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December 4, 2019

Re: Early treatment efficacy of S-adenosylmethionine in patients with intrahepatic cholestasis: A systematic review (Manuscript No: 51365)

To the Editorial Office,

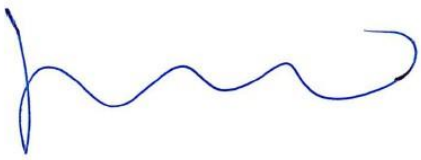
On behalf of myself and my co-authors, we are pleased to enclose the above referenced manuscript for resubmission to World Journal of Hepatology.

We thank the reviewers for their insightful comments, and we believe that these have now been fully addressed, where possible, in this revised version of the manuscript. Please find detailed responses to each comment in the table at the end of this letter. In addition to addressing these comments, we have implemented the style changes requested by the Editor. All alterations we have made have been clearly denoted by highlighted text in the enclosed revised manuscript.

We hope that the manuscript now meets the requirements of World Journal of Hepatology and look forward to hearing from you at your earliest convenience.

Respectfully,

José M Mato



Reviewer	Comment	Author response
1	None	None
2	Excellent updated systematic review	None
3	In this manuscript the authors reported data of a systematic review on the Early treatment efficacy of S-adenosylmethionine in patients with intrahepatic cholestasis. I appreciate this work. However, I think that among the limitations, should also be reported the small sample size both in term of study number and cohort included.	We have added a sentence on sample size in the limitations section of the discussion on page 17. Both the number of studies and the number of patients are discussed, as requested.
	When the authors reported the reference number 2, should be added also the reference "Expanding etiology of progressive familial intrahepatic cholestasis. Henkel SA, Squires JH, Ayers M, Ganoza A, Mckiernan P, Squires JE. World J Hepatol. 2019 May 27;11(5):450-463.", because this type of cholestasis represents an important chapter in this field. Some reference should be updated: I suggest to replace the number 12 with Testino et al. Minerva Gastroenterol Dietol. 2018 Sep;64(3):187-189.	We thank the reviewer for this comment. We have now added both the Henkel 2019 and Testino 2018 references to the manuscript (refs 3 and 14, respectively). However, please note that we suggest the Lu and Mato 2012 reference (formerly ref 12, now ref 13) should not be removed from the manuscript entirely as it contains information not found in the Testino 2018 reference, including details on AdoMet biochemistry.
4	One point the authors did not highlight was source of AdoMet used in studies. While it is assumed that pharmaceutical grade (fully validated and tested) AdoMet was used in these clinical studies. This should be discussed in the paper. E.g., could differences in early efficacy be linked to source/type of AdoMet?	All the studies in this review used pharmaceutical grade AdoMet. As such, we have added the following statement on page 16: *"Finally, all the studies included in this review used pharmaceutical grade AdoMet; it is uncertain whether similar findings would be observed from AdoMet formulations of different quality or from alternative manufacturing techniques"*
	The majority of the studies highlighted in this review are old – over 20 years old. E.g., the two randomized, double-blinded clinical trials. Is there some significance to the fact that the early efficacy of AdoMet in treatment IHC has not been further investigated in the field?	We thank the reviewer for this insightful comment. While it is notable that some of the references are over 20 years old, four of the nine included studies were published between 2013 and 2018. We believe it is unlikely that there is any significance in the fact that the early efficacy of AdoMet has not been further investigated; on this topic, we have already noted in the discussion on page 17 that "*prospective, randomized, placebo-controlled clinical studies are needed to establish the speed of onset of AdoMet efficacy, and the subsequent clinical impact on patient outcomes, in the treatment of specific liver diseases"*.

	It is recommended that the authors include original research papers for biological effects of AdoMet indicated in Figure 1. For example, cite papers showing the anti-inflammatory, TNF lowering, IL-10 producing, ROS decreasing, etc….properties of Adomet.	Original research manuscripts have been cited for the biological effects of AdoMet in Figure 1 as requested.
	It is appreciated that the authors provided an extensive discussion of the limitations of this paper. It is likely that the underlying cause of IHC is important in determining early efficacy. Is it also possible that severity and duration of IHC could impact outcomes? Maybe a small discussion on this topic could be added.	We have already mentioned in the discussion section on page 17 that *"we included studies of patients with a broad variety of underlying chronic liver diseases, and we recognize that the heterogeneity of the studied populations was a confounding factor that may mask the true treatment effects in specific underlying diseases."* However, we have now added further information to this paragraph on page 17 to acknowledge that differences in the severity and duration of IHC in the different studies could have had an impact on clinical outcomes and that not all patients with IHC have a deficiency in AdoMet synthesis.