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

Jiang QY *et al.* NLR and PLR prediction models

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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.

**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 aera 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 ≥ 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/μl) (adjusted OR: 4.30), absolute monocyte count (> 0.29 k/μl; adjusted OR: 2.34), and platelet count (> 145 k/μl) (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.

**REFERENCES**

1 **Garon EB**, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn MJ, Felip E, Lee JS, Hellmann MD, Hamid O, Goldman JW, Soria JC, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Roach C, Emancipator K, Gandhi L; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372**: 2018-2028 [PMID: 25891174 DOI: 10.1056/NEJMoa1501824]

2 **Ott PA**, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, Rugo HS, Cohen RB, O'Neil BH, Mehnert JM, Lopez J, Doi T, van Brummelen EMJ, Cristescu R, Yang P, Emancipator K, Stein K, Ayers M, Joe AK, Lunceford JK. T-Cell-Inflamed Gene-Expression Profile, Programmed Death Ligand 1 Expression, and Tumor Mutational Burden Predict Efficacy in Patients Treated With Pembrolizumab Across 20 Cancers: KEYNOTE-028. *J Clin Oncol* 2019; **37**: 318-327 [PMID: 30557521 DOI: 10.1200/JCO.2018.78.2276]

3 **Martins F**, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, Shabafrouz K, Ribi C, Cairoli A, Guex-Crosier Y, Kuntzer T, Michielin O, Peters S, Coukos G, Spertini F, Thompson JA, Obeid M. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 2019; **16**: 563-580 [PMID: 31092901 DOI: 10.1038/s41571-019-0218-0]

4 **Bajwa R**, Cheema A, Khan T, Amirpour A, Paul A, Chaughtai S, Patel S, Patel T, Bramson J, Gupta V, Levitt M, Asif A, Hossain MA. Adverse Effects of Immune Checkpoint Inhibitors (Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors): Results of a Retrospective Study. *J Clin Med Res* 2019; **11**: 225-236 [PMID: 30937112 DOI: 10.14740/jocmr3750]

5 **Das S**, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer* 2019; **7**: 306 [PMID: 31730012 DOI: 10.1186/s40425-019-0805-8]

6 **Postow MA**, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med* 2018; **378**: 158-168 [PMID: 29320654 DOI: 10.1056/NEJMra1703481]

7 **Larkin J**, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015; **373**: 23-34 [PMID: 26027431 DOI: 10.1056/NEJMoa1504030]

8 **He Y**, Zhang X, Jia K, Dziadziuszko R, Zhao S, Deng J, Wang H, Hirsch FR, Zhou C. OX40 and OX40L protein expression of tumor infiltrating lymphocytes in non-small cell lung cancer and its role in clinical outcome and relationships with other immune biomarkers. *Transl Lung Cancer Res* 2019; **8**: 352-366 [PMID: 31555511 DOI: 10.21037/tlcr.2019.08.15]

9 **Joshi SS**, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA Cancer J Clin* 2021; **71**: 264-279 [PMID: 33592120 DOI: 10.3322/caac.21657]

10 **Ayers M**, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, Albright A, Cheng JD, Kang SP, Shankaran V, Piha-Paul SA, Yearley J, Seiwert TY, Ribas A, McClanahan TK. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest* 2017; **127**: 2930-2940 [PMID: 28650338 DOI: 10.1172/JCI91190]

11 **Jiang P**, Gu S, Pan D, Fu J, Sahu A, Hu X, Li Z, Traugh N, Bu X, Li B, Liu J, Freeman GJ, Brown MA, Wucherpfennig KW, Liu XS. Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response. *Nat Med* 2018; **24**: 1550-1558 [PMID: 30127393 DOI: 10.1038/s41591-018-0136-1]

