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REVIEW

The association between immunoinflammatory biomarkers NLR, PLR, LMR and nonalcoholic fatty liver disease: a systematic review and meta-analysis

Yunyi Yang[1] · Xiaoli He[1] · Shufa Tan[2] · Xiaoxiao Qu[1] · Weijin Huang[1] · Jiayuan Cai[1] · Jiawen You[1] · Xinyi Fu[1] · Yanming He[1] · Hongjie Yang[1]

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disorder closely linked to metabolic syndrome. Identifying novel, easily measurable biomarkers could significantly enhance the diagnosis and management of NAFLD in clinical settings. Recent studies suggest that immunoinflammatory biomarkers—specifically, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR)—may offer diagnostic value for NAFLD. However, the effectiveness of these biomarkers has not been comprehensively assessed in this patient population. This systematic review and meta-analysis aimed to evaluate the association between these immunoinflammatory biomarkers and NAFLD. As of August 8, 2024, databases including PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus were systematically searched to compare NLR, PLR, and LMR levels in NAFLD patients and healthy controls. Study quality was assessed using the Newcastle–Ottawa Scale, and standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated (PROSPERO registry number: CRD42024580812). A total of 20 studies were included in the meta-analysis. Results indicated that NAFLD patients had significantly higher NLR levels (SMD = 0.43; 95% CI 0.28–0.58; $p < 0.001$) and lower PLR levels (SMD = − 0.29; 95% CI − 0.41 to − 0.17; $p < 0.001$) compared to controls. However, no significant difference in LMR was observed between NAFLD patients and controls(SMD = 0.08; 95% CI − 0.00 to 0.17; $p = 0.051$). These findings suggest that NLR and PLR may hold promise as diagnostic markers for NAFLD, while LMR appears to have limited diagnostic utility. Further research is warranted to explore the potential role of these biomarkers in tracking disease progression.

Keywords NAFLD · Fatty liver · NLR · PLR · LMR

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
LMR	Lymphocyte-to-monocyte ratio
NOS	Newcastle–ottawa scale
SMDs	Standardized mean differences
CIs	Confidence intervals
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
NASH	Non-alcoholic steatohepatitis
OSAHS	Obstructive sleep apnea–hypopnea syndrome
MELD	Model for end-stage liver disease

Yunyi Yang and Xiaoli He have been contributed equally to this work and should be considered as co-first authors.

✉ Yanming He
heyanming176@163.com

✉ Hongjie Yang
yueyangnfm@163.com

[1] Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, No. 110 Ganhe Road, Shanghai 200437, China

[2] Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a pathological condition marked by the abnormal accumulation of fat within liver cells, without involvement of alcohol or other

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specific liver-damaging agents [1, 2]. NAFLD often coexists with metabolic syndrome, a collection of metabolic issues such as insulin resistance, obesity, high blood pressure, and dyslipidemia [3, 4]. In recent years, NAFLD has become a major factor contributing to the global burden of liver disorders. Current research indicates that NAFLD affects around 25.24% of people worldwide, with the highest rates found in the Middle East and South America, and the lowest in Africa [5]. Furthermore, NAFLD greatly elevates the likelihood of progression to liver fibrosis, cirrhosis, and hepatocellular carcinoma, thus posing a significant global public health concern [6, 7].

Despite significant advancements in research on NAFLD, its exact pathophysiological mechanisms remain only partially understood. Nonetheless, increasing evidence points to immune-mediated inflammation as a key factor in both the onset and progression of NAFLD [8–10]. Within this framework, several immunoinflammatory markers, such as the NLR, PLR, and LMR, have attracted substantial interest in recent years. These markers offer insight into the complex relationship between immune responses and inflammation [11, 12]. Elevated NLR, PLR, and LMR have been identified in a variety of inflammation-related diseases, including cardiovascular disorders, thyroid conditions, colorectal cancer, lymphoma, and bladder cancer [13–18].

In individuals with NAFLD, alterations in these inflammatory biomarkers may reflect the extent of both inflammation and immune response. These variations are frequently linked to the severity of hepatic fibrosis, liver dysfunction, and the potential for disease advancement [19, 20]. Although many studies have examined the correlation between NLR, PLR, LMR, and NAFLD, the results have been inconsistent [21–25]. Discrepancies in findings may be attributed to differences in sample sizes, ethnic diversity, and research methods across studies [26].

In light of these uncertainties, this systematic review and meta-analysis aim to thoroughly evaluate and integrate existing data to examine the associations between NLR, PLR, LMR, and NAFLD. The goal of this study is to enhance the early detection and management of high-risk patients, thereby contributing to improved clinical outcomes.

Materials and methods

This research was carried out in full compliance with the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [27].

Search strategy

A comprehensive search was conducted across PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus databases, encompassing all relevant studies published from the inception of each database through August 8, 2024. The search utilized the following terms: "NAFLD," "nonalcoholic fatty liver disease," "non-fatty liver disease," "neutrophil-to-lymphocyte ratio" (NLR), "platelet-to-lymphocyte ratio" (PLR), and "lymphocyte-to-monocyte ratio" (LMR). To ensure thoroughness, we combined key terms with medical subject headings (MeSH). Additionally, this review was registered with PROSPERO under registration number CRD42024580812.

Selection criteria

We utilized the PICOS framework (Population, Intervention, Comparator, Outcome, and Study Design) to identify relevant studies:

- Population: Adults (aged 18 and older) diagnosed with non-alcoholic fatty liver disease (NAFLD), including all stages such as simple steatosis (NAFL), non-alcoholic steatohepatitis (NASH), and advanced fibrosis.
- Intervention: Measurement of NLR, PLR, or LMR through peripheral blood samples using standard clinical laboratory methods.
- Comparator: NAFLD patients compared to individuals without NAFLD.
- Outcome: Evaluation of biomarker levels and their relationship with the presence and progression of NAFLD, particularly regarding hepatic fibrosis.
- Study Design: Retrospective, prospective, and cross-sectional research designs.

Inclusion criteria:

1. Studies involving participants aged 18 and above.
2. Diagnosis of NAFLD verified through imaging (ultrasound, MRI, CT), liver biopsy, or validated non-invasive scoring methods.
3. Studies providing data on at least one of the biomarkers (NLR, PLR, or LMR).

Exclusion criteria:

1. Participants with significant alcohol intake (> 30 g/day for men, > 20 g/day for women).
2. Studies addressing secondary causes of liver disease, such as viral hepatitis, autoimmune hepatitis, drug-induced liver injury, or hereditary liver disorders.
3. Animal studies.
4. Publications categorized as reviews, opinions, case reports, case series, editorials, or letters.

Data extraction and quality assessment

Two independent reviewers evaluated the titles and abstracts of the identified studies to determine their eligibility according to the inclusion and exclusion criteria. Any disagreements between the reviewers were settled through discussion, and if necessary, a third reviewer was consulted to make the final decision. Studies that passed the initial screening underwent a full-text review, and those that satisfied all the criteria were included in the meta-analysis.

The data extracted from each study included the following: author, publication year, country, study design, sample size, NAFLD stage, characteristics of the control group, and the mean values with standard deviations for NLR, PLR, and LMR. Any discrepancies in data extraction were resolved in collaboration with a third reviewer.

The quality of the included studies was evaluated using the Newcastle–Ottawa Scale (NOS) [28], which assesses studies based on three key domains: selection (study population, representativeness, and inclusion criteria), comparability (control of confounding factors), and outcome/exposure (methods of measurement and adequacy of follow-up). The NOS assigns scores ranging from 0 to 9, with higher scores reflecting better study quality. Any disagreements encountered during the quality assessment process were resolved by reaching a consensus with the involvement of a third reviewer.

