Dear Pr Garcia-Olmo,

Herein, we are submitting to the World Journal of Gastroenterology, a revised version of our paper titled "*High tacrolimus intra-patient variability is associated with graft rejection and de novo DSA occurence after liver transplantation*"" (Manuscript NO 37368).

We have answered to the reviewer's comments as follow:

Reviewer 1 :

Del Bello et al analyzed the risk factors of graft rejection, and de novo DSAs occurrence after liver transplantation and found that high tacrolimus intra-patient variability is one of the predictors. I have some comments.

1. What is the interval or indication to check the DSA after liver transplantation?
   In this retrospective study, all patients were screened for HLA antibodies at 3 and 12 months post transplantation, and thereafter every each years.
   Moreover, additionnal screening for anti-HLA antibodies were performed in case of graft dysfunction or suspicion of graft rejection.
   This was added in the Patients and Method section.
2. The authors described that "non-adherence to Tac seems to be the main cause of IPV in pediatric and adolescent liver transplantation". Is it also true in adults? Is the cause of high IPV related with non-adherence or non-compliance in the present study? Please discuss about it.
   The role of Tac-IPV was not well studied in adult liver transplant recipients until now. However, several data in adult kidney transplant recipients argue for the role of non-adherence or non-compliance as the main cause of Tac-IPV. In our study, we cannot conclude definitively concerning this point due to the lack of evaluation of medical adherence in this retrospective study
   As requested, this limitation was discussed.

Reviewer 2

Major comments This is a very interesting study design but lacking of the basic molecular data support such as genotype CYP3A4, CYP3A5 and multi-drug resistant 1 (MDR1). The author only used with the statistical method univariate and multi-variate analysis to explore the result. As we know, the HLA tapping is much difference from the donors between LDLT and DDLT. Tacrolimus concentration is closely related to the liver graft from the donors particularly when the recipients have difference genotypes in CYP3A4, CYP3A5 and MDR1.

We thank the reviewer for this very interesting comment. In this retrospective study we investigated the use of Tac-IPV to identify patients with a high rejection risk. The interest of Tac-IPV lies in its ease and its cost, unlike pharmacogenomics assays. Moreover, several studies have put forward the role of pharmacogenomic to quickly reach the therapeutic range, but not to follow intra-patient variability of tacrolimus. These point were added in the discussion section.

Minor comments

Abstract: Un-structural present and lacking of conclusion at the end of abstract.

As requested the abstract was modified.

Introduction: In reference " (1) (2) (3)" needs to be revise

As requested references were revised

In reference "(4) (5; 6)" it is not acceptable.

As requested, references were revised

Patients and Methods: 1. Donors' age at transplantation is ranged from 9 to 85, the author needs to describe more detail

As requested, a more granular information concerning donor's age was completed.

2. It is a LDLT or DDLT study needs to describe which should be impact the inter-individual and intra-individual variability

In this study, all donors were DDLT. This was added in the Patients and Methods, and in the results.

In reference " (18) (19) (20)" needs to be revise

As requested, references were revised

Discussion: 1. In reference " (14) (11) (22) (23)" it is a wrong list.

As requested, references were revised

"The use of once-daily tacrolimus compared to a twice daily formulation has been found to improve adherence and IPV (11) (28). However, in our study, no significant difference between these Tac formulations was observed." The author needs to describe and explain more detail.

As requested this point was discussed

The total number of patients receiving tacrolimus once daily is 164, but your study mentioned 116 cases were included. What's it?

As mentionned in the Table 1, five patients received once-daily Tacrolimus immediately transplantation, and 42 additional patients were switched for once-daily Tacrolimus during the follow-up. The cumulative incidence of patients under Tacrolimus once-daily was detailled in each point.

Reviewer 3

Figure 2 of the histograms should be implemented with the standard deviation. The section of the limitations should be expanded. Very interesting paper from a very good transplantation center!

We thank the reviewer for this comments. However the fig 2 represents the number of patients by Tac-IPV distribution. So we couldn’t use standard deviation in this type of figure.