The point-by-point responses to the concerns of the reviewers are as follows:

Reply to reviewer 1:

Overall very well written manuscript. Some minor language polishing should be corrected. And the figures are too small, please update the images.

Reply: Thanks very much for your enlightening suggestion. We have revised the language in the article. Limited to the submission system. The picture of the article is now provided in the word version. I will submit a pdf version later. Such pictures will be much clearer.

Reply to reviewer 2:

This is an interesting study of transcriptional landscape of PD-1, PD-L1 and PD-L2 correlated genes in hepatocellular carcinoma. This study is well designed and the manuscript is well written. Minor comments:• The sentence "The potential regulating network of PD-1/PD-L1/PD-L2 signaling in immune escape still remains unclear" is not syntactically correct, please rewrite it.

Reply: Thanks very much for your enlightening suggestion, We have rewritten this sentence

• The aim of the study needs to be indicated as the "The immune checkpoint of PD-1/PD-L1/PD-L2 has been suggested to be an effective target of immunotherapy in a variety types of cancer" does not point out what the aim of the study was.

Reply: Thanks very much for your kind reminding. We have rewritten the aim of the abstract in the manuscript

• "clusterprofiler" instead of "clusterprofier" •

Reply: Thank you for your pertinent review. We have change this mistake.

- Please provide more details in regards with the TCGA datasets used to analyze the PD-1/PD-L1/PD-L2 gene expression profile in different clinical groups and include the number of patients per clinical group.

Reply: Thanks very much for your enlightening suggestion, We have added the patients number in the Result section.

• Please indicate the names of the genes in full: calcium voltage-gated channel subunit alpha1 E (CACNA1E), catenin beta 1 (CTNNB1), ryanodine receptor 2 (RYR2), tumor suppressor protein p53 (TP53), titin (TTN).

Reply: Thanks very much for your kind reminding, the full name of the gene have added in the manuscript.

• Please indicate the process followed to carry out the enrichment analysis.

Reply: Thank you for your pertinent review, the process of enrichment analysis have added in the methods section.

 • Please provide the list of the 7 PD-L1/PD-L2 interacting and the 39 PD-1 associated genes.

• Please indicate the genes correlated to PD-1 and PD-L1/PD-L2 involved in the pathways listed in the table 2.

• Please provide potential molecular mechanisms involved in the alteration of PD-1 gene expression mediated by mutations of the CACNA1E, CTNNB1, RYR2, TP53 and TTN as well as for the correlation between high PD-L1 expression with TP53 mutations and the association of PD-L2 expression with TTN.

• The sentence "In addition, prognosis of in Kras-p53 induced lung cancer was improved via regulating MEK and PD-1/PD-L1 immune checkpoint" requires clarification.

• Please propose potential immunotherapeutic approaches in the sentence "The underlying mechanisms of critical mutations such as TP53, TTN and CTNNB1 in modulating PD-1 signaling might provide novel strategies for immunotherapies."

Reply: Thanks very much for your kind reminding, We added the effect of mutations on immunotherapy after the sentence.

• "role instead of "tole" • "correlated with outcome" instead of "to correlated with outcome" • Please confirm the accuracy of the sentence "It has been reported that CD8 cytotoxic T lymphocytes greatly increase PD-L1 expression on cancer cell-line" • "The combined inhibition…" instead of "The combination inhibition…"

Reply: Thanks very much for your kind reminding, We fixed the error in the above sentence.

• Please provide more accurate and detailed figure legends: Figure 1. A, PD-1/PD-L1/PD-L2 expression in different "recurrence" events. B, PD-1/PD-L1/PD-L2 expression "in different stage". C, Prognostic analysis of PD-1/PD-L1/PD-L2, median expression of gene was selected as the cut-off point. Figure 3. …were used to selected the co-expression gene. A, Soft threshold selected in the WGCNA analysis. 14 was selected as the threshold. C, protein-protein interaction of the co-expression genes in the STRING datasets. D, Biological process of GO analysis in the co-expression gene. Figure 4. PD-1/PD-L1/ PD-L2 expression and immune infiltration. The left heatmap showed the immune infiltration score in LIHC, the middle heatmap showed the relationship between gene expression and immune infiltration, and the right heatmap showed the relation among immune infiltration. Figure 5, correlation between PD-1/PD-L1/PD-L2 expression and immune checkpoints gene.

Table 1: mutation instead of muation Table 2: GO analysis for PD-1/PD-L1/PD-L2 co-expression gene.

Reply: Thanks very much for your enlightening suggestion, all of the figure and table legend have been rewritten.