Peer Review File

Article information: https://dx.doi.org/10.21037/tp-23-119

Review comments-Reviewer A

Comment 1: Lines 264 to 265, figure 3D) shows that fibroblast, monocyte and CTL are more highly infiltrated in both cluster 1 and 2.

Response: Your reminder is much appreciated. Immunotherapy is a prominent area in cancer treatment. However, neuroblastoma, due to its low mutation burden and lack of T-cell infiltration, is considered immunologically "cold"[1]. Higher abundance of CD8+ T-cells has also been correlated with favorable prognosis and long-term survival in neuroblastoma [2]. As we mentioned in the result, $CD8^+$ T cells and dendritic cells were more highly infiltrated in cluster 1 (Figure 3D), implying that there may be an increased immune cell infiltration and activate the immune response in the tumor microenvironment if the dormancy signature is higher. As you mentioned, it is true that fibroblasts have a higher MCP-Score in the Figure3D. However, we did not observe any significant differences between the two clusters. Our focus lies on the infiltrating cells that exhibit notable distinctions between the two clusters, such as CTLs (CD8+ T cells).

Comment 2: Figure s3A, what does group 1/2/3/4 mean?

Response: Thank you for your wonderful suggestion. It was our negligence not to mark it clearly. To further clarify the role of CDKN2A and BMP7, 24 samples of NB tissues were gathered from patients who had received curative surgery between 2015 and 2016 at Tianjin Medical University Cancer Institute and Hospital. This cohort of NB patients was enrolled and divided into early (<2 years) and late (≥2 years) recurrence groups. One case of early recurrence and one case of late recurrence were randomly assigned in each group (Figure s3A). We corrected them in the revised manuscript. (see Page11 Line24, Page23, Line2-3)

Comment 3: Lines 381 to 383, this sentence is confusing. Please rephrase it.

Response: We thank the reviewer for pointing out this issue. As mentioned in our manuscript, although there are methods now available to predict neuroblastoma prognosis such as INSS, histologic category, and DNA ploidy, there is still a lack of effectively accurate method to prevent or predict recurrence. (see Page12 Line5-7)

Comment 4: Lines 422 to 482, the authors introduced the background of six dormancy-associated genes, but the relationship between the background of these genes and the findings of this study was not clearly indicated.

Response: We have added the aforementioned results to the discussion to highlight the

novelty and significance of our model.

The nomogram is a reliable tool for NB clinical diagnosis and therapy evaluation. These results indicated that the 6-gene signature had a powerful capacity to predict NB prognosis, which had certain guiding significance in decision-making for clinical treatment.

Due to tumor dormancy, most high-risk neuroblastomas present with widespread metastatic disease at diagnosis and either do not respond to conventional therapies initially or ultimately relapse after treatment. But each of these individual gene mentioned above can be modulated by various factors, a gene signature comprising various genes is recommended. In this study, a dormancy-associated gene signature, including CDKN2A, BHLHB3, CDKN2B, MAPK14, CDKN1B, and BMP7, was established. The gene signature showed a strong capacity to predict NB patient prognosis and had certain guiding significance in decision-making for clinical treatment. Through the nomogram, physicians might predict the overall survival more accurately and offer a reasonable personalized therapy for improving the survival of NB patients. After more clinical validation, patients in the high-risk group could be given more attention and intensive treatment, while excessive treatment should be avoided for low-risk group patients. (see Page15 Line6-18)

Comment 5: Line 52, ArrayExpres2s should be revised as ArrayExpress.

Response: Thank you for the detailed comments. We have corrected them in the revised manuscript. (see Page2 Line22)

Comment 6: I have searched the PubMed database with a search algorithm of "neuroblastoma[ti] and nomogram[ti]" and found that 14 studies have investigated the prognosis of neuroblastoma with nomogram. Please address the strength or novelty of this study in the discussion section.

Response: As you have mentioned, several nomograms related to neuroblastoma have been developed. However, whether dormancy is linked to the prognosis of neuroblastoma remains unknown. In our study, we made an important discovery that dormancy-related genes are associated with the prognosis of neuroblastoma. To our knowledge, we are the first to construct a nomogram based on these genes, which demonstrated excellent prognostic predictive power (as shown in Figure 7C). We have added the aforementioned results to the discussion to highlight the novelty and significance of our model. (see Page15 Line6-18)

References

1. Jw A, Mpd A, Gamt A, Ak B, Sn A, Jjm A: The immune landscape of neuroblastoma: Challenges and opportunities for novel therapeutic strategies in pediatric oncology. European Journal of Cancer 2021, 144:123-150.
2. Mina M, Boldrini R, Citti A, Romania P, Fruci D: Tumor-infiltrating T lymphocytes improve clinical outcome of therapy-resistant neuroblastoma. Oncoimmunology 2016,

4(9): e1019981.

Review comments-Reviewer B

1. Please define below abbreviation in Abstract.

27 immunity. Finally, sex, age, International Neuroblastoma Staging System (INSS)
28 stage, and *MYCN* status were identified as independent overall survival-related

R: Thank you for pointing this out, which we neglect in our original manuscript. We have added abbreviation in Abstract and Introduction in the revised manuscript (page 2, line 28, page 3, line 20)

2. Check if any references are missing in this sentence since you've mentioned "previous studies".

20 been confirmed. For example, higher expression of CDKN2A and BMP7 was found
21 in tumor tissues of the late recurrence group in line with previous studies. However,

R: We agree with the reviewer's comments. We have added 3 references in the revised manuscript (page 15, line 28).

3. Please define HR and CI in Figure 4 legends.

R: Thank you for pointing this out. We have added the definitions in the revised manuscript (page 27, line 9).

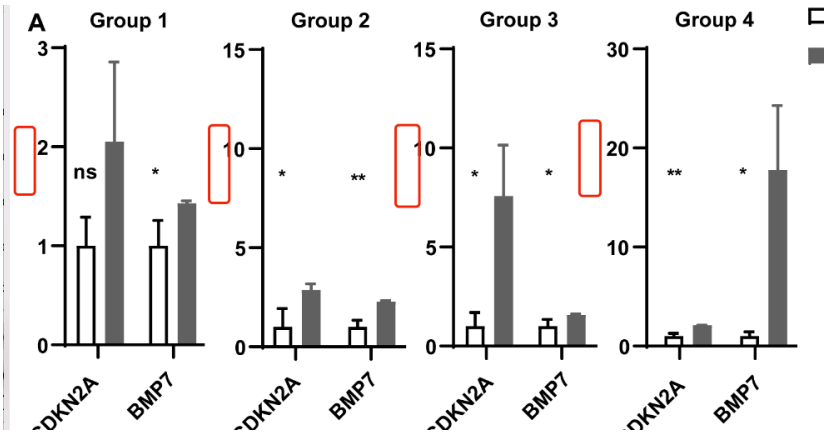
4. Please define OS, HR, and CI in Figure 7 legends.

R: Thank you for pointing this out. We have added the definitions in the revised manuscript (page 28, line 11-12).

5. Please define BP and CC in Figure S1 legends.

R: Thank you for pointing this out. We have added the definition in the revised manuscript (page 29, line 6).

6. Figure S3: Please check if descriptions of Y-axis are missing in the figure.



R: As you recommended, we have added descriptions of Y-axis in the Figure s3-revised.

7. Please define all abbreviations in Table S1 footnote.

R: Thank you for pointing this out. We have added abbreviation in Table S1 in the revised manuscript (page 32).