Dear **Prof. Tarnawsk,**

We thank the referees for their careful reading our manuscript and for giving us many useful comments. In response to the referees' comments, we have revised the manuscript: **ID 42016**. We look forward to the publication of our manuscript in the *World Journal of Gastroenterology*.

Response to Reviewer 1:
Thank you for your detailed comments. They have helped us improve our manuscript.

Comment 1: The Authors should try to analyze also the risk factors for the occurrence of complications.

Reply: We agree with the reviewer's concerns on this point. In accordance with the reviewer's comment, we have added the following text in the text (p.12, lines 27-32).

"Risk factors for the occurrence of complications
According to any grade AE, no significant differences between patients with and without adverse events were found with respect to clinical characteristics. According to ≥Grade 3 AE, 2 patients with portal vein thrombosis were diagnosed as having Child-Pugh class B and had a history of previous variceal bleeding with subsequent endoscopic treatment."

Response to Reviewer 2:

Thank you for your detailed comments. They have helped us improve our manuscript.

Comment 1: It is to be cleared if the dose of this drug can be increased in case of big splenomegaly, and if the treatment can be continued all over the life

Reply: We agree that additional information on the administration of increased dose and long term as the reviewer suggested would be valuable. However, there is no study about administration of long term. Therefore, we have added about "the dose of this drug" in the following text and Ref (p.13, lines 21-25).

"Based on the results of this phase 2b study, a dose-related increase in the maximum platelet count and duration of the maintenance of the increase in platelet count was reported[15]. When the dose of this treatment drug can be increased in case of severe splenomegaly, a treatment response may be achieved."

"15 Tateishi R, Seike M, Kudo M, Tamai H, Kawazoe S, Katsube T, Ochiai T, Fukuhara T, Kano T, Tanaka K, Kurokawa M, Yamamoto K, Osaki Y, Izumi N, Imawari M. A randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. J Gastroenterol. 2018. [Epub ahead of print] [PMID: 30105510 DOI: 10.1007/s00535-018-1499-2] "

Response to Reviewer 3:
Thank you for your detailed comments. They have helped us improve our manuscript.

Comment 1: According to the authors, the study was retrospective. However, several characteristics of design such as the fixed times of blood sampling (1, 5, 12 and 28 days), the fact that doses of other drugs administered prior to enrollment were unchanged and blood transfusions were not administered during lusutrombopag administration are only possible in a prospective study with a predefined design and inclusion and exclusion selection criteria or in a retrospective study if patients selection is performed according to these criteria.

Reply: We agree with the reviewer's concerns on this point. In accordance with the reviewer's comment, we have changed the following text (p.7, lines2-5 and 17-20).

"This study enrolled thrombocytopenic patients, who received oral lusutrombopag (3.0 mg/day for 7 days), and from whom blood samples to analyze changes in platelet counts were collected on days 1, 5, 12 (or the maximum count), and 28, according to the manufacturer's prescription guidelines."
"patients with hematologic disease, past history of thromboembolism, who underwent blood or platelet transfusions in the previous 2 weeks, or those who had changes in their doses of conventional drugs were excluded."

Comment 2: If this is the case, how many patients had been treated with lusutrombopag from February 2015 to March 2018 in the four study's centers and how many patients were excluded from the study because a blood sample was not available or they receipt a treatment or a transfusion?

Reply: We agree with the reviewer's concerns on this point. In accordance with the reviewer's comment, we have added the following text (p.9, lines 21-28).
"A total of 59 patients were treated with lusutrombopag from February 2015 through March 2018 in the four study centers. Of these, 6 patients did not meet the above

inclusion criteria (3 patients received an insufficient dose of the trial drug during the period of the study, 2 patients had a change in the doses of their conventional drugs, and 1 patient received a platelet transfusion before day 12). When we assessed the remaining 53 patients for eligibility, 3 patients were excluded because of missing data regarding their splenic volume and/or their blood samples."

Comment 3: In most clinical trials of lusutrombopag, the main outcome was the number of patients who needed a blood transfusion. The change in the platelet count was a secondary outcome. In the present manuscript, to study a variable as the percentage of patients who receipt a blood transfusion is not possible due to the possible patient selection bias described in the previous paragraph. How many patients treated with lusutrombopag needed a blood transfusion and were not included in the study? What was the spleen size of these patients? Limitations of the main variable used in this study (change in the platelet count) should be discussed by the authors.

Reply: A total of 59 patients had been treated with lusutrombopag from February 2015 through March 2018 in the four study's centers. Of these, 9 patients did not meet the above inclusion criteria. One patient had received a platelet transfusion before day 12. Furthermore, strategies to reduce or avoid platelet transfusions not achieved by the present study where only the relationship between the response to lusutrombopag and splenic volume has been showed.
In accordance with the reviewer's comment, we have added the following text (p.10, lines 25-32 and p.11, lines 1) (p.15, lines 1-6)

"Thrombocytopenic patients received blood transfusions
In the non-responder group (n = 10), 2 patients received platelet transfusion prior to an elective invasive procedure. One patient was a woman with HCV-related liver cirrhosis, and the splenic volume was 890 ml. Her on pre-treatment, post-treatment, and post-platelet transfusion platelet counts were 4.1, 5.5, and 6.5 $\times 10^4$/μl, respectively. Another patient was a man with HBV-related liver cirrhosis, and the splenic volume was 1720 ml. His platelet count on pre-treatment, post-treatment, and post-platelet transfusions were 4.0, 4.8, and 5.2 $\times 10^4$/μl, respectively."

