Applied Artificial Intelligence Research

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The Application of Artificial Intelligence in Tumor Immunotherapy: Integrating Multi-Omics Data to Achieve Efficacy Prediction and Combination Strategies

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ARTICLEINFO

Keywords:
Artificial Intelligence
Tumor Immunotherapy
Multi-Omics
Efficacy Prediction
Combination Therapy
Machine Learning

ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, yet only a minority of patients achieve durable clinical benefit due to primary or acquired resistance. This heterogeneity necessitates precise predictive biomarkers and rational combination strategies. The rapid accumulation of multi-omics data-including genomics, transcriptomics, radiomics, pathomics, and microbiomics-offers unprecedented opportunities to decode tumor-immune interactions. Artificial intelligence, particularly machine learning and deep learning, excels at integrating high-dimensional, heterogeneous data to build interpretable efficacy prediction models and accelerate the discovery of synergistic combination regimens. In this review, we systematically summarize AI-based multimodal integration frameworks (e.g:deep multimodal fusion, graph neural networks, and single-cell omics models) and key technologies. We critically analyze the types and characteristics of multi-omics data used in immunotherapy prediction. Furthermore, we discuss AI-driven applications in personalized stratification, combination therapy target discovery, and drug synergy prediction. Finally, we identify current bottlenecks-including interpretability, data standardization, clinical validation, and model generalizability-and propose future directions. This review provides a systematic reference for transitioning from empirical treatment to data-driven precision immunotherapy.

1.Introduction

Immune checkpoint inhibitors (ICIs), which include anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death 1/ligand 1 (PD-1/PD-L1), have significantly altered the course of treatment for a number of cancers, including renal cell carcinoma, advanced melanoma, and non-small cell lung cancer[1]. However, actual data reveals that in the US, only roughly 12% of the population can benefit from ICI treatment, and less than 40% of individuals with advanced cancer match the requirements[2]. In gastric cancer, PD-1 inhibitor monotherapy achieves an objective response rate of only 11-15%[3]. Two fundamental clinical challenges are highlighted by this extreme heterogeneity in therapeutic efficacy: first, how to accurately identify patients who may benefit in advance to prevent ineffective exposure and immune-related adverse events; and second, how to develop the best combination treatment strategy to increase the responder population and prolong survival given the prevalence of primary or acquired resistance.

It is challenging for single-dimensional biomarkers to adequately reflect the complexity of the response to tumour immunotherapy since it is regulated at numerous levels by intrinsic tumour properties, the immune microenvironment, the host's general health, and external environmental factors. Tumour mutational burden (TMB), microsatellite instability, and programmed death-ligand 1 (PD-L1) expression have all been included in clinical guidelines, but their predictive sensitivity and specificity are subpar, with frequent false positives and false negatives. Recent meta-analyses have shown that PD-L1 demonstrates predictive value in only 28.9% of FDA approvals, and conventional biomarker-based approaches achieve limited accuracy in clinical practice[4]. The deeper explanation for this is that the immune response is a multifaceted interactive network that includes transcriptional programs, genomic changes, immune cell infiltration status, intercellular spatial topology, systemic metabolism, and gut

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https://doi.org/10.65455/q72yq328
Received 22 May 2026; Received in revised form 28 May 2026; Accepted 16 June 2026; Available online 24 June 2026
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microbiota composition. Therefore, characterising the immune response with a single type of omics feature is far from adequate.

The rapid advancement of high-throughput sequencing, mass spectrometry imaging, digital medical imaging, and liquid biopsy technologies has greatly increased the availability of multi-omics data, providing a thorough genetic map for systematically analysing the tumor-immune interaction.Recent reviews have systematically summarized emerging predictive biomarkers spanning genomics, proteomics, metabolomics, and their synergistic roles in patient stratification[5]. Simultaneously, deep learning based on architectures like convolutional neural networks, graph neural networks, and Transformers, as well as traditional machine learning represented by random forests and gradient boosting machines, have demonstrated strong abilities in fitting high-dimensional nonlinear data and learning cross-modal representations[6,7]. It is anticipated to overcome the limit of single-omics prediction and produce novel biological insights by algorithmically integrating multi-source data, such as genomes, transcriptomics, proteomics, imaging, pathology, and even microbiomics, at either the feature or decision level. Furthermore, AI has great promise for predicting the synergistic effects of medications and simulating the behaviour of signalling networks during disruptions, creating new opportunities for the rational development of immunotherapy combinations[8].