12 **Cabrita R**, Lauss M, Sanna A, Donia M, Skaarup Larsen M, Mitra S, Johansson I, Phung B, Harbst K, Vallon-Christersson J, van Schoiack A, Lövgren K, Warren S, Jirström K, Olsson H, Pietras K, Ingvar C, Isaksson K, Schadendorf D, Schmidt H, Bastholt L, Carneiro A, Wargo JA, Svane IM, Jönsson G. Author Correction: Tertiary lymphoid structures improve immunotherapy and survival in melanoma. *Nature* 2020; **580**: E1 [PMID: 32238929 DOI: 10.1038/s41586-020-2155-6]

13 **Jiang Q**, Chen Z, Meng F, Zhang H, Chen H, Xue J, Shen X, Liu T, Dong L, Zhang S, Xue R. CD36-BATF2\MYB Axis Predicts Anti-PD-1 Immunotherapy Response in Gastric Cancer. *Int J Biol Sci* 2023; **19**: 4476-4492 [PMID: 37781029 DOI: 10.7150/ijbs.87635]

14 **van der Kooij MK**, Suijkerbuijk KPM, Aarts MJB, van den Berkmortel FWPJ, Blank CU, Boers-Sonderen MJ, van Breeschoten J, van den Eertwegh AJM, de Groot JWB, Haanen JBAG, Hospers GAP, Piersma D, van Rijn RS, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van Zeijl MCT, Wouters MWJM, Dekkers OM, Kapiteijn E. Safety and Efficacy of Checkpoint Inhibition in Patients With Melanoma and Preexisting Autoimmune Disease : A Cohort Study. *Ann Intern Med* 2021; **174**: 641-648 [PMID: 33587686 DOI: 10.7326/M20-3419]

15 **Fountzilas E**, Lampaki S, Koliou GA, Koumarianou A, Levva S, Vagionas A, Christopoulou A, Laloysis A, Psyrri A, Binas I, Mountzios G, Kentepozidis N, Kotsakis A, Saloustros E, Boutis A, Nikolaidi A, Fountzilas G, Georgoulias V, Chrysanthidis M, Kotteas E, Vo H, Tsiatas M, Res E, Linardou H, Daoussis D, Bompolaki I, Andreadou A, Papaxoinis G, Spyratos D, Gogas H, Syrigos KN, Bafaloukos D. Real-world safety and efficacy data of immunotherapy in patients with cancer and autoimmune disease: the experience of the Hellenic Cooperative Oncology Group. *Cancer Immunol Immunother* 2022; **71**: 327-337 [PMID: 34164709 DOI: 10.1007/s00262-021-02985-6]

16 **Alexander S**, Swami U, Kaur A, Gao Y, Fatima M, Ginn MM, Stein JE, Grivas P, Zakharia Y, Singh N. Safety of immune checkpoint inhibitors in patients with cancer and pre-existing autoimmune disease. *Ann Transl Med* 2021; **9**: 1033 [PMID: 34277833 DOI: 10.21037/atm-20-8124]

17 **Abu-Sbeih H**, Faleck DM, Ricciuti B, Mendelsohn RB, Naqash AR, Cohen JV, Sellers MC, Balaji A, Ben-Betzalel G, Hajir I, Zhang J, Awad MM, Leonardi GC, Johnson DB, Pinato DJ, Owen DH, Weiss SA, Lamberti G, Lythgoe MP, Manuzzi L, Arnold C, Qiao W, Naidoo J, Markel G, Powell N, Yeung SJ, Sharon E, Dougan M, Wang Y. Immune Checkpoint Inhibitor Therapy in Patients With Preexisting Inflammatory Bowel Disease. *J Clin Oncol* 2020; **38**: 576-583 [PMID: 31800340 DOI: 10.1200/JCO.19.01674]

18 **Michailidou D**, Khaki AR, Morelli MP, Diamantopoulos L, Singh N, Grivas P. Association of blood biomarkers and autoimmunity with immune related adverse events in patients with cancer treated with immune checkpoint inhibitors. *Sci Rep* 2021; **11**: 9029 [PMID: 33907229 DOI: 10.1038/s41598-021-88307-3]

