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Peripheral blood cell counts as predictors of immune-related adverse events in cancer patients receiving immune checkpoint inhibitors: a systematic review and meta-analysis

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Background: In recent years, immune checkpoint inhibitors (ICIs) have shown significant efficacy in treating various malignancies and have become a key therapeutic approach in cancer treatment. However, while ICIs activate the immune system, they can also induce immune-related adverse events (irAEs). Due to the variability in the frequency and severity of irAEs, clinical management faces a significant challenge in balancing antitumor efficacy with the risk of irAEs. Predicting and preventing irAEs during the early stages of treatment has become a critical research focus in cancer immunotherapy. This study aims to evaluate the predictive value of peripheral blood cell counts for irAEs.

Methods: Studies meeting the inclusion criteria were identified through database searches. The standardized mean difference (SMD) was used to compare continuous blood cell counts. For studies that did not provide adjusted odds ratios (ORs) and 95% confidence intervals (CIs), crude ORs for categorized blood cell counts were calculated. The study protocol was registered on PROSPERO (CRD42024592126).

Results: The meta-analysis included 60 studies involving 16,736 cancer patients treated with ICIs. Compared to patients without irAEs, those experiencing irAEs had significantly higher baseline continuous ALC (SMD = 0.12, 95% CI = 0.01-0.24), while ANC (SMD = -0.18, 95% CI = -0.28 to -0.07) and PLR (SMD = -0.32, 95% CI = -0.60 to -0.04) were significantly lower. Similarly, categorized blood cell counts indicated that higher baseline ALC (OR = 2.46, 95% CI = 1.69-3.57) and AEC (OR = 2.05, 95% CI = 1.09-3.85), along with lower baseline NLR (OR = 0.64, 95% CI = 0.50-0.81) and PLR (OR = 0.63, 95% CI = 0.48-0.82), were associated with an increased risk of irAEs. Subgroup analysis further identified cutoff values for ALC (2×10^9/L), NLR (5 or 3), and PLR (180) as better predictors of irAEs.

Conclusion: Higher baseline ALC and AEC, along with lower baseline ANC, NLR, and PLR, are associated with an increased risk of irAEs. However, further research is needed to determine the optimal cutoff values and to explore the efficacy of blood cell counts in predicting specific types of irAEs.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42024592126.

KEYWORDS

immune checkpoint inhibitors, immunotherapy, immune-related adverse events, blood cell count, biomarker, risk factor

Introduction

Cancer immunotherapy has emerged as a breakthrough in the treatment of various malignancies. ICIs, which target PD-1/PD-L1 and CTLA-4 pathways, work by blocking inhibitory signals, activating T cells, and reinvigorating antitumor immune responses. However, by enhancing host immune responses and disrupting immune homeostasis, ICIs can promote inflammatory activity, potentially leading to inflammation-related damage in multiple organs (1). This manifests as a range of clinical symptoms collectively called irAEs, commonly affecting various organ systems, including the skin, endocrine, respiratory, and gastrointestinal systems (2). The incidence of irAEs is relatively high, and certain severe complications can significantly affect patients' quality of life and prognosis (3). Effectively managing irAEs without compromising the antitumor efficacy of ICIs or the long-term survival of patients remains a clinical challenge (4). Notably, patients who develop irAEs often experience better cancer outcomes (5–7). Therefore, assessing individual risk for toxicity in advance is crucial, as early intervention and management of irAEs can help ensure that high-risk patients continue ICI treatment and benefit from it.

As the use of ICIs in cancer treatment continues to expand, there is an increasing need for reliable and validated biomarkers to predict irAEs (8). Factors such as drug selection, gender, laboratory indicators, pre-existing comorbidities, and tumor mutation burden (TMB) have been identified as potential predictors of irAEs (9–11). However, these factors are often difficult to apply widely in clinical practice due to limited accuracy or high testing costs. Easily measurable and cost-effective markers like blood cell counts have garnered increasing attention. Circulating blood cell counts—such as absolute lymphocyte count (ALC), neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR)—have shown potential for predicting both the efficacy of cancer immunotherapy and the risk of irAEs (11–15). However, current research on the relationship between blood cell counts and irAEs has yielded inconsistent results, with many studies limited by small sample sizes or single-center analyses and lacking systematic reviews and quantitative assessments.

Through a systematic review and meta-analysis, this study aims to evaluate the predictive value of peripheral blood cell counts for irAEs in cancer patients receiving ICIs. Additionally, we seek to identify clinically relevant cutoffs for these blood cell counts, providing evidence-based support for clinical practice.

Abbreviations: ICIs, Immune checkpoint inhibitors; irAEs, immune-related adverse events; SMD, standardized mean difference; ORs, odds ratios; CIs, confidence intervals; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; TMB, tumor mutational burden; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AEC, absolute eosinophil count; PLT, platelet count; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; AE, adverse event; SD, standard deviation; TCR, T cell receptor; Tregs, Regulatory T cells; ANA, anti-nuclear antibody; anti-dsDNA, anti-double-stranded DNA; MBP, major basic protein; IL-5, interleukin-5; IL-4, interleukin-4; IL-13, interleukin-13; TNF-α, tumor necrosis factor-alpha; CIP, ICI-related pneumonitis; PMN-MDSCs, polymorphonuclear myeloid-derived suppressor cells; IL-1, interleukin-1; IL-6, interleukin-6.

Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The study protocol was registered on PROSPERO (CRD42024592126). The objective was to assess the predictive value of peripheral blood cell counts for irAEs in cancer patients receiving ICIs.

Search strategy

We conducted a comprehensive literature search in PubMed, Ovid Medline, Embase, and Cochrane Library databases, with a

search cutoff date of August 24, 2024. The search terms included "immune checkpoint inhibitor", "immune-related adverse events", "neutrophils", "lymphocytes", "monocytes", "eosinophils", "platelets", "neutrophil to lymphocyte ratio", "platelet to lymphocyte ratio", "monocyte to lymphocyte ratio", "lymphocyte to monocyte ratio", "risk factors". The detailed search strategy is available in Supplementary Table 1.

Inclusion and exclusion criteria

The inclusion criteria were established as follows (1): Studies included patients with cancer treated with ICIs; (2) The incidence of irAEs was reported; (3) The study evaluated blood cell counts as a predictive factor for irAEs; (4) The study was a randomized clinical trial, retrospective clinical study, or case-control study.

The exclusion criteria were established as follows: (1) Studies involving *in vitro* or *in vivo* experiments. (2) Lack of available data on continuous blood cell counts, categorized blood cell counts by cut-off, or ORs associated with irAEs. (3) Case reports or case series with a sample size of less than 10.

Literature screening, data extraction

Two researchers independently screened the titles and abstracts based on the inclusion and exclusion criteria. The full texts were further evaluated if the abstracts lacked sufficient detail or the data could not be extracted. Any disagreements between the two reviewers were resolved through discussion with a third investigator. Data from the eligible studies were extracted into a standardized form, including study characteristics (e.g., author, year, design), patient characteristics (e.g., age, sex, cancer type), blood cell count-related variables (including absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute eosinophil count (AEC), platelet count (PLT), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and monocyte to lymphocyte ratio (MLR)), as well as the incidence of irAEs either overall or by specific subtypes. These blood cell counts and percentages were recorded at baseline, before the initiation of ICI therapy. The continuous or categorized values of these blood cell counts were collected in terms of adverse event (AE) and non-AE groups. ORs with corresponding 95% CIs were also collected when available. Multivariate or adjusted ORs were preferentially included; otherwise, univariate ORs were included or calculated based on the original data from the article.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) tool. Any discrepancies were resolved through the involvement of a third party until a consensus was reached.

