

Dear Editor

Thank you very much for giving us the opportunity to revise our manuscript entitled: "Autoimmune hepatitis: old or new? A systematic review in older patients" (Manuscript NO: 47389) (The title of the paper has been modified in the revised version of the manuscript)

We have appreciated the comments of the Editor and the Reviewers and addressed them in both our letter and the resubmitted manuscript. Please find our point-by-point responses below.

We hope that these answers satisfy the concerns of the Reviewers and that our paper is now suitable for publication in the World Journal of Gastroenterology.

Best Regards

Marilena Durazzo

Reviewer #1 (02441161)

The authors performed a systematic review of the literature on autoimmune hepatitis treatment in the elderly. Their study confirmed that conventional treatment is effective in elderly patients and efficacy appears even greater than in the young subjects. And Early start of treatment is recommended to achieve remission and to avoid progression. There are some Grammar mistakes, like those, drug induced (drug-induced), were (was): Information including the first author name, publication year, country, study design, total sample size, number of elderly patients, follow-up time were also extracted for each included study. Out (Out of): Out the 15 remaining studies, clicical (The clinical): However, clinical presentation first line (first-line): first line treatment...

We apologise for our spelling and grammar mistakes that have been amended in the revised version of the manuscript (changes highlighted in blue). Moreover, English language editing was performed by one of the co-authors (see attached certificate) to improve readability and to ensure the manuscript text conforms to WJG standards (changes highlighted in red). Finally, the title of the manuscript has been slightly changed.

1. "Drug induced" was replace by "drug-induced" (page 6 line 18)
2. The sentence "Information ...was" has been replaced by "data...were" (page 7 lines 19-21)
3. "Out the" was changed in "Out of the" (page 8 line 3)
4. "However, clinical presentation" was changed in "The clinical presentation" (page 8 line 10)
5. "First line" was replace with "first-line" (page 8 line 23)

Reviewer 2 (03210617)

In this manuscript, Marilena Durazzo et al performed a systematic review of the available literature on AIH treatment in elderly patients. The following issues need to be considered:

1. *Does the literature of different diagnostic criteria affect the results of the review?*

Diagnostic criteria for AIH differed in the included studies. Specifically, five studies used the 1999 revised IAIHG criteria, both diagnostic scoring systems were used by Zhang Y et al, while the study by Zachou K et al used the 2008 simplified IAIHG criteria. This has been specified in the revised version of the manuscript (page 8 lines 17-19) (changes highlighted in light-blue). Moreover, we have also underlined in the Discussion that heterogeneity exists among studies in the diagnostic criteria (page 11 line 15)(changes highlighted in light-blue). We agree with the Reviewer that the use of different diagnostic criteria may affect results of systematic reviews. However, the only study that used different diagnostic criteria (Zachou K) did not significantly contribute to our analysis and conclusions as it assessed the performance of an alternative first-line treatment with prednisolone plus MMF.

2. *Are the characteristics of autoimmune hepatitis and the response to treatment different among elderly patients of different age groups? For example, the difference between 60-year-old patients and 80-year-old patients.*

We agree with the Reviewer that AIH both characteristics and response to treatment may vary in elderly patients of different age groups. Unfortunately, six out of the seven included studies did not further stratified elderly patients in different age subgroups. Therefore, we are unable to provide results on this relevant point and this limit of the review has been acknowledged in the Discussion (page 11 line 16)(changes highlighted in yellow).

3. Are there any differences in response to treatment among different ethnic groups of elderly patients with autoimmune hepatitis?

In our systematic review, two studies (Schramm C and Czaja AJ) included Caucasian patient only, while all patients were Chinese in the study by Zhang Y. Response rate to therapy was similar in the Czaja and Zhang Y studies, but greater in the Schramm C study. No information on ethnicity was provided by the other studies. This has been reported in the results (page 9 lines 14-18)(changes highlighted in purple), though no final conclusion can be drawn on the effect of ethnicity on the response to treatment given the paucity of available data.

Reviewer #3 (01548565)

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease, potentially leading to liver cirrhosis and hepatic failure. AIH carries a poor prognosis, but it responds well to steroids and azathioprine therapy, but the best treatment in elderly patients remains unclear. It has been reported that an higher incidence of AIH in older patients in the last decades, data concerning its treatment are still limited. This systematic review tailored on this subgroup of patients, aiming to assess the efficacy and safety of treatment options for AIH in this population. Although treatment options of AIH in elderly patients are challenging, this review supports the use of steroids and azathioprine, being safe and effective in inducing remission. However, sample sizes were small, and the quality of the included studies relatively low. There was heterogeneity between studies in the definition of outcomes, cluster classification, disease severity and comorbidities. Larger clinical studies are needed to establish whether the specific subgroup of elderly patients may benefit from a different therapeutic approach. As the results, the conclusion is Accept (General priority).

We thank the Reviewer for suggesting to accept our paper for publication. We are aware that the small sample sizes and the heterogeneity of the included studies as well as the relatively low quality of the evidence are limits of our systematic review and this has been underscored in the abstract (page 3 lines 23-24), the core tip (page 4 lines 7-8), the discussion (page 11 lines 17-18), and the Research Highlights (page 13 lines 1-8)(changes were highlighted in green).

Response to the Editor:

The text of manuscript has been revised according to the Editorial WJG guidelines and requirements (changes were highlighted in orange). Required certificates/documents were provided. In addition, both Figure 1 and the Appendix were uploaded as separate files. Finally, the Tables have been modified and now tables fit on one page each (landscape).