BMC Gastroenterology

SYSTEMATIC REVIEW Open Access

Prognostic value of platelet-to-lymphocyte ratio in hepatocellular carcinoma patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis

Qingtian Zhou[1], Zewen Jiang[2], Tingting Ye[1], Li Yu[1], Qinglian Wang[1], Pin Lin[1] and Yanfeng Shao[1*]

Abstract

Background The prognostic significance of the Platelet–to–Lymphocyte Ratio (PLR) in patients with hepatocellular carcinoma (HCC) undergoing treatment with immune checkpoint inhibitors (ICIs) remains uncertain. A systematic review and meta–analysis was conducted to assess the prognostic value of PLR in HCC patients receiving ICIs.

Methods Potential eligible studies that explored the role of pretreatment PLR in HCC patients received ICIs treatment were retrieved using PubMed, Embase, and the Cochrane Library databases up to March 31, 2024. The Newcastle–Ottawa Scale was used to assess the study quality. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were utilized to investigate the correlation between PLR and both overall survival (OS) and progression–free survival (PFS). Subgroup analysis along with assessments for publication bias and sensitivity were performed to identify any sources of heterogeneity and to confirm the reliability of the pooled outcomes.

Results A total of 15 studies were analyzed, with the aggregate findings showing that elevated PLR levels were associated with poorer OS (HR: 1.79, 95%CI: 1.44–2.22, $P < 0.001$) and PFS (HR: 1.80, 95%CI: 1.40–2.30, $P < 0.001$) in HCC patients treated with ICIs. Moreover, the subgroup analyses did not alter the direction of results for OS and PFS. Publication bias and sensitivity analysis revealed that there was no significant publication bias among the articles and the pooled results were robust.

Conclusion These results show that elevated PLR is related to worse survival in patients with HCC treated with ICIs. PLR may therefore represent an effective indicator of prognosis in HCC undergoing ICIs treatment.

Trial registration This study is registered with the International Platform of Registered Systematic Review and Meta–analysis Protocols (INPLASY202450079).

Keywords Platelet–to–Lymphocyte ratio, Meta, Prognosis, Hepatocellular carcinoma, Immune checkpoint inhibitors

*Correspondence:
Yanfeng Shao
jxmipsen@163.com
[1]Department of Gastroenterology, The Third Affiliated People's Hospital of Fujian University of Traditional Chinese Medicinee, No. 363, Guobin Avenue, Fuzhou City, Fujian Province, China
[2]Department of Infectious Diseases, The 900 Hospital of the Joint Logistics Team of the Chinese PLA, Fuzhou, Fujian, China

Introduction

Liver cancer is expected to be the sixth most frequently diagnosed cancer and the fourth leading cause of cancer–related deaths globally, with over 840,000 new cases and 780,000 fatalities each year [1]. Hepatocellular carcinoma (HCC) constitutes 75–85% of primary liver cancer cases and is associated with a grim prognosis [2]. Despite advancements in diagnosis, staging, and treatment, HCC has a high recurrence rate of about 70%, and overall survival (OS) showing minimal improvement over the past two decades [3, 4]. In recent years, there has been rapid progress in the development of molecular targeted therapy and immunotherapy for the treatment of HCC. The approval of anti–programmed cell death–1 (PD–1) antibodies, nivolumab and pembrolizumab as immune checkpoint inhibitors (ICIs) has expanded the treatment options for HCC [5, 6].

The systemic treatment landscape for HCC is continuously evolving, with a growing emphasis on combination therapies involving ICIs and anti-angiogenic agents or tyrosine kinase inhibitors. Recent clinical trials and real-world studies have demonstrated that such combinatorial approaches may improve response rates and survival outcomes in advanced HCC patients [7–11]. These developments underscore the importance of identifying effective biomarkers to optimize treatment selection and monitor therapeutic efficacy.

However, responses to ICIs vary among individuals, and not all advanced patients benefiting from them [12, 13]. Identifying predictive biomarkers remains a high priority, particularly considering the expanding indications for and increasing use of ICIs [14, 15]. The current recommended strategy involves assessing PD–L1 expression and tumor mutational burden (TMB) to anticipate the efficacy of ICIs [16, 17]. However, not all patients with high PD–L1 and TMB expression could benefit from ICIs [18]. Therefore, the search for prognostic biomarkers to forecast treatment response and long–term survival in HCC patients receiving ICIs is deemed crucial.

Inflammation is a well–recognized characteristic of aggressive cancer, reflecting both the fundamental nature of the tumor and the interactions between the tumor and the host [19]. Recently, there has been widespread interest in meta–analyses of the prognostic value of peripheral blood inflammation–based indicators such as the lymphocyte–to–monocyte ratio (LMR) [20, 21], neutrophil–to–lymphocyte ratio (NLR) [22–25], and C–reactive protein (CRP) [26, 27] in cancer patients undergoing immunotherapy with ICIs. The platelet–to–lymphocyte ratio (PLR), a new combined metric calculated by dividing the platelet count by the lymphocyte count, predicts unfavorable outcomes / is associated with worse prognosis [28], renal cell cancer [29], and head and neck malignancies [30] receiving ICIs treatment. However, the use of PLR to indicate prognosis in patients with HCC treated with immunotherapy remains inconsistent [31, 32]. To further investigate this issue, we conducted a meta–analysis to evaluate the prognostic significance of pretreatment PLR in patients with hepatocellular carcinoma who received ICIs.

Methods

The review was performed following the Preferred Reporting Items for Systematic Reviews and Meta–Analyses (PRISMA) guidelines [33].

Search strategy and selection criteria

This study is registered with the International Platform of Registered Systematic Review and Meta–analysis Protocols (INPLASY202450079). A comprehensive search was conducted across PubMed, Embase, and the Cochrane Library databases without language restrictions to identify relevant studies investigating the correlation between PLR and the prognosis of HCC patients undergoing immunotherapy with ICIs. The search period spanned from the inception of the databases until March 31, 2024. The search strategy incorporated combinations of the following terms using Boolean operators AND and OR: "platelet to lymphocyte ratio" OR "platelet–lymphocyte ratio" OR "PLR", "immune checkpoint inhibitors" OR "immunotherapy" OR "PD–1" OR "PD–L1", "hepatocellular carcinoma" OR "liver cancer", "prognosis" OR "prognostic" OR "survival". Additionally, references cited in the selected publications were screened to identify any additional pertinent studies. No deviations from the registered protocol were made.

