Responds to the Reviewers' comments

Reviewer #1 (03475479)

Authors evaluated the risk factor of PTDL, and showed that pre-treatment serum IL-12(p70) level is associated with the development of PTDL. Furthermore authors showed that PTDL is associated with poorer prognosis in HCC patients. This report is interesting, but several issues remain to be addressed.

1. Authors should show the proportion of living-donor LT.

Response: OK. No living-donor LT was included (page 6).

2. HBV-HCC patients were main cohort. Authors should describe HBV status such as HBV-DNA, HBeAg positivity or anti-viral treatment in pre- and post LT.

Response: OK. HBV status were added in Table 1 (page 24). HBV patients received standard anti-virus protocol post-LT as we described before (1) (page 6).

3. HCC recurrence was frequent in present cohort. Authors should describe the indication of LT in HCC patients and the diagnostic methods.

Response: Yes. Hangzhou criteria was used as an indication of LT in HCC patients. Hangzhou criteria was defined as: (I) total tumor diameter no more than 8 cm; (II) total tumor diameter more than 8 cm, with pathological grade I or II and preoperative alpha fetoprotein (AFP) level no more than 400 ng/mL, simultaneously. The diagnosis of recurrence was based on imaging appearance (2) (page 6). The 1- and 3-y cumulative patient survival rates in HCC recipients were 84.3% and 60.0%, respectively.

4. Authors should discuss the role of anti-lipid therapy for PTDL.

Response: Thanks for the suggestion. We added an additional discussion in page 10 line 14-18.

References

1. Lu D, Zhuo J, Yang M, Wang C, Pan L, Xie H, Xu X, Zheng S. The association

between donor genetic variations in one-carbon metabolism pathway genes and hepatitis B recurrence after liver transplantation. Gene 2018; 663: 121-125 [PMID: 29627528 DOI: 10.1016/j.gene.2018.03.071]

2. Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, Yan S, Wu L, Geng L, Ke Q, Gao F, Tu Z, Wang W, Zhang M, Shen Y, Xie H, Jiang W, Wang H, Zheng S. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. Gut 2016; 65(6): 1035-1041 [PMID: 25804634 DOI: 10.1136/gutjnl-2014-308513]

Reviewer #2 (02440884)

The clinical study is focused on the prediction of dyslipidemia after liver transplantation. In a very good clinical setting the pro-inflammatory cytokine IL-12 was identified as a potential marker predicting post-transplant dyslipidemia (PTDL). Dendritic cells are suggested as the important source of IL-12.

1. Comments 1. The pathophysiological cascade that IL-12 triggers the metabolomics profile is suggested by the data, but additional experimental work is necessary. This point should be clearly addressed in the section Discussion.

Response: Thanks for the comment. We definitely agree with the reviewer and add this point in the discussion (page 11).

Reviewer #3 (00051373)

A great study design and manuscript written for investigating the association of recipients' metabolic inflammation status with post-liver transplantation dyslipidemia.

Response: Thanks a lot!

Reviewer #4 (00503243)

This is a very interesting manuscript on clinical factors and cytokines influencing the post liver transplant lipid abnormalities. The manuscript is well written and the study has been well conducted. The statistical analysis has been also well conducted. The conclusion on the role of IL-12 (p70) is new and interesting.

1. My only question is on the role of other cytokines. The authors documented the role of IFN-alpha2 and IFN-beta but their relevance seems to disappear at the multivariate analysis. What about the other cytokines that in different conditions are responsible of lipid abnormalities. Some comments in the discussion should be added.

Response: Thanks for the suggestion. We reviewed the literatures and made an additional discussion about the other cytokines in the revised manuscript (page 11).

Reviewer #5 (00071178)

1. The most important problem in this article is the statements about HCC. To suggest that there is a relationship between HCC recurrence and posttransplant dyslipidemia, there should be no difference in preoperative HCC characteristics between the two groups. Therefore, both groups should be compared in terms of tumor number, tumor size, vascular invasion and tumor histology. If there is no difference between the groups, it can be claimed that there is a relationship between tumor recurrence and dyslipidemia.

Response: Thanks a lot for the constructive suggestions. Accordingly, we performed a comparison between the two groups and found no significant difference in the HCC characteristics between the two groups (page 8).

Table S1

	PTDL (n=108)	Non-PTDL (n=61)	*P*
Multiple tumor (n, %)	64 (59.3)	33 (54.1)	0.515
Size of largest tumor (cm)	4.0 (2.5, 6.0)	3.5 (2.0, 5.3)	0.147
Vascular invasions (n, %)	31 (28.7)	19 (31.1)	0.738
Moderately or poorly differentiated (n, %)	54 (50.0)	26 (42.6)	0.358
AFP > 400 ng/mL (n, %)	29 (26.9)	15 (24.6)	0.738
Within Milan criteria (n, %)	47 (43.5)	30 (49.2)	0.478

Within Hangzhou criteria (n, %)	81 (75.0)	48 (78.7)	0.588

2. MedCalc for Windows version 4.2 Although not specified in the statistical method section, kaplan-meier analysis was used for survival analysis. The authors stated that they are using medcalc 4.2 version, but is this package program still in use? I couldn't be sure of that.

Response: Thanks for the carefully review. We used Kaplan-Meier analysis for survival analysis, which was added in the statistical method section (page 7). We also made a correction in the revised manuscript that we used MedCalc for Windows version 11.4.2.0 (page 7).

3. The authors should state which p values (obtained univariate analysis) are included in the multivariate analysis.

Response: OK. Variables with statistical significance ($P < 0.05$) in univariate analysis were entered into a stepwise multivariate regression analysis (page 7).