December 4, 2025

Dear Editor(s) of ***International Journal of Molecular Sciences***,

We are pleased to submit our manuscript entitled "Identification of Immune&Driver molecular subtypes optimizes chemotherapy and immunotherapy strategies for gastric cancer", which we wish to be considered for publication in your journal, ***International Journal of Molecular Sciences***.

Immunotherapy has emerged as a promising treatment modality for gastric cancer. However, its efficacy varies significantly across molecular subtypes, due to the heterogeneous immune microenvironments and genomic alterations within subgroups. In this study, Immune&Driver molecular subtypes of gastric cancer were established by systematically integrating multi-omics data from immune-related and driver genes. Molecular subtypes were characterized from genomic instability and immune landscape. Their anti-cancer drug sensitivity and response to immunotherapy, particularly anti-PD-1 and anti-CTLA-4 therapies, were predicted and validated in four gastric cancer cohorts and four melanoma cohorts. Finally, an immunotherapy prediction model was developed by training four melanoma immunotherapy cohorts across seven machine-learning algorithms.

Our findings revealed two molecular subtypes, CS1 and CS2, with differential associations to patient outcomes undergoing radiation therapy in gastric cancer. The CS1 subtype was linked to a better prognosis, while CS2 represented a poorer prognostic phenotype. The CS1 subtype displayed enhanced genomic instability, marked by higher mutation rates and chromosomal alterations, suggesting a more aggressive tumor biology. In contrast, CS2 exhibited higher immune activity, with a higher density of immune cell infiltrates and increased expression of immune checkpoint molecules and chemokines, which may contribute to a more robust immune response against the tumor. Furthermore, the CS1 subtype demonstrated heightened sensitivity to FDA-approved chemotherapy drugs, such as crizotinib, gefitinib, and osimertinib. CS2 was more responsive to FDA-approved immune-related drugs, containing niraparib, talazoparib, and venetoclax. CS2 was more responsive to anti-PD-1 therapy, with the combination of anti-PD-1 and anti-CTLA-4 showing superior efficacy compared to anti-PD-1 monotherapy. Additionally, the Logistboost model was identified as the optimal model for robustly predicting immunotherapy responses based on the transcriptional expression of CS biomarkers. Therefore, immune&Driver molecular subtypes offer valuable insights into personalized treatment approaches, where chemotherapy and immunotherapy can be tailored to specific subgroups.

This manuscript is a full-length work that has not been concurrently submitted for publication in print or electronic format elsewhere. No part of the manuscript has been published or will be published elsewhere prior to its publication in ***International Journal of Molecular Sciences***. This submission has the consent of all co-authors of the paper. The manuscript has undergone editing by several professionals and a specialist language editing company (International Science Editing) to prevent any potential academic or grammatical errors.

Sincerely yours,

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