer. Thank you for your suggestion. The results of all relevant studies are summarized in the chapter «GUT-MUSCLE AXIS IN CIRRHOSIS».

3. It is suggested to refer to the literatures for clinical studies on the treatment of patients with cirrhosis with intestinal dominant flora, and supplement if necessary.

Authors' response.

Dear Reviewer. Thank you for your suggestion. Tables 1-4, as well as in the text, present the effect of various drugs on the composition of gut microbiota in cirrhosis.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Decreased barrier function of the gut and liver, gut dysbiosis, and small intestinal bacterial overgrowth (SIBO) can lead to increased blood levels of ammonia, lipopolysaccharides, pro-inflammatory mediators, and myostatin. These factors have complex negative effects on muscle mass and function. Drug

interventions that target the gut microbiota (long-term use of rifaximin, lactulose, lactitol, or probiotics) positively affect most links of the compromised gut-muscle axis in patients with cirrhosis by decreasing the levels of hyperammonemia, bacterial translocation, and systemic inflammation and correcting gut dysbiosis and SIBO. The exact mechanisms underlying the development of sarcopenia in patients with cirrhosis have not yet been established. Among the factors contributing to the development of sarcopenia in cirrhosis, disorders of the metabolic function of the liver, decreased appetite, increased muscle autophagy, increased serum myostatin (a protein that blocks muscle growth), catabolic effects of systemic inflammation induced by bacterial translocation from the gut, and low testosterone levels were found. This study aims to review the prospects for therapy targeted to gut microbiota for the sarcopenia in cirrhosis. Overall, this is an interesting study that may be helpful for the clinical management of sarcopenia in cirrhosis subjects. I have several concerns as follow: 1. Gut dysbiosis in patients with cirrhosis, and Small intestinal bacterial overgrowth in cirrhosis. More direct evidence/introduction were needed in these two sections. These two sections only introduce the gut bacterial issue in cirrhosis. How to transform to sarcopenia? Please address it.

Authors' response.

Dear Reviewer. Thank you for your suggestion. The mechanisms of association of gut dysbiosis and SIBO with sarcopenia are described in the chapter "Gut-muscle axis in cirrhosis" and presented in Figure 1.

2. A table is also needed for section "Treating gut microbiota in patients with cirrhosis: prebiotic disaccharides lactulose and lactitol"

Authors' response.

Dear Reviewer. Thank you for your suggestion. The Table 3 on this topic was added.

3. The title "Treating gut microbiota in patients with cirrhosis: rifaximin" may not be suitable. The included studies were related to some other disorders, eg, Alzheimer's disease, Irritable bowel syndrome, Symptomatic uncomplicated diverticular disease, Chronic Kidney Disease, Gut diseases, Ulcerative colitis, Crohn's disease. The same issue in the next several sections.

Authors' response.

Dear Reviewer. We wanted to first briefly describe the general effects of these drugs on the links of the gut-muscle axis, and then to specify them in cirrhosis, making a dialectical transition from the general to the specific.

4. In fact, the data on the fecal transplantation is rather limited, whereas the knowledge on rifaximin, prebiotic disaccharides and probiotics is rather informative. Therefore, the conclusion regarding these treatments needs reconstructed. Probably, rifaximin, prebiotic disaccharides and probiotics should also be mentioned in detailed, and fecal transplantation is a promising future direction instead.

Authors' response.

Dear Reviewer. Thank you for your suggestion. The Conclusion section has been edited.

5. A schematic diagram regarding the treatments (rifaximin, prebiotic disaccharides, probiotics and fecal transplantation) is helpful for the readers to better understanding the concept of this review.

Authors' response.

Dear Reviewer. Thank you for your suggestion. The Figure 2 on this topic was added.

Round 2

Specific Comments To Authors: Reviewers' comments Manuscript ID: 84675 Title:Sarcopenia in cirrhosis: prospects for therapy targeted to gut microbiota Comments： Decreased muscle mass and function, also known as sarcopenia, is common in patients with cirrhosis and is associated with a poor prognosis. Although the pathogenesis of this disorder has not been fully elucidated, a disordered gut-muscle axis probably plays an important role. Decreased barrier function of the gut and liver, gut dysbiosis, and small intestinal bacterial overgrowth (SIBO) can lead to increased blood levels of ammonia, lipopolysaccharides, pro-inflammatory mediators, and myostatin. These factors have complex negative effects on muscle mass and function. Drug interventions that target the gut microbiota (long-term use of rifaximin, lactulose, lactitol, or probiotics) positively affect most links of the compromised gut-muscle axis in patients with cirrhosis by decreasing the levels of hyperammonemia, bacterial translocation, and systemic inflammation and correcting gut dysbiosis and SIBO. However, although these drugs are promising, they have not yet been investigated in randomized controlled trials specifically for the treatment and prevention of sarcopenia in patients with cirrhosis. No data exist on the effects of fecal transplantation on most links of gut-muscle axis in cirrhosis; however, the results of animal experimental studies are promising. It is a topic of interest to the researchers in the related areas ， but the paper needsome improvements before acceptance for publication.My detailed comments are as follows: 1. There are still too many references,they should be shorten to 80 references at most.In addition.The some of 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. 2.The conclusion should be concise and only summarize the most important contribution of the research. Pelase make some revisions of the parts of references， and conclusion again.After making some revisions,the paper may be considered for publication.

Authors' response.

Dear editor and reviewer. Thank you for your recommendations. We have edited the reference list. It contains more than 85% of references to articles published within the last 10 years, and the rest cannot be replaced by newer ones. We have removed all

irrelevant references, trying to keep those that will be useful to readers in order to expand their knowledge on citation topics. Although this number is slightly higher than most of the reviews published in the World Journal of Gastroenterology (196 versus 130-170), we do not think that this is a problem. The Conclusions section of our manuscript has 3 sentences and 82 words, we have shortened it as best we could and it only summarize the most important contribution of the research.