19 **Valpione S**, Pasquali S, Campana LG, Piccin L, Mocellin S, Pigozzo J, Chiarion-Sileni V. Sex and interleukin-6 are prognostic factors for autoimmune toxicity following treatment with anti-CTLA4 blockade. *J Transl Med* 2018; **16**: 94 [PMID: 29642948 DOI: 10.1186/s12967-018-1467-x]

20 **Guzman-Prado Y**, Ben Shimol J, Samson O. Body mass index and immune-related adverse events in patients on immune checkpoint inhibitor therapies: a systematic review and meta-analysis. *Cancer Immunol Immunother* 2021; **70**: 89-100 [PMID: 32648164 DOI: 10.1007/s00262-020-02663-z]

21 **Shah KP**, Song H, Ye F, Moslehi JJ, Balko JM, Salem JE, Johnson DB. Demographic Factors Associated with Toxicity in Patients Treated with Anti-Programmed Cell Death-1 Therapy. *Cancer Immunol Res* 2020; **8**: 851-855 [PMID: 32350001 DOI: 10.1158/2326-6066.CIR-19-0986]

22 **Young AC**, Quach HT, Song H, Davis EJ, Moslehi JJ, Ye F, Williams GR, Johnson DB. Impact of body composition on outcomes from anti-PD1 +/- anti-CTLA-4 treatment in melanoma. *J Immunother Cancer* 2020; **8** [PMID: 32747470 DOI: 10.1136/jitc-2020-000821]

23 **Di Giacomo AM**, Grimaldi AM, Ascierto PA, Queirolo P, Del Vecchio M, Ridolfi R, De Rosa F, De Galitiis F, Testori A, Cognetti F, Bernengo MG, Savoia P, Guida M, Strippoli S, Galli L, Mandala M, Parmiani G, Rinaldi G, Aglietta M, Chiarion-Sileni V. Correlation between efficacy and toxicity in pts with pretreated advanced melanoma treated within the Italian cohort of the ipilimumab expanded access programme (EAP). *J Clin Oncol* 2013; **31** [DOI: 10.1200/jco.2013.31.15\_suppl.9065]

24 **Xing P**, Zhang F, Wang G, Xu Y, Li C, Wang S, Guo Y, Cai S, Wang Y, Li J. Incidence rates of immune-related adverse events and their correlation with response in advanced solid tumours treated with NIVO or NIVO+IPI: a systematic review and meta-analysis. *J Immunother Cancer* 2019; **7**: 341 [PMID: 31801636 DOI: 10.1186/s40425-019-0779-6]

25 **Jing Y**, Liu J, Ye Y, Pan L, Deng H, Wang Y, Yang Y, Diao L, Lin SH, Mills GB, Zhuang G, Xue X, Han L. Multi-omics prediction of immune-related adverse events during checkpoint immunotherapy. *Nat Commun* 2020; **11**: 4946 [PMID: 33009409 DOI: 10.1038/s41467-020-18742-9]

26 **Haratani K**, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, Kaneda H, Hasegawa Y, Tanaka K, Takeda M, Nakagawa K. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. *JAMA Oncol* 2018; **4**: 374-378 [PMID: 28975219 DOI: 10.1001/jamaoncol.2017.2925]

27 **Wang Y**, Abu-Sbeih H, Mao E, Ali N, Ali FS, Qiao W, Lum P, Raju G, Shuttlesworth G, Stroehlein J, Diab A. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. *J Immunother Cancer* 2018; **6**: 37 [PMID: 29747688 DOI: 10.1186/s40425-018-0346-6]

28 **Bomze D**, Hasan Ali O, Bate A, Flatz L. Association Between Immune-Related Adverse Events During Anti-PD-1 Therapy and Tumor Mutational Burden. *JAMA Oncol* 2019; **5**: 1633-1635 [PMID: 31436791 DOI: 10.1001/jamaoncol.2019.3221]