Statistical analysis

We calculated the standardized mean difference (SMD) and its 95% confidence interval (CI). SMD is used to quantify the difference between two groups (e.g., NAFLD vs. non-NAFLD) in standard deviation units. This allows for meaningful comparisons between studies, even if they use different measurement scales. an SMD of 0.2 usually indicates a small difference, 0.5 indicates a moderate difference, and 0.8 or higher indicates a large difference. Forest plots were also drawn to assess potential differences in NLR, PLR, and LMR values between NAFLD patients and non-NAFLD populations (significance level set at $p < 0.05$). For studies that provided data in the form of medians with interquartile ranges or medians with ranges, established techniques were applied to convert these figures into means and standard deviations [29].

Heterogeneity was evaluated using the Q statistic, with a significance threshold set at $p < 0.10$. In instances of significant heterogeneity, a random-effects model was applied [30]. To assess the reliability of the meta-analysis results, sensitivity analyses were performed. Publication bias was examined using Egger's test, and funnel plots were employed for visual inspection of any bias.

Subgroup analyses were also performed to investigate the relationship between effect sizes and factors such as study design, geographic location, and the presence of comorbid conditions. All statistical analyses were carried out using Stata 17 software (Stata Corporation, College Station, TX, USA) to ensure the precision and reliability of the data.

Results

Literature selection and inclusion of study characteristics

Figure 1 presents the PRISMA flowchart detailing the study selection process. Out of an initial set of 1591 articles, 820 were removed due to duplication. A thorough screening of the remaining 771 articles led to the exclusion of irrelevant studies, resulting in 20 studies with a low risk of bias being included in the final analysis [21, 23, 25, 31–47].

Table 1 outlines the main characteristics of the studies included, which involved a total of 25,252 individuals diagnosed with NAFLD and 41,940 control subjects without NAFLD. The research was conducted across various countries, with the majority of studies originating from China [23, 25, 34, 39–41, 43–45], followed by the United States [21, 46], Turkey [31, 33], and Egypt [32, 35]. Additional studies were carried out in Poland [36], Mexico [37], Iran [38], South Korea [47], and Romania [42].

Regarding study design, 9 studies were cross-sectional [21, 23, 33, 34, 38–41, 45], 9 were retrospective [25, 31, 36, 37, 42–44, 46, 47], and 2 were prospective [32, 35]. A total of 17 studies [21, 23, 25, 31–37, 39, 40, 42–46] examined NLR levels in both NAFLD patients and control groups, while 12 studies [21, 23, 25, 36, 37, 39–41, 43, 45–47] compared PLR levels, and 7 studies [21, 23, 38–40, 45, 47] analyzed LMR levels.

The quality of the included studies was assessed using the NOS, with most studies receiving scores between 6 and 8, indicating that the research was of moderate to high methodological quality.

NLR

Seventeen studies [21, 23, 25, 31–37, 39, 40, 42–46] provided data on NLR values, encompassing 30,419 NAFLD patients and 19,705 individuals without NAFLD. Due to significant heterogeneity among these studies ($I^2 = 98\%$, $p < 0.001$), a random-effects model was applied for the analysis (Fig. 2). The pooled analysis showed that NLR levels were significantly elevated in NAFLD patients compared to non-NAFLD individuals (SMD = 0.43; 95% CI = 0.28–0.58, $p < 0.001$).

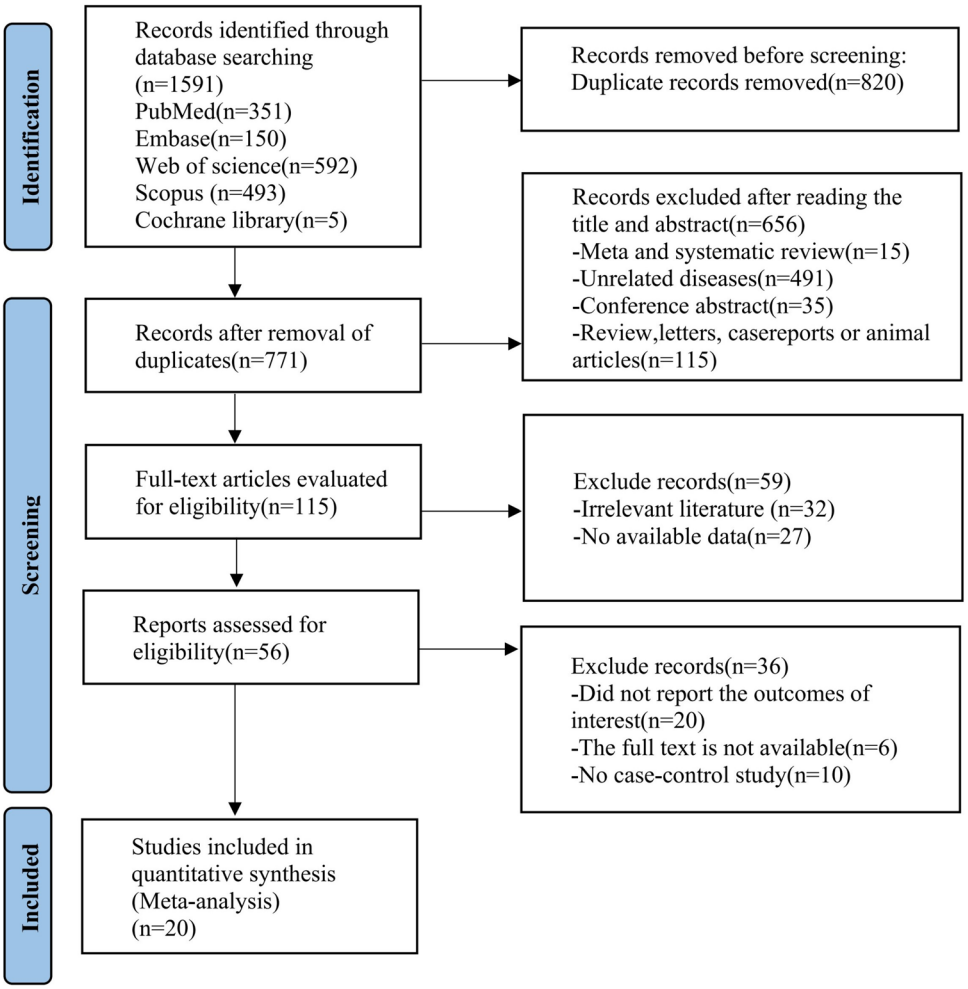

Fig. 1 The PRISMA flow chart summarizing the literature search, and study selection process

Four studies[32, 34, 44, 46] specifically explored the progression from NAFLD to NASH or advanced liver fibrosis. While some studies reported significant increases in NLR (Supplementary Fig. 1), the overall effect size was not statistically significant (SMD = 0.76; 95% CI = − 0.34 to 1.85). Sensitivity analyses excluding various studies revealed minimal fluctuations in pooled effect sizes and confidence intervals, demonstrating the robustness of the findings (Supplementary Fig. 2).

Subgroup analyses based on geographic regions indicated that Turkey (SMD = 0.89, 95% CI = − 0.24 to 2.01; $I^2 = 90.3\%$, $p < 0.001$), Egypt (SMD = 2.55, 95% CI = − 0.80 to 5.91; $I^2 = 99.5\%$, $p < 0.001$), China (SMD = 0.07, 95% CI = − 0.08 to 0.22; $I^2 = 97.0\%$, $p < 0.001$), the USA (SMD = 0.14, 95% CI = 0.07 to 0.21; $I^2 = 80.3\%$, $p = 0.024$), and other regions (SMD = 0.25, 95% CI = − 0.15 to 0.65; $I^2 = 75.7\%$, $p = 0.016$; Fig. 3A). The overall pooled effect size remained significant (SMD = 0.43, 95% CI = 0.28 to 0.58), though substantial heterogeneity existed across regions and countries.

