Dear Editors,

Name of journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13291

Thank you for the constructive comments provided by the reviewers regarding the manuscript "Management of Patients with Hepatitis C Infection and Renal Disease". I and my co-authors have gone over all of them carefully and have addressed them to the best of our ability and have provided a point by point response as well as a revised manuscript with changes highlighted with red color. The title of the article has been shortened. We have modified the manuscript and references according to the journal format, and as per the editorial team's comments. The powerpoint file of Figure 1 and 2 is provided.

Reviewer 00505728

Interesting review. Minor points the first sentence in core tips ie decreased graft and patient survival should be referenced. Additionally next to last line of first paragraph of introduction Importantly the liver related morbidity...general population should be referenced Section of pharmocologic issues. The authors comment of IFN alfa 2A having a restricted volume of distribution and the PEG-IFN having a larger volume of distribution. The numbers quoted show the opposite In the Ribavirin cection RBC is used when it should be RBV Sobosbuvir and simeprevir-based therapy section "and weal" drug interactions needs to be revised eg which would have Section of mixed cryoglobulinemia second paragraph 41 degrees C should be 4 The authors probably shopuld comment that a large percentage of individuals with hepatitis C develop diabetesd mellitus and the renal disease may be secondary to DM or without hepatitis C type of changes.

Responses:

Citations are added in the first paragraph as recommended. We prefer not to make citations in the core tips. The volume of distribution (Vd) of PEG-IFN 2A is 2-12 L, and the Vd of PEG-IFN 2B is 0.9 L/kg. The units are different. Typo errors have been corrected as suggested Association between HCV and DM is an important issue. A short paragraph on this has been added.

Reviewer 00503175

Article ?Management of patients with hepatitis C infection and renal disease“ by Bunchorntavakul C et al. is according to my opinion, acceptable for publication. This article is very interesting for persons involved in area of hepatitis C infection and end-stage renal disease (ESRD). The authors explained influence of HCV infection on the kidney function especially in the patients with already impaired renal function (patients with ESRD and patients with kidney transplantation). They made an overview of therapeutic management of HCV in these patients. First they started

with well known drugs for HCV infection as interferons, pegylated interferons and ribavirin. Also they made attention to new drugs as direct acting antivirals. They presented dosage modification for patient with renal impairment who needs intereferon or/and ribavirin. Also they presented pharmacokinetic and metabolic parameters of selected direct acting antivirals. The special focus was made on management of HCV in patients with ESRD and in the kidney transplant recipients. At the end they made an overview about influence of hepatitis C virus on kidney, especially mixed cryoglobulinemia-associated glomerulonephritis. According to me this article is worthwhile for publishing.

Responses:

Thank you very much

Reviewer 00289581

The manuscript under review "Management of Patients with Hepatitis C Infection and Renal Disease" covers a high priority topic and deserves publication with some minor revision required. In general it is very long and come be summarized in many sections. For example: 1. Epidemiology section, the second paragraph has numerous stats which could go in a Table or condensed. 2. Mixed Cryoglobulinemia, I am unclear why you defined the three Types of MC and the methods for cryoglobulin measurement. 3. Management of Transplant and Hepatitis C, what is the effect of a decrease in immunosuppression? This was unclear. 4. A summary at the end is needed

Responses:

Thank you very much.

Due to the rarity of the condition, we try to give the readers some background on cryoglobulinemia. The paragraphs on epidemiology and cryoglobulinemia have been shortened as suggested. Similar to the management of HCV in liver transplant recipients, DAA with drug-drug interactions with immunosuppressive agents may be able to utilized with great cautions. Although the dose of immunosuppressive agents may be decreased, but the drug levels during HCV treatment must be closely monitored and keeping in the same range as standard post-transplant protocol. This strategy may be applicable for newer DAA to minimize the risk of graft rejection. As we mentioned in the manuscript, boceprevir- or telaprevir-based therapies are not recommended for KT recipients due to the need of IFN, and IFN-free regimens are preferred. The summary will be same as the core tips. This manuscript is already too long so we try to avoid redundancy.

Reviewer 00503199

According to this reviewer the manuscript needs minor changes. 1. Core tips: specify that DAA use in severe renal impairment cannot be recommended 2. Be more precise to treatment according to HCV genotype (which drug can be used in each genotype 3. Diagnosis of HCV

infection in cases of cryoglobulinemia: Are antibodies a sensitive method? Do we need to do other tests (e.g PCR?) and in which occasion?

Responses:

A sentence about not recommending DAA for ESRD has been added in the core tips as suggested. As the treatment of HCV is rapidly evolving, we recommend the readers to follow IDSA/AASLD guideline for the specific regimen for each HCV genotype (Website and references are provided in the manuscript). Further, treatment recommendation for HCV genotype 3 in patients with severe renal disease is unclear at this stage. Currently, PEG-IFN plus RBV for 24 weeks can be utilized. Sofosbuvir plus RBV with or without PEG-IFN, which is currently recommended for genotype 3 patients with normal renal function, cannot be recommended for patients with severe renal disease at this stage. We think the sensitivity of antibody testing is acceptable for everyday clinical practice. Due to space limitation and rarity of the condition, we could not discuss thoroughly for the laboratory details of cryoglobulinemia.