Statistical analysis

The primary outcome of the meta-analysis was the predictive value of blood cell counts for irAEs. In instances where studies reported median and range for continuous blood cell counts instead of mean and standard deviation (SD), the authors utilized the formula provided by Hozo et al. to convert these values into means and SDs (16). The SMD was employed to assess the differences in continuous blood cell counts between the irAE and non-irAE groups. For studies that provided categorized blood cell counts based on specified cutoff values, the authors calculated the OR and 95% CI. The authors summarized crude and adjusted ORs to report the pooled ORs and corresponding 95% CIs. To further investigate the sources of heterogeneity between studies, subgroup analyses were conducted, considering the following potential confounding factors: cutoff values, irAEs type, cancer type, ICI type, and patient ethnicity. Statistical heterogeneity was assessed using the I^2 statistic, where $I^2 \geq 50\%$ indicated the presence of heterogeneity. A fixed-effects model was applied in the absence of heterogeneity; otherwise, a random-effects model was utilized. Sensitivity analyses were conducted by systematically omitting individual studies to evaluate their impact on the overall results. Publication bias was assessed using the Egger test. Statistical analyses were performed using Stata15.0 software.

Results

Study selection

A systematic search conducted across four databases identified 7836 potential studies. After removing duplicates and a comprehensive review of titles, abstracts, and full texts, 60 studies (17–76) were ultimately included in the analysis (Figure 1).

Research characteristics

Table 1 presents the features of the 60 studies included in this analysis, all published from 2018 to 2024, with 42 originating from Asia. Among these, 23 studies were from China, 17 from Japan, and 1 each from South Korea and Singapore. The remaining 18 studies were conducted in the United States (10 studies), Spain(2 study), Australia (2 study), Belgium (1 study), Germany (1 study), Switzerland (1 study) and Italy (1 study). Regarding cancer types, 22 studies specifically recruited patients with lung cancer, while 5 studies focused exclusively on liver cancer. Additionally, 4 studies included only renal cell carcinoma or urothelial carcinoma, 2 studies exclusively involved melanoma, and 1 study each targeted esophageal cancer, pancreatic cancer, gastric cancer, and head and neck squamous cell carcinoma. The remaining 24 studies included mixed cancer populations. Among the 60 studies, 21 focused exclusively on the irAEs associated with PD-1 inhibitors, while 6 assessed the irAEs linked to PD-L1 inhibitors. Additionally, 15 studies examined the irAEs related to both PD-1 and PD-L1

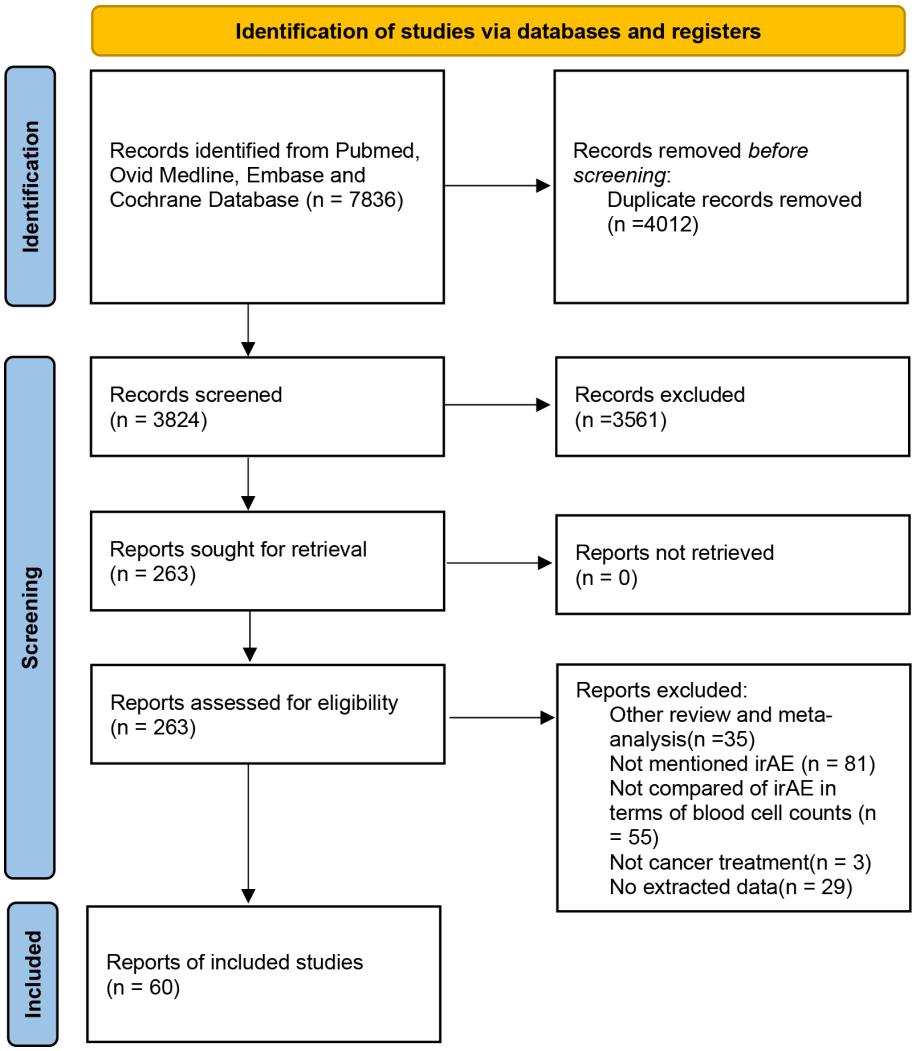

FIGURE 1
The flowchart of study screening.

inhibitors. The remaining 18 studies included assessments of irAEs from PD-1/PD-L1 and CTLA-4 inhibitors. In terms of the types of irAEs, 43 studies assessed all categories of irAEs, while 6 studies specifically reported on cardiovascular adverse events, 4 focused solely on immune-related pneumonia, 3 exclusively on dermatologic adverse events, 2 on endocrine adverse events, and 1 each on colitis-related and renal adverse events.

Meta-analysis

Our meta-analysis comprised 16,736 patients, featuring a median sample size of 169 per study, ranging from 41 to 1,548 (Supplementary Table 2). A total of 4210 irAE cases were documented, resulting in a median incidence rate of 31.71%, with rates ranging from 3.62% to 74.63%. 35 studies reported the incidence rates of various subtypes of irAEs (Supplementary Table 3). Dermatologic disorders were the most commonly observed irAE, with incidence rates varying between 2.57% and 58.54%. The incidence rates for pneumonia, endocrine disorders, gastrointestinal conditions, and liver injury were 0.69% to 24.83%, 1.79% to 31.11%, 0.97% to 20.30%, and 0.26% to 25.21%, respectively.

Predictive significance of continuous blood cell counts for irAEs

A total of 28 studies reported continuous blood cell counts for both the irAE and non-irAE groups, with 21 studies providing baseline blood cell count levels for each group and 12 studies presenting ORs for continuous blood cell counts in predicting irAEs. By synthesizing all studies reporting continuous blood cell counts to predict irAEs, we found that higher ALC (SMD=0.12, 95% CI=0.01-0.24, Table 2, Figure 2B) (OR=1.30, 95%CI=1.05-1.60, Table 3, Figure 2D), along with lower ANC (SMD=-0.18 95% CI=-0.28 to -0.07, Table 2, Figure 2A) and PLR (SMD=-0.32 95% CI=-0.60 to -0.04, Table 2, Figure 2C), were associated with a higher incidence of irAEs.

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TABLE 1 Characteristics of the included studies.

