Point-by-point Response to Reviewer Comments

To

The Editors

World Journal of Hepatology

Dear Editors,

We would like to thank you for considering our manuscript for publication in the World Journal of Hepatology. We would also like to thank the reviewers for taking the time to review our manuscript and helping us improve the quality of our work. Please note that all the reviewer comments have been addressed in the re-submitted version of the manuscript and a point-by-point response has been provided for the reviewer comments. The manuscript has been thoroughly revised again to ensure data accuracy and reporting. Additionally, the manuscript has been revised again by a native English speaker for grammatical errors. All authors agree to the resubmitted version of the manuscript and have no conflict of interest to report.

Please feel free to reach out to me at any time regarding this manuscript at dush.dahiya@gmail.com

Sincerely,

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Reviewer Comments

Reviewer #1

In brief: The total number of LT hospitalizations with AP increased from 305 in 2007 to 610 in 2019. There was a rising trend of Hispanic (16.5% in 2007 to 21.1% in 2018, p-trend=0.0009) and Asian (4.3% in 2007 to 7.4% in 2019, p-trend=0.0002) LT hospitalizations with AP, while a decline was noted for Blacks (11% in 2007 to 8.3% in 2019, p-trend=0.0004). Furthermore, LT hospitalizations with AP had an increasing comorbidity burden as the Charlson Comorbidity Index (CCI) score ≥3 increased from 41.64% in 2007 to 62.30% in 2019 (p-trend<0.0001). We did not find statistically significant trends in inpatient mortality, mean length of stay (LOS), and mean total healthcare charge (THC) for LT hospitalizations with AP despite rising trends of complications such as sepsis, acute kidney failure [AKF], acute respiratory failure [ARF], abdominal abscesses, portal vein thrombosis [PVT], and venous thromboembolism [VTE]. Between 2007–2019, 6,863 LT hospitalizations with AP were compared to 5,649,980 non-LT AP hospitalizations. LT hospitalizations with AP were slightly older (53.5 vs 52.6 years, p=0.017) and had a higher proportion of patients with CCI≥3 (51.5% vs 19.8%, p<0.0001) compared to the non-LT cohort. Additionally, LT hospitalizations with AP had a higher proportion of Whites (67.9% vs 64.6%, p<0.0001) and Asians (4% vs 2.3%, p<0.0001), while the non-LT cohort had a higher proportion of Blacks and Hispanics. Interestingly, LT hospitalizations with AP had lower inpatient mortality (1.37% vs 2.16%, p=0.0479) compared to the non-LT cohort despite having a higher mean age, CCI scores, and complications such as AKF, PVT, VTE, and the need for blood transfusion. However, LT hospitalizations with AP had a higher mean THC ($59,596 vs $50,466, p=0.0429) than the non-LT cohort. The authors have structured the manuscript very well. I have two reservations: 1. Please state the novelty of your results because it does not seem to be different from the literature 2. Please discuss in detail why the outcome of the LT group is better despite unfavorable odds.

Author Response: Thank you so much for taking the time to review our manuscript. We highly appreciate your effort and enthusiasm in helping us improve the quality of our work. Our response is as follows:

1. You have raised an excellent point. Some of our findings are consistent with published literature as we mention in the manuscript. However, our findings are novel in numerous ways. Although studies investigating Acute Pancreatitis (AP) in Liver Transplant (LT) patients do exist in the United States (US), they are primarily limited to single-center experiences. This limits the data available and applicability to a larger US population which is very diverse in terms of age and race demographics. Additionally, those studies are unable to provide an overall perspective of different hospitals in the US. In our study, the data was derived from a large, national, multi-ethnic database in the US. Hence, the results of our study are applicable to all hospitalizations in the US. Furthermore, our study also provided trends of hospitalization characteristics, complications, and clinical outcomes for AP in LT at a national level, which are unavailable in any other study. Through a comparative analysis, we are able to provide hepatologists with real-world data on individuals at high risk of adverse clinical outcomes and complications. Finally, we also identified predictors of inpatient mortality for LT hospitalizations with AP thereby helping identify individuals at high risk of mortality early. We have added this to the discussion section of the manuscript.

2. Thank you for an excellent question. This was a very important and interesting finding of our study. In current literature, there continues to be a significant paucity of data on mortality for AP in LT recipients, particularly at a national level in the US. In our study, we did not find a statistically significant trend for inpatient mortality in LT hospitalizations with AP. After a comparative analysis, LT hospitalizations with AP had lower inpatient mortality rates compared to the non-LT cohort despite a higher mean age, greater comorbidity burden, and higher proportion of patients with complications. The exact reason for lower inpatient mortality rates in LT hospitalizations with AP is currently unknown, but it may, in part, be due to increased vigilance for complications in these hospitalizations, overall improvements in management strategies, and a multi-disciplinary team approach for management of these highly complex patients. However, due to limitations associated with the NIS database, we are unable to determine the exact cause. Our study advocates for the need of additional research on this topic to ultimately prevent mortality. We have added this to the discussion section of the manuscript.

Reviewer #2

Specific comments to authors: Dahiya and co-others in this article report on ‘Acute Pancreatitis in Liver Transplant Hospitalizations in the United States’’. The manuscript is properly written, and of clinical interest although the authors need to address some points as follows:

Author Response: Thank you for taking the time to review our manuscript and helping us improve the quality of our work. We highly appreciate your efforts and enthusiasm.

- To enrich the results the authors need to add some predictor of mortality in liver transplant patients with AP such as: status of immunosuppression, presence of viral infection, presence of obesity, hyperlipidemia, biliary complications, performance of ERCP.

Author Response: Thank you for an excellent point. Ideally, we would have liked to add additional data on predictors of mortality for LT hospitalizations with AP. However, we were significantly limited by intrinsic limitations and availability of data from the NIS database. The NIS database does not contain any information on the hospital course, hospital treatments, treatment aspects of the disease, time from procedure to development of complications, procedural complications (pre, intra, and post), intraprocedural operator preferences, or performance of any procedure. In table 5, we have already listed the significant predictors of mortality. Furthermore, we have expanded the limitations section of the manuscript to incorporate this point.

-Please add P-value for the trend in the number of liver transplant patients admitted with AP through different years.

Author Response: Thank you for a great point. For the total number of hospitalizations, we report absolute numbers only for each calendar year rather than a trend. Hence, the p-value is not required. This data gives gastroenterologists real-world information on the actual number of LT hospitalizations with AP in the US each year.

-You repeatedly mentioned in the introduction, discussion and in the conclusion that ‘the development of post-LT pancreatitis may lead to increased risk of graft failure’. This statement was not supported in your results and there was no mention of the association between AP and graft failure.

Author Response: Thank you for bringing it to our attention. We agree with you and apologize for the error. This NIS does not contain any data on graft failure and this outcome was not analyzed in our study. We have addended the manuscript extensively to reflect this point.

- Regarding table 3 and 4: in the text you reported that you are comparing between liver transplant patients with AP and non-transplant patients with AP. Meanwhile in the tables’ headings you mentioned that the comparison is between liver transplant patients with AP and liver transplant patients without AP. Which one do you mean? Thanks

Author Response: Thank you for bringing it to our attention. We apologize for the error. We have edited the table legends and table headings in the manuscript appropriately.