Inclusion criteria consisted of studies that (1) enrolled patients with HCC confirmed by histopathology, (2) presented hazard ratios (HR) and 95% confidence intervals (CI) for OS or progression–free survival (PFS), or contained adequate data to compute HR and 95% CI, (3) involved the administration of any form of ICIs, and (4) reported the specified cut–off value of PLR prior to immunotherapy.

Exclusion criteria encompassed (1) letters, review articles, editorial, conference abstracts, expert opinion, study protocol, guidelines, case reports or case series; (2) animal studies and non–relevant studies; (3) duplicate or inaccessible full texts.

Two reviewers independently screened the literature according to the above criteria, and the different opinions encountered during the research screening process were resolved through discussion or by the third reviewer.

Extraction of data and evaluation of quality

Two researchers meticulously reviewed eligible studies to gather details such as the first author's last name, region, patients' age and gender, number of patients,

cut–off value, duration of follow–up, treatment methods, and survival analysis. The summary HR with 95% CI was derived from each study, with a preference for HR data from multivariate analysis when both univariate and multivariate analyses were conducted. If multivariate analyses were not available, results from univariate analysis were deemed acceptable. The quality of primary studies was evaluated independently by three investigators using the Newcastle–Ottawa Quality Assessment Scale (NOS) [34]. Studies with NOS scores > 6 out of a total of 9 points were regarded as high quality.

Additionally, we also reviewed study quality across the three key domains of the NOS: selection, comparability, and outcome assessment. Most studies scored well in the selection and outcome domains. However, comparability was often limited, as several studies did not perform adequate adjustment for known prognostic confounders. Moreover, information regarding blinding of outcome assessment and handling of missing data was inconsistently reported, which may introduce potential bias. These methodological issues were taken into consideration when interpreting the pooled results.

Statistical analysis

Data on HR and 95% CI were gathered either directly from individual articles or computed as described previously if not shown directly [35]. Statistical heterogeneity in the combined results was evaluated using Cochran's Q and I^2 methods [36]. If I^2 was less than 50% and P>0.10, heterogeneity was considered not significant. Given the anticipated clinical and methodological variability among studies, a random–effects model was applied for all pooled analyses regardless of the level of statistical heterogeneity. Subgroup analyses were conducted based on country, treatment, sample size, cut–off value, and types of Cox regression analysis. Evaluation for publication bias involved Egger's test, Begg's test, and a funnel plot, with statistical significance defined as a p–value below 0.05. Additionally, a sensitivity analysis was carried out sequentially excluding each study to assess its impact on the overall results. Statistical analysis was performed using Stata 12.0.

Results

Characteristics of selected studies

Figure 1 presents a flow chart illustrating the selection process. A total of 240 potentially relevant articles were found through the database search, out of which 220 were excluded after reviewing titles and abstracts. After further screening of the full text of the remaining 20 publications, 5 articles were excluded for lack of cut–off value or available data. Finally, 15 articles were selected for the meta–analysis [31, 32, 37–49]. The characteristics of the 15 included studies are detailed in Table 1. All these studies were deemed of high quality based on the NOS criteria (see Supplementary Table S1). Among these studies, 10 were carried out in China, 2 in the USA, 1 in Korea, and 2 were multicentre. The cutoff values for PLR varied from 96.42 to 300, with 13 articles having cutoff values below 300. The sample sizes ranged from 46 to 442 patients. Out of the 15 studies included, 11 assessed OS, while 13 assessed PFS.

The relationship between PLR and OS was examined in HCC patients receiving ICIs

A total of 11 studies involving 2059 patients investigated the link between baseline PLR levels and OS [31, 32, 37–40, 43, 45–48]. The analysis showed moderate heterogeneity (I^2 = 49.5%, P = 0.031) among the studies, leading to the use of a random effect model for pooled analysis. The combined data indicated a significant association between higher PLR levels and poorer OS, with a pooled HR estimate of 1.79 (95% CI: 1.44–2.22, P < 0.001; Fig. 2). Subgroup analyses indicated that elevated PLR was negatively associated with OS in China (HR: 2.08, 95% CI: 1.51–2.86, P < 0.001) and other region (HR: 1.54, 95% CI: 1.28–1.86, P < 0.001). In the analysis of combination therapy, pooled HR for patients receiving ICIs was 1.68 (95% CI: 1.44–1.97, P < 0.001) and 1.89 (95% CI: 1.24–2.88, P = 0.003) for patients treated with ICIs combined with other treatment strategies. Moreover, when PLR ≥ 140, pooled HR for OS was 1.56 (95% CI: 1.32–1.85, P < 0.001) and when PLR <140, pooled HR for OS was 2.22 (95% CI: 1.48–3.33, P < 0.001). Following stratification based on sample size, the combined HR was 1.54 (95% CI: 1.34–1.77, P < 0.001) for sample size > 120 and 2.99 (95% CI: 2.08–4.29, P < 0.001) for sample size < 120. In the analysis of types of Cox regression analysis, pooled HR for univariate analysis was 1.58 (95% CI: 1.30–1.91, P < 0.001) and 2.17 (95% CI: 1.39–3.40, P = 0.001) for multivariate analysis. These results are shown in Table 2. In summary, the subgroup variables region, combination therapy, the value of cut–off cancer, sample size, analysis method did not alter the direction of results for OS. Sample size may be a potential source of OS heterogeneity. When the sample size < 120, the adverse association between higher PLR levels and OS appeared more pronounced in smaller sample size studies.

