# Peer Review File

Authors describe the expression of SOX11 in multiple tumors and with detail i renal cell carcinoma. The amount of information preclude the comprehension of some details in the clinical and pathological characterization of the casuistic. It is difficult to understand if all tumors are clear cell, for how long patients were followed and treated, etc. The expression levels of SOX11 in cell culture would be a secondary information or a matter for another manustript. As a transcription factor, SOX11 should be expressed in the nucleus, but it is not the case for some of the pictures. I suggest authors to split the data in two: One experimental and one clinical. It would clear more the role of SOX11 in renal cell cancer.

Comment 1: It is difficult to understand if all tumors are clear cell, for how long patients were followed and treated, etc.
Reply 1: We download clear cell renal cell carcinoma data from the TCGA database and the GEO database (Line91-96: The methods of the manuscript have been described), the duration of treatment was found in the tumor until the patient's death, and the patient was followed up for 4000 days. (The abscissa of the KM curve is labeled)
Changes in text: We have added instructions to Methods (Line 99): Patient's follow-up duration extends for a period of 4,000 days.

Comment 2: The expression levels of SOX11 in cell culture would be a secondary information or a matter for another manuscript.
Reply 2: We have placed the data that SOX11 expression in cells as supplementary material as principal information.
Changes in text: We have revised Figure 2, and the data that SOX11 expression in cells has been placed in the supplementary materials.

Comment 3: As a transcription factor, SOX11 should be expressed in the nucleus, but it is not the case for some of the pictures. SOX11.
Reply 3: We have replaced the IHC picture in Figure 2.
Changes in text: We have replaced Figure 2 and modified the legend (line 561-565 and line 602-607).

Comment 4: I suggest authors to split the data in two: One experimental and one clinical.
Reply 4: Thank you for the precious advice proposed by the reviewers; considering that dividing the data into two parts would disrupt the expressive logic of the article, we have not separated it into sections.
Changes in text: no

Comment 5: It would clear more the role of SOX11 in renal cell cancer.

Reply 5: In our discussion of the manuscript also delved into this inadequacy, and in my future research, I shall continue to explore the role of SOX11 within renal cell carcinoma.

Changes in text: In our discussion of the manuscript also delved into this inadequacy (Line378-380: However, given that this study relied solely on bioinformatic analysis, further experimental investigations are necessary to explore the role of SOX11 in KIRC.)

1. Please provide the full names of the abbreviated terms in the highlight box. And please note that the box should be no more than 250 words.

   Reply: We have revised it in manuscript.

2. Please provide the full name of "TIMER" in the abstract and "mRNA" "RNAseq" "TPM" "cDNA" "TBS" "ANOVA" "LSD" "CI" "HR" in the main text. Please also check through your article to make sure **all** the abbreviated terms have been defined when they **FIRST** appear in the Abstract and the main text.

   Reply: We have checked all the abbreviated terms and revised the manuscript.

3. It is suggested to double check the full name of "DEGs" "RT-qPCR" "CESC" "LIHC" in the manuscript.

   between SOX11 expression and clinical pathological features. Differential gene expression (DEGs) were

   normal renal tubular cells and renal cancer cells, we conducted real-time polymerase quantitative chain reaction (RT-qPCR). Immunohistochemical (IHC) staining confirmed differential protein expression of bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and adenocarcinoma (CESC), cholangiocarcinoma (CHOL), diffuse large B-cell lymphoma (DLBC), (HNSC), kidney renal clear cell carcinoma (KIRC), brain lower grade glioma (LGG), hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), ovarian serous

   Reply: We have revised it in manuscript.

4. The name you mentioned in the following sentence does not match the corresponding reference. Please check and revise.

   "In the context of prostate cancer, Huang et al. demonstrated that overexpression of SOX11 enhances the invasiveness of cancer cells by suppressing vimentin

expression (32)."

32. Hirokawa YS, Kanayama K, Kagaya M, et al. SOX11-induced decrease in vimentin and an increase in prostate cancer cell migration attributed to cofilin activity. Experimental and Molecular Pathology 2020;117:104542.

Reply: We have revised it in manuscript.

5. Figures and Tables
   - **All abbreviations** in figures/tables and legends should be explained. "SOX11" "TCGA" "GTEx" "ROC" "TPM" "AUC" "CI" "TPR" "FPR" "HR" in Figure 1, and "SOX11" in Table 1 for example. Please check all abbreviations and provide the full names in the corresponding legends.

     Reply: We have revised it in figures/tables and legends.

   - There is no "ns" in Figure 1, while it is explained in Figure 1 legend.

     Reply: We have revised it in manuscript.

   - Please indicate how data are presented in Figure 1E-1G, Figure 9C-9H and Figure 10.

     HR = 1.56 (1.09 - 2.23)

     Reply: We have revised it in manuscript.

   - Please unify the description in Figure 1F.

     Disease Specific Survival
     HR = 1.97 (1.32 - 2.94)

     (F) The disease-free survival (DFS) curve

     Reply: We have revised it in manuscript.

   - Please check if "KICH" needs to be added in the following sentence.

     "Significant upregulation of SOX11 was observed in various cancer tissues, including adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and adenocarcinoma (CESC), cholangiocarcinoma (CHOL), diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), … as well as uterine carcinosarcoma (UCS)."

     Reply: We have added it in manuscript.