Furthermore, significant overall effect sizes were identified across various study designs, including retrospective studies (SMD = 0.18, 95% CI = 0.01 to 0.34; $I^2 = 88.5\%$, $p < 0.001$), prospective studies (SMD = 2.55, 95% CI = -0.80 to 5.91; $I^2 = 99.5\%$, $p < 0.001$), and cross-sectional studies (SMD = 0.14, 95% CI = -0.01 to 0.29; $I^2 = 97.4\%$, $p < 0.001$). The overall effect size remained significant (SMD = 0.43, 95% CI = 0.28 to 0.58; $I^2 = 98.0\%$, $p < 0.001$; Fig. 3B).

When dividing NAFLD patients based on the presence of comorbidities, the combined effect size was significant in those without comorbidities (SMD = 0.48, 95% CI = 0.32 to 0.64), while it was not significant in those with comorbid conditions (SMD = 0.01, 95% CI = − 0.52 to 0.53). The overall pooled effect size was SMD = 0.43 (95% CI = 0.28 to 0.58), which was statistically significant (Fig. 3C). Lastly, Egger's test did not indicate significant publication bias ($p = 0.071$; Fig. 4), suggesting no major publication bias.

Table 1 Baseline characteristics of the included studies

First author	Year	Study area	Design	Diagnostic method	Control			Case			NOS score
						N	NLR PLR LMR (Mean ± SD)		N	NLR PLR LMR (Mean ± SD)	
Yilmaz H	2015	Turkey	Retrospective	Biopsy	healthy population	35	1.90 ± 0.70 NR NR	NASH	38	3.44 ± 1.29 NR NR	8
Abdel-Razik A	2016	Egypt	Prospective	Imaging (Ultrasound)	healthy population	150	1.8 ± 0.8 NR NR	NASH	120	2.6 ± 1.1 NR NR	8
								NAFLD	753	1.9 ± 0.7 NR NR	
Kahraman NK	2016	Turkey	Cross-section	Imaging (Ultrasound)	T2DM	38	1.6 ± 0.37 NR NR	T2DM + NAFLD	32	1.9 ± 1.33 NR NR	7
Chen J	2019	China	Cross-section	Biopsy	healthy population	15	1.50 ± 0.48 NR NR	NASH	48	2.06 ± 0.67 NR NR	7
								NAFLD	24	2.31 ± 0.69 NR NR	
Hanafy AS	2019	Egypt	Prospective	Imaging (Ultrasound)	healthy population	100	1.6 ± 0.1 NR NR	NAFLD	272	2.97 ± 0.37 NR NR	8
Michalak A	2020	Poland	Retrospective	Imaging (Ultrasound)	healthy population	68	1.97 ± 1.09 154.88 ± 64.92 NR	NAFLD	92	3.4 ± 2.84 182.78 ± 128.93 NR	6
Purón-González E	2021	Mexico	Retrospective	Imaging (Ultrasound)	healthy population	81	1.7 ± 1.6 121 ± 43.2 NR	NAFLD	69	1.7 ± 1.8 94 ± 50.26 NR	7
Kohsari M	2022	Iran	Cross-section	The history of disease and consumption of related medication	healthy population	5214	NR NR 13.0 ± 4.7	NAFLD	1003	NR NR 13.9 ± 5.0	7
Jilin M	2022	China	Cross-section	Imaging (Ultrasound)	healthy population	1075	0.23 ± 0.10 130.06 ± 44.65 1.90 ± 0.94	NAFLD	1248	0.29 ± 0.11 120.35 ± 40.29 1.79 ± 0.70	7
Zhao Y	2022	China	Cross-section	Histological examination or imaging techniques	healthy population	3683	1.77 ± 0.59 117.22 ± 35.62 4.83 ± 1.41	NAFLD	4465	1.82 ± 0.73 93.33 ± 35.72 5.09 ± 1.78	7

Table 1 (continued)

First author	Year	Study area	Design	Diagnostic method	Control			Case			NOS score
						N	NLR PLR LMR (Mean ± SD)		N	NLR PLR LMR (Mean ± SD)	
Chen M	2022	China	Cross-section	Imaging (Ultrasound)	Non-NAFLD group	3413	1.72 ± 0.69 74.00 ± 26.47 NR	NAFLD	1085	1.71 ± 0.63 66.20 ± 20.82 NR	7
Zhou Y	2022	China	Retrospective	Imaging (Ultrasound)	Non-NAFLD group	3413	1.72 ± 0.69 74.00 ± 26.47 NR	NAFLD	1085	1.71 ± 0.63 66.20 ± 20.82 NR	7
Cucoranu DC	2023	Targu Mures	Retrospective	Imaging (CT)	Non-NAFLD group	42	2.6 ± 1.26 NR NR	NAFLD	73	2.8 ± 2.07 NR NR	5
Li X	2023	China	Retrospective	Imaging (Ultrasound)	schizophrenia (SCZ)	140	1.76 ± 0.77 122.05 ± 46.91 NR	SCZ + NAFLD	170	1.6 ± 0.67 110.28 ± 39.78 NR	6
Liu CF	2023	Taiwan, China	Retrospective	Fibroscan model	Non-NAFLD group	2474	2.1 ± 0.04 NR NR	NAFLD	1355	2.1 ± 0.04 NR NR	7
								Advanced Liver Fibrosis	162	2.2 ± 0.07 NR NR	
Liu Q	2023	China	Cross-section	Imaging (Ultrasound)	Non-NAFLD group	4540	1.61 ± 0.62 125.00 ± 41.35 5.86 ± 1.95	NAFLD	2178	1.53 ± 0.56 116.07 ± 34.8 6.27 ± 1.90	6
Chen G	2024	USA	Retrospective	FibroScan model	Non-NAFLD group	3905	2.03 ± 0.99 124.84 ± 45.25 NR	NAFLD	2504	2.13 ± 1.00 114.53 ± 41.28 NR	7
								Advanced Liver Fibrosis	267	2.30 ± 1.07 109.99 ± 47.41 NR	
Choe EK	2024	South Korea	Retrospective	Imaging (Ultrasound)	Non-NAFLD group	3676	NR 153.9 ± 53.2 6.8 ± 2.3	NAFLD	2253	NR 137.1 ± 47.7 6.7 ± 2.1	8
Liu K	2024	USA	Cross-section	US Fatty Liver Index	Non-NAFLD group	7496	2.08 ± 1.06 131.84 ± 50.07 3.99 ± 1.55	NAFLD	3325	137.1 ± 47.7 6.7 ± 2.1 2.27 ± 1.14	6
Wang G	2024	China	Cross-section	Imaging (Ultrasound)	Non-NAFLD group	2382	1.91 ± 0.87 128.1 ± 42.7 5.92 ± 1.94	NAFLD	2631	1.84 ± 0.72 122.1 ± 39.0 6.23 ± 1.96	7