Author	Published year	Country	Cancer	Immune checkpoint inhibitors	irAE type	Peripheral blood biomarker
Dwight H Owen	2018	United States	lung cancer	Nivolumab, Pembrolizumab,Atezolizumab	All types of irAE	NLR, PLR
Yoshiyuki Nakamura	2019	Japan	melanoma	Nivolumab, Pembrolizumab	All types of irAE	ANC, ALC, AMC, AEC, NLR
Alberto Pavan	2019	Italy	lung cancer	Nivolumab, Pembrolizumab,Atezolizumab	All types of irAE	NLR, PLR
Yu Nakanishi	2019	Japan	lung cancer	Nivolumab, Pembrolizumab	Interstitial lung disease	ANC, ALC, NLR
Jun Fukihara	2019	Japan	lung cancer	Nivolumab, Pembrolizumab	Pneumonitis	NLR
Yeonghee Eun	2019	Korea	lung cancer, melanoma, lymphoma and others	Pembrolizumab	All types of irAE	ANC, NLR
Koichiro Ogihara	2020	Japan	urothelial carcinoma	Pembrolizumab	ir-SAE	NLR
Lihong Peng	2020	China	lung cancer	Nivolumab, Pembrolizumab, Toripalimab, Sintilimab	All types of irAE	NLR
Shilpa Grover	2020	United States	melanoma	Nivolumab, Pembrolizumab,Ipilimumab	Colitis	NLR
Kazuo Kobayashi	2020	Japan	renal cell carcinoma	Nivolumab	All types of irAE	ANC, ALC, PLT, NLR, PLR
Ganessan Kichenadasse	2020	Australia	lung cancer	Atezolizumab	All types of irAE	NLR
Xiangling Chu	2020	China	lung cancer	Not specified, including anti–PD-1, anti-PD-L1 inhibitors	Pneumonitis	ANC, ALC, AMC, AEC
Zsofia D Drobni	2020	United States	lung cancer, melanoma, renal cell carcinoma, head and neck carcinoma and others	Not specified, including anti–PD-1, anti-PD-L1, anti-CTLA4 inhibitors	Myocarditis	ANC, ALC, AMC, PLT, NLR
Melissa Y Y Moey	2020	United States	lung cancer	Nivolumab, Pembrolizumab,Atezolizumab	Major adverse cardiac events	PLT, NLR
Ryosuke Matsukane	2021	Japan	lung cancer, renal cell carcinoma, head and neck carcinoma, melanoma	Nivolumab, Pembrolizumab	All types of irAE	NLR, PLR
Eduard Roussel	2021	Belgium	renal cell carcinoma	Nivolumab	All types of irAE	NLR
Xiaona Fan	2021	China	gastric and colorectal cancers	Not specified, including anti–PD-1 inhibitor	All types of irAE	NLR, PLR, MLR
Pei Yi Lee	2021	Singapore	lung cancer, renal cell carcinoma, nasopharyngeal carcinoma, melanoma	Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, Tremelimumab	All types of irAE	ANC, ALC, PLT, NLR, PLR
Despina Michailidou	2021	United States	lung, skin, genitourinary, gastrointestinal, sarcoma, hematological malignancy, head and neck, breast carcer	Nivolumab, Pembrolizumab, Cemiplimab, Atezolizumab, Durvalumab, Avelumab, Ipilimumab, Tremelimumab	All types of irAE	ANC, ALC, AMC, NLR, PLR, MLR
Ashish Manne	2021	United States	lung cancer, melanoma	Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, Ipilimumab,	All types of irAE	ANC, ALC, PLT, NLR, PLR

(Continued)

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TABLE 1 Continued

Author	Published year	Country	Cancer	Immune checkpoint inhibitors	irAE type	Peripheral blood biomarker
Airi Fujimoto	2021	Japan	lung cancer	Nivolumab, Pembrolizumab,Atezolizumab	All types of irAE	ANC, ALC, NLR
Rilan Bai	2021	China	lung cancer, melanoma, liver cancer, esophageal cancer, urothelial cancer, gastric cancer, hypopharyngeal cancer, nasopharyngeal cancer, colon cancer, pancreatic cancer, orbital malignancy	Nivolumab, Pembrolizumab, Toripalimab, Sintilimab, Tislelizumab, Camrelizumab, Atezolizumab, Ipilimumab	All types of irAE	AEC, PLT
Lea Daniello	2021	Germany	lung cancer	Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab	All types of irAE	NLR
Dan-Yun Ruan	2021	China	advanced gastric cancer	Toripalimab	All types of irAE	NLR
Yuequan Shi	2021	China	lung cancer	Not specified, including anti–PD-1, anti-PD-L1, anti-CTLA4 inhibitors	All types of irAE	ANC, ALC, AEC, NLR, PLR
Shinobu Takayasu	2022	Japan	lung cancer, renal-urinary cancer, head and neck cancer, malignant melanoma, gastric cancer, esophageal cancer and others	Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, Ipilimumab	Adrenal insufficiency	AEC
Kei Sonehara	2022	Japan	lung cancer	Nivolumab, Pembrolizumab,Atezolizumab	All types of irAE	NLR, PLR
Toshifumi Tada	2022	Japan	hepatocellular carcinoma	Atezolizumab	All types of irAE	NLR
Mioko Matsuo	2022	Japan	head and neck squamous cell carcinoma	Nivolumab	All types of irAE	NLR, PLR
Lijun Zhao	2022	China	lung, esophagus, gastrointestinal	Nivolumab, Pembrolizumab, Camrelizumab, Toripalimab	ir-SAE	NLR, PLR
Manuel Sánchez Cánovas	2022	Spain	melanoma and lung cancer	Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab	Thrombosis	NLR
Xue Chen	2022	China	solid tumors	Not specified, including anti–PD-1, anti-PD-L1 inhibitor	Cardiotoxicity	NLR, PLR, MLR
Xiaohui Jia	2022	China	lung cancer	Not specified	Pneumonitis	ANC, ALC, AEC, PLT, NLR, PLR
Yingying Yu	2022	China	liver Cancer	Nivolumab, Camrelizumab, Sintilimab	All types of irAE	ANC, ALC, AMC, PLT, NLR, PLR
Afaf Abed	2022	Australia	lung cancer	Nivolumab, Pembrolizumab,Atezolizumab	All types of irAE	ALC, NLR, PLR
Hiroyuki Inoue	2022	Japan	esophageal cancer	Nivolumab	All types of irAE	ALC, NLR, PLR, MLR
Xiaojuan Lu	2022	China	lung cancer	Not specified, including anti–PD-1 inhibitor	All types of irAE	NLR, PLR

(Continued)

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TABLE 1 Continued

Author	Published year	Country	Cancer	Immune checkpoint inhibitors	irAE type	Peripheral blood biomarker
Yan Ma	2022	China	lung, esophageal carcinoma, liver cancer, head and neck cancer, genital system cancer, colorectal cancer, gastric carcinoma, urogenital carcinoma, cutaneous soft tissue carcinoma, melanoma, gallbladder carcinoma and bile duct carcinoma	Nivolumab, Sintilimab, Camrelizumab, Atezolizumab	All types of irAE	AEC, NLR, PLR
Zhening Zhang	2022	China	esophageal, gastric, colon cancer	Nivolumab, Pembrolizumab, Zimberelimab, Camrelizumab, Sintilimab, Tislelizumab, Toripalimab, Atezolizumab, Sugemalimab, Envafolimab, Nivolumab, Ipilimumab, Cadolinimab	All types of irAE	NLR, PLR, LMR
Si Wu	2022	China	lung cancer, stomach cancer, esophageal cancer, liver cancer, colorectal and others	Nivolumab, Pembrolizumab, Camrelizumab, Sintilimab, Toripalimab, Tislelizumab, Atezolizumab, Durvalumab	Cardiovascular adverse events	NLR
Ako Gannichida	2022	Japan	lung cancer, renal cell carcinoma, head and neck carcinoma, melanoma, gastric cancer	Nivolumab	Hypothyroidism	NLR
Cho-Han Chiang	2022	United States	head and neck cancer, gastrointestinal cancer, hepatobiliary cancer, pancreatic cancer, lung cancer, skin cancer, breast cancer, gynecologic cancer, renal and genitourinary, bone and connective tissue and others	Not specified, including anti–PD-1, anti-PD-L1, anti-CTLA4 inhibitors	Cardiotoxicity	PLR
Zhiyao Bao	2022	China	lung cancer	Nivolumab, Pembrolizumab, Toripalimab, Cindilimab, Atezolizumab, Durvalumab Tislelizumab, Camrelizumab	Renal	ANC, ALC, AMC, AEC, NLR, PLR, LMR
Yan Wu	2022	China	lung cancer	Not specified, including anti–PD-1, anti-PD-L1 inhibitor	All types of irAE	AEC, NLR
Yue Linda Wu	2022	United States	hepatocellular carcinoma	Atezolizumab	All types of irAE	NLR, PLR
Cassie Pan	2023	United States	head and neck squamous cell carcinoma, salivary gland cancer	Pembrolizumab	ir-SAE	ANC, ALC, NLR
Xin Qiu	2023	China	pancreatic cancer	Pembrolizumab, Sintilimab, Toripalimab	All types of irAE	NLR, PLR, LMR