"Our final objective was to minimize the administration of transfusion for reducing the incidence of bleeding events in thrombocytopenic patients. However, strategies to reduce or avoid platelet transfusions not achieved by the present study where only the relationship between the response to lusutrombopag and splenic volume has been showed."

Comment 4: Logistic regression has been made using dichotomous independent variables. Dichotomization of continuous variables has been performed using median values. Why median values were selected as cut-off points instead of using splines?. Why were continuous variables such as platelet or leucocyte counts not included in the regression model as numeric variables?. Are the p-values obtained in the logistic regression analysis different if independent numeric variables are used without categorization?

Reply:
The reason of median values selected as cut-off points instead of using splines is that We were interested in analysis by dichotomous independent variables using median values rather than analyzing by independent numeric variables.
When independent numeric variables are used without categorization, the *P*-value is below.

	single regression model			
	n	OR	95% CI	P-value
Splenic volume (per 1)	50	0.995	0.992 , 0.998	**0.002**
Splenic volume (per 10)	50	0.954	0.926 , 0.983	**0.002**
Splenic volume (per 100)	50	0.626	0.463 , 0.846	**0.002**
Sex_Female (vs. Male)	50	5.400	0.621 , 46.959	0.126
Age (per 1)	50	1.015	0.948 , 1.085	0.675
PLT ($\times 10^4/\mu l$) (per 1)	50	1.114	0.580 , 2.142	0.746
HB (per 1)	50	1.457	1.024 , 2.072	**0.036**
BUN (per 1)	50	0.949	0.846 , 1.064	0.370
Child score (per 1)	50	1.077	0.682 , 1.702	0.750

WBC (per 1)	50	1.001	1.000 , 1.002	**0.026**
WBC (per 100)	50	1.110	1.012 , 1.217	**0.026**
WBC (per 1000)	50	2.837	1.129 , 7.127	**0.026**
weight (per 1)	50	0.945	0.893 , 1.001	0.054
Ammonia (per 1)	50	0.994	0.979 , 1.009	0.439
Ammonia (per 10)	50	0.941	0.808 , 1.097	0.439

	multiple regression model 1： forced entry		
	OR	95% CI	P-value
Splenic volume (per 1)			
Splenic volume (per 10)			
Splenic volume (per 100)	0.651	0.465 , 0.913	**0.013**
Sex_Female (vs. Male)	—		
Age (per 1)	—		
PLT (×10^4/μl) (per 1)	—		
HB (per 1)	1.231	0.792 , 1.913	0.356
BUN (per 1)	—		
Child score (per 1)	—		
WBC (per 1)			
WBC (per 100)			
WBC (per 1000)	1.101	0.986 , 1.229	0.087
weight (per 1)	—		
Ammonia (per 1)			
Ammonia (per 10)	—		

	multiple regression model 2： Forward selecton		
	OR	95% CI	P-value
Splenic volume (per 1)			
Splenic volume (per 10)			

Splenic volume (per 100)	0.635	0.469 , 0.859	**0.003**
Sex_Female (vs. Male)	—		
Age (per 1)	—		
PLT (×10^4/μl) (per 1)	—		
HB (per 1)	n.e.		
BUN (per 1)	—		
Child score (per 1)	—		
WBC (per 1)			
WBC (per 100)			
WBC (per 1000)	n.e.		
weight (per 1)	—		
Ammonia (per 1)			
Ammonia (per 10)	—		

Comment 5: According to univariate analysis showed in table 2 the p-value of white blood cells was 0.044. Is this a mistake? If not, why this variable was not considered in multivariate analysis?

Reply: We mistakenly wrote in the Table 2. We corrected it.

Comment 6: In the abstract and core tip sections, the authors state that splenic volume influences the response to lusutrombopag or that larger spleen size appears to reduce the effect of lusutrombopag in terms of platelet count. These statements are not supported by data from the manuscript where only a statistical association has been showed (not a cause-effect relationship).

Reply: We showed that splenic volume was associated with a change in platelet count ($r = -0.524$, $P = 0.001$). Splenic volume increase was negatively related to changes in the platelet count. Correlation between change in platelet count and splenic volume are supported by data from. Please see the result (p.1, line 1-4) and Figure 3.

However, the response to lusutrombopag, which mean strategies to reduce or avoid platelet transfusions, were not achieved by the present study. To make this point clearer, we changed the abstract, core tip sections, and the text (p. 12, lines 10).

“CONCLUSION:
Splenic volume influences change in platelet counts after administration of lusutrombopag in patients with chronic liver disease. ”

“Core tip:
Splenic volume influences change in platelet counts after administration of lusutrombopag in patients with chronic liver disease. Splenic volume increase was negatively related to changes in the platelet count. ”

Thank you again for your comments on our manuscript. I trust that the revised manuscript is now suitable for publication in the *World Journal of Gastroenterology*.

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