NR no record

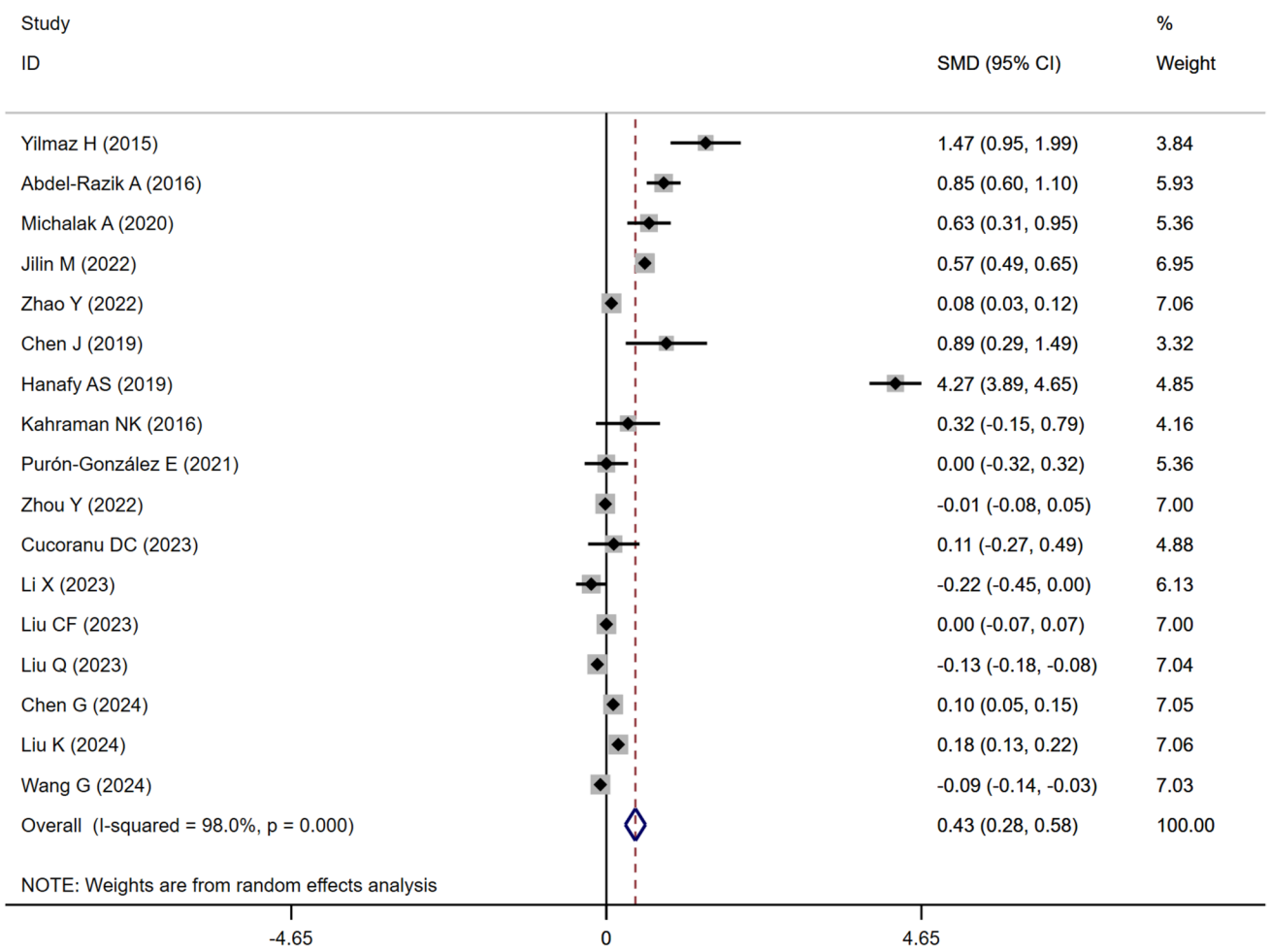

Fig. 2 Forest plot comparing NLR levels in NAFLD patients and controls

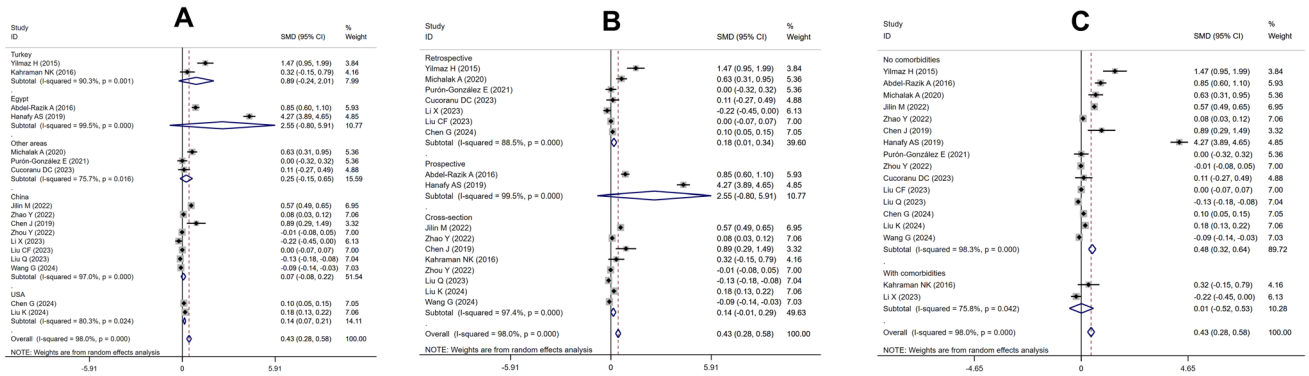

Fig. 3 Forest plot of subgroup analysis comparing NLR levels in NAFLD patients and controls. **A** regional analysis; **B** study type analysis; **C** presence of comorbidities analysis)

PLR

Twelve studies [21, 23, 25, 36, 37, 39–41, 43, 45–47] reported PLR values, covering 31,313 NAFLD patients and 20,299 controls (Table 1). The meta-analysis forest plot indicated that PLR levels were significantly lower in NAFLD patients compared to controls (SMD = − 0.29, 95% CI = − 0.41 to − 0.17; $I^2 = 97.3\%$, $p < 0.001$; Fig. 5).

