**Peer Review File**

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**Reviewer A**

**Comment 1**: Considering the notorious variability between oral squamous cell carcinoma and squamous cell carcinomas in other anatomical areas of the head and neck, it would be interesting to have a subgroup analysis of the validity of the IRGS in OSCC.
**Response:** We are grateful for your consideration of this manuscript. Your affirmation is the biggest driving force for our work.

**Comment 2**: In concert with the previous comment, there is also a shift in the epidemiology of HNSCC, from older/smoking/drinking/HPV- cases to younger/non-smoker/HPV+ cases. A subgroup analysis of IRGS performance in these cases would also be interesting.
**Response:** Thank you very much for your comment and consideration of our manuscript. Your affirmation is the biggest driving force for our work.

**Comment 3**: In figure 6A-B and in some manuscript, text passages the authors seem to include/consider fibroblasts as 'immune cells' alongside dendritic cells. To this reviewer this is not correct, as fibroblasts (particularly CAFs) albeit capable of expressing immune-modulating mediators are stromal cells.
**Response:** Thank you very much for your comment. We agree with your opinion. Although fibroblasts have the function of expressing immune-modulating mediators, they are stromal cells. We are grateful to you for pointing out our negligence. We revised the unclear description in the manuscript (Page 10, Line 282).

**Comment 4**: Still in Figure 6A there are a noticeable inverse correlation between PMN signature and IRGS score, which considering other immune cell signature/infiltration sown in this figure suggests a myeloid/monocytic cell highly-infiltrated tumor with some degree of desmoplasia (high infiltration by fibroblasts). In HNSCC there is evidence already associating this phenotype to a worse prognosis and poorer response to treatment. It would be interesting to have the authors comment on this, particularly on the specific contribution of the IRGS signature with the tumor/stroma ratio in the microenvironment.
**Response:** Thank you very much for your comment. There are articles associate high infiltration by fibroblasts to a worse prognosis and poorer response to treatment.

However, both monocytic cells and fibroblasts are heterogeneous. Tumor microenvironment varies greatly in different stages of different individual and also varies greatly across time and space. So, it is difficult to reflect changes in a subpopulation from one data set. In addition, much of the analysis of the immune microenvironment comes from bioinformatics and there is inevitably some noise in the process of analysis.

**Comment 5**: In figure 5A there is a considerable number of T1/T2 deceased patients (and considering this is a cohort of T1/T2 HNSCC) are in the 'mid portion' and 'left hand portion' of the graph, corresponding to an intermediary/low IRGS score. It would be interesting to have the authors comments on this.
**Response:** Thanks very much for your comment. There is a considerable number of T1/T2 deceased patients (and considering this is a cohort of T1/T2 HNSCC) are in the 'mid portion' and 'left hand portion' of the graph, corresponding to an intermediary/low IRGS score. This fully proves that this evaluation system is independent of T stage. It shows that patients with low T stage may also have a poor prognosis and reveals the limitation of TNM stage.

**Comment 6**: For the purpose of clinical translatability using currently-used immunotherapeutic approaches, it would be interesting to assess the correlation of IRGS genes and the expression of PD-1, PD-L1 and CTLA4 immune checkpoints. This information could provide a new perspective on selection of cases for immunotherapy with currently-available molecules.
**Response:** We are grateful for your consideration of this manuscript. Your affirmation is the biggest driving force for our work.

