Date: 01-15-2022.

To,

Editor

World Journal of Gastrointestinal Surgery.

Subject: Resubmission of manuscript "Letter to the editor- Immunotherapy after liver transplantation: Where are we now?" ID: 73526

Respected,

The authors, thank you for the opportunity to resubmit the manuscript. We have made the revision in the manuscript, as per the reviewer comments and also explained below. We hope you consider our work for publication.

Thank you.

Yours sincerely,

Corresponding Author.

Reviewer #1:

The author commented on the study of Kin PA and colleagues with respect to immunotherapy and its risk of graft rejection that underwent liver transplantation for HCC. They pointed out the initiation of immunotherapy within a short duration of transplant and the expression of PD-L1 on the graft lymphocytes are the risk factors for graft rejection in liver transplant patients receiving immunotherapy. Proper patient selection is quintessential in initiating immunotherapy, thus preventing lethal graft rejection. This view has certain clinical reference value.

Thank you for the comments. We appreciate it.

Reviewer #2:

Is there literature of immunotherapy and graft rejection in other transplantation? What can we learn from those? -Could you comment on which studies are needed to answer the question on characteristics associated with good outcome after immunotherapy -is there an expected difference in graft rejection with ctla4 versus pd1? -what should be the focus of future studies on immunotherapy in liver transplant?

Thank you for the comments. We addressed as below

The overall rejection rates following immunotherapy are 29-54% and 25%, respectively, in patients who underwent solid organ transplantation and LT[4-6]. Kidney (40%) is associated with higher rates of graft rejection than liver (35%) and heart (20%)[3].

Compared with CTLA-4 inhibitors, PD-1 inhibitors are associated with higher rates of graft rejection and graft loss in LT recipients[7, 8]. Kittai et al reported graft rejection in 4 of 8 patients treated with anti-PD-1, whereas no rejections were detected in patients receiving anti-CTLA-4 therapy.

A higher dose of immunotherapy medication, a shorter interval between LT and immunotherapy initiation, expression of PD-L1 on the graft lymphocytes, and a previous GVHD history are positively related with the risk of and response to graft rejection[4]. Studies on patient characteristics such as gender, age, pathological type of primary tumor, donor type, type, and duration of ischemia during LT and post-operative hepatitis virus status of the patient are necessary to learn the factors associated with favorable outcomes after immunotherapy. Proper patient selection is quintessential to prevent lethal graft rejection. Hence, a close collaboration among oncologists and transplant specialists is encouraged when handling patients who require immunotherapy. However, prospective studies focusing on (i) although the PD-1 pathway is dominant in establishing immune tolerance, whether anti-PD-1 and anti-CTLA-4 antibodies are associated with graft rejection[9] (ii) the treatment of immunotherapy related graft rejection and its efficacy (iii) is there any difference in treatment modality between immunotherapy related graft rejection and isolated graft rejection, are required beforehand to recommend immune checkpoint inhibitors in transplant recipients.