Relationship between the PLR and PFS in HCC patients treated with ICIs

The impact of PLR on PFS was assessed in 13 studies with 1673 patients [31, 32, 37, 39–45, 47–49]. The pooled data demonstrated that patients with elevated PLR had inferior OS compared to those with lower PLR levels (HR: 1.80, 95% CI: 1.40–2.30, P < 0.001). A moderate level of significant heterogeneity (I^2 = 53.3%, P = 0.012) was identified, leading to the utilization of a random–effect model

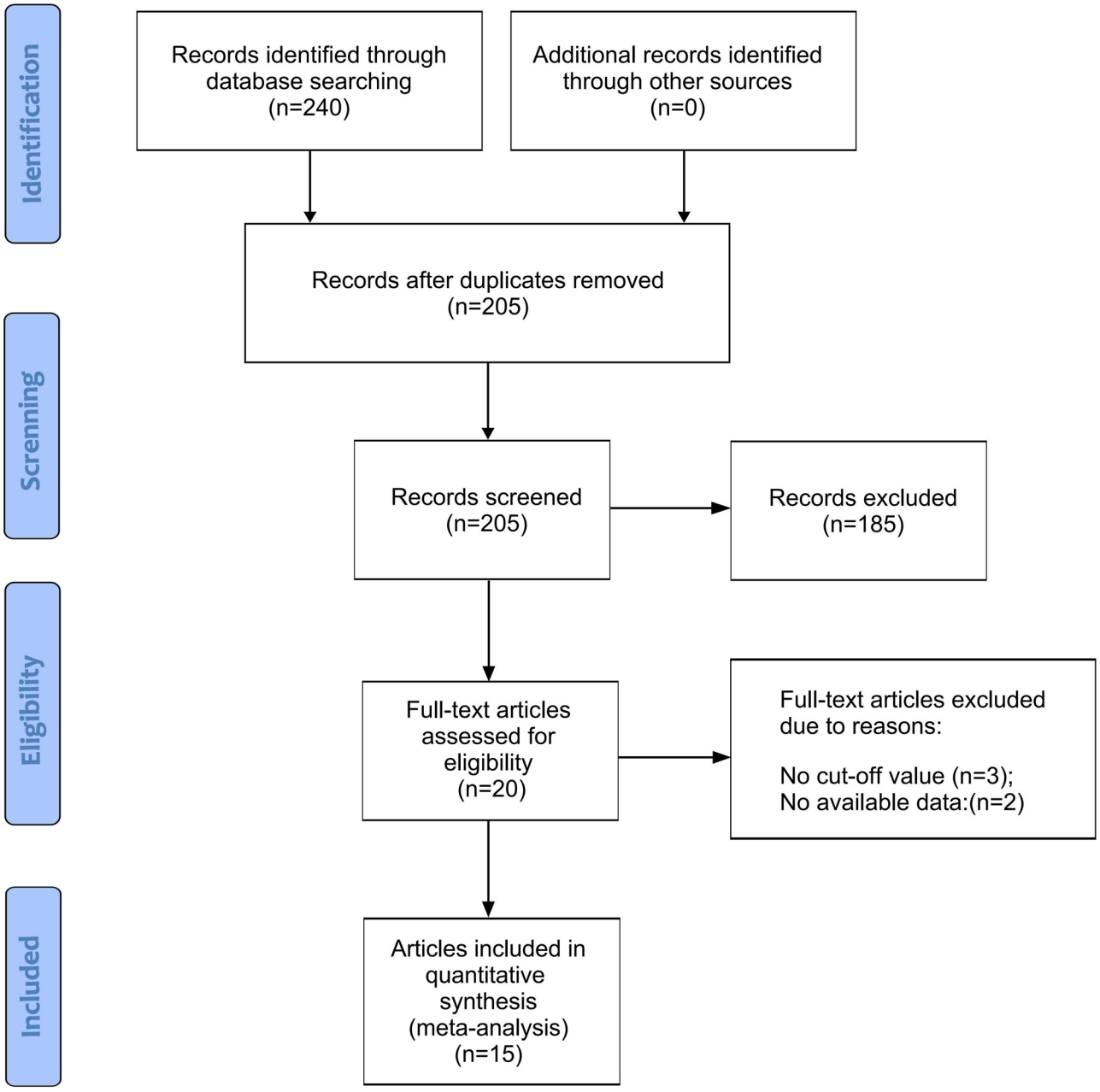

Fig. 1 Flow chart of the meta–analysis

for the analysis (Fig. 3). Subgroup analyses showed that increased PLR predicted poor PFS among patients in China (HR: 2.00, 95% CI: 1.42–2.80, $P<0.001$) and other region (HR: 1.44, 95% CI: 1.09–1.91, $P=0.01$). In the analysis of combination therapy, pooled HR for patients treated with ICIs was 2.11 (95% CI: 1.38–3.22, $P=0.001$), 1.63 (95% CI: 1.19–2.22, $P=0.002$) for patients receiving ICIs combined with other treatment strategies. Moreover, when PLR ≥ 140, pooled HR for PFS was 1.86 (95% CI: 1.33–2.58, $P<0.001$) and when PLR <140, pooled HR for PFS was 1.73 (95% CI: 1.14–2.63, $P=0.011$). Following stratification by sample size, pooled HR was 1.38 (95% CI: 1.08–1.77, $P=0.011$) for sample size > 120 and 2.11 (95% CI: 1.51–2.94, $P<0.001$) for sample size < 120. In the analysis of types of Cox regression analysis, pooled HR for univariate analysis was 1.48 (95% CI: 1.10–1.99, $P=0.009$) and 2.25 (95% CI: 1.72–2.95, $P<0.001$) for multivariate analysis. The findings can be found in Table 3. Overall, the subgroup variables, including region, combination therapy, the value of cut–off, sample size and analysis method did not alter the direction of results for PFS and may not be a potential source of heterogeneity.