The research aims to thoroughly evaluate how artificial intelligence technologies combine multi-omics data in order to predict the efficacy of immunotherapy and design combination methods. We will discuss, in order, the multi-omics aspects of immunotherapy, the main techniques of AI-integrated predictive models, AI-driven discoveries of combination therapies, and the main obstacles currently encountered in order to offer a comprehensive reference for in-depth research and translational implementation in this multidisciplinary field.

Structure and highlights of this review: This review comprehensively evaluates how AI technologies integrate multi-omics data for immunotherapy efficacy prediction and combination strategy design. Section 2 systematically characterizes multi-omics dimensions relevant to immunotherapy response, supported by a summary table. Section 3 delineates AI-integrated predictive models, comparing traditional machine learning, deep multimodal fusion strategies (early, intermediate, late), and single-cell/spatial omics approaches, with a comparative table of fusion strategies. Section 4 discusses AI-driven discovery of combination therapies Section 5 analyzes current challenges Section 6 concludes with core findings and future 3-5 year directions. This review provides a systematic reference for basic research, algorithm development, and clinical translation in this interdisciplinary field.

2.Multi-omics characteristics related to the efficacy of immunotherapy

The foundation of creating high-performance predictive models is fully extracting features with biological discriminative capability. Multiple biological dimensions are involved in immunotherapy sensitivity and resistance, and each layer of data contains distinct prediction cues.

2.1.Genomic and transcriptomic biomarkers

The first predicted indicators to be used were biomarkers at the genetic level of tumours. A tumor's total number of non-synonymous somatic mutations is represented by its TMB, and a high TMB increases the likelihood of neoantigen generation, which facilitates immune identification. In a thorough examination of TMB, PD-L1, and T-cell-inflamed gene expression profile (GEP) in a pan-cancer cohort, Cristescu and colleagues discovered that GEP and TMB are comparatively independent in predicting pembrolizumab effectiveness and that their combination can more effectively stratify patients[9]. By using transcriptome data to generate an immune prediction score, Auslander and colleagues were able to predict metastatic melanoma more accurately than a single TMB. This study highlights the equivalent importance of immune escape modules caused by intrinsic defects in tumour signalling pathways[10]. Through extensive immunogenomic research, Jiang and colleagues found characteristics of T cell rejection and malfunction that can independently predict anti-PD-1 treatment responses in a variety of cancer types[11]. These findings show how transcriptome and genomic properties are complementary and redundant, which severely restricts algorithmic dimensionality reduction and variable selection[12,13].

2.2.Tumor microenvironment and single-cell omics

The phenotypic and functional state of immune cells within the tumour microenvironment is the real "executive layer" that ultimately governs the immune response. Using single-cell RNA sequencing (scRNA-seq), the dynamic lineages of myeloid cells, natural killer cells, invading T cells, and other cells may be accurately identified. Zhang and associates discovered a "T cell resilience" state that highly expressed particular transcription factors by integrating scRNA-seq data from many immunotherapy groups. This state can predict objective responses and survival advantages of anti-PD-1 therapy across different tumour types and is independent of traditional exhaustion markers[14]. This finding raises the predictive dimension to the dynamic level of cell states from static cell proportions. Furthermore, important antigen-specific information is provided by the clonal diversity of the T cell receptor (TCR) repertoire, amplified clonotypes, and neoantigen-specific recognition, which are new input variables for AI modelling[15].

2.3.Radiomics, pathomics, and spatial omics

Conventional pathology slides stained with haematoxylin and eosin (H&E) offer a wealth of information about cancer cell morphology, stromal responses, and immune cell spatial distribution—tasks that are perfect for deep learning picture recognition. Johannet and colleagues used machine learning techniques to extract features and build models from H&E pathology images of advanced melanoma in order to predict

immunotherapy response beyond PD-L1 expression and to visualise the significant contributions of tumor-infiltrating lymphocyte density and spatial distribution[16]. Such techniques do not require additional molecular testing, are low-cost, and widely accessible. Spatial transcriptomics and multiplex immunofluorescence as spatial omics can also map molecular expression to tissue spatial coordinates, reveal neighborhood relationships between immune cells and tumor cells, tertiary lymphoid maturity, and more elaborate topological properties[5,17].

