PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Systematic review with a meta-analysis: Clinical effects of statins on the reduction of portal hypertension and variceal haemorrhage in cirrhotic patients
AUTHORS	Wan, Sizhe; Huang, Chenkai; Zhu, Xuan

VERSION 1 – REVIEW

REVIEWER	Cui Xiaobing Shenzhen Hospital of Southern Medical University, China
REVIEW RETURNED	21-Mar-2019

GENERAL COMMENTS	This review focus on effect of statin therapy on portal hypertension and variceal bleeding. By including SEVEN RCT and ONE retrospective cohort, the authors conclude that statin use might decrease portal hypertension and the risk of variceal bleeding. The study “Flores, 2014”(Ref. 28) was published as a poster in The Liver Meeting 2014, which having the same authors and institution of the other study “Pollo-Flores 2015”(Ref. 29). There is a risk to using overlapping data.

REVIEWER	Kristen Tecson Baylor Heart and Vascular Institute, USA
REVIEW RETURNED	28-Mar-2019

GENERAL COMMENTS	Please note that this is a statistical review. Search Results: Please elaborate on the 12 studies that were excluded for lack of interesting results - as it is currently written, it seems this method could have introduced bias. You may want to immediately refer the reader to Figure 1 for the 44 full articles that were deemed ineligible; based on the text only, the reader has no explanation. Description of Included studies: For a meta-analysis that included 7/8 RCTs, it was shocking to see only 28% of patients were exposed to statin. Please make mention that the vast majority of the sample size was driven by the observational study, in which there were many nonusers. Additionally, what were the durations of statins for the other 2 studies not mentioned in this section? Throughout results/limitations: Please explain to the readers what these high levels of heterogeneity mean for their inferences of the results and elaborate in the limitations section.

	Limitations: You mention that you adjusted for confounders, but this was not mentioned in the methods section. Please add. Please also comment on the available degrees of freedom and model (in)stability for incorporating these variables. Please also make it clear throughout that the RRs are adjusted. Please comment on the Flores and Polloflores studies each having 0 event counts in the control arms as well as the 95% confidence intervals that range from 0 - 242 (wow!! I don't know if I've seen confidence intervals for RRs that wide in press before). Please discuss continuity corrections, and add this as a source of bias to your limitations. Perhaps you should also consider Poisson regression to overcome this small event count problem.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Q: The study “Flores, 2014”(Ref. 28) was published as a poster in The Liver Meeting 2014, which having the same authors and institution of the other study “Pollo-Flores 2015”(Ref. 29). There is a risk to using overlapping data.

A: Dear reviewer, thanks for your advice. Although the two studies were from the same authors and institutions, the inclusion criteria and research samples in the two studies were still different by communicating with the authors. So they are not overlapping data.

Reviewer: 2

Q: Please elaborate on the 12 studies that were excluded for lack of interesting results - as it is currently written, it seems this method could have introduced bias. You may want to immediately refer the reader to Figure 1 for the 44 full articles that were deemed ineligible; based on the text only, the reader has no explanation.

A: Dear reviewer, thanks for your advice. We explain this in “Search Results” section
“because they did not clearly report the number of patients with improved in portal hypertension and variceal haemorrhage ”

Q: Description of Included studies: For a meta-analysis that included 7/8 RCTs, it was shocking to see only 28% of patients were exposed to statin. Please make mention that the vast majority of the sample size was driven by the observational study, in which there were many nonusers. Additionally, what were the durations of statins for the other 2 studies not mentioned in this section?

A: We included 7 RCTs and one cohort study. In that cohort study, 2,062 patients who were not exposed to statins were included, thus lowering the final statistic. Excluding this cohort study, the remaining 7 RCTs included 404 patients with cirrhosis, 42% of whom were exposed to statins. “Mohanty 2016” did not explicitly mention the duration of statins (PMID: 26484707). In the “Abraldes 2016”, the duration of statin treatment was 2 years (PMID: 26774179).

Q: Throughout results/limitations: Please explain to the readers what these high levels of heterogeneity mean for their inferences of the results and elaborate in the limitations section.

A: I explained the high levels of heterogeneity in the limitations section of the “Discussion” through the track changes mode.
“In some of the results, we have a large heterogeneity, which may be due to the inconsistency of the inclusion and exclusion criteria we included in the study. In addition, patients with various etiologies of cirrhosis were not researched separately because of insufficient information, which may explain the substantial heterogeneity. So we performed a subgroup analysis to try to eliminate this difference, significantly reducing heterogeneity in some subgroup analyses.”

Q: Limitations: You mention that you adjusted for confounders, but this was not mentioned in the methods section. Please add. Please also comment on the available degrees of freedom and model (in)stability for incorporating these variables. Please also make it clear throughout that the RRs are adjusted.

A: I am very sorry that this is a clerical error. I originally meant that “although individual studies adjusted for various confounders (e.g., age, sex, CTP score, and MELD score), there are residual confounders that could not be completely adjusted remained”. The manuscript has been modified through the track changes mode.

Q: Please comment on the Flores and Polloflores studies each having 0 event counts in the control arms as well as the 95% confidence intervals that range from 0 - 242 (wow!! I don't know if I've seen confidence intervals for RRs that wide in press before). Please discuss continuity corrections, and add this as a source of bias to your limitations.

A: I have commented in the limitations section of the “Discussion” through the track changes mode.
“In the two studies, the 0 event counts in the control group may be due to the fact that the placebo used in the control group is not a drug such as NSBB that has been proven to have a reduced portal pressure, leading to a wide 95% confidence intervals. The quality assessment of the RCT suggests that the quality of the two studies is acceptable, so we have no good reason to exclude these studies. The number of patients included in some studies is insufficient, so continuity corrections is not used, which may increase the risk of bias.”