Table 1 Characteristics of studies included in this meta–analysis

Study, year	Country	Sample size	Age (median or mean ± SD or range)	Gender (M/F)	Follow–up (months)	Treatment	Cut–off	Survival outcome	Analysis	NOS
Akce et al. 2020	USA	57	66	44/13	median:6	Anti–PD–1	135	PFS	M	8
Awiwi et al. 2022	USA	55	66 (36–80)	45/10	median:7.9	Atezolizumab + Bevacizumab	230	PFS	M	8
Chon et al. 2022	Korea	121	63 (57–71)	100/21	median:8.5	Atezolizumab + Bevacizumab	150	OS, PFS	U, U	7
Guo et al. 2024	China	98	NR	86/12	NR	ICIs + TACE + TKIs	98.89	OS, PFS	M, M	7
Huang et al. 2022	China	110	54.5 (31–84)	100/10	NR	Anti–PD–1	140	OS, PFS	M, M	7
Jia et al. 2023	China	117	58	106/11	median:15.1	Anti–PD–1	131	OS, PFS	M, U	8
Li et al. 2022	China	114	53 (24–79)	102/12	median:10.6	Anti–PD–1 + Lenvatinib + TACE	96.42	OS, PFS	U, U	7
Liu et al. 2023	China	104	65	86/18	NR	Anti–PD–1	227	PFS	U	6
Mei et al. 2021	China	442	52 (21–75)	382/60	median:13.7	Anti–PD–1	136.8	OS	U	7
Muhammed et al. 2022	Multicentre	362	65 (15–87)	284/78	NR	ICIs	300	OS, PFS	M, M	8
Wang et al. 2022	China	48	62 (31–80)	38/10	median:9.5	Atezolizumab + Bevacizumab	230	PFS	M	8
Wang et al. 2024	China	208	56.02 ± 10.89	193/15	median:15.56	Anti–PD–1 + targeted drugs	100	OS	U	7
Wu et al. 2022	Multicentre	281	66 (59–73)	233/47	median:6.88	Atezolizumab + Bevacizumab	300	OS, PFS	M, M	9
Yang et al. 2023	China	46	NR	39/7	median:8.0	Regorafenib + ICIs	133	OS, PFS	M, U	8
Zhao et al. 2022	China	160	58 (26–86)	129/31	NR	ICIs + TKIs	145.25	OS, PFS	U, U	6

Notes: M, multivariate; U, Univariate; ICIs, immune checkpoint inhibitors; TACE, transcatheter arterial chemoembolization; TKIs, tyrosine kinase inhibitors; OS overall survival; PFS progression–free survival; NOS Newcastle–Ottawa Scale; NR not reported