(Continued)

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TABLE 1 Continued

Author	Published year	Country	Cancer	Immune checkpoint inhibitors	irAE type	Peripheral blood biomarker
Airi Fujimoto	2023	Japan	lung cancer	Nivolumab, Pembrolizumab, Atezolizumab, Ipilimumab	All types of irAE	NLR, PLR
Masafumi Haraguchi	2023	Japan	lung cancer, urological cancer, melanoma, head and neck cancer, gastric cancer	Nivolumab, Pembrolizumab, Atezolizumab, Ipilimumab	All types of irAE	ALC, AEC, NLR
Wei-Ting Hu	2023	China	lung cancer	Not specified, including anti–PD-1 inhibitor	All types of irAE	ANC, ALC, AEC, NLR
Tarun Mehra	2023	Switzerland	lung cancer, melanoma, renal cell carcinoma, head and neck carcinoma, hepatocellular carcinoma, urothelial carcinoma, hodgkin-lymphoma, colorectal cancer	Nivolumab, Pembrolizumab, Atezolizumab, Ipilimumab	All types of irAE	AEC
Jiayi Gao	2023	China	lung cancer	Not specified, including anti–PD-1, anti-PD-L1 inhibitor	All types of irAE	NLR, PLR, LMR
Weitong Gao	2023	China	lung cancer	Nivolumab, Pembrolizumab, Camrelizumab, Sintilimab, Tislelizumab, Toripalimab, Atezolizumab, Durvalumab, Ipilimumab	All types of irAE	ANC, ALC, AMC, AEC, NLR, PLR, MLR
Sirish Dharmapuri	2023	United States	hepatocellular carcinoma	Not specified, including anti–PD-1, anti-CTLA4 inhibitors	All types of irAE	NLR, PLR
Lucía Teijeira	2023	Spain	lung cancer, melanoma, renal cell carcinoma, head and neck carcinoma,urothelial carcinoma, gastric adenocarcinoma, colorectal adenocarcinoma, malignant pleural mesothelioma, pancreatic adenocarcinoma, merkel cell carcinoma	Nivolumab, Pembrolizumab, Cemiplimab, Atezolizumab, Durvalumab, Avelumab	All types of irAE	ALC
Akifumi Kuwano	2024	Japan	hepatocellular carcinoma	Atezolizumab	All types of irAE	ANC, ALC, AEC, PLT, NLR, PLR
Jingting Wang	2024	China	lung cancer, head and neck cancer, gastric carcinoma, urothelial carcinoma,colorectal cancer, reproductive systemcancer, liver cancer, gallbladder carcinoma and bile duct carcinoma, melanoma and others	Nivolumab, Pembrolizumab, Camrelizumab, Sintilimab, Atezolizumab, Durvalumab	All types of irAE	AEC, NLR, MLR
Meng Yang	2024	China	urothelial carcinoma	Tislelizumab	All types of irAE	NLR, PLR, MLR
Baishen Zhang	2024	China	lung cancer	Atezolizumab, Durvalumab	All types of irAE	NLR, PLR

(Continued)

TABLE 1 Continued

Author	Published year	Country	Cancer	Immune checkpoint inhibitors	irAE type	Peripheral blood biomarker
Masahiko Sue	2024	Japan	lung cancer, gastrointestinal cancer, head and neck cancer, kidney cancer,melanoma, liver cancer, genital cancerand others	Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, Avelumab, Ipilimumab	All types of irAE	NLR

irAE, immune-related adverse event; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AEC, absolute eosinophil count; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; LMR, lymphocyte to monocyte ratio.

Predictive significance of categorized blood cell counts for irAEs

A total of 40 studies reported categorized blood cell counts for both the irAE and non-irAE groups, with 20 of these studies providing data on the number of patients with lower or higher blood cell counts in each group and 28 studies reporting calculated ORs for categorized blood cell counts in predicting irAEs using either univariate or multivariate models. By synthesizing all studies that reported categorized blood cell counts in predicting irAEs, we found that higher ALC (OR=2.46 95%CI=1.69-3.57, Table 4, Figure 3A) and AEC (OR=2.05 95%CI=1.09-3.85, Table 4, Figure 3B), as well as lower NLR (OR=0.64 95%CI=0.50-0.81 Table 4, Figure 3C) and PLR (OR=0.63 95%CI=0.48-0.82, Table 4, Figure 3D), were associated with a higher incidence of irAEs.

Subgroup analysis

To explore potential sources of heterogeneity among the studies, we performed a subgroup analysis based on categorized blood cell counts. Among the different cutoff values for blood cell counts, an ALC of 2 or higher was significantly associated with an increased incidence of irAEs (OR = 2.28, 95% CI = 1.27–4.07, Table 5). No optimal cutoff value has yet been identified for AEC. An NLR of 5 or 3 or lower was significantly associated with an increased incidence of irAEs (OR = 0.39, 95% CI = 0.29–0.53, Table 6; OR = 0.63, 95% CI = 0.43–0.93, Table 6). Additionally, a PLR of 180 or lower was significantly associated with an increased incidence of irAEs (OR = 0.65, 95% CI = 0.45–0.95, Table 7).

Additionally, we performed a subgroup analysis based on specific types of irAEs. The results indicated that higher AEC values were associated with an increased incidence of pneumonitis (OR = 3.15, 95% CI = 1.82–5.45, Table 8), while lower PLR values were associated with an increased incidence of cardiovascular injury (OR = 0.65, 95% CI = 0.45–0.95, Table 7).

Subgroup analysis based on cancer type revealed that higher ALC (OR = 3.34, 95% CI = 1.45–7.68, Table 5) and AEC (OR = 3.15, 95% CI = 1.82–5.45, Table 8) were associated with an increased incidence of irAEs in lung cancer patients. Additionally, lower NLR was associated with an increased incidence of irAEs in lung cancer patients (OR = 0.59, 95% CI = 0.40–0.86, Table 6).

We conducted a subgroup analysis based on the type of ICI. Among the 40 studies that evaluated continuous blood cell counts, 12 studies evaluated PD-1 inhibitors alone, 3 studies evaluated PD-L1 inhibitors alone, 10 studies assessed both PD-1 and PD-L1 inhibitors, 2 studies evaluated both PD-1 and CTLA-4 inhibitors, and 13 studies evaluated PD-1, PD-L1, and CTLA-4 inhibitors simultaneously. In patients receiving PD-1 inhibitors, lower NLR values were associated with a higher incidence of irAEs (OR=0.47, 95% CI=0.26-0.87, Table 6).