Macroscopic features of tumours, including as general heterogeneity, necrosis, fibrosis, and marginal infiltration, can be seen using non-invasive imaging techniques like computed tomography (CT) and magnetic resonance imaging (MRI). In order to successfully build a predictive model for the response to anti-PD-1 therapy, Trebeschi and colleagues used CT radiomics to extract numerous quantitative features from baseline and early treatment CT scans of non-small cell lung cancer and melanoma. They discovered that immune responders frequently have more compact and homogeneous tumour phenotypes[18]. The benefit of radiomics is its capacity for non-invasive, real-time, and thorough evaluation, which makes it especially useful for monitoring dynamic efficacy and identifying pseudoprogression[19,20].

2.4.Microbiomics and systemic multi-omics dimensions

By controlling the intestinal immunological milieu, the makeup of the gut microbiota can affect systemic anti-tumor immunity, according to recent research. A microbiome-based predictive model was built by Limeta and colleagues after they performed a meta-analysis of published microbiome data and confirmed the correlation between favourable responses to ICIs and certain microbial diversity and taxonomic abundance (such as Akkermansia muciniphila and Bifidobacterium)[21]. Exosomes, circulating immune cell subsets, soluble immune regulatory factors, and the dynamic alterations of circulating tumour DNA (ctDNA) in peripheral blood are all possible multi-omics dimensions that offer opportunities for non-invasive long-term surveillance.

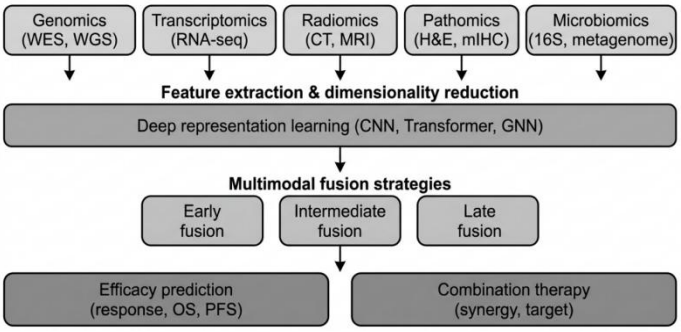


Fig 1. Schematic overview of multi-omics data integration with artificial intelligence for immunotherapy efficacy prediction and combination strategy design

A causally linked multi-level regulatory network is formed by the aforementioned multi-omics properties rather than being isolated from one another. Litchfield et al. thoroughly illustrated through extensive meta-analyses how T cell-intrinsic factors (like some exhaustion programs) and tumor-intrinsic factors (like antigen presentation and interferon signalling) jointly determine sensitivity to immune checkpoint blockade. This clearly shows that no single omics layer can fully explain the variations in response and that only the integration of multi-dimensional features can truly capture the full complexity of immune responses.This offers a basic biological foundation for cross-modal integration with AI[4].

Table 1. Summary of multi-omics data types for immunotherapy efficacy prediction

Omics Type	Data Category	Prediction Targets	Advantages	Limitations
Genomics	WES, WGS	TMB, neoantigen load, HLA type, specific mutations	Direct genetic evidence, stable	Low sensitivity alone, fails to capture dynamic changes
Transcriptomics	RNA-seq, microarray	GEP, immune cell fraction, exhaustion signatures	Reflects functional state	Susceptible to batch effects, requires fresh/frozen tissue
Radiomics	CT, MRI	Tumor heterogeneity, shape, texture, necrosis	Non-invasive, longitudinal, cheap	Indirect biological readout, modality-dependent
Pathomics	H&E slides, mIHC	TIL density/spatial distribution, tumor-stroma interface	Preserves spatial context, widely available	Requires digital scanners, subjective feature selection
Microbiomics	16S rRNA, metagenomics	Microbial diversity, specific taxa (e.g., Akkermansia)	Systemic immune modulation potential	Highly variable across cohorts, causal inference difficult
Single-cell omics	scRNA-seq, scATAC-seq	Cell state, clonal expansion, ligand-receptor pairs	Unprecedented resolution	High cost, sparse data, computational complexity