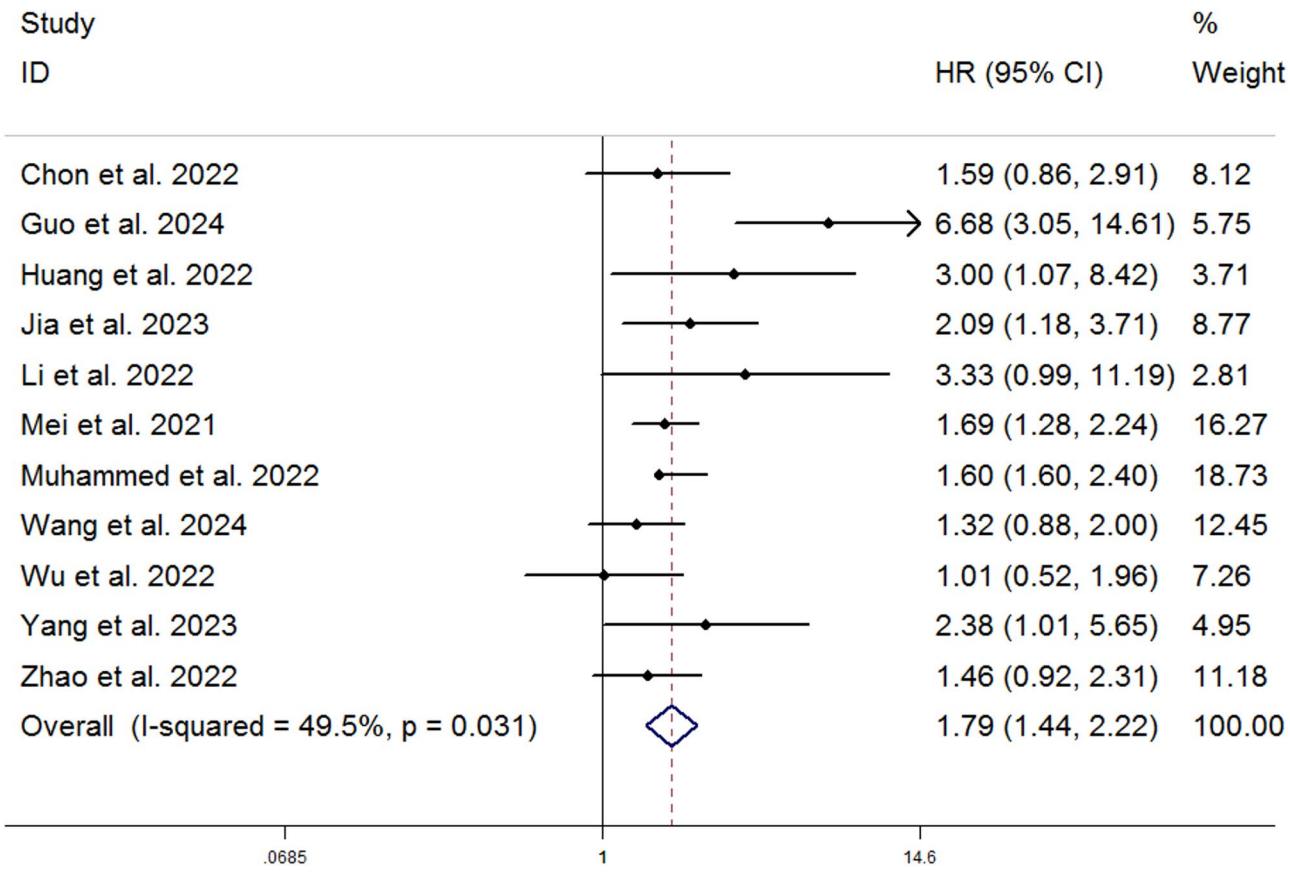

Fig. 2 Forest plot of the relationship between high PLR and OS

Table 2 Subgroup analyses of OS

Subgroup	NO. of studies	HR (95% CI)	*P*	Heterogeneity		Model
				I^2 (%)	Ph	
Country						
China	8	2.08 (1.51–2.86)	<0.001	57.8	0.02	Random
Other	3	1.54 (1.28–1.86)	<0.001	42.7	0	Random
Combination therapy						
Yes	7	1.89 (1.24–2.88)	0.003	66.3	0.007	Random
NO	4	1.68 (1.44–1.97)	<0.001	0	0.573	Random
Cuf–off						
≥ 140	5	1.56 (1.32–1.85)	<0.001	0	0.501	Random
< 140	6	2.22 (1.48–3.33)	<0.001	66.1	0.012	Random
Sample size						
> 120	6	1.54 (1.34–1.77)	<0.001	0	0.742	Random
< 120	5	2.99 (2.08–4.29)	<0.001	31.7	0.21	Random
Analysis						
Univariate	5	1.58 (1.30–1.91)	<0.001	0	0.638	Random
Multivariate	6	2.17 (1.39–3.40)	0.001	69.8	0.005	Random

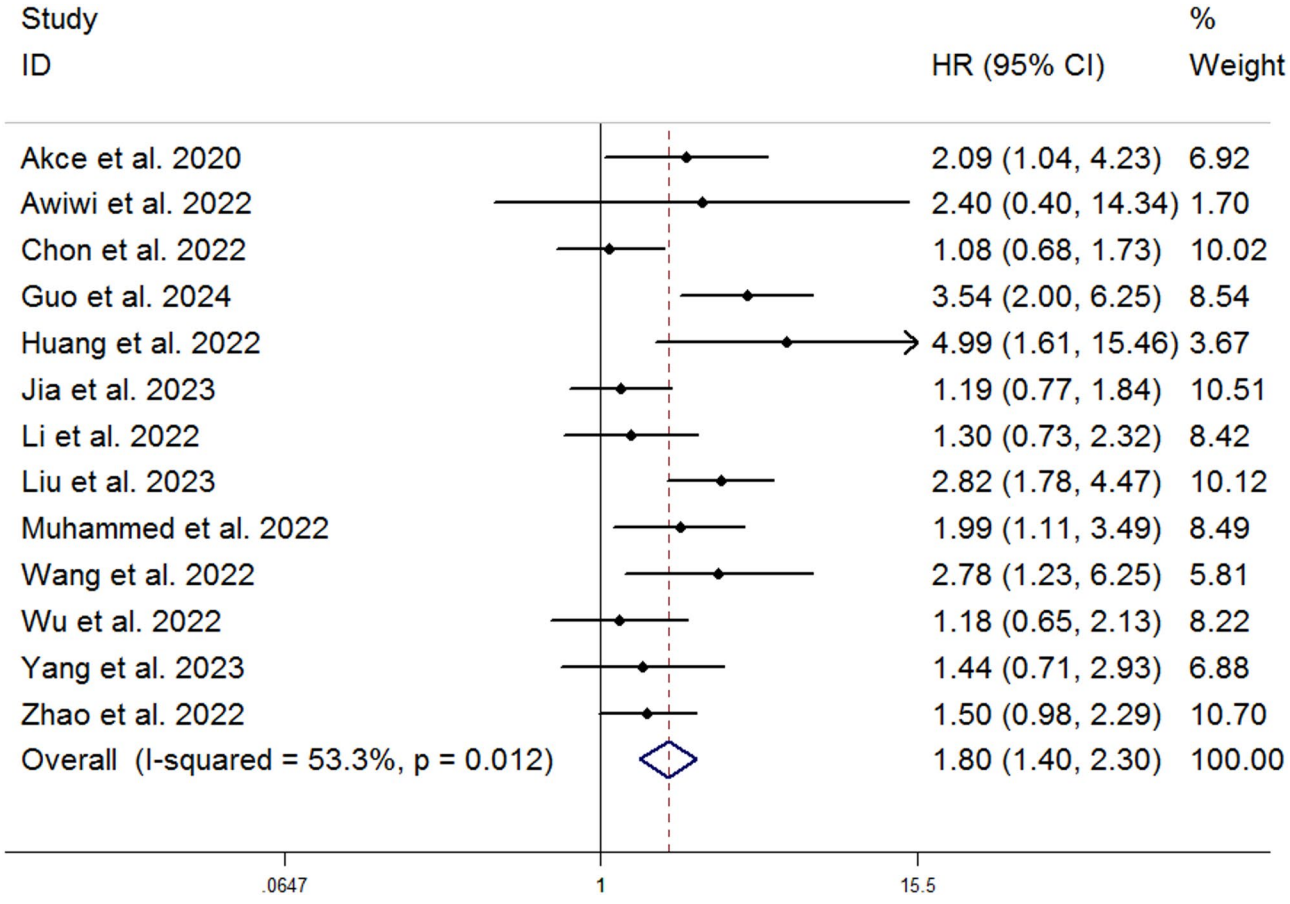

Fig. 3 Forest plots of studies evaluating the association between high PLR and PFS

Publication bias and sensitivity analyses

Publication bias was assessed using a funnel plot, Begg's test, and Egger's test. The symmetrical shape of the funnel plots for the impact of PLR on OS and PFS indicated no potential publication bias in these studies, as depicted in Fig. 4. This finding was corroborated by the results of Begg's test and Egger's test. The analysis in Figs. 5 and 6 revealed that there was no significant publication bias in the studies concerning PLR and pooled OS (Begg's test, $P = 0.087$; Egger's test, $P = 0.155$) and PFS (Begg's test,