Finally, the subgroup analysis based on the publication region categorized the studies into those from Asian and non-Asian countries. In Asian countries, higher ALC values (OR=3.36, 95% CI=1.36-8.27, Table 5) and AEC values (OR=2.42, 95% CI=1.10-5.33, Table 8), as well as lower NLR values (OR=0.57, 95% CI=0.42-0.76, Table 6) and PLR values (OR=0.63, 95% CI=0.44-0.91,

TABLE 2 Meta-analysis investigating the association between continuous blood cell counts and irAEs: Comparison of mean values for continuous variables between groups.

Blood cell	Studies (n)	SMD (95% CI)	p-value	I^2	p-value Egger's test
ANC	11	-0.18 (-0.28, -0.07)	0.001	4.70	0.901
ALC	11	0.12 (0.01,0.24)	0.037	38.30	0.887
AMC	3	0.16 (-0.05,0.37)	0.125	8.60	0.623
AEC	5	0.13 (-0.20,0.46)	0.441	72.20	0.427
PLT	6	-0.11 (-0.28,0.05)	0.174	0.00	0.583
NLR	17	-0.38 (-1.04,0.27)	0.249	98.50	0.812
PLR	7	-0.32 (-0.60,-0.04)	0.026	70.90	0.827

Bolded values indicate $p < 0.05$.

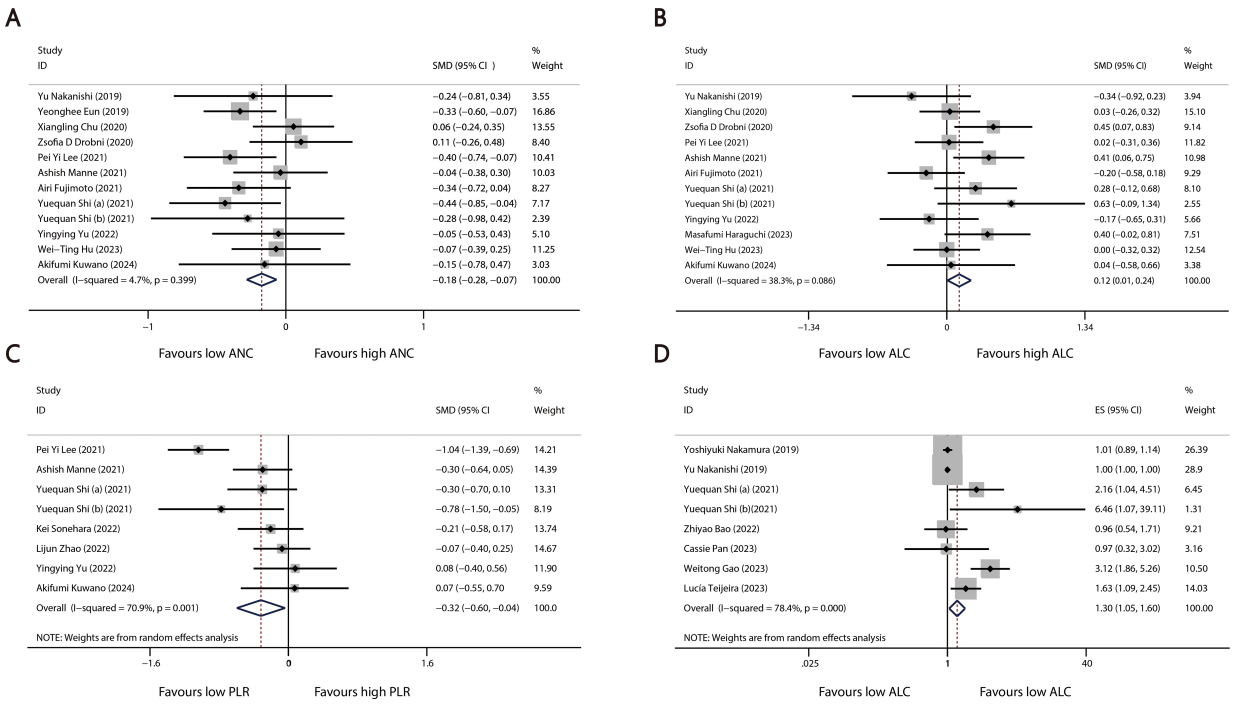

FIGURE 2
Forest plots comparing the association between continuous blood cell counts and irAEs: **(A)** Comparison of mean continuous ANC between groups. **(B)** Comparison of mean continuous ALC between groups. **(C)** Comparison of mean continuous PLR between groups. **(D)** Pooled ORs derived from continuous ALC data.

Table 7), were associated with a higher incidence of irAEs. In non-Asian countries, higher ALC values (OR=2.30, 95% CI=1.53-3.47, Table 5) and lower PLR values (OR=0.61, 95% CI=0.42-0.88, Table 7) were also associated with an increased incidence of irAEs.

Sensitivity analysis

We conducted a sensitivity analysis to explore potential sources of heterogeneity. For continuous ALC in predicting irAEs, heterogeneity was significantly influenced by each study, likely due to the limited number of studies included (Supplementary Figure 1D). All other combined results were relatively robust (Supplementary Figure 1).

Quality assessment and publication bias assessment

We considered 51 studies to be of high quality, while the remaining 9 studies had NOS scores ranging from 5 to 6. Egger's test indicated a potential publication bias for the studies calculating the combined OR for categorized AEC (P = 0.032).

Discussion

Through an extensive meta-analysis, we analyzed 60 studies involving 16,736 cancer patients and found that peripheral blood

TABLE 3 Meta-analysis investigating the association between continuous blood cell counts and irAEs: Comparison of ORs for continuous variable values between groups.

Blood cell	Studies (n)	OR (95% CI)	p-value	I^2 (%)	p-value Egger's test
ANC	5	0.95 (0.87,1.04)	0.249	66.5	0.338
ALC	7	1.30 (1.05,1.60)	0.016	78.4	0.049
AMC	3	0.54 (0.21,1.38)	0.198	72.8	0.175
AEC	6	1.49 (0.66,3.32)	0.335	58.5	0.455
NLR	10	1.02 (0.97,1.07)	0.511	55.5	0.153
PLR	3	0.998 (0.995, 1.002)	0.356	61.0	0.225
MLR	3	0.90 (0.81, 1.01)	0.069	0.0	0.500

Bolded values indicate $p < 0.05$.

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TABLE 4 Meta-analysis investigating the association between categorized blood cell counts and irAEs.

Blood cell	Studies (n)	OR (95% CI)	p-value	I^2 (%)	p-value Egger's test
ANC	3	0.68 (0.41,1.13)	0.141	0.0	0.903
ALC	6	2.46 (1.69,3.57)	0.000	0.0	0.348
AEC	6	2.05 (1.09,3.85)	0.026	82.1	0.032
PLT	4	0.85 (0.45,1.61)	0.623	72.7	0.845
NLR	33	0.64 (0.50,0.81)	0.000	71.7	0.686
PLR	23	0.63 (0.48,0.82)	0.001	62.0	0.776
MLR	8	0.82 (0.49,1.38)	0.461	77.4	0.669

Bolded values indicate $p < 0.05$.

cell counts could serve as potential biomarkers for predicting adverse events.