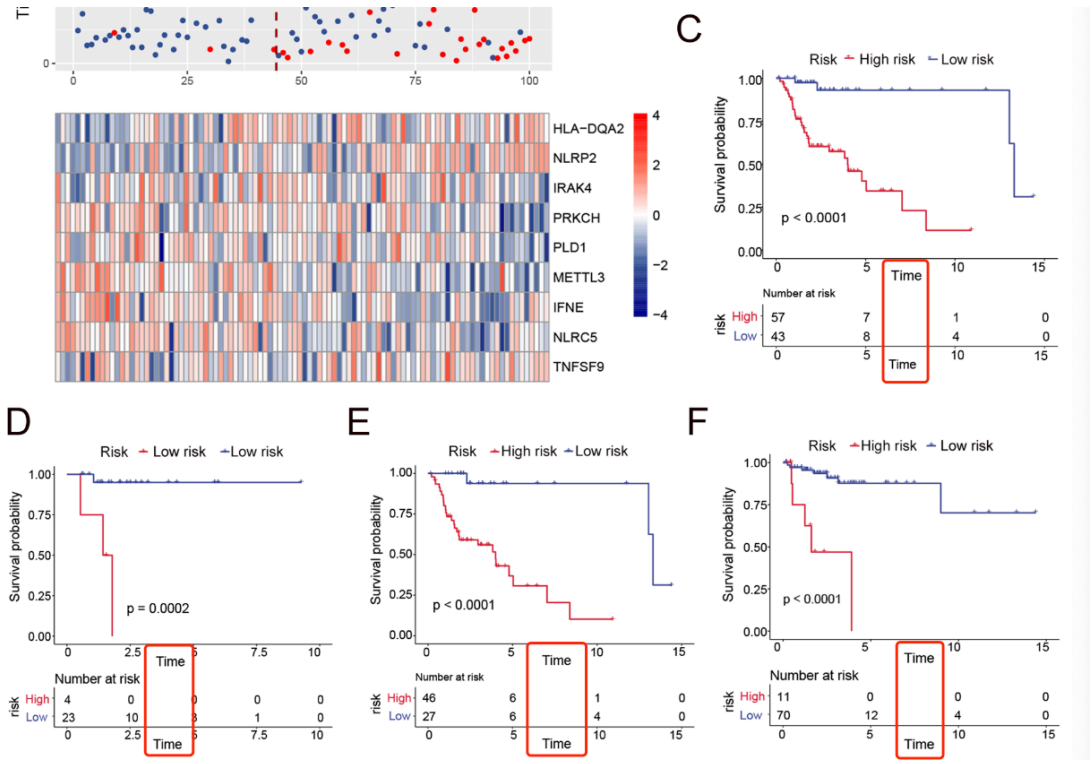
**Reviewer B**

**Comment 1:** Figure 1
Please double check whether it is necessary to capitalize the word.

628 coefficient profiles. **D.** 10-fold cross-validation FOR the tuning parameter

**Response:** Thanks for your careful reading. We have revised the word as you suggested.

**Comment 2:** Figure 2
Please provide the unit of the x-axis.




**Response:** Thanks for your careful reading. The unit of the x-axis is year.

**Comment 3:** Figure 3

Please provide the unit of the x-axis for Figure 3B-C, 3E-F.

**Response:** Thanks for your careful reading. The unit of the x-axis is year. We have revised the Figure 3 in the manuscript.

**Comment 4**: Figure 4

a) Figures, tables and videos should be cited consecutively in the text and numbered in the order in which they are discussed. Figure 4H should be cited after figure 4G, please revise.

cohort, and outperformed than other clinical recognized risk factors (**Figure 4A-C**). The IRGS score C-index was higher than other clinicopathological parameters (**Figure 4H**). Thus, the IRGS score could accurately predict survival in patients with early-stage HNSCC. Subsequently, we also determined the predictive performance of the IRGS score in the validation and clinical cohorts. The IRGS scores achieved AUCs for estimating 3-, 5-year OS of 0.766 and 0.822 in the validation cohort and 0.755 and 0.714 in the independent clinical cohort (**Figure 4D & E**). The C-index further confirmed the predictive value of the IRGS score compared with other clinical factors (**Figure 4F & G**).

b) Figure 4I was not cited, please indicated. It should be cited after 4H.

**Response:** Thanks very much for your comment. We have revised the manuscript as you suggested.

**Comment 5**: Figure 5

It seems that these symbols were no showed in the figure 5, please check.

between IRGS score and 7 metagenes in the training cohort. *, ** and ***

represent P < 0.05, P < 0.01, and P < 0.001, respectively.

**Response:** Thanks for your careful reading. We have revised the mistake.

**Comment 6**: Supplementary Table 1

Please provide the unit of age.

| | | | |
|---|---|---|---|
| Age | | | |
| ≤60 | 39 (39.0) | 28 (57.1) | 42 (51.9) |
| >60 | 61 (61.0) | 21 (42.9) | 39 (48.1) |

**Response:** Thanks very much for your comment. We have provided the unit of age and revised the table.

**Comment 7**: Supplementary figures

Each supplementary figure should follow after each figure legend, please adjust.

**Supplementary materials**

**Supplementary figures**

**Supplementary figure 1.** Subgroup analyses of IRGS in Training set (TCGA, N=100)

**Supplementary figure 2.** Subgroup analyses of IRGS in validaiton set (GSE65858, N=49)

**Supplementary figure 3.** Subgroup analyses of IRGS in external validation cohort (N=81)

**Response:** Thanks very much for your comment. We have adjusted the manuscript as you suggested.

**Comment 8**: References/Citations

a) Reference 34 was not cited in the main text, please revise.

*Please note that it should be cited between 33 and 35.

b) References 10 and 16 are the same, please delete one of them and revise both the citation in main text and reference list's order.

**Response:** Thanks very much for your comment. We have revised the manuscript as you suggested.