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## Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: Markers predicting immune-checkpoint inhibitor efficacy and immune-related adverse events

Qiu-Yu Jiang, Ru-Yi Xue

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### Abstract

We conducted a comprehensive review of existing prediction models pertaining to the efficacy of immune-checkpoint inhibitor (ICI) and the occurrence of immune-related adverse events (irAEs). The predictive potential of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in determining ICI effectiveness has been extensively investigated, while limited research has been conducted on predicting irAEs. Furthermore, the combined model incorporating NLR and PLR, either with each other or in conjunction with additional markers such as carcinoembryonic antigen, exhibits superior predictive capabilities compared to individual markers alone. NLR and PLR are promising markers for clinical applications. Forthcoming models ought to incorporate established efficacious models and newly identified ones, thereby constituting a multifactor composite model. Furthermore, efforts should be made to explore effective clinical application approaches that enhance the predictive accuracy and efficiency.

**Key Words:** Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Immune-checkpoint inhibitor; Immune-related adverse event

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**Core Tip:** The negative correlation between high baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and the effectiveness of immune-checkpoint inhibitor (ICI) treatment has been confirmed in non-small cell lung cancer, melanoma, and hepatocellular carcinoma. However, there is a scarcity of studies investigating the prediction of immune-related adverse events (irAEs) occurrence. By incorporating NLR and PLR with other potential risk factors, it is possible to enhance the predictive accuracy of both ICI response and irAEs occurrence through the development of joint prediction models. This approach can aid in the selection of appropriate candidates for ICIs.

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## INTRODUCTION

Monoclonal antibodies targeting immune checkpoints, commonly known as immune-checkpoint inhibitors (ICIs), have significantly transformed cancer therapy and are now widely used in cancer treatment. Despite the notable advancements in patient outcomes across various cancer types, it is important to acknowledge that only a minority of patients receiving ICI therapies experience a sustained response. Among patients with melanoma, a malignancy known for its high responsiveness to ICI, a significant proportion, ranging from 60% to 70%, fail to exhibit an objective response to anti-PD-1 therapy. Furthermore, within the subset of responders, approximately 20% to 30% eventually encounter tumor relapse and progression[1,2].

Despite the considerable advantages that ICIs have provided to patients, the excessive activation of the immune system to enhance antitumor immunity can have both positive and negative consequences. One such consequence is the emergence of immune-related adverse events (irAEs), which are frequently observed in individuals undergoing ICI treatment[3,4]. Studies have shown that approximately 30%-60% of patients experience irAEs, with around 10%-20% experiencing more severe irAEs (grade three or four)[3-5]. The majority of irAEs primarily affect the colon, liver, lungs, pituitary gland, thyroid, and skin, although there have been rare instances of adverse events involving the heart, nervous system, and other organs[6].

The occurrence and intensity of irAEs vary among different immune checkpoint therapies. Anti-PD-1 therapy was demonstrated to be safer compared to anti-CTLA-4 therapy. In patients diagnosed with melanoma, administration of ICIs before any other treatment resulted in grade three or four irAEs in 27.3% of patients using anti-CTLA-4 and 16.3% of patients using anti-PD-1[7]. Combination of both anti-CTLA-4 and anti-PD-1 for advanced melanoma significantly increased both the frequency and severity of irAEs, showing a high-grade irAEs rate of 55% among patients[7]. In addition to variations in the frequency and severity of irAEs, the administration of ICIs also leads to irAEs that exhibit differences in terms of organ manifestation. Specifically, anti-CTLA-4 therapy is associated with a higher incidence of hypophysitis and more severe cases of colitis, whereas anti-PD-1 therapy is linked to a greater occurrence of pneumonitis, thyroiditis, and nephritis[3,6].

## PREDICTION MODELS OF ICI EFFICACY AND IRAES OCCURANCE

The identification of predictive biomarkers is imperative in order to discern patients who may experience favorable outcomes or adverse events as a result of ICI. There are many predictive models of immunotherapy reactivity. Several biomarkers related to the tumor microenvironment, such as PD-L1, CD8+ T cell infiltration, and microsatellite instability, have been utilized in clinical settings to identify appropriate candidates for immunotherapy[8,9]. However, their sensitivities and specificities vary and lack uniformity. Currently, diverse immune cell-associated signatures have been developed to enhance the prognostication of immunotherapy effectiveness. According to the TIGER database, the signatures T cell-inflamed GEP[10], CAF[11], TAM M2[11], IFNG[11], CD8[11], CD274[11], TLS[12], TLS-melanoma[12], T cell dysfunction[11], T cell exclusion[11] and MDSC[11] exhibited an overall area under curve (AUC) of 0.6632, 0.6059, 0.5928, 0.5806, 0.6594, 0.6140, 0.6495, 0.6586, and 0.6078, respectively. Despite their recognition, these signatures still do not demonstrate satisfactory predictive efficacy. Future investigations could potentially explore the identification of additional signatures or the recombination of existing models using diverse detection methods to further enhance efficiency. As an example, our previous research[13] has successfully developed a novel immunohistochemistry model that incorporated three activated CD4+ memory T cell-related genes (CD36, BATF2, and MYB) along with traditional biomarkers CD8 and PD-L1. This combined model has demonstrated enhanced predictive capability (AUC = 0.821) in the context of immunotherapy for gastric cancer patients.