29 **Tyan K**, Baginska J, Brainard M, Giobbie-Hurder A, Severgnini M, Manos M, Haq R, Buchbinder EI, Ott PA, Hodi FS, Rahma OE. Cytokine changes during immune-related adverse events and corticosteroid treatment in melanoma patients receiving immune checkpoint inhibitors. *Cancer Immunol Immunother* 2021; **70**: 2209-2221 [PMID: 33481042 DOI: 10.1007/s00262-021-02855-1]

30 **Lim SY**, Lee JH, Gide TN, Menzies AM, Guminski A, Carlino MS, Breen EJ, Yang JYH, Ghazanfar S, Kefford RF, Scolyer RA, Long GV, Rizos H. Circulating Cytokines Predict Immune-Related Toxicity in Melanoma Patients Receiving Anti-PD-1-Based Immunotherapy. *Clin Cancer Res* 2019; **25**: 1557-1563 [PMID: 30409824 DOI: 10.1158/1078-0432.CCR-18-2795]

31 **Tarhini AA**, Zahoor H, Lin Y, Malhotra U, Sander C, Butterfield LH, Kirkwood JM. Baseline circulating IL-17 predicts toxicity while TGF-β1 and IL-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. *J Immunother Cancer* 2015; **3**: 39 [PMID: 26380086 DOI: 10.1186/s40425-015-0081-1]

32 **Bins S**, Basak EA, El Bouazzaoui S, Koolen SLW, Oomen-de Hoop E, van der Leest CH, van der Veldt AAM, Sleijfer S, Debets R, van Schaik RHN, Aerts JGJV, Mathijssen RHJ. Association between single-nucleotide polymorphisms and adverse events in nivolumab-treated non-small cell lung cancer patients. *Br J Cancer* 2018; **118**: 1296-1301 [PMID: 29695768 DOI: 10.1038/s41416-018-0074-1]

33 **Queirolo P**, Dozin B, Morabito A, Banelli B, Carosio R, Fontana V, Ferrucci PF, Martinoli C, Cocorocchio E, Ascierto PA, Madonna G, Simeone E, De Galitiis F, Antonini Cappellini GC, Marchetti P, Guida M, Tommasi S, Ghilardi L, Merelli B, Fava P, Osella-Abate S, Guidoboni M, Romani M, Ferone D, Spagnolo F, Pistillo MP; Italian Melanoma Intergroup (IMI). CTLA-4 gene variant -1661A>G may predict the onset of endocrine adverse events in metastatic melanoma patients treated with ipilimumab. *Eur J Cancer* 2018; **97**: 59-61 [PMID: 29743138 DOI: 10.1016/j.ejca.2018.04.005]

34 **Dubin K**, Callahan MK, Ren B, Khanin R, Viale A, Ling L, No D, Gobourne A, Littmann E, Huttenhower C, Pamer EG, Wolchok JD. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. *Nat Commun* 2016; **7**: 10391 [PMID: 26837003 DOI: 10.1038/ncomms10391]

35 **Andrews MC**, Duong CPM, Gopalakrishnan V, Iebba V, Chen WS, Derosa L, Khan MAW, Cogdill AP, White MG, Wong MC, Ferrere G, Fluckiger A, Roberti MP, Opolon P, Alou MT, Yonekura S, Roh W, Spencer CN, Curbelo IF, Vence L, Reuben A, Johnson S, Arora R, Morad G, Lastrapes M, Baruch EN, Little L, Gumbs C, Cooper ZA, Prieto PA, Wani K, Lazar AJ, Tetzlaff MT, Hudgens CW, Callahan MK, Adamow M, Postow MA, Ariyan CE, Gaudreau PO, Nezi L, Raoult D, Mihalcioiu C, Elkrief A, Pezo RC, Haydu LE, Simon JM, Tawbi HA, McQuade J, Hwu P, Hwu WJ, Amaria RN, Burton EM, Woodman SE, Watowich S, Diab A, Patel SP, Glitza IC, Wong MK, Zhao L, Zhang J, Ajami NJ, Petrosino J, Jenq RR, Davies MA, Gershenwald JE, Futreal PA, Sharma P, Allison JP, Routy B, Zitvogel L, Wargo JA. Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. *Nat Med* 2021; **27**: 1432-1441 [PMID: 34239137 DOI: 10.1038/s41591-021-01406-6]