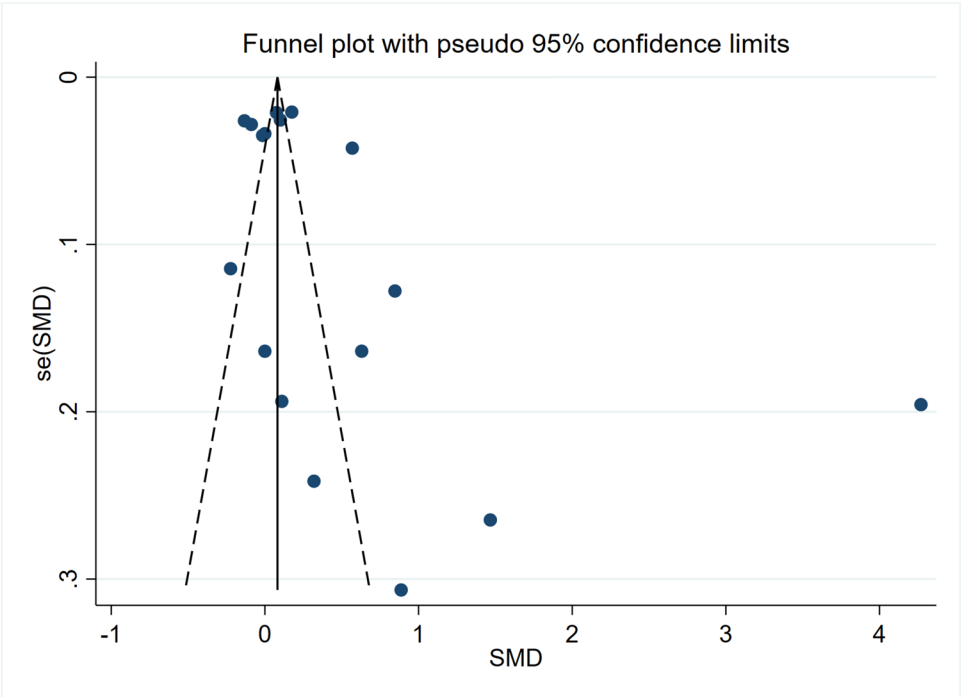

Fig. 4 Funnel plot for assessing publication bias in NLR levels

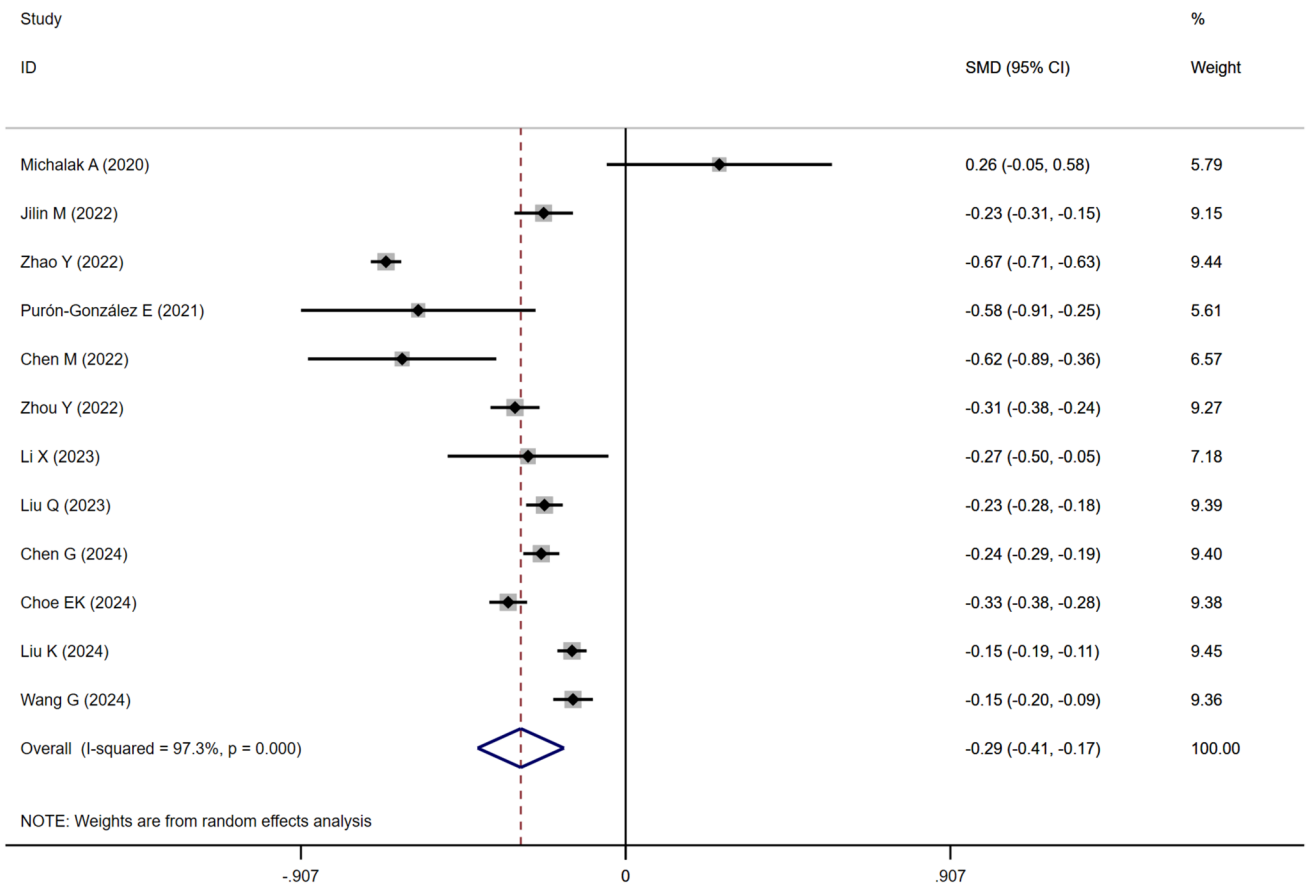

Fig. 5 Forest plot comparing PLR levels in NAFLD patients and controls

Sensitivity analyses confirmed the robustness and reliability of these results (Supplementary Fig. 3).

In the subgroup analysis based on geographic region (Fig. 6A), results were particularly significant for China (SMD = − 0.35, 95% CI = − 0.54 to − 0.16; I^2 = 98.0%, p < 0.001) and the United States (SMD = − 0.19, 95% CI = − 0.28 to − 0.11; I^2 = 85.1%, p < 0.001), demonstrating significantly lower PLR levels in NAFLD patients from these areas. In contrast, studies from other regions did not show statistically significant results (SMD = − 0.22, 95% CI = − 0.60 to 0.16; I^2 = 87.2%, p < 0.001).

When examining the effect of study design (Fig. 6B), both retrospective (SMD = -0.25, 95% CI = − 0.37 to − 0.14; I^2 = 80.7%, p < 0.001) and cross-sectional studies (SMD = − 0.33, 95% CI = − 0.51 to − 0.15; I^2 = 98.4%, p < 0.001) consistently showed a significant decrease in PLR levels among NAFLD patients. The overall effect size across all study designs (SMD = − 0.29, 95% CI = − 0.41 to − 0.17; I^2 = 97.3%, p < 0.001) highlighted a clear pattern, demonstrating the impact of study design on PLR outcomes.

Subgroup analyses also evaluated the effect of comorbidities on PLR levels. Regardless of the presence of comorbid conditions, NAFLD patients exhibited significantly lower PLR levels. In patients with comorbidities, the effect size was SMD = − 0.44 (95% CI = − 0.79 to − 0.10, p < 0.001), while in those without comorbidities, the effect size was SMD = − 0.27 (95% CI = − 0.40 to -0.14, p < 0.001) (Fig. 6C).

Finally, Egger's test for publication bias yielded a p-value of 0.833, indicating no evidence of significant bias (Fig. 7).

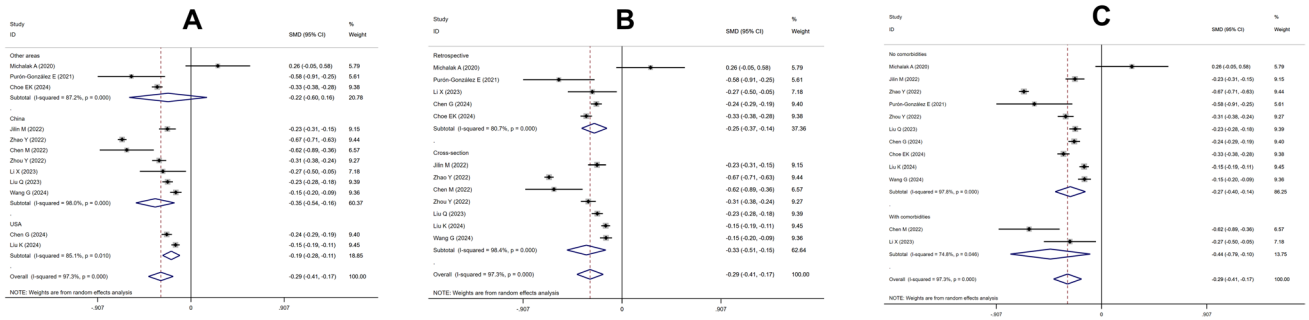

Fig. 6 Forest plot of subgroup analysis comparing PLR levels in NAFLD patients and controls. **A** regional analysis; **B** study type analysis; **C** presence of comorbidities analysis)