In contrast, studies of signatures linked to irAEs are relatively lacking. Previous retrospective series have identified various clinical characteristics, germline and somatic genetic features, microbiome composition, and circulating biomarkers that are associated with an increased risk of developing irAEs. Specifically, factors such as pre-existing autoimmune disease[14-18], sex and body mass index[19-22], response to ICI[5,23-28], circulating cytokines and immune cells[19,29-31], inherited genetic variants[32,33], and microbiome[34-36] have been previously implicated in the prediction

of irAEs.

## PREDICTION MODELS BASED ON NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET-TO-LYMPHOCYTE RATIO

In the latest edition of the *World Journal of Gastrointestinal Oncology*, Dharmapuri *et al*[37] presented a noteworthy retrospective study titled "Baseline neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as potential predictors of immune treatment-related toxicity in hepatocellular carcinoma". This study involved the analysis of 361 patients who received ICI monotherapy or combination therapy for hepatocellular carcinoma (HCC) between 2016 and 2020. The patients' basic clinical characteristics, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), steroid usage, presence of underlying diseases, and treatment regimens were examined. The researchers made the discovery that NLR and PLR can be used as predictive indicators for immune treatment related toxicity in HCC. It was found that high baseline NLR (> 5) and PLR (> 300) are associated with a decreased incidence of grade  $\geq 2$  irAEs, while lower baseline NLR (< 5) and PLR (< 300) may serve as predictive biomarkers [odds ratio (OR) = 0.26;  $P = 0.011$ ] for the occurrence of irAEs in HCC patients undergoing treatment with ICIs. Similarly, it has been reported that within a cohort of 470 patients with diverse solid tumors who underwent ICI therapy, higher baseline ALC (> 2.6 k/ $\mu$ L) (adjusted OR: 4.30), absolute monocyte count (> 0.29 k/ $\mu$ L; adjusted OR: 2.34), and platelet count (> 145 k/ $\mu$ L) (adjusted OR: 2.23) were found to be associated with a higher incidence of irAEs[18]. The NLR and PLR have also been reported to predict prognosis in various fatal diseases such as gastric cancer[38], non-small cell lung cancer (NSCLC)[39], colorectal cancer[40], and acute myocardial infarction[41] in previous studies. Furthermore, these markers have proven to be valuable in the prediction of ICI response[42-46] and irAEs[47], encompassing NSCLC and HCC. Consequently, they have gained extensive utilization as indicators of inflammation for the anticipation of immunotherapy response and irAEs.

The present research not only examined the individual predictive capabilities of NLR and PLR, but also investigated their collective predictive abilities, as well as their combined predictive abilities when used in conjunction with other indicators. Chen *et al*[48] found that NLR combined with carcinoembryonic antigen demonstrated superior predictive efficacy in determining the effectiveness of immunotherapy at either week 6 or 12 post-treatment in patients with NSCLC, compared to NLR alone. Similarly, Kartolo *et al*[49] proposed that combining NLR with PLR resulted in improved prediction of overall survival (OS) or progression-free survival in patients with melanoma and NSCLC who were undergoing anti-PD-1 therapy, surpassing the predictive capabilities of either indicator used independently. The study conducted by Lu *et al*[50] revealed that the combination of PLR and NLR demonstrated superior predictive ability for OS in stage III/IV NSCLC patients undergoing immunotherapy, compared to PLR alone. However, there is currently no identified composite model that incorporates these two factors along with other predictors to forecast the risk of irAEs. This presents a promising avenue for future research.

## CONCLUSION

Considering the prevailing research trend in the current literature, which involves the development of integrated models for multiple risk factors, it is plausible to combine markers such as NLR and PLR, which have been independently linked to prognosis or irAEs in patients undergoing immunotherapy, with other recently identified or pre-existing markers. This amalgamation can be employed to enhance the effectiveness and precision of individual predictions, while also facilitating the selection of the most suitable model for clinical translation, in comparison to previous prediction models. Gaining insight into the fundamental mechanisms of inflammatory markers, such as NLR and PLR, as prognostic indicators, also enables the enhancement and fine-tuning of the model to effectively tackle prevailing obstacles related to immune therapy response rates and frequent adverse reactions. Furthermore, as highlighted by the author, it is imperative to conduct prospective large-scale cohort studies to authenticate the predictive efficacy of models integrating markers like NLR and PLR, and to propose appropriate detection techniques that are applicable in clinical settings, thereby expediting the translation of these findings into practical clinical applications.

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