36 **McCulloch JA**, Davar D, Rodrigues RR, Badger JH, Fang JR, Cole AM, Balaji AK, Vetizou M, Prescott SM, Fernandes MR, Costa RGF, Yuan W, Salcedo R, Bahadiroglu E, Roy S, DeBlasio RN, Morrison RM, Chauvin JM, Ding Q, Zidi B, Lowin A, Chakka S, Gao W, Pagliano O, Ernst SJ, Rose A, Newman NK, Morgun A, Zarour HM, Trinchieri G, Dzutsev AK. Intestinal microbiota signatures of clinical response and immune-related adverse events in melanoma patients treated with anti-PD-1. *Nat Med* 2022; **28**: 545-556 [PMID: 35228752 DOI: 10.1038/s41591-022-01698-2]

37 **Dharmapuri S**, Özbek U, Jethra H, Jun T, Marron TU, Saeed A, Huang YH, Muzaffar M, Pinter M, Balcar L, Fulgenzi C, Amara S, Weinmann A, Personeni N, Scheiner B, Pressiani T, Navaid M, Bengsch B, Paul S, Khan U, Bettinger D, Nishida N, Mohamed YI, Vogel A, Gampa A, Korolewicz J, Cammarota A, Kaseb A, Galle PR, Pillai A, Wang YH, Cortellini A, Kudo M, D'Alessio A, Rimassa L, Pinato DJ, Ang C. Baseline neutrophil-lymphocyte ratio and platelet-lymphocyte ratio appear predictive of immune treatment related toxicity in hepatocellular carcinoma. *World J Gastrointest Oncol* 2023; **15**: 1900-1912 [PMID: 38077640 DOI: 10.4251/wjgo.v15.i11.1900]

38 **Fang T**, Wang Y, Yin X, Zhai Z, Zhang Y, Yang Y, You Q, Li Z, Ma Y, Li C, Song H, Shi H, Zhang Y, Yu X, Gao H, Sun Y, Xie R, Xue Y. Diagnostic Sensitivity of NLR and PLR in Early Diagnosis of Gastric Cancer. *J Immunol Res* 2020; **2020**: 9146042 [PMID: 32211444 DOI: 10.1155/2020/9146042]

39 **Mandaliya H**, Jones M, Oldmeadow C, Nordman II. Prognostic biomarkers in stage IV non-small cell lung cancer (NSCLC): neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and advanced lung cancer inflammation index (ALI). *Transl Lung Cancer Res* 2019; **8**: 886-894 [PMID: 32010567 DOI: 10.21037/tlcr.2019.11.16]

40 **Kang Y**, Zhu X, Lin Z, Zeng M, Shi P, Cao Y, Chen F. Compare the Diagnostic and Prognostic Value of MLR, NLR and PLR in CRC Patients. *Clin Lab* 2021; **67** [PMID: 34542964 DOI: 10.7754/Clin.Lab.2021.201130]

41 **Liu J**, Ao W, Zhou J, Luo P, Wang Q, Xiang D. The correlation between PLR-NLR and prognosis in acute myocardial infarction. *Am J Transl Res* 2021; **13**: 4892-4899 [PMID: 34150072]

42 **Diem S**, Schmid S, Krapf M, Flatz L, Born D, Jochum W, Templeton AJ, Früh M. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer* 2017; **111**: 176-181 [PMID: 28838390 DOI: 10.1016/j.lungcan.2017.07.024]