3.Artificial intelligence integrates multi-omics to achieve efficacy prediction

3.1.Traditional machine learning models

In the early stages of multi-omics data integration, traditional machine learning techniques including logistic regression, elastic net, random forest, and support vector machine are often used because to their excellent interpretability and low overfitting risk. In a group of patients with metastatic melanoma receiving pembrolizumab, Liu et al. developed an integrated prediction model based on Bayesian logistic regression and Cox regression. By incorporating a number of variables, including clinical characteristics (like lactate dehydrogenase, age), genomic mutations (like BRAF, NRAS, etc.), TMB, and GEP, this model greatly improved the prediction accuracy for overall survival in an independent validation set[22]. This work shows that, if the input features

are biologically acceptable, merging multi-omics data can still yield prediction performance that is superior than that of single variables, even when using extremely basic models. Kim and colleagues, focusing on metastatic gastric cancer, identified multiple molecular subtypes through the integration of whole-exome and transcriptome analyses, underscoring the significance of using statistical models for multivariable integration. They found that high TMB and inflammatory features can only identify the patient groups most likely to benefit when assessed together[23]. More recently, multi-tensor AI/ML approaches have been applied to discover whole-transcriptome predictors of survival in response to immunotherapy from multi-omic clinical data[24].

3.2.Deep learning and multimodal fusion strategies

When working with ever-larger and more complex types of data, deep learning provides the potential for end-to-end joint learning. In multimodal data fusion, three methods are commonly employed: early fusion, intermediate fusion, and late fusion. Although early fusion is simple and uncomplicated, it is vulnerable to intermodal noise. It enters raw data into a single network by concatenating it from multiple sources.Although flexible, late fusion ignores cross-modal interactions and trains sub-models independently on each modality, only performing weighted integration at the output layer. Conversely, intermediate fusion has the most potential since it captures high-order cross-modal correlations in a learnable space and realises feature interaction in the network's hidden layers[25,26].

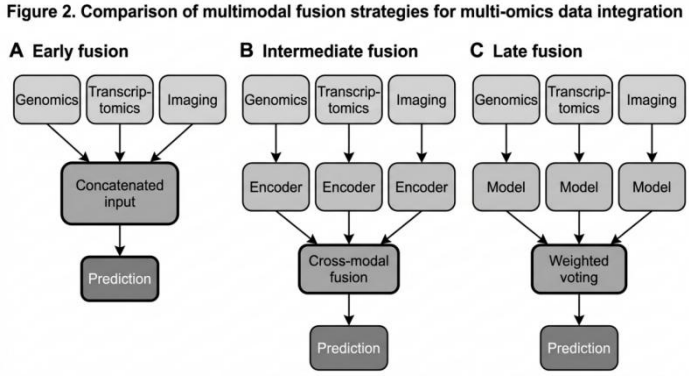


Fig 2. Comparison of multimodal fusion strategies for multi-omics data integration

Vanguri and coworkers employed a multimodal fusion paradigm to predict immunotherapy for non-small cell lung cancer by combining information from TMB, H&E pathology slides, CT imaging, and genetic changes (such as TP53 and KRAS). After deep representations were extracted using separate encoders, attention-weighted interactions were performed at the fusion layer to achieve joint prediction. The consistency index of the multimodal model showed the complementary value across modalities, and it was significantly superior to any single-modality model.Similar designs are progressively becoming the norm for AI prediction models. The key is to figure out how to design encoding networks that are specific to each kind of data, such as Transformers for omics sequences and convolutional networks for image processing, and how to use gating mechanisms or cross-modal attention to automatically learn modality weights.