Table 3 Subgroup analyses of PFS

Subgroup	NO. of studies	HR (95% CI)	*P*	Heterogeneity		Model
				I^2 (%)	Ph	
Country						
China	8	2.00 (1.42–2.80)	<0.001	63	0.008	Random
Other	5	1.44 (1.09–1.91)	0.01	11.4	0.341	Random
Combination therapy						
Yes	8	1.63 (1.19–2.22)	0.002	49.3	0.054	Random
NO	5	2.11 (1.38–3.22)	0.001	60.4	0.039	Random
Cuf–off						
≥ 140	8	1.86 (1.33–2.58)	<0.001	54.3	0.032	Random
< 140	5	1.73 (1.14–2.63)	0.011	61.2	0.036	Random
Sample size						
> 120	4	1.38 (1.08–1.77)	0.011	1.4	0.385	Random
< 120	9	2.11 (1.51–2.94)	<0.001	54.6	0.024	Random
Analysis						
Univariate	6	1.48 (1.10–1.99)	0.009	52.1	0.064	Random
Multivariate	7	2.25 (1.72–2.95)	<0.001	36	0.153	Random

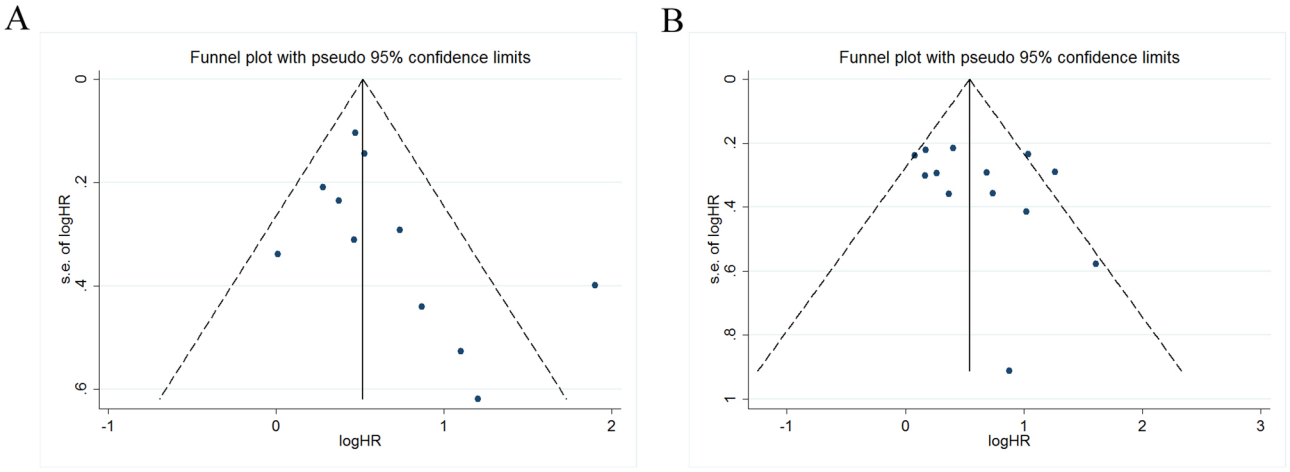

Fig. 4 Funnel plot. Correlation of high PLR with OS (**A**) and PFS (**B**)

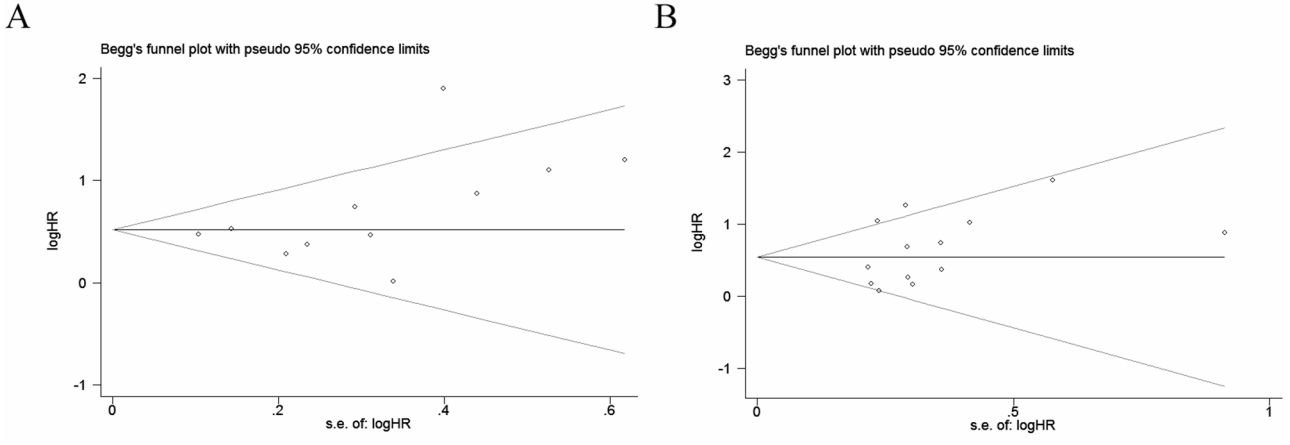

Fig. 5 Begg's publication bias funnel plots. Correlation of high PLR with OS (**A**) and PFS (**B**)

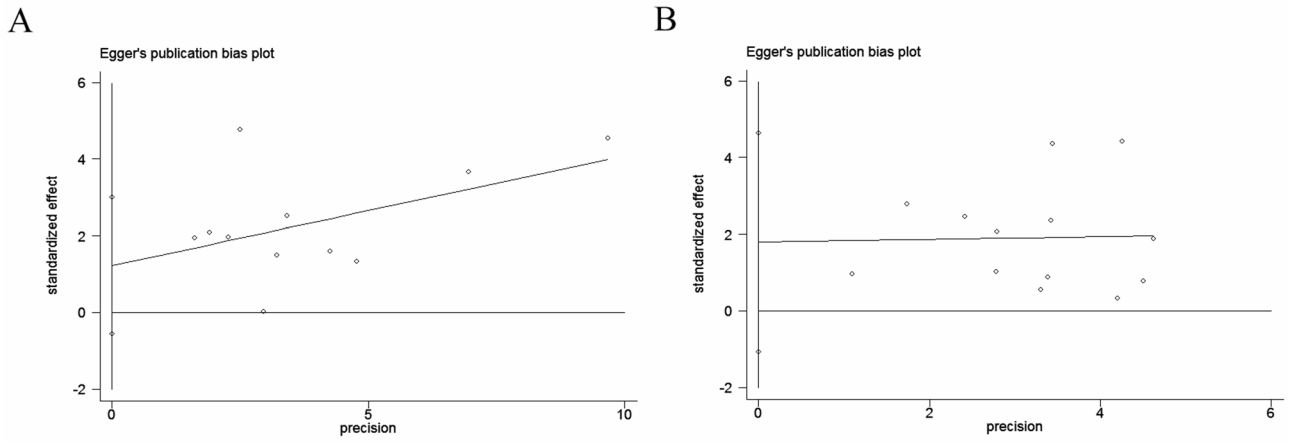

Fig. 6 Egger's publication bias funnel plots. Correlation of high PLR with OS (**A**) and PFS (**B**)