43 **Platini H**, Ferdinand E, Kohar K, Prayogo SA, Amirah S, Komariah M, Maulana S. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Prognostic Markers for Advanced Non-Small-Cell Lung Cancer Treated with Immunotherapy: A Systematic Review and Meta-Analysis. *Medicina (Kaunas)* 2022; **58** [PMID: 36013536 DOI: 10.3390/medicina58081069]

44 **Wu M**, Liu J, Wu S, Liu J, Wu H, Yu J, Meng X. Systemic Immune Activation and Responses of Irradiation to Different Metastatic Sites Combined With Immunotherapy in Advanced Non-Small Cell Lung Cancer. *Front Immunol* 2021; **12**: 803247 [PMID: 34970277 DOI: 10.3389/fimmu.2021.803247]

45 **Wu YL**, Fulgenzi CAM, D'Alessio A, Cheon J, Nishida N, Saeed A, Wietharn B, Cammarota A, Pressiani T, Personeni N, Pinter M, Scheiner B, Balcar L, Huang YH, Phen S, Naqash AR, Vivaldi C, Salani F, Masi G, Bettinger D, Vogel A, Schönlein M, von Felden J, Schulze K, Wege H, Galle PR, Kudo M, Rimassa L, Singal AG, Sharma R, Cortellini A, Gaillard VE, Chon HJ, Pinato DJ, Ang C. Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios as Prognostic Biomarkers in Unresectable Hepatocellular Carcinoma Treated with Atezolizumab plus Bevacizumab. *Cancers (Basel)* 2022; **14** [PMID: 36497316 DOI: 10.3390/cancers14235834]

46 **Muhammed A**, Fulgenzi CAM, Dharmapuri S, Pinter M, Balcar L, Scheiner B, Marron TU, Jun T, Saeed A, Hildebrand H, Muzaffar M, Navaid M, Naqash AR, Gampa A, Ozbek U, Lin JY, Perone Y, Vincenzi B, Silletta M, Pillai A, Wang Y, Khan U, Huang YH, Bettinger D, Abugabal YI, Kaseb A, Pressiani T, Personeni N, Rimassa L, Nishida N, Di Tommaso L, Kudo M, Vogel A, Mauri FA, Cortellini A, Sharma R, D'Alessio A, Ang C, Pinato DJ. The Systemic Inflammatory Response Identifies Patients with Adverse Clinical Outcome from Immunotherapy in Hepatocellular Carcinoma. *Cancers (Basel)* 2021; **14** [PMID: 35008350 DOI: 10.3390/cancers14010186]

47 **Pavan A**, Calvetti L, Dal Maso A, Attili I, Del Bianco P, Pasello G, Guarneri V, Aprile G, Conte P, Bonanno L. Peripheral Blood Markers Identify Risk of Immune-Related Toxicity in Advanced Non-Small Cell Lung Cancer Treated with Immune-Checkpoint Inhibitors. *Oncologist* 2019; **24**: 1128-1136 [PMID: 31015312 DOI: 10.1634/theoncologist.2018-0563]

48 **Chen Y**, Wen S, Xia J, Du X, Wu Y, Pan B, Zhu W, Shen B. Association of Dynamic Changes in Peripheral Blood Indexes With Response to PD-1 Inhibitor-Based Combination Therapy and Survival Among Patients With Advanced Non-Small Cell Lung Cancer. *Front Immunol* 2021; **12**: 672271 [PMID: 34054853 DOI: 10.3389/fimmu.2021.672271]

49 **Kartolo A**, Holstead R, Khalid S, Emack J, Hopman W, Robinson A, Baetz T. Serum neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in prognosticating immunotherapy efficacy. *Immunotherapy* 2020; **12**: 785-798 [PMID: 32657234 DOI: 10.2217/imt-2020-0105]

50 **Lu X**, Wan J, Shi H. Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios are associated with the efficacy of immunotherapy in stage III/IV non-small cell lung cancer. *Oncol Lett* 2022; **24**: 266 [PMID: 35782904 DOI: 10.3892/ol.2022.13386]

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