Lymphocytes, particularly T and B cells, play a crucial role in the pathogenesis of irAEs. T cells, especially the CD4+ and CD8+ subsets, are central to the immune responses triggered by ICIs (77–79). Immune checkpoint blockade enhances T cell activity and proliferation, potentially leading to a breakdown in self-tolerance. This overactivation may expand autoreactive T cell clones that can recognize and attack healthy tissues (80, 81). Studies have shown that some tumors and normal tissues share identical T cell receptor (TCR) sequences (82). ICIs can induce diversification of the TCR repertoire, generating autoreactive T cells that target normal tissue antigens (79). T cell infiltration into damaged tissues has also been observed in cases of myocarditis and skin toxicities (79, 83). Regulatory T cells (Tregs) play a critical role in maintaining peripheral tolerance by suppressing autoreactive T cells (84, 85). ICIs may reduce Treg populations, disrupting the balance between effector T cells and Tregs, thereby enhancing immune responses against self-antigens and promoting autoimmune phenomena (86). After ICI treatment, activated B cells may generate autoantibodies targeting self-antigens, leading to tissue damage and inflammatory responses (87). This mechanism is particularly evident in irAEs such as thyroid dysfunction, where

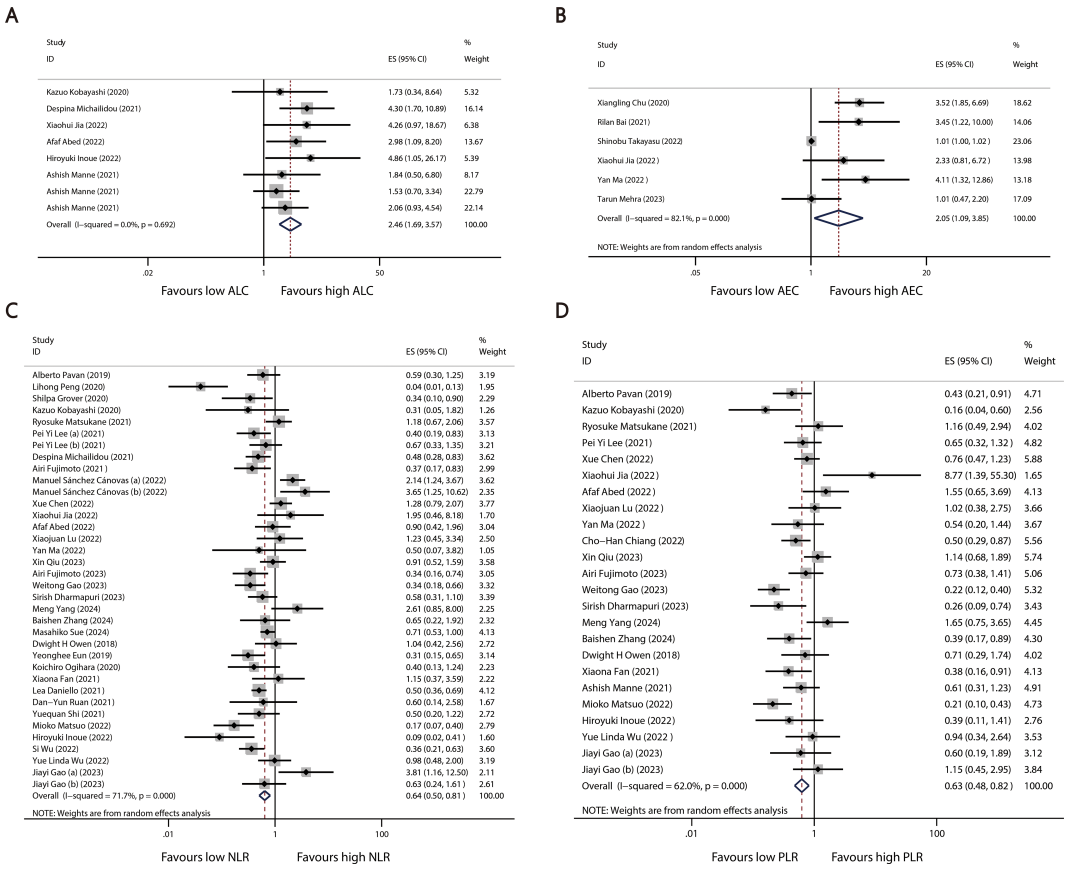

FIGURE 3
Forest plots comparing the association between categorized blood cell counts and irAEs: **(A)** ALC **(B)** AEC **(C)** NLR **(D)** PLR.

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TABLE 5 Subgroup Analysis of Categorized ALC.

Subgroup	N studies	OR (95% CI)	I^2 (%)	p-value for heterogeneity
cutoff				
0.6	1	1.84 (0.50, 6.79)	–	0.360
1	1	1.53 (0.70, 3.34)	–	0.286
1.015	1	4.86 (0.97, 24.21)	–	0.054
1.635	1	4.26 (0.97, 18.67)	–	0.054
2	**3**	**2.28 (1.27, 4.07)**	**0.0**	**0.006**
2.6	1	4.30 (1.70, 10.88)	–	0.002
irAE type				
All types of irAE	**5**	**2.36 (1.61, 3.48)**	**0.0**	**0.000**
pneumonitis	1	4.26 (0.97, 18.67)	–	0.054
cancer type				
renal Cell Carcinoma	1	1.73 (0.34, 8.64)	–	0.507
mixed cancer	**2**	**2.19 (1.40, 3.43)**	**0.0**	**0.001**
lung cancer	**2**	**3.34 (1.45, 7.68)**	**0.0**	**0.005**
esophageal cancer	1	4.86 (0.97, 24.21)	–	0.054
drug				
PD-1	2	2.91 (0.93, 9.10)	0.0	0.066
PD-1/PD-L1	1	2.98 (1.09, 8.17)	–	0.034
PD-1/PD-L1/CTLA-4	**3**	**2.32 (1.51, 3.56)**	**0.0**	**0.000**
region				
Asian	**3**	**3.36 (1.36, 8.27)**	**0.0**	**0.009**
non-Asian	**3**	**2.30 (1.53, 3.47)**	**0.0**	**0.000**

Bolded values indicate $p < 0.05$.

affected patients often exhibit elevated levels of anti-thyroid autoantibodies (88). Furthermore, interactions between autoreactive T cells and B cells facilitate the formation of immune complexes, such as anti-nuclear antibody (ANA)-antigen complexes and anti-double-stranded DNA (anti-dsDNA) antibody-antigen complexes, which activate the complement system, triggering inflammation and exacerbating tissue damage (87). Additionally, pro-inflammatory cytokines produced by T cells and B cells, such as IL-17, TNF-α, and IFN-γ, amplify systemic inflammation and contribute to organ-specific damage (89, 90). The results of our meta-analysis indicate that elevated levels of peripheral blood lymphocytes are associated with an increased incidence of irAEs (OR=2.46, 95% CI=1.69-3.57). High circulating lymphocyte levels may reflect enhanced immune surveillance and signify sustained anti-tumor activity. However, this heightened immune surveillance may also lead to the recognition of self-antigens, potentially triggering autoimmune responses.

Eosinophils have traditionally been associated with allergic reactions and parasitic infections (91); however, recent research suggests that these cells also play diverse roles in anti-tumor immunity and autoimmunity. Eosinophils can recruit tumor-specific CD8+ T cells into the tumor microenvironment by secreting chemokines such as CCL5, CXCL9, and CXCL10, and induce macrophage polarization toward the M1 phenotype (92), thereby enhancing the immune system's ability to recognize and destroy tumor cells. In a melanoma mouse model, depletion of regulatory T cells significantly increased eosinophil infiltration, which was associated with tumor regression (93). Eosinophils can also exert direct cytotoxic effects on tumor cells by releasing substances like major basic protein (MBP), demonstrating potent tumor-killing activity in melanoma cells (92, 94). Numerous studies have shown that elevated eosinophil levels are linked to stronger anti-tumor immune responses and better prognosis in patients receiving ICI therapy (95, 96). Eosinophils contribute to these processes by secreting chemokines that promote the recruitment and activation of tumor-specific CD8+ T cells (93). After ICI treatment, CD4+ T cells release interleukin-5 (IL-5), stimulating eosinophil production in the bone marrow, which subsequently leads to their accumulation in peripheral blood and infiltration into tumor tissues (93). While eosinophils may contribute to favorable therapeutic outcomes, their accumulation in healthy tissues is also implicated in the development of irAEs (90, 97). Eosinophils produce various pro-inflammatory cytokines and chemokines,

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TABLE 6 Subgroup Analysis of Categorized NLR.