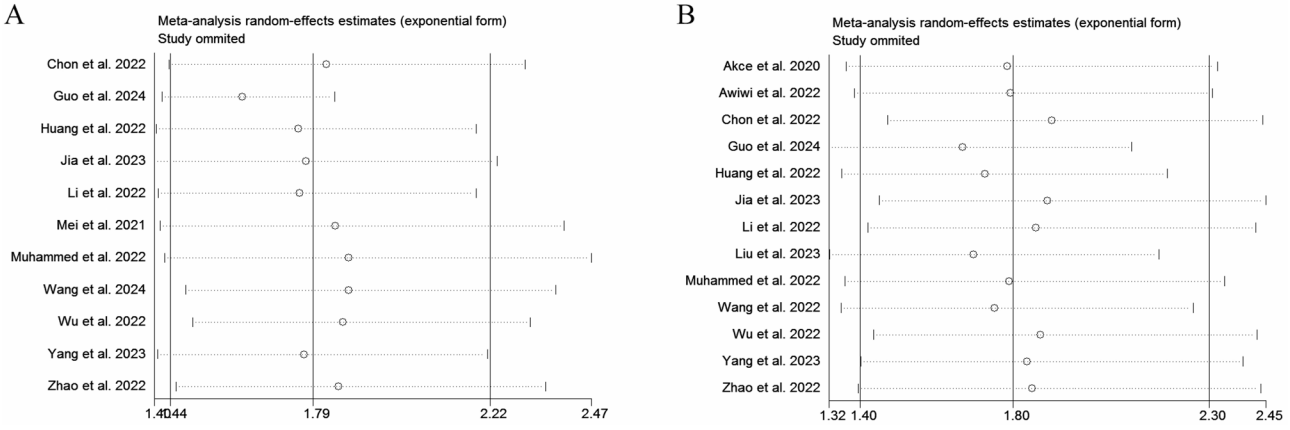

Fig. 7 Sensitivity analysis for the meta–analysis. Correlation of high PLR with OS (**A**) and PFS (**B**)

$P = 0.360$; Egger's test, $P = 0.195$). Sensitivity analysis, illustrated in Fig. 7, demonstrated that the pooled HR remained consistent even when individual studies were each removed from the analysis.

Discussion

In recent years, immunotherapy, particularly ICIs such as nivolumab and pembrolizumab, has shown promising therapeutic effects in advanced HCC patients [50]. Although clinical outcomes can vary among different patients, the search for effective biomarkers as targets for therapy remains essential for predicting the optimal response to immunotherapy. PLR is a widely studied pre–treatment hematological biomarker that may reflect the balance between inflammation and immune status. Studies have demonstrated that PLR can serve as an adverse prognostic factor in both localized and metastatic HCC [51, 52], as well as in various other types of cancer treated with ICIs [28–30]. However, the role of PLR as a prognostic marker in HCC patients receiving immunotherapy remains a topic of debate.

This meta–analysis, comprising 15 articles involving 2323 patients, explored the association between PLR and prognosis in HCC patients undergoing treatment with ICIs. The findings showed that high PLR levels in HCC patients were linked to shorter overall survival and PFS after immunotherapy. Subgroup analyses based on cut–off values, sample sizes, regions, types of therapy, and methods of Cox regression analysis yielded consistent results with the pooled findings. These results suggest that increased PLR may serve as an independent prognostic indicator for HCC patients treated with ICIs.

The link between inflammation and cancer has been extensively studied [53]. Pro–inflammatory factors are released from tumour cells and systemic inflammation promotes the proliferation, migration, and invasion of tumour cells by inhibiting apoptosis and promoting angiogenesis [54, 55]. One common and straightforward method to measure this connection is through a basic blood test which can determine the PLR. Patients with high PLR levels often exhibit thrombocytosis and/or lymphopenia. Tumour–associated platelets release growth factors and small molecules such as ADP, serotonin, and

thromboxane A_2 (TXA_2), which facilitate tumour growth and invasion (51). Activated platelets can also extravasate into the tumour microenvironment via focal adhesion kinase (FAK) to fuel tumour growth [56]. Lymphocytes are crucial for the body's immune defense against cancer, and a decrease in lymphocytes is typically seen as a sign of weakened immunity [57]. Lymphocytes are essential elements of both the innate and adaptive immune systems, forming the cellular foundation of immune surveillance and response mechanisms. The interaction between CD8 + and CD4 + T–lymphocytes can trigger tumor cell apoptosis within the immune system's antitumor response [58]. A high PLR indicates elevated platelet levels, while low levels of lymphocytes are linked to increased tumor invasion and metastasis, leading to poorer survival rates. Recent studies have suggested that the movement of the PD–L1 protein from tumor cells to platelets may restrict the infiltration of CD4 + and CD8 + T lymphocytes [59]. Platelet levels in the bloodstream might reflect the presence of PD–L1 on tumors, potentially reducing the effectiveness of ICIs. These findings offer insights into the potential use of PLR as a prognostic marker for the success of immunotherapy.