Table 2. Comparison of multimodal fusion strategies

Fusion Strategy	Principle	Advantages	Disadvantages	Applicable Scenarios
Early fusion	Concatenate raw features from all modalities at input level	Simple, easy to implement	Ignores modality heterogeneity; vulnerable to noise	Modalities are well-aligned and low-dimensional
Intermediate fusion	Learn cross-modal interactions in hidden layers (e.g., attention, gating)	Captures high-order correlations; flexible	Complex architecture; requires large data	Heterogeneous, high-dimensional multi-omics data
Late fusion	Train separate models per modality, combine outputs (e.g., voting, averaging)	Robust to missing modalities; interpretable	No cross-modal interaction during training	Modalities are independent or confidence scores available

3.3.Single-cell and spatial omics models

More advanced AI techniques are needed because to the extreme sparsity and multi-dimensional nature of single-cell data. In a common paradigm based on aggregative modelling of single-cell representations, Zhang et al. learned the T cell state space from scRNA-seq using autoencoders and kernel techniques, then converted the patient-level cell state distributions into predictive labels[24]. As spatial omics has grown, graph neural networks have been used to model tissue sections as cell-node graphs, capture intercellular adjacency relationships and ligand-receptor signalling, and obtain overall microenvironment graph-level representations by learning node embeddings for prediction[17]. The spatial integration of in situ multimolecular characteristics of tissues is a perfect fit for this design[4].

3.4.Interpretability and generalization

The lack of confidence in "black-box" models is one of the obstacles in clinical applications. Approaches such as feature attribution based on SHAP (Shapley Additive Explanations) or integrated gradients, as well as attention weight visualisation, can be used to identify the components that truly affect predictions in multi-omics models. For example, heatmaps can support established immune exclusion phenotypes by displaying tumor–stromal interfaces and immune cell-dense regions that are most associated with immunological responses in pathological deep learning models[27]. This "interpretability—discovery—validation" closed loop not only enhances model transparency but may also guide the development of novel biomarkers (such as specific cell states and geographic features) and act as a vital conduit for AI to feed back into immunobiology.

Due to differences in technological platforms and the population diversity of immunotherapy cohorts, models are

very susceptible to overfitting or performance collapse. It is still challenging to fully reuse models across cancer types, according to pan-cancer analysis[9], which necessitates the creation of transfer learning and domain adaptation algorithms to align different data distributions. Thorough external independent validation, temporal validation, and prospective clinical trials (such AI-based stratified enrolment basket trials) are the gold standard for confirming the robustness of a model[28].

4.Artificial intelligence-driven combination therapy strategy

4.1.Identification of resistance mechanisms

Resistance bottlenecks can be identified by multi-omics analysis in addition to predicting responses. Litchfield et al. noted that some resistant tumours concurrently show defects in the interferon-γ pathway along with upregulation of alternative immune inhibitory molecules (such as LAG-3 and TIGIT), based on the identification of determinants of immune sensitivity and resistance. This suggests that PD-1 inhibitors in conjunction with corresponding immune co-inhibitory receptor antagonists may reverse resistance. These multi-omics-driven theories are currently being confirmed by further preclinical research. In order to accomplish quantitative ranking from omics to targets, AI can methodically incorporate gene dependency and drug perturbation datasets (like the Cancer Dependency Map).

4.2.Drug synergy prediction

AI models that can predict synergy from available omics perturbation data are tremendously beneficial because large-scale in vitro drug combination screening is quite expensive. In order to predict the sensitivity of particular cancer cell lines to anticancer drugs and the synergy scores of drug combinations, Kuenzi and colleagues created the DrugCell model, which is based on deep neural networks and jointly encodes the molecular profiling of tumour cells and the chemical structure of drugs[16]. This model paved the way for the adaptation of similar frameworks to immune–tumor co-culture models.Inputting multi-omics characteristics of cancer cell lines, immune cell activation signalling pathways, and drug target profiles into deep synergistic models shows promise for virtual screening that more closely reflects true in vivo immune combination effects, even though the prediction of synergy fully simulating tumor–immune–stromal interactions is still in its early stages.A mechanistically explainable AI model has recently been developed for predicting synergistic cancer therapy combinations, offering greater transparency in synergy prediction[29]. Furthermore, AI-enhanced synergistic chemo-immunotherapy is being translated from mechanistic insights to clinical practice[8].

4.3.Personalized combination matching

Using patient-specific multi-omics profiles to match appropriate combo medicines is one of AI's greatest benefits. In the future, a closed loop could be built by first screening high-risk groups that might be resistant to single-drug therapy using patients' multi-omics data using efficacy prediction models; then, for the resistant omics characteristics of this group, looking for the best synergistic combinations in a database of drug synergy prediction models and combining a safety prediction module to rule out high-risk toxicities. The initial idea of offering various immunotherapy approaches based on molecular feature categorisation has already been expressed in Kim et al.'s multi-omics classification research of gastric cancer[23]. Personalised combination therapy recommendations based on a thorough risk-benefit analysis can be produced by incorporating specific clinical factors, such as liver and kidney function and co-medications, through the integration of electronic health records.