Subgroup	N studies	OR (95% CI)	I^2 (%)	p-value for heterogeneity
cutoff				
2	1	0.91 (0.52, 1.59)	–	0.741
2.7	1	0.60 (0.14, 2.58)	–	0.492
2.86	1	0.37 (0.17, 0.82)	–	0.014
3	**5**	**0.39 (0.29, 0.53)**	**0.0**	**0.000**
3.01	1	3.65 (1.25, 10.64)	–	0.018
3.1	1	1.28 (0.79, 2.07)	–	0.315
3.2	2	0.87 (0.24, 3.19)	83.5	0.830
3.28	1	1.95 (0.46, 8.18)	–	0.363
3.35	1	0.40 (0.13, 1.24)	–	0.111
3.4	1	0.31 (0.05, 1.87)	–	0.202
3.401	1	0.09 (0.02, 0.41)	–	0.002
3.56	1	1.23 (0.45, 3.34)	–	0.687
3.8	1	1.18 (0.67, 2.07)	–	0.564
4	2	1.21 (0.41, 3.55)	91.6	0.735
5	**12**	**0.63 (0.43, 0.93)**	**65.4**	**0.021**
5.3	1	0.48 (0.28, 0.83)	–	0.008
6.505	1	0.17 (0.07, 0.41)	–	0.000
8.58	1	0.501 (0.07, 3.81)	–	0.504
irAE type				
All types of irAE	**27**	**0.58 (0.46, 0.73)**	**63.5**	**0.000**
colitis	1	0.34 (0.11, 1.02)	–	0.054
thrombosis	1	2.39 (1.47, 3.87)	–	0.000
cardiovascular injury	2	0.68 (0.20, 2.37)	91.4	0.549
pneumonitis	1	1.95 (0.46, 8.18)	–	0.363
ir-SAE	1	0.40 (0.13, 1.24)	–	0.111
cancer type				
lung cancer	**13**	**0.59 (0.40, 0.86)**	**67.7**	**0.006**
melanoma	1	0.34 (0.11, 1.02)	–	0.054
renal cell carcinoma	1	0.31 (0.05, 1.87)	–	0.202
mixed cancer	11	0.71 (0.48, 1.06)	79.9	0.097
pancreatic cancer	1	0.91 (0.52,1.59)	–	0.741
hepatocellular carcinoma	2	0.73 (0.44, 1.22)	13.9	0.236
urothelial carcinoma	2	1.02 (0.16, 6.43)	81.3	0.981
gastric cancer	1	0.60 (0.14, 2.58)	–	0.492
esophageal cancer	1	0.09 (0.02, 0.41)	–	0.002
drug				
PD-1	**12**	**0.47 (0.26, 0.87)**	**79.2**	**0.017**
PD-L1	2	0.87 (0.48, 1.57)	0.0	0.635

(Continued)

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TABLE 6 Continued

Subgroup	N studies	OR (95% CI)	I^2 (%)	p-value for heterogeneity
drug				
PD-1/PD-L1	9	1.00 (0.63, 1.58)	77.0	0.993
PD-1/CTLA-4	**2**	**0.51 (0.29, 0.88)**	**35.8**	**0.015**
PD-1/PD-L1/CTLA-4	**8**	**0.50 (0.38, 0.66)**	**71.7**	**0.000**
region				
Asian	**24**	**0.57 (0.42, 0.76)**	**71.1**	**0.000**
non-Asian	9	0.83 (0.55, 1.25)	74.7	0.363

Bolded values indicate $p < 0.05$.

TABLE 7 Subgroup Analysis of Categorized PLR.

Subgroup	N studies	OR (95% CI)	I^2 (%)	p-value for heterogeneity
cutoff				
114.271	1	8.77(1.39, 55.32)	–	0.021
135	3	0.93(0.44, 1.96)	69.5	0.846
143	1	0.22(0.12, 0.40)	–	0.000
150	1	0.61(0.31, 1.26)	–	0.160
156	1	0.16(0.04, 0.62)	–	0.008
163	1	0.76(0.47, 1.23)	–	0.263
180	**5**	**0.65(0.45, 0.95)**	**33.9**	**0.028**
180.68	1	0.54(0.20, 1.45)	–	0.221
185	1	0.39(0.17, 0.89)	–	0.026
200	1	1.02(0.38, 2.74)	–	0.969
237	1	0.71(0.29, 1.74)	–	0.454
240	1	1.16(0.47, 2.84)	–	0.745
243	1	0.39(0.11, 1.40)	–	0.148
300	2	0.50(0.14, 1.75)	66.0	0.277
320	1	0.21(0.10, 0.44)	–	0.000
436	1	0.89(0.43, 1.83)	–	0.744
irAE type				
All types of irAE	**20**	**0.60(0.45, 0.80)**	**61.0**	**0.001**
cardiovascular injury	**2**	**0.63(0.42, 0.95)**	**20.8**	**0.027**
pneumonitis	1	8.77(1.39, 55.32)	–	0.021
cancer type				
lung cancer	9	0.72(0.44, 1.17)	68.6	0.182
renal cell carcinoma	1	0.16(0.04, 0.62)	–	0.008
mixed cancer	**8**	**0.55(0.39, 0.76)**	**42.6**	**0.000**
pancreatic cancer	1	1.14(0.68, 1.90)	–	0.615
hepatocellular carcinoma	2	0.50(0.14, 1.75)	66.0	0.277

(Continued)

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TABLE 7 Continued

Subgroup	N studies	OR (95% CI)	I^2 (%)	p-value for heterogeneity
cancer type				
urothelial carcinoma	1	1.65(0.75, 3.64)	–	0.215
esophageal cancer	1	0.39(0.11, 1.40)	–	0.148
drug				
PD-1	8	0.61(0.33, 1.11)	74.6	0.106
PD-L1	2	0.57(0.24, 1.35)	41.6	0.203
PD-1/PD-L1	6	0.74(0.55, 1.01)	4.4	0.055
PD-1/CTLA-4	1	0.26(0.09, 0.75)	–	0.012
PD-1/PD-L1/CTLA-4	6	0.61(0.34, 1.07)	73.0	0.083
region				
Asian	**16**	**0.63(0.44, 0.91)**	**68.9**	**0.012**
non-Asian	**7**	**0.61(0.42, 0.88)**	**34.1**	**0.009**

Bolded values indicate $p < 0.05$.

including interleukin-4 (IL-4), IL-5, interleukin-13 (IL-13), and tumor necrosis factor-alpha (TNF-α) (98). These mediators not only recruit additional immune cells to sites of inflammation but also sustain and amplify the inflammatory response. In patients undergoing ICI therapy, increased eosinophil infiltration has been observed in tissues affected by irAEs, such as the skin, lungs, and gastrointestinal tract (99–101). Eosinophils express a variety of surface markers and receptors, such as CD30 and PD-L1, which

TABLE 8 Subgroup Analysis of Categorized AEC.