Although PLR has shown good prognostic value in HCC patients receiving ICI treatment, its clinical application needs to be compared and discussed together with other known biomarkers. Indicators such as PD–L1 expression, tumor mutation burden (TMB), and microsatellite instability (MSI) have been incorporated into the treatment modalities of various cancers, but they often rely on expensive and tissue–based tests. Compared with these methods, PLR has obvious advantages. It is non–invasive, low–cost, and based on blood routine tests, allowing for repeated dynamic monitoring. Moreover, it has wider applicability in resource–poor environments. However, the non–specific characteristics of PLR also limit its application. It may be affected by infection, chronic inflammation or liver dysfunction unrelated to malignant tumors, and its value as an independent biomarker may be limited. However, PLR can serve as a useful adjunct to other prognostic factors or as part of a comprehensive prognostic model, especially when molecular testing is not feasible. Future studies should compare PLR with established biomarkers and evaluate its role in patient selection, risk stratification or treatment monitoring during immunotherapy.

There were several limitations to this meta–analysis. Firstly, the majority of the studies included were conducted in Asia, with only four conducted in Europe, which may affect the extrapolation of the results. Second, inconsistencies were noted in the cutoff values used across studies. The lack of standardized cutoff points and unclear methods for establishing them in many studies added to this limitation. Although we pooled the results according to PLR > 140 in the subgroup analysis, bias may exist because using diverse cut–off values potentially lead to different conclusion in the same study, which may influence the pooled results of this analysis. Third, most enrolled studies were retrospective studies with non–randomized design, which may lead to bias in the results. Although we used hazard ratios from multivariable models when available, the adjusted covariates were not consistent across studies, which may affect the comparability of pooled effect estimates.

Moreover, despite conducting subgroup analyses, the presence of moderate heterogeneity (I^2 = 49.5% for OS, 53.3% for PFS) warrants discussion. Several potential sources of heterogeneity were identified across the included studies. The cut–off values for PLR varied widely (96.42–300), which may affect the stratification of patients into prognostic groups. Second, treatment regimens differed across studies, including anti–PD–1 monotherapy, atezolizumab plus bevacizumab, and ICIs combined with TKIs or TACE, each with different mechanisms and efficacies. Third, baseline patient characteristics such as the underlying etiology of HCC (HBV–related vs. non–HBV), disease stage, and prior systemic or locoregional treatments were often inconsistently reported, limiting cross–study comparability. The follow–up durations varied substantially, potentially affecting survival outcome reporting.

While the subgroup analyses based on treatment strategy, country, cut–off value, and sample size, we acknowledge that the data reported in many studies were insufficient to perform formal meta–regression analyses to quantify the effect of these covariates. Therefore, this limitation has been explicitly noted. Future studies providing more granular individual–level data may allow for a more refined exploration of heterogeneity using meta–regression models.

An additional source of heterogeneity and limitation to the clinical utility of PLR lies in the lack of a standardized cut–off value across studies. In this meta–analysis, PLR thresholds ranging from 96.42 to 300. This variability complicates the interpretation of what constitutes a "high" versus "low" PLR, and limits direct comparisons between studies. To explore the impact of cut–off variability, we conducted a subgroup analysis using 140 as a threshold, which was close to the median of the reported cut–off values among the included studies. We acknowledge that this threshold was selected empirically and lacks a unified biological or clinical rationale. Given these challenges, future studies are encouraged to adopt more consistent methods to define PLR thresholds, potentially through ROC curve analysis, percentile–based standardization.

Although all included studies were deemed high quality based on NOS scoring, the reliance on a summary score

may obscure specific methodological limitations. Some studies lacked explicit multivariate adjustment for known prognostic variables, potentially introducing confounding bias. The details on blinding of outcome assessment and handling of incomplete follow–up data were often absent. Use of the QUIPS tool in future meta–analyses may offer a more rigorous and tailored approach to bias evaluation in prognostic factor research.

The PLR as a simple and feasible potential biomarker, helps to evaluate the prognosis of HCC patients treated with ICIs. Its low cost and non-invasive features make it promising in environments lacking advanced molecular diagnostics. Nevertheless, the lack of standardized thresholds and limited understanding of its biological basis remain the most significant challenges at present. Future research should focus on validating PLR in prospective cohorts and exploring its integration with other biomarkers. In the coming years, PLR may become part of a broader study guiding individualized immunotherapy strategies for HCC.

Conclusion

In summary, our study results suggest that PLR may serve as a potential prognostic indicator of OS and PFS in HCC patients treated with ICIs. Elevated PLR levels are associated with poorer survival outcomes. Given that PLR is low–cost and easy to measure, it could be widely utilized for risk stratification in HCC patients undergoing ICIs treatment following validation in large prospective studies.

Abbreviations

PLR	Platelet–to–Lymphocyte Ratio
HCC	Hepatocellular Carcinoma
ICIs	Immune checkpoint inhibitors
HRs	Hazard ratios
CIs	Confidence intervals
OS	Overall survival
PFS	Progression–free survival
PD–1	Anti–programmed cell death–1
TMB	Tumor mutational burden
LMR	Lymphocyte–to–monocyte ratio
NLR	Neutrophil–to–lymphocyte ratio
CRP	C–reactive protein
NOS	Newcastle–Ottawa Quality Assessment Scale
TXA_2	Thromboxane A_2
FAK	Focal adhesion kinase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04028-1.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We are grateful for the useful comments and suggestions from anonymous referees.

Author contributions

Q.Z. and Y.S. were responsible for conceptualization, methodology, software, formal analysis, resources, data curation, writing-original draft, writing-review and editing, project administration, supervision; Z.J. and Q.W. were responsible for methodology, investigation, resources, data curation, visualization; L.Y. and T.Y. were responsible for methodology, data curation, writing-original draft, writing-review and editing; P.L. and Y.S. were responsible for conceptualization, methodology, writing-original draft, writing-review and editing, project administration.

Funding

This study was supported by the Provincial Clinical Key Specialty Construction Project (Traditional Chinese Medicine) "Gastroenterology" of Fujian Provincial Health Commission in 2023 ([2023]1163) and the construction project for the Traditional Chinese Medicine Inheritance Studio at Fujian University of Traditional Chinese Medicine ([2023]56).

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

As a meta–analysis, our paper did not require any referral to our institutional clinical ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 11 December 2024 / Accepted: 23 May 2025
Published online: 06 June 2025

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