4.4.Integration with adaptive clinical trials

AI-driven combination strategies may eventually deeply integrate with adaptive clinical trial designs by generating digital twins based on multi-omics data, updating patients' response probabilities to combination therapies in real time, and expediting the screening of effective combinations while reducing the risk of ineffective exposure. Even while this strategy now faces significant challenges in regulatory science and causal inference, it is certainly a long-term goal of precision immuno-oncology.

5.Challenges and future directions

5.1.Data heterogeneity and standardization

Batch effects and data heterogeneity in multi-omics data, which come from different platforms, batches, and centers, have a major impact on the transferability of models.Many published models are now hard to replicate due to a lack of open benchmark datasets, metadata description guidelines, and standardised preprocessing standards. At the infrastructural level, there is an urgent need to establish large-scale, multi-center, multi-omics immunotherapy common databases (like TCIA, Immune-Related Atlas) and standardised analysis methods.

5.2.Missing modalities and model robustness

Although all modalities are assumed to be completely present in multimodal models, it is frequently the case in clinical practice that some tests are absent. Strong fusion frameworks that can handle missing modalities are therefore needed, such as multimodal missing data completeness and dynamic weighting techniques based on variational inference.However, careful algorithm design is also needed to determine how best to balance the contributions of each modality so that low-dimensional but clinically significant factors are not overpowered by high-dimensional imaging or omics data.

5.3.Clinical validation and regulatory hurdles

The great majority of prediction models lack support from the highest level of evidence in evidence-based medicine and are only internally verified in retrospective cohorts. Randomised controlled trials or umbrella studies that integrate AI stratification and use patient clinical outcomes as endpoints to verify the model's efficacy are essential for bridging the gap between research and clinical practice. Regulatory agencies have already begun discussing evaluation frameworks for AI-based diagnostic and treatment decision systems[3].

5.4.Interpretability and bias mitigation

Clinicians must understand the logic of the model while making decisions. Future research should focus on enhancing interpretability methods theoretically and creating visual interactive interfaces for clinical applications. AI model outputs should be openly displayed alongside key driving characteristics (such as diseased regions, gene mutations, and microbial abundance) in order to promote confidence.

Racial, regional, and socioeconomic biases in training data may cause AI prediction models to perform badly in minority populations, exacerbating health inequities. Bias audits and fairness limits must be integrated throughout the whole AI development process to ensure that multi-omics-driven precision immunotherapy may truly yield "universally precise" results.

6.Conclusion

This review systematically demonstrates that the integration of multi-omics data with artificial intelligence is fundamentally reshaping precision prediction and decision-making in tumor immunotherapy. Each omics layer-from genomics, transcriptomics, and single-cell profiling to radiomics, pathomics, and microbiomics-provides distinct but complementary codes of the immune response. AI, particularly deep multimodal fusion and graph neural networks, serves as an indispensable decoder of these multi-level, non-linear signals. Key advantages of mainstream AI algorithms include the ability to handle missing modalities, learn cross-modal correlations, and offer interpretability through attention mechanisms or SHAP analysis. However, major obstacles hindering clinical translation include batch effects and data heterogeneity, lack of standardized benchmarks, limited prospective validation, and algorithmic bias. Over the next 3-5 years, critical research directions should prioritize: establishing large-scale, multi-center, standardized multi-omics immunotherapy cohorts; developing robust fusion frameworks resilient to missing modalities; embedding interpretability and fairness constraints into model design; and conducting prospective clinical trials (e.g:umbrella or basket designs) to validate AI-driven stratification. The academic contribution of this review lies in providing a systematic, critical, and forward-looking reference for subsequent basic research, algorithm development, and clinical translation at the intersection of multi-omics, AI, and immuno-oncology.

Author contributions Gang Liu is the sole author of this article and is responsible for all aspects of the work: study conception and design, data collection and analysis, and drafting and revision of the manuscript.

Funding No funding was received for this work.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The author declares no conflict of interest.

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