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Li-Jun Cui

Science Editor, Editorial Office,

Editors-in-Chief: Clara Balsano, PhD, Wan-Long Chuang, MD, PhD, Lucia Pacifico, MD
World Journal of Hepatology,

January 10th, 2018

Re: World Journal of Hepatology Manuscript NO: 37321 entitled

"Outcomes of Kidney Transplantation in Patients with Hepatitis B Virus Infection: A Systematic Review and Meta-analysis"

Dear Editor,

Thank you for the thoughtful input and review of our manuscript. The reviewers' inputs are extremely helpful. We believe as a result of this review, our study would have more value for your readers. We revised the manuscript based on the reviewer's suggestions. We have attached our point by point response.

As the invitation and our status Number ID: 03475636 as a contributor to the F6Publishing system, we are thankful that it is acknowledged by waiving of the publication fee for "Review Articles" authored and submitted that are accepted for publication in the BPG journals.

Thank you for your time and consideration. We look forward to hearing from you.

With many thanks for your attention, I remain.

Sincerely yours,

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Response to Reviewer

Reviewer: 1

Comment to the author

Title: Outcomes of Kidney Transplantation in Patients with Hepatitis B Virus Infection: A Meta-analysis. The authors of this paper presented the result of a systematic literature review that was conducted to identify studies assessing outcomes of kidney transplantation in patients with HBV. The authors concluded that HBsAg-positive status in kidney transplant recipients was significantly associated with graft and recipient poor outcomes with increased risk of mortality and increased risk of allograft loss. Overall the paper is very well-written and they did very impressive data analysis and statistical tests to reach to their conclusion.

Response: We thank you for reviewing our manuscript. We really appreciated your input.

Comment #1

I think there was a serious heterogeneity of the study population, they did not take consideration of the presence of comorbidity, the experience of the surgical team and the experience of the transplant center (as far as the number of renal transplant/year), no mention of the type and quality of the renal graft (cadaveric versus live donor) and no data about the donors? All these information and data can shift the results in different direction.

Response: We agree with the reviewer. Thus, we included the data on mean age, sex, immunosuppression regimen, the type of donor in the tables as well as performed additional analyses and included in the manuscript. We found that the associations of HBsAg positive status with increased risks of mortality and allograft failure after kidney transplantation were affected by the donor type. We also performed meta-analysis limited only to studies with adjusted analysis for confounders, the pooled OR of mortality was 1.27 (95% CI, 1.06-1.51). We appreciated the reviewer's input. The data on the experience of the transplant center (as far as the number of renal transplant/year) in included studies were limited and we accept this as a limitation in our meta-analysis.

We have added the information in our manuscript as following in **bold**:

"When meta-analysis was limited only to studies with adjusted analysis for confounders[36, 53, 54], the pooled OR of mortality was 1.27 (95% CI, 1.06-1.51, I²= 85). Meta-regression showed significant negative correlations between mortality risk after kidney transplantation in HBsAg-positive patients and year of study (slopes = -0.062, p =0.001, Figure 3). Meta-regression showed no significant impact of donor type on the association between HBsAg-positive status and increased risk of mortality after kidney transplantation (p =0.11)."

Comment #2

The authors did not comment on the reason/reasons for high mortality in the HBsAg-positive recipients, was that related to the graft quality, surgical technique, patient-related issues or related to re-activation of the HBV in the liver! I am sure they can look into these details in particular the number of the papers they did review and included in the study was not huge!

Response: We agree with the reviewer comment. Thus, we look into included studies. High mortality in the HBsAg-positive recipients has been related to liver complications. Compared to the HBsAg-negative recipients, HBsAg-positive recipients carry a higher risk of hepatic complications including chronic hepatitis, liver failure, fibrosing cholestatic hepatitis, and hepatocellular carcinoma. In addition, immunosuppression after kidney transplantation may also put patients at higher risks of HBV reactivation. Although antiviral treatment has been shown to reduce mortality after kidney transplantation due to decrease in liver complications [18, 21, 54], in the era of antiviral therapies, Lee et al[54] recently showed that deaths from liver complications still remained a significant problem accounting for 40% of deaths in HBsAg patients and 22.2% of all mortalities that occurred in recipients treated with antiviral agents [54]. We have included this information in the discussion of the manuscript. The data on the graft quality, surgical technique in HBsAg-positive recipients were limited and we accepted this in our limitation.

Reviewer: 2

Comments to the Author

This article was well-organized and provided valuable information on managing kidney transplants with HBV infection. If surveillance strategies and treatment policy available, it would be better and more complete.

Response: We thank you for reviewing our manuscript. We really appreciated your input. We agree with the reviewer that these are important data. Although data on surveillance strategies and treatment policy are limited, we look into the data on impact of antiviral treatments on patient survival after kidney transplantation in patients with HBsAg-positive and have added the information in our manuscript as following in bold:

"Impact of Antiviral Treatments on Patient Survival after Kidney Transplantation in Patients with HBsAg-positive

Of 9 studies(1-9), 3 studies(3, 4, 7) provided data on prophylactic antiviral treatment for HBV. When meta-analysis was limited only to studies with HBs Ag-positive recipients (>50%) treated with prophylactic antiviral treatment for HBV, the pooled OR of mortality was 3.85 (95% CI, 0.91-16.23, I²= 50%). In a recent study by Lee et al(4), which 81% of HBs Ag-positive recipients were treated with prophylactic antiviral treatment, HBsAg-positive status was significantly associated with increased risk of mortality after kidney transplantation with adjusted HR of 2.37 (95% CI, 1.16-4.87).

Yap et al.(3) demonstrated that recipients treated with nucleoside/nucleotide analogues had significantly better patient survival, when compared to those who were not on treatment (83% vs. 34% at 20 years, $p = 0.006$). In patients who had lamivudine-resistant HBV, the investigators showed that treatment with adefovir or entecavir was effective with a three-log reduction in HBV DNA by 6 months. When compared to patients who were treated with lamivudine or adefovir, Lee et al.(4) demonstrated that those treated with new generation antiviral agent entecavir had better patient survival (log-rank, $p = 0.050$)."

Thank you for great and helpful suggestions.

Sincerely,

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