   - There is no "*" "***" in Figure 2, while it is explained in Figure 2 legend.
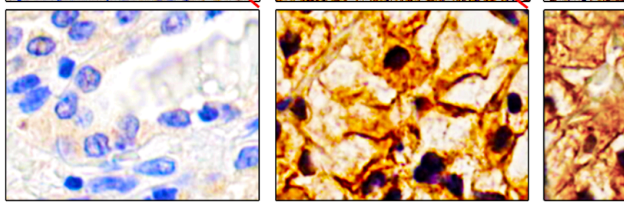
     Reply: We have revised it in manuscript.

   - Please double check the full name of "IHC" in Figure 2 legend.

showing immunohistochemica (IHC) s

Reply: We have revised it in manuscript.

- Please indicate the magnification in the second row of Figure 2A.



Reply: We have indicated the magnification in the second row of Figure 2A.

- Please add unit for Age in Figure 3A.

 Reply: We have added unit for Age in Figure 3A.

- Please double check the highlighted content in the following sentence.

"Regarding OS along with PFI, the expression levels of SOX11 were higher among deceased patients than those among surviving patients with statistical significance (Figure 3)."
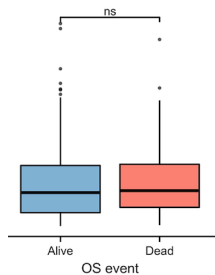


Reply: We have revised it in manuscript (line: 240)

- It is suggested to unify to use "ECM Proteoglycans" in Figure 5D.

**D**

[Reactome] Ecm Proteoglycans

Reply: We have revised it in manuscript (line: 260)

- There is no "ns" in Figure 6, while it is explained in Figure 6 legend.

 Reply: We have revised it in manuscript.

- Please unify the cell names in Figure 6A and the text.

"Specifically, it was positively correlated with CD8 T lymphocytes (r = 0.102, $P$ = 3.28E-02), CD4 T cells (r = 0.32, $P$ = 2.12E-12), as well as neutrophils (r = 0.142, $P$ = 2.38E-03)."

| CD8+ T cell | CD4+ T cell |
|---|---|
| partial.cor = 0.102 p = 3.28e-02 | partial.cor = 0.32 p = 2.12e-12 |

Reply: We have revised it in manuscript.

- Please revise the **P value** in the text.

If 0.001≤ P value <0.01, report the specific P value to 3 decimal places, e.g., "P=0.001" or "P=0.009".

If P value≥0.01, report the specific P value to 2 decimal places, e.g., "P=0.01" "P=0.06" "P=0.10" "P=0.90".

*"SOX11 expression levels were associated with immune infiltrating cells in tumors, including CD8 T cells (P = 0.0265), dendritic cells (P = 0.0081), mast cells (P < 0.001), NK CD56bright cells (P = 0.0014), NK CD56dim cells (P = 0.0254), NK cells (P < 0.001), pDC (P < 0.001), Tcm (p = 0.0082), Tem (P < 0.001), Tgd (P < 0.001), Th1 (P = 0.0146), Th17 (P = 0.0049), and Th2 (P < 0.001) (Figure 6C)."*

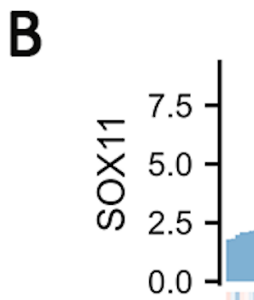Reply: We have revised it in manuscript.

- Please double check Figure 7I-7L legend.

M2 Macrophage (I, J) Neutrophil and (K, L) Dendritic cell.
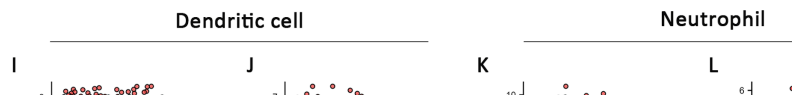


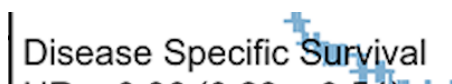Reply: We have double checked Figure 7I-7L legend.

- Please double check the description of the y-axis in Figure 8B.



Reply: We have double checked the description of the y-axis in Figure 8B.

- It is suggested to unify the description in Figure 10A-10F.

The disease-free survival (DFS) curve of (A) ZC3H13, (B) IGF2BP1, (C) FTO, (D) METTL14, (E) IGF2BP2,



Disease Specific Survival

Reply: We have revised it in manuscript (line: 620).

- The unit is repeated in Table 2, please remove.

| Pathologic T stage, n (%) | | |
|---|---|---|
| T1&T2 | 189 (34.9%) | 161 (29.8%) |
| T3&T4 | 81 (15%) | 110 (20.3%) |

Reply: We have removed the unit in Table 2.

- Please add unit for Age in Table 2.

Reply: We have added the unit in Table 2.

- Please check the Table 1 title in the manuscript.

**Table 1:** Primer sequences of SOX11 and β-actin.

Reply: We have revised the Table 1 title in manuscript (line: 624).

6. Supplementary

- **All abbreviations** in the supplementary figure and legend should be explained. Please provide the full name of "mRNA" "SOX11" "ANOVA" "LSD" "SEM" in Supplementary Figure 1 legend.

Reply: We have revised in manuscript

- **A summarized legend** for a figure with different parts should be provided, followed by legends for each part. Please provide the summarized legend for Supplementary Figure 1.

Reply: We have revised in manuscript

- Please indicate the meaning of "****" in Supplementary Figure 1 legend.

Reply: We have revised Supplementary Figure 1 legend in manuscript