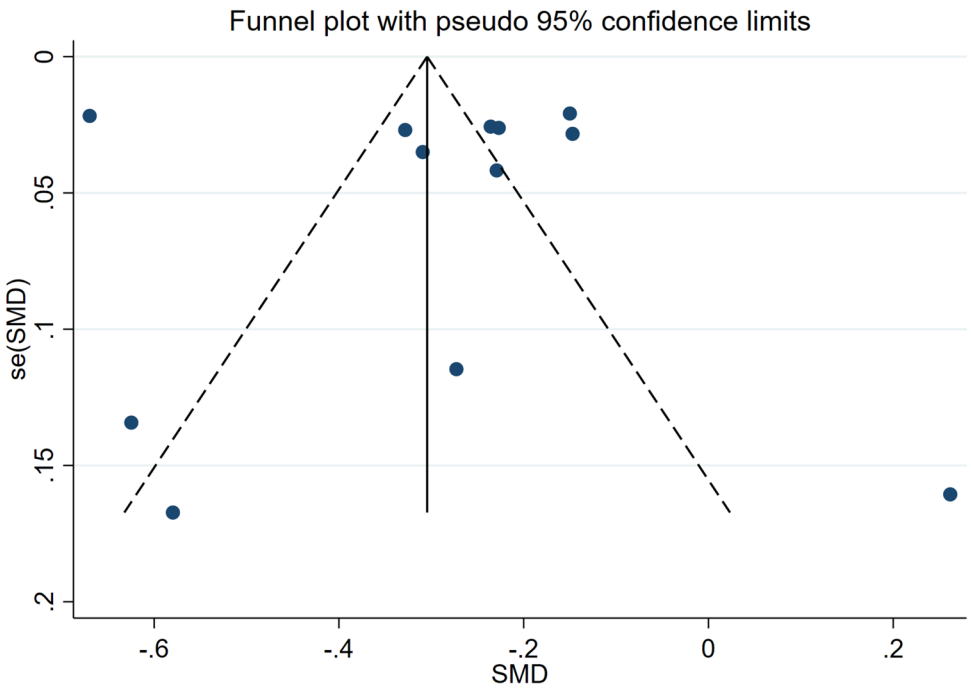

Fig. 7 Funnel plot for assessing publication bias in PLR levels

LMR

Seven studies [21, 23, 38–40, 45, 47] reported LMR values, encompassing 17,103 patients with NAFLD and 28,848 control subjects (Table 1). The forest plots presented mixed findings: while some studies [23, 38, 40, 45] showed significantly higher LMR levels in NAFLD patients compared to controls, others [21, 39, 47] either found no significant difference or reported lower LMR levels (Fig. 8). Overall, the meta-analysis did not yield statistically significant results (SMD = 0.08, 95% CI = − 0.00 to 0.17), indicating that LMR may not be a reliable biomarker for inflammation or disease progression in NAFLD patients, and its use in clinical settings should be approached cautiously. Sensitivity analyses confirmed the stability of these findings, as excluding individual studies produced minimal changes in the overall effect size (Supplementary Fig. 4).

In the subgroup analyses by region (Fig. 9), both in China and other areas, slight variations in LMR levels were observed in individual studies; however, the combined effect sizes remained statistically insignificant (SMD = 0.08, 95% CI = − 0.00 to 0.17). This suggests that LMR levels do not differ significantly between NAFLD patients and controls.

Finally, Egger's test for publication bias returned a *p*-value of 0.683, indicating no evidence of significant publication bias (Fig. 10). Although some studies reported changes in LMR, the current evidence does not support LMR as a consistent or reliable biomarker for NAFLD. Further high-quality research is needed to confirm these findings.

Discussion

This systematic review and meta-analysis aimed to evaluate the association between three immuno-inflammatory biomarkers—NLR, PLR, and LMR—and NAFLD. The results revealed that NLR levels were significantly higher in NAFLD patients compared to non-NAFLD controls. Although some studies reported an increase in NLR as NAFLD progressed to NASH or advanced liver fibrosis, the overall pooled effect size was not statistically significant, suggesting that NLR may have limited value as a marker for disease progression in NAFLD. For PLR, the analysis indicated significantly lower levels in NAFLD patients compared to controls, with this trend being especially pronounced in studies from China and the US. Sensitivity analyses confirmed the robustness of these findings. Lastly, regarding LMR, although a few studies reported elevated LMR levels in NAFLD patients compared to controls, the overall effect

