Point-to point Response Letter

Comments from editor:

1 Scientific quality: The manuscript describes a retrospective study of gene signature associated with stromal infiltration for diffuse large B-cell lymphoma. The topic is within the scope of the WJCC. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: The author found two genes, FN1 and SPARC, cooperatively expressed in DLBCL, which may be novel therapeutic targets for DLBCL, however, there are some issues should be addressed according to the comments of reviewer 02544757; and (3) Format: There are 8 figures. A total of 31 references are cited, including 22 reference published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B. The authors provided the Non-Native Speakers of English Editing Certificate. 3 Academic norms and rules: The authors provided the biostatistics statement and institutional review board approval form. The written informed consent was waived. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an unsolicited manuscript. This study is supported by Natural Science Foundation of Chongqing. The topic has not previously been published in the WJCC. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. And (2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s). 6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

Reply: We thank the editors and reviewer's efforts for our manuscript, and the integral documents were prepared in the revision version, and the point-to-point response were shown in below, and the supporting information was also supplied in the submitting system.
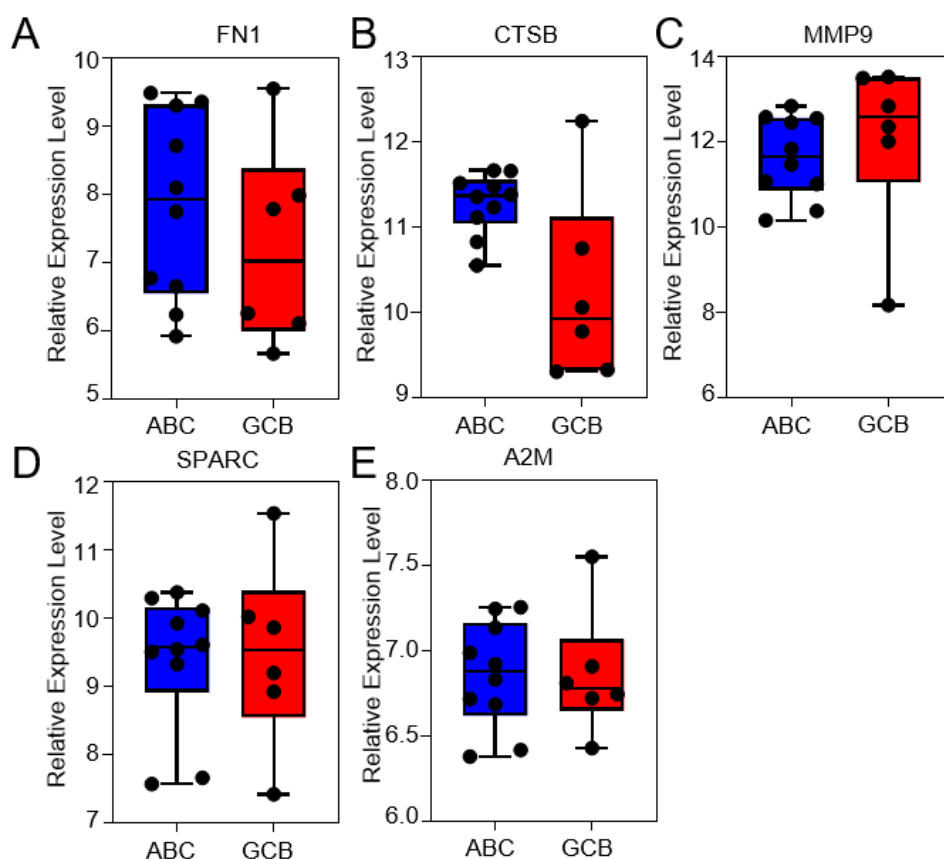
Reviewer

Through analyzing the e GSE60 dataset in DLBCL and using principal components analysis (PCA) plot, the authors identified five genes were closely associated with tumor stage and stromal infiltration in DLBCL. The author also found two genes, FN1 and SPARC, cooperatively expressed in DLBCL, which may be novel therapeutic targets for DLBCL. Although the current manuscript showed five genes may be associated with the development of DLBCL, there are many issues should be addressed. My comments are in the following

1. The author first used the GSE60 dataset to evaluate different gene expressions in DLBCL and normal tissue. Do the differentially expressed genes in DLBCL could further be divided into germinal center (GC) B-like or activated B-like DLBCL? I think this is important because the gene expressions in these two groups are different.

