Response to Reviewers

Journal: World Journal of Gastroenterology

Manuscript No: 53539

Manuscript Title: A systematic review of primary sclerosing cholangitis with increased IgG4 levels: a distinct clinical subtype and its implications

Reviewer #1: *This is a very well written and designed review paper concerning the analysis of clinical phenotype, differential diagnosis, response to therapy and pathogenic mechanisms associated with Primary Sclerosing Cholangitis (PSC) with elevated serum and/or tissue IgG4 subclass. The authors give an extensive overview about the prevalence, diagnosis of PSC with high level of IgG4, differential diagnosis of sclerosing cholangitis with high IgG4 levels and cholangiocarcinoma. The authors give very good overview about the pathogenic mechanisms in PSC with high IgG4 level, about genetic associations, the role of IgG4 antibodies, the role of cytokines and chemokines in pathogenesis. The authors conclude that PSC patients with high IgG4 levels have a distinct clinical phenotype and need discrimination from IgG4 related sclerosing cholangitis. The presence of IgG4 may represent chronic activation to persistent antigenic exposure in genetically predisposed individuals. The authors have reviewed and analyzed a large amount of literature (114 references). It should be mentioned that two Figures and 4 excellent Tables give a good overview about this topic.*

Thank you for this positive review of our manuscript. There are no comments to address.

Reviewer #2: *This is a comprehensive review article dealing with PSC with high IgG4 levels. I'd like to appreciate authors' effort for accomplishing this perfect work.*

1. *I recommend add words 'systematic review' in the title to emphasize its perfectness.*
2. *The literature search strategy may become more easy to understand with illustrating it in a decision tree figure.*

Thank you for your comments. We have adjusted the title as recommended to "A systematic review of primary sclerosing cholangitis with increased IgG4 levels: a distinct clinical subtype and its implications". We have added a decision tree to illustrate the literature strategy and is newly labelled as Figure 1.

Reviewer #3: This manuscript provides an overview on primary sclerosing cholangitis with increased IgG4 levels.

1. The Core Tip should be shortened (according to the Guidelines for Authors).

2. Section "Cholangiocarcinoma (CCA)": Ca-19-9 -> CA19-9. Section "Pathogenic Mechanisms in PSC high IgG4": A "Figure 3" is mentioned but not provided (- did you mean "Figure 2"?).
3. Table 3: "If they then meet criterion R, then they diagnosis becomes definite" - this footnote requires correction.
4. Figure legend 1 should be improved (with more information on your patient).
5. Some sentences are grammatically unclear (e.g., Abstract, Results: "Serum IgG4:IgG1 ratios and novel IgG4:IgG RNA ratio report excellent discrimination but requires external validation", "The immunological drivers underlying prominent IgG4 antibodies in PSC are incompletely defined, although a role for HLA class-II, T-helper2 and T-regulatory cytokines and chemokines have been demonstrated").

Thank you for these comments. We have shortened to core tips as recommended. Figure 3 should have said Figure 2; an extra figure has now been added as per Reviewer 2, so it is now labelled Figure 3. We have corrected the footnote in Table 3. We have added further clinical information for the legend and labels for the image in Figure 1 (now Figure 2). The sentences mentioned in the core tips have been removed, and those in the abstract and main text have been expanded for better readership.

Reviewer #4: Authors reviewed the literature in order to summarize the differences between 2 entity, namely PSC with increased IgG4 and IgG4 related SC. My comments:

1. Authors should have emphasized that this is not a generally excepted and so establish discrimination but, is a proposal for clinically subclassifying PSC based on the literature findings.
2. The manuscript must be redacted by omitting the repetitions and overlapping sections.
3. The resolution of figure 1 is inadequate, and the pathologic findings should be marked on the figure.
4. The expression of figure3 on page should be figure2, since there is no figure3.

Thank you for these comments. This is a proposal for clinically subclassifying PSC based on review of the literature, the evolution of clinical trial design in PSC to include serum IgG4 levels, and current clinical practice to risk stratify in many European and UK tertiary high-volume PSC centres (led by members of IPSCSG and UK-PSC groups). We have added a sentence to the introduction to reinforce this. Sections with repetition have been deleted (e.g. serum IgG1:IgG4 ratios and PCR and immunology sections in the core tips, abstract, main text). Given the other 6 reviewers positive comments as to the excellent detail in the content of the manuscript we have not shortened other sections. We have replaced the original image with a tiff of higher resolution, provided clinical details in the legend and marked pathological findings as recommended. We have re-labelled the figures to reflect the correct order (this is now Figure 2A and B).

Reviewer #5: The authors performed systemic review of primary sclerosing cholangitis and IgG4. The manuscript was informative and useful.

1. Figure 1 shows MRCP of IgG4-SC type 2. Was this photo referred from the literatures? Or was it from the authors' institute? If the photo was provided by the authors, it would be helpful to add clinical features to evaluate it. Was ERCP performed to the patient of Figure 1?

The Figure was an image from our institute. We have replaced the original image with a tiff of higher resolution, provided clinical details in the legend and marked pathological findings as recommended. We have re-labelled the figures to reflect the correct order (this is now Figure 2A and B). The patient responded well to steroids and then relapsed and required second line azathioprine. ERCP was done to brush the CBD stricture and brushings were negative for dysplasia.

Reviewer #6: This manuscript, 53539, provides the review of factors underlying primary sclerosing cholangitis (PSC), chronic progressive liver disease characterized by the elevated IgG4 subtype. Based on the extensive review of the available literature data, the conclusion is that PSC-high IgG4 has a distinct clinical phenotype from that of IgG-4-related sclerosing cholangitis (IgG4-SC), and hence requires careful assessment of clinical features, organ involvement and tissue morphology. This is an interesting contribution, which clearly lays out the methods for differential diagnosis of PSC from that of IgG4-SC. The paper is well written, and the presented data are amply justified by the accompanied figures and tables.

Thank you for this positive review of our manuscript. There are no comments to address.

Reviewer #7: An interesting and clearly review to summarize the clinical phenotype, disease associations, differential diagnosis, response to therapy and pathogenic mechanisms underlying PSC-high IgG4 subtype.

There are no comments to address.