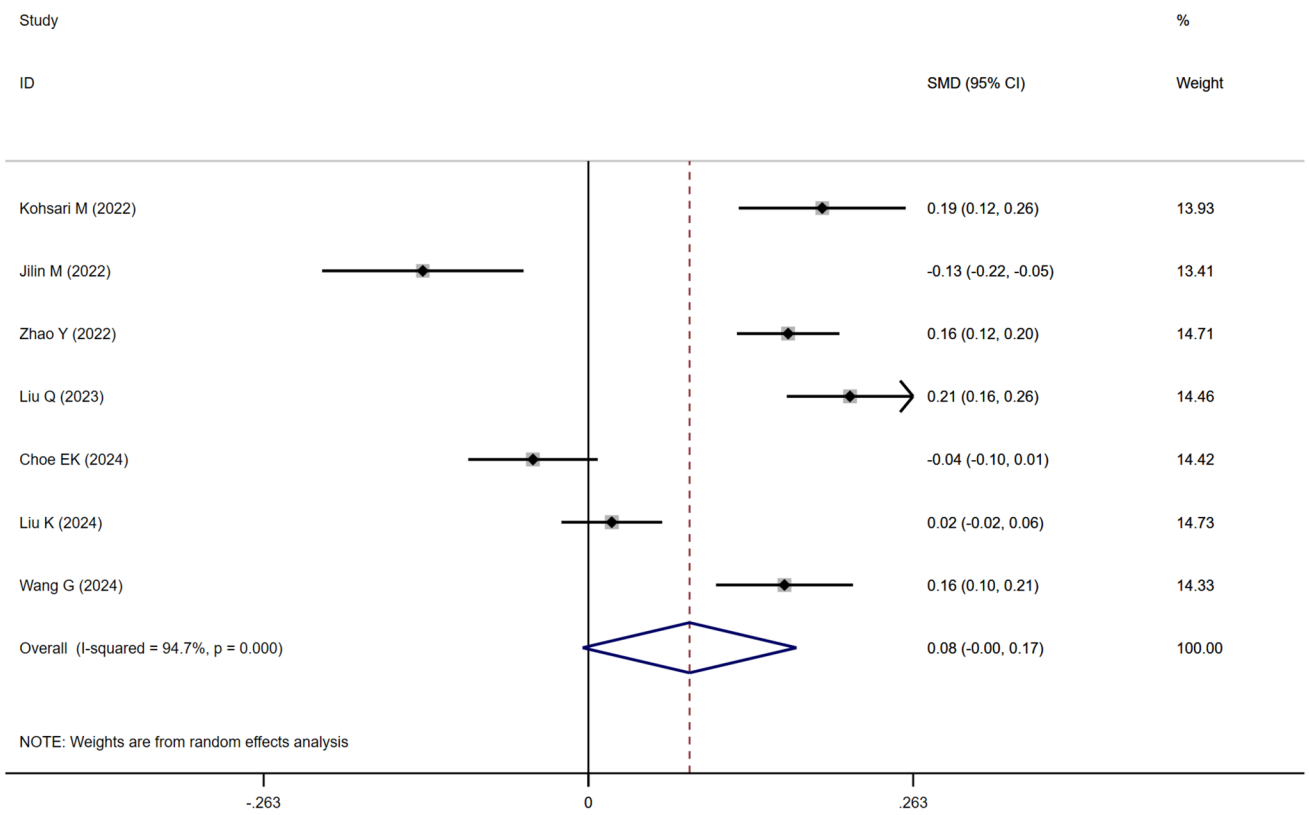

Fig. 8 Forest plot comparing LMR levels in NAFLD patients and controls

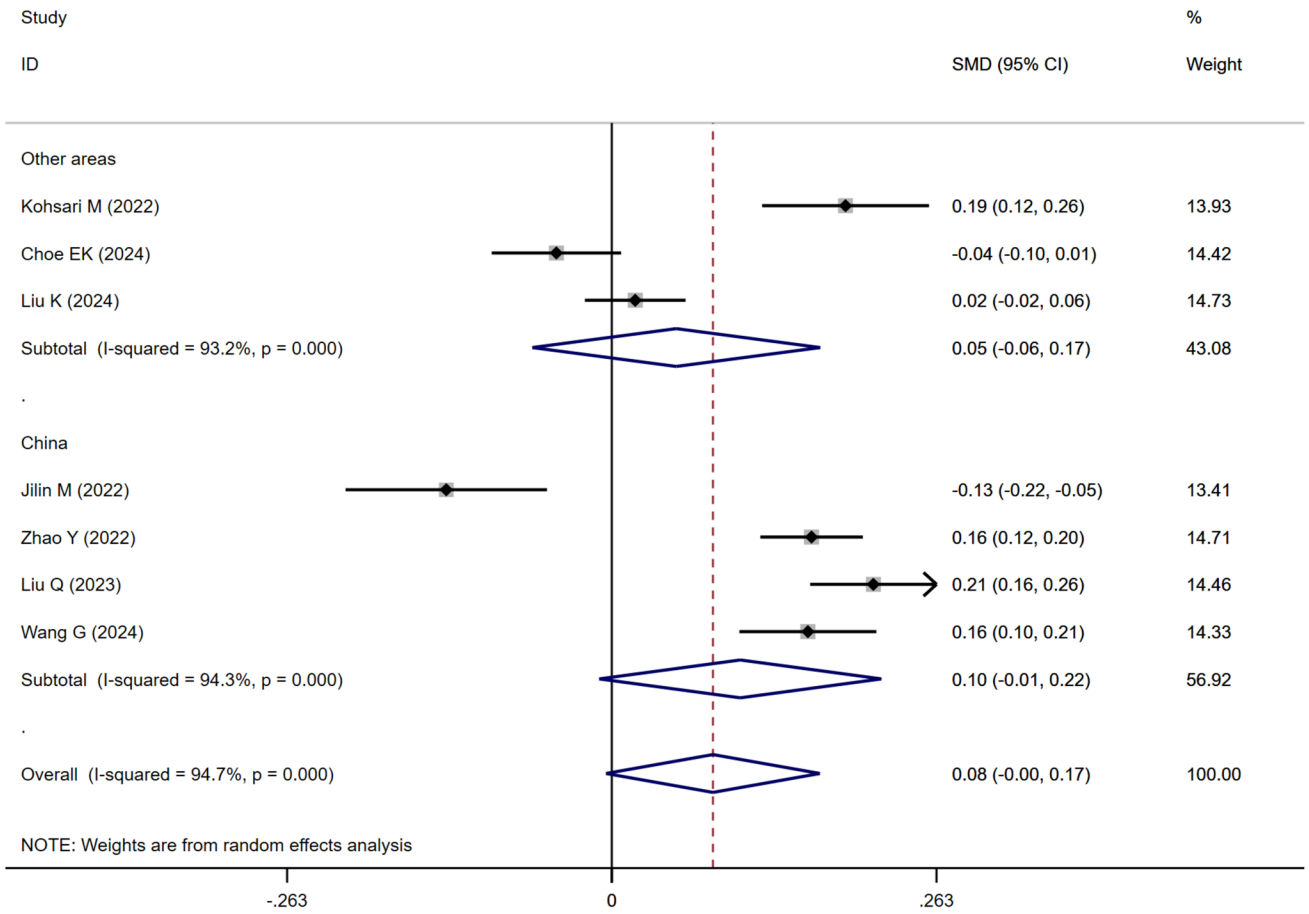

Fig. 9 Forest plot of subgroup analysis comparing LMR levels in NAFLD patients and controls

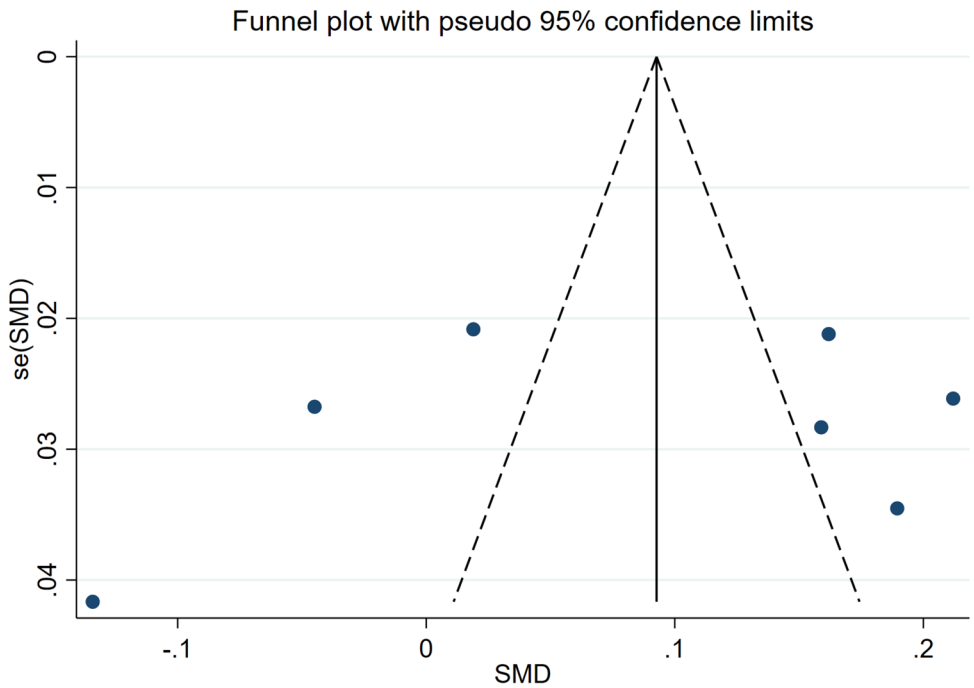

Fig. 10 Funnel plot for assessing publication bias in LMR levels

sizes did not reach statistical significance. Subgroup analyses by region also did not reveal significant differences, and sensitivity analyses further suggested that LMR has limited diagnostic utility in NAFLD.

Chronic low-grade inflammation plays a pivotal role in the development and progression of NAFLD, driven by intricate pathophysiological mechanisms influenced by both intrahepatic and extrahepatic factors. Within the liver, key contributors include mitochondrial dysfunction and disruptions in lipid metabolism, both intracellular and extracellular, which result in oxidative stress and lipotoxicity. These factors activate inflammatory pathways and induce cellular apoptosis [48]. In addition to liver-specific factors like lipotoxicity, innate immune responses, and apoptotic pathways, hepatic inflammation is also affected by extrahepatic influences such as adipose tissue dysfunction and alterations in the gut microbiota [49]. Various immune cell types are implicated in NAFLD progression, and their presence correlates with the severity of hepatic steatosis, fibrosis, inflammation, and cell damage [50]. Elevated NLR not only reflects the imbalance between pro-inflammatory neutrophils and anti-inflammatory lymphocytes but may also suggest a more complex immune response. Higher NLR levels have been associated with increased production of interleukin-6 and tumor necrosis factor-α, which are linked to bacterial translocation and elevated neutrophil counts. At the same time, activated immune cells produce cytokines and reactive oxygen species, which can impair lymphocyte function, contributing to immune dysregulation [36, 51]. Several clinical studies have demonstrated that high NLR levels are predictive of mortality in cirrhosis patients, particularly those with decompensated cirrhosis, where NLR was shown to predict bacterial infections even though it was not significantly related to the Model for End-Stage Liver Disease (MELD) score or cirrhosis stage [52–54]. Lesmana et al. [55] examined the differences in NLR values across various degrees of fatty infiltration and fibrosis using transient elastography (TE) with controlled attenuation parameter (CAP), a gold-standard diagnostic tool for assessing both fatty infiltration and fibrosis. Their study found that the mean NLR for patients with mild fatty infiltration was 1.492, while for those with moderate to severe fatty infiltration, the mean NLR increased to 2.198. In patients without significant fibrosis, the average NLR was 1.744, whereas for those with significant fibrosis, the mean NLR was 2.617. In addition, a study by Agata Michalak et al. concluded that an NLR threshold of 2.034 is optimal for diagnosing NAFLD [36]. Further research by Ahmed Abdel-Razik et al. demonstrated that the highest sensitivity and specificity for identifying NASH were achieved with an NLR threshold of 2.05 [32].