Reply: Thank the reviewer's constructive suggestion. Just as the reviewer pointed out, GCB-like DLBCL was significantly different from the ABC-like DLBCL. We further conducted the analysis of the five gene signatures in GCB and ABC-like DLBCL, just as the supporting Figure S1 showed, the five gene signatures including FN1, CTSB,

MMP9, SPARC and A2M expression in GCB-like DLBCL samples were not significantly different from the ABC-like DLBCL samples. To be noted, the five gene signatures were obtained from the overall DLBCL samples, including some subtypes. Therefore, the five gene signatures were general regulators in DLBCL.

supporting Figure S1

2. *The author used the STRING to identify five hub overexpressed genes in DLBCL. The legends of Figure 2B-F are needed to describe the data validation from TCGA dataset.*
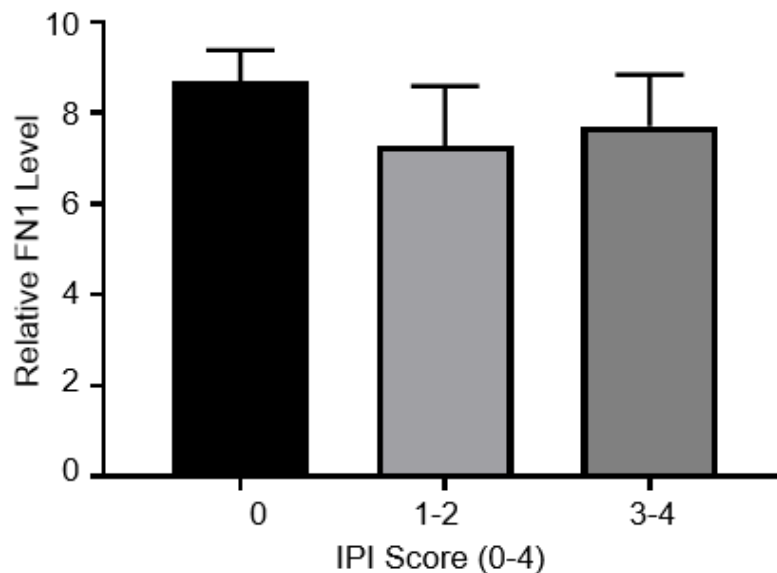**Reply:** Thank you for the reviewer's reminder, and we revised the legend of Figure 2B-F was validated in TCGA dataset. Thank you very much for your careful review again.

3. *The author studied the five hub genes that were higher expressed in late stages than in early stages. The FN1 gene expression had a stage-dependent increase. Are there any significant differences (P value) when comparing stage 2, 3 or 4 to stage 4? In addition, is FN1 gene expression also associated with high IPI scores in DLBCL?*
Reply: Thank you for the careful review. Just as the reviewer pointed out, FN1 expression has a potential association with the patient stage, but due to the limitation of samples in DLBCL patients, the statistical analysis was insignificant, therefore there was no remarks in the Figure 3. The second issue pointed out by the reviewer is a good question, and we conducted the potential association between FN1 expression and IPI scores. Just as shown in supporting Figure S2, the DLBCL samples were divided into

three groups with the IPI score value 0, 1-2, 3-4 respectively, and the result showed that the FN1 expression showed no significantly difference in three groups with different IPI scores, suggesting that FN1 was an independent factor compared with the common IPI score system.

supporting Figure S2

4. In figure 5-8, the overexpression of 5 genes had different Spearman's relationship to stromal score or CAF. It is better to describe high, moderate, or low correlations of every genes, respectively. In addition, it is better to arrange other experiments to validate these correlations.

Reply: Thank you the reviewer's insightful opinion. In Figure 5, the results showed the close association between the five genes with stromal score, an important tumor microenvironment analysis. Based on the significant association, and considering the importance of CAFs in the stromal analysis, we further conducted the correlation analysis between the five gens and CAFs. Meanwhile, in order to further validate the correlation, we conducted the correlation analysis in MCP-counter method and TIDE method, therefore the close correlation was credible. And in the further work, we would conduct further experiments *in vitro* and in *vivo*.