Subgroup	N studies	OR (95% CI)	I^2 (%)	p-value for heterogeneity
cutoff				
0.045	1	4.11(1.32, 12.86)	–	0.015
0.125	1	3.52(1.85, 6.69)	–	0.000
0.155	1	2.33(0.81, 6.72)	–	0.118
0.175	1	3.45(1.22, 10.00)	–	0.021
0.198	1	1.01(1.00, 1.02)	–	0.049
0.2	1	1.01(0.47, 2.20)	–	0.974
irAE type				
pneumonitis	**2**	**3.15(1.82, 5.45)**	**0.0**	**0.000**
All types of irAE	3	2.26(0.88, 5.80)	63.7	0.089
adrenal insufficiency	1	1.01(1.00,1.02)	–	0.049
cancer type				
lung cancer	**2**	**3.15(1.82, 5.45)**	**0.0**	**0.000**
mixed cancer	4	1.66(0.85, 3.25)	72.9	0.142
drug				
PD-1/PD-L1	**2**	**3.65(2.09, 6.39)**	**0.0**	**0.000**
PD-1/PD-L1/CTLA-4	4	1.42(0.83, 2.45)	60.7	0.204
region				
Asian	**5**	**2.42(1.10, 5.33)**	**85.7**	**0.028**
non-Asian	1	1.01(0.47, 2.20)	–	0.974

Bolded values indicate $p < 0.05$.

facilitate their interaction with T cells and enhance a Th2-skewed immune response characterized by increased production of IL-4 and IL-5. This interaction may result in allergic-like reactions in patients receiving ICIs (102). The Th2-biased immune response can further exacerbate tissue inflammation and damage, contributing to the development of irAEs. Our meta-analysis indicates that elevated peripheral blood eosinophil levels are associated with an increased incidence of irAEs(OR=2.05, 95%CI=1.09-3.85). Initially, high eosinophil levels may correlate with effective anti-tumor immune responses. However, their prolonged presence and activation can provoke harmful autoimmune reactions. ICI-related pneumonitis (CIP) often presents as bilateral ground-glass opacities or nodules, with eosinophils frequently observed (100). Additionally, a small number of eosinophils can be detected in bronchoalveolar lavage fluid (103). Our subgroup analysis revealed that elevated AEC are associated with an increased incidence of pneumonia (OR = 3.15, 95% CI = 1.82-5.45), suggesting that eosinophils may play a significant role in the development of CIP. Although the specific mechanisms underlying the relationship between eosinophils and CIP remain unclear, it is essential to be vigilant regarding the potential risk of CIP in patients with baseline eosinophilia.

NLR and PLR are recognized markers of inflammation, playing a pivotal role in assessing the effectiveness and prognosis of immune checkpoint inhibitor therapy (8, 104). In our study, a low NLR (OR=0.64, 95%CI=0.50-0.81)and PLR(OR=0.63, 95%CI=0.48-0.82) were associated with an increased incidence of irAEs. An elevated NLR typically indicates a chronic inflammatory state characterized by increased levels of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) and tumor-associated neutrophils (62), which can suppress the anti-tumor function of lymphocytes, thereby weakening the immune response against tumors (105, 106). Besides their role in hemostasis, platelets also play a critical role in immune modulation (107). They release pro-inflammatory cytokines and chemokines upon activation, such as interleukin-1 (IL-1), TNF-α, and interleukin-6 (IL-6) (108). These mediators are essential for enhancing local inflammatory responses and recruiting immune cells, including monocytes and T cells, to sites of inflammation (109). Platelet activation is associated with chronic inflammatory states and can inhibit lymphocyte function, impairing the anti-tumor immune response (110). In contrast, a high lymphocyte count typically signifies a robust immune response capable of effectively combating tumors. Thus, lower NLR and PLR, indicating reduced neutrophil and platelet levels alongside a high lymphocyte count, reflect sustained anti-tumor activity and suggest an increased risk of developing irAEs. Although previous literature indicates that elevated PLR is associated with an increased risk of cardiovascular events (111, 112), our subgroup analysis revealed that a lower PLR (OR = 0.65, 95% CI = 0.45-0.95) is associated with a higher incidence of immune-related cardiovascular adverse events. It is important to note that immune-related cardiovascular events differ significantly from traditional cardiovascular events in their underlying mechanisms, placing greater emphasis on the role of immune and inflammatory responses in disease development. The bidirectional changes in PLR may reflect the complex immune-inflammatory mechanisms involved in different cardiovascular events, indicating that patients with varying PLR levels may face distinct immune-related risk profiles.

This study demonstrates that peripheral blood cell counts (such as ALC, AEC, NLR, and PLR) are strongly associated with irAEs and can serve as early predictive markers for patients undergoing immunotherapy. Regular monitoring of these biomarkers enables the timely identification of high-risk patients and facilitates early intervention. For instance, an increase in lymphocyte count may suggest immune system overactivation (71), potentially signaling the onset of irAEs, while elevated eosinophil count may be closely linked to immune-related pneumonia (23). These biomarkers predict the occurrence of irAEs and help assess their severity, thus guiding treatment adjustments (113). Increased NLR and PLR may indicate immune activation, enabling clinicians to adjust the immunotherapy dose or temporarily pause treatment. For patients who have already developed irAEs, regular monitoring of hematological markers helps assess immune response control and determine the need for immunosuppressive agents to manage adverse reactions. The use of hematological biomarkers supports personalized treatment management. By integrating clinical characteristics with peripheral blood cell counts, clinicians can more effectively balance treatment efficacy and safety (8, 114).

The application of these biomarkers in clinical practice faces several challenges. First, their sensitivity and specificity in predicting irAEs require further validation. Factors such as patient population, tumor type, immune checkpoint inhibitors, treatment timing, regimen, and detection methods may influence biomarker performance, resulting in variability across different populations (38, 113, 115, 116). Second, clinical thresholds for hematological biomarkers have not been standardized, and cutoff values vary significantly across studies, introducing uncertainty in their application. Our meta-analysis suggests that the optimal cutoff values for ALC, NLR, and PLR are 2×10^9/L, 3 or 5, and 180, respectively, while no clear standard exists for AEC. These critical values are influenced by factors such as study population, leading to heterogeneity in results. Therefore, future multicenter, large-scale prospective studies are needed to establish optimal clinical standards for these biomarkers.

Our study presents several significant strengths. First, it includes a substantial sample size, comprising 60 studies and 16,736 cancer patients, thereby enhancing the reliability of our conclusions. Second, we assessed continuous and categorical blood cell counts, strengthening our findings' robustness. Third, we performed comprehensive subgroup analyses according to varying blood cell counts cutoffs, specific irAEs (such as pneumonitis and cardiovascular injury), cancer types, ICIs, and patient demographics. Fourth, all included studies were of moderate to high quality, and sensitivity analyses further validated the stability of our results. Finally, we identified a commonly used cutoff value for blood cell counts, which offers valuable guidance for clinical practice, although this finding requires further validation.

Our study has several significant limitations that require careful consideration. First, since our analysis primarily relies on retrospective studies, there is a potential for selection bias and heterogeneity, which could affect the generalizability of our findings. Second, the substantial variability in blood cell counts cutoff values across different studies indicates a lack of consensus on an optimal threshold, thereby limiting its applicability in clinical

practice. Third, this meta-analysis includes only published studies, which raises concerns about publication bias, given that unpublished negative results may skew our findings. Fourth, the scarcity of reports on specific irAE subtypes, such as cardiovascular events and pneumonia, limits our ability to evaluate the predictive capacity of blood cell counts for these adverse events. Finally, the heterogeneity among studies, especially in the analysis of continuous blood cell counts, may compromise the reliability of our results. Although subgroup and sensitivity analyses were performed to explore sources of heterogeneity, the limited number of studies and the diversity in study design, populations, and reporting methods may still leave some heterogeneity unexplained.

Conclusion

In conclusion, our meta-analysis revealed a significant association between higher baseline ALC and AEC, and lower baseline PLR and NLR, with an increased risk of developing irAEs. However, the predictive value of blood cell counts varies across different types of irAEs, highlighting the need for additional subgroup analyses when evaluating the efficacy of peripheral biomarkers. The commonly used cutoff values (ALC = 2×10^9/L, NLR = 3 or 5, PLR = 180) require further consensus to establish the optimal cutoff for future clinical guidance. Overall, our findings suggest that blood cell counts may serve as a valuable predictor of irAEs, and further research is warranted to evaluate its role in personalized immunotherapy management.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

XZ: Conceptualization, Data curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. BZ: Writing – original draft. DL: Writing – original draft. YY: Writing – original draft. SL: Writing – original draft. RZ: Writing – original draft. YL: Writing – original draft. LP: Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1528084/full#supplementary-material

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