



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47009

**Title:** Association of proton pump inhibitors with the risk of hepatic encephalopathy in advanced liver disease: A meta-analysis

**Reviewer's code:** 03477219

**Reviewer's country:** Italy

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-03-13 11:17

**Reviewer performed review:** 2019-03-14 10:04

**Review time:** 22 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input checked="" type="checkbox"/> Yes
			<input type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

Authors aim is the evaluation the risk of HE development in patients with advances liver disease. The paper is interesting, but deserves several concerns: different type of study are considered. In particular there are conference abstracts. These studies,



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generally, have no definitive conclusions and in this case could provide misleading results. I suggest to eliminate abstract from the analysis, being result slight similar The study by Lin et al is aimed to assess the role of PPI in a particular setting: the acute HBV infection on chronic liver disease. This is, maybe, the case of an Acute HE and not the C-type HE. Please explain As well known HE is frequently consequent a precipitating event. Please clarify and add results following this suggestion As authors report correctly, the presence of MHE was not assessed in all studies analyzed and this could underestimate the risk of overall HE. This is in my opinion a great limitation of the study.

#### INITIAL REVIEW OF THE MANUSCRIPT

##### *Google Search:*

- The same title
- Duplicate publication
- Plagiarism
- No

##### *BPG Search:*

- The same title
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- No



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**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47009

**Title:** Association of proton pump inhibitors with the risk of hepatic encephalopathy in advanced liver disease: A meta-analysis

**Reviewer's code:** 00009492

**Reviewer's country:** Japan

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-03-13 23:43

**Reviewer performed review:** 2019-03-23 14:58

**Review time:** 9 Days and 15 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

This review article states an association of proton pump inhibitors with the risk of hepatic encephalopathy in advanced liver disease. The data of this article is well written and summarized. However, the data about the association of proton pump inhibitors



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with the risk of hepatic encephalopathy are different among the existing articles and among various countries. Authors should discuss why such variable data are available.

**Major Criticism** 1. The prevalence of *H. pylori* infection and the degree of gastric atrophy differ among various countries. *H. pylori* infection causes lower expression of proton pump and successful eradication increases its expression. The effect of PPI is different between *H. pylori* negative and positive subjects. These factors influence largely the level of acid secretion and the effect of proton pump inhibitors. Therefore, authors should focus on these factors to review an association of proton pump inhibitors with the risk of hepatic encephalopathy, even if direct association is not demonstrated.

Gut. 2010 Jul;59(7):874 Am J Physiol Gastrointest Liver Physiol. 2014 Apr 1;306(7):G606 Gut. 2006 Feb;55(2):152 Aliment Pharmacol Ther. 2006 Nov 15;24(10):1445 2. Proton pump inhibitors are mainly metabolized by liver metabolizing isozyme CYP2C19 including extensive metabolizer, poor metabolizer and intermediate type. Tsai CF et al. reported that rabeprazole is not associated with an increased risk of hepatic encephalopathy. Therefore, it is difficult to unify easily such an association among all proton pump inhibitors. Please describe possible association between this isozyme and effect of PPI. Aliment Pharmacol Ther. 2013 Nov;38(9):1129 Turk J Gastroenterol.

2016 Sep;27(5):408 Aliment Pharmacol Ther. 2012 Apr;35(7):810 **Minor Criticism** 1. Introduction section. At present, several factors have been identified that lower the incidence of HE, such as infection, constipation, gastrointestinal bleeding, and the use of some nervous system drugs. Is this sentence correct? 2. Introduction section. High-quality evidence from Europe and China was published in 2018. Authors refer to a lot article in this review from various areas. Therefore, this sentence should be deleted.

**INITIAL REVIEW OF THE MANUSCRIPT**



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## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 47009

**Title:** Association of proton pump inhibitors with the risk of hepatic encephalopathy in advanced liver disease: A meta-analysis

**Reviewer's code:** 02441154

**Reviewer's country:** Taiwan

**Science editor:** Jia-Ping Yan

**Reviewer accepted review:** 2019-03-19 22:08

**Reviewer performed review:** 2019-04-01 21:37

**Review time:** 12 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
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		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

The aim of this meta-analysis was to evaluate the pool risk of hepatic encephalopathy in patients with advanced disease who use proton pump inhibitors (PPIs). My specific comments are as follows: Comment 1. Methods, P5, line 9: Please clearly describe when



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is the date of database inception. Comment 2. P6, Methods: What were the purposes of PPI use (prophylactic use or non-prophylactic use) in these included studies? How many studies included patients using PPIs for prophylaxis of some diseases? Comment 3. P22, Results: Please show the Forest plot evaluating the association between PPI and hepatic encephalopathy with stratification analyses based on prophylactic and non-prophylactic uses of PPIs. Comment 4. P22, Results, P22, Figure 5. The rate ratios of in-hospital case control studies and current-definition cohort studies are quite different (3.51 vs 1.36). Please explain the difference in the Discussion section. The rate ratios concerning the association between PPI use and hepatic encephalopathy in the in-hospital case control studies might be over-estimated because these studies included patients using PPIs for upper gastrointestinal bleeding, and upper gastrointestinal bleeding was a risk factor of hepatic encephalopathy. Comment 5. Discussion: Do the results of this meta-analysis change the clinical practice for PPI use in patients with advanced disease? What are the scenarios that PPIs are over-used in current practice? Comment 6. Discussion: Please include selection bias as a limitation in these included studies.

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Plagiarism

No