In our meta-analysis, we found that NLR levels were significantly elevated in NAFLD patients compared to healthy controls, consistent with existing literature [25, 31, 32, 34–36]. This indicates that elevated NLR is a key marker of metabolic liver disease and systemic inflammation. However, when NAFLD progressed to NASH or advanced liver fibrosis, changes in NLR levels were no longer significant, in line with previous studies [44]. This suggests that while NLR is strongly associated with the risk of NAFLD, its relationship with the progression to advanced fibrosis is less clear. Fibrosis involves a dynamic process of tissue deposition and degradation during liver injury, where the accumulation of extracellular matrix can exceed the liver's capacity to remove fibrotic tissue over time [56]. Despite this, evidence suggests that elevated NLR may accompany the shift from simple steatosis to steatohepatitis, highlighting the critical role of inflammation in these stages [57]. Furthermore, in our analysis, we conducted subgroup analyses based on comorbidities, with a particular focus on diabetes, a critical factor in the development and progression of NAFLD. Diabetes, especially type 2 diabetes, is frequently associated with insulin resistance, which not only disrupts systemic metabolism but also directly promotes hepatic fat accumulation and exacerbates inflammatory responses [58]. In diabetic individuals, these metabolic disturbances within the liver, coupled with a sustained inflammatory state, may result in more pronounced changes in NLR, making it a more sensitive biomarker for NAFLD progression. Moreover, diabetes accelerates NAFLD progression through mechanisms such as abnormal fatty acid metabolism, oxidative stress, and increased hepatic fibrosis, all of which contribute to more severe liver injury and inflammation.

In NAFLD, increased platelet activation significantly contributes to disease progression by promoting both prothrombotic and proinflammatory conditions. Platelets induce hepatic sinusoidal endothelial cells to release large quantities of chemokines, which subsequently facilitate the recruitment of neutrophils and lymphocytes, exacerbating liver damage and fostering the development of fibrosis [59, 60]. It is well known that circulating lymphocyte levels tend to decrease in inflammatory conditions [61]. Interestingly, our analysis showed that PLR was lower in NAFLD patients compared to controls without NAFLD, which contrasts with the expectation that inflammation would elevate PLR levels. This finding suggests a more complex relationship between platelet activity and immune regulation in liver disease. In NAFLD, chronic liver inflammation and fibrosis can lead to dysregulated immune responses, which might impair platelet activation [62]. This could result in lower PLR levels, despite the ongoing inflammatory processes. Additionally, platelet activation may be counterbalanced by increased lymphocyte activity or other immune system changes [63, 64]. These immune alterations, possibly driven by metabolic disturbances, insulin resistance, or oxidative stress, could play a key role in influencing PLR levels. The reduced PLR could reflect changes in platelet function or represent a

compensatory response to ongoing chronic inflammation. Previous research has indicated a U-shaped nonlinear association between PLR and NAFLD, suggesting a more intricate relationship [21]. Moreover, a study by Chen et al. [41] found a close relationship between PLR and the occurrence of NAFLD in patients with obstructive sleep apnea–hypopnea syndrome (OSAHS). Subgroup analyses showed that PLR had predictive value for NAFLD in individuals with a body mass index (BMI) below 28 kg/m^2 but not in those with a BMI of 28 kg/m^2 or higher. Conversely, Duan et al. [65] reported that PLR was not significantly associated with the development of NAFLD in obese children. Our meta-analysis aligns with previous clinical studies [25, 40, 41, 43, 45–47], suggesting that PLR may act as a protective factor in NAFLD. However, the causal relationship between PLR and NAFLD, as well as the underlying mechanisms, remains unclear and warrants further investigation. These findings emphasize the possibility that PLR's role may vary in different pathological contexts, highlighting the need for future studies to explore this complex biological mechanism more thoroughly.

Given the well-established connection between NAFLD and metabolic syndrome, we propose that NLR and PLR could be valuable tools in predicting key components of the syndrome. Both biomarkers reflect systemic inflammation and immune dysregulation, which are central to the development of metabolic disorders [21]. Specifically, NLR has been linked to insulin resistance, while PLR correlates with obesity and dyslipidemia [66, 67]. These findings suggest that NLR and PLR may not only serve as biomarkers for hepatic inflammation and fibrosis, but also as indicators of broader metabolic dysfunction in NAFLD patients. However, further studies are needed to confirm these associations and assess the clinical utility of these biomarkers in routine practice, particularly for metabolic syndrome risk stratification. The incorporation of NLR and PLR into clinical protocols could provide a more comprehensive evaluation of NAFLD, especially in patients with comorbid conditions such as obesity and type 2 diabetes.

The results of our meta-analysis indicate that NLR and PLR may have practical applications in the early diagnosis of NAFLD. Elevated NLR was strongly associated with a heightened risk of NAFLD, while lower PLR likely reflects alterations in immune regulation and platelet function within the disease context. Beyond their diagnostic utility, NLR and PLR offer promise in the early detection, risk stratification, and monitoring of NAFLD progression. These biomarkers are easily measurable through routine blood tests, which could enable clinicians to detect NAFLD in its earliest stages, particularly in high-risk populations such as individuals with obesity, metabolic syndrome, and type 2 diabetes. Early detection of NAFLD is essential, as it allows for timely intervention and lifestyle modifications that can halt disease progression. These biomarkers can complement imaging techniques like ultrasound or MRI, which primarily assess liver fat content and fibrosis, by providing valuable insights into inflammation and immune system activation. Moreover, NLR and PLR could assist in risk stratification by identifying individuals at higher risk of developing more severe forms of liver disease, such as NASH and cirrhosis. Changes in NLR and PLR are closely associated with increased liver inflammation and fibrosis, both of which are critical factors in determining disease severity and prognosis. Consequently, these biomarkers could serve as invaluable tools for guiding clinical decisions on the intensity of monitoring and the need for more aggressive therapeutic interventions. Finally, NLR and PLR could have significant implications for monitoring treatment responses in NAFLD patients. Changes in these biomarkers may reflect improvements in liver inflammation and fibrosis in response to lifestyle modifications such as weight loss, dietary changes, or increased physical activity. Moreover, NLR and PLR could serve as valuable indicators for assessing the effectiveness of pharmacological therapies, particularly those targeting insulin resistance or systemic inflammation. Thus, incorporating these biomarkers into clinical practice could optimize the diagnostic pathway, reducing reliance on invasive procedures and improving overall disease management.

In our study, LMR did not show a statistically significant association with NAFLD, which warrants further consideration. Several factors may explain this result. Firstly, variations in the study populations, such as differences in age, gender, comorbidities, or the severity of liver disease, might influence the ability of LMR to accurately reflect NAFLD. Additionally, sample size limitations in specific subgroups may have affected the statistical power of our analysis, preventing the detection of a true relationship. Another possible explanation is that LMR, although an established immuno-inflammatory biomarker, might not exhibit the same sensitivity or specificity for NAFLD as NLR and PLR. The relationship between LMR and NAFLD could be influenced by additional factors, such as the stage of liver disease or the presence of other liver pathologies, which were not fully accounted for in this study. Further research with larger sample sizes and more comprehensive assessments of disease