Comments to: Prognostic and chemotherapeutic implications of a novel four-gene pyroptosis model in head and neck squamous cell carcinoma

The authors sought to assess the prognostic and predictive value of "four-gene pyroptosis score" in patients with head and neck squamous cell carcinoma (HNSCC). Conducting chemotherapy sensitivity assays in HNSCC cell lines is the strength of this study. Weaknesses of this study are listed below.

1. Selections of the four genes (Caspase-1, Caspase-3, Gasdermin D, Gasdermin E) are not well supported. For example, on line 66-67, the authors mentioned that "GSDMD and CASP1 are also reported to implicate in mediating pyroptosis or chemotherapeutic responses of HNSCC(16-18)". However, ref 16 didn't investigate GSDMD or CASP1, ref 17 reported that GSDMD can enhance cisplatin-induced apoptosis, not pyroptosis. For ref 18, I don't understand why it was cited. Similarly, on line 73-74, "As aforementioned, four pyroptosis-related genes, GSDMD, CASP1, GSDME, and CASP3, have been reported to play crucial roles in HNSCC progression(15-17, 24)." Based on the cited references, the rationality of choosing GSDMD and CASP1 is weak.

2. Please explain why "these pooled signatures are incapable of reflecting the pyroptosis activity in the tumors" (line 69-70)? However, a formulated PRGscore can be "reflective of pyroptotic activity" (ling 39)?

3. Results should be better explained. According to Figure 2, we can see that the prognostic values of CASP1 and GSDMD are low. Comparing Figure 3C to Figure 2B, the impact of PRGscore on survival is less significant than the impact of CASP3 and GSDME. From Figure 4C, it should be concluded that there was no significant difference when comparing high-PRGscore to low-PRGscore patients in the chemotherapy cohort (**P=0.05**, Log-rank test, Fig. 4C; hazard ratio of PRGscore=0.175, **P=0.057**, Fig. 4D).

4. It is possible that the performance of a two-gene pyroptosis score based on CASP3 and GSDME is similar to that of the four-gene score. Have you studied the performance of a two-gene score?

5. Immunophenoscore (IPS) could predict response to immunotherapy. However, a significant difference in IPS between PRGscore-low and PRGscore-high patients could

not lead to a conclusion that “individuals with elevated PRGscore or increased pyroptosis gene expression showed increased responsiveness to immunotherapy targeting PD1, CTLA4, or the combination of CTLA4 and PD” (line 231-233). This result should be shown and interpreted in a better way.

Minor issues:

1. Legends to supplementary figures are missing.

2. It should be Fig. S3C to S3**G**, not “Fig S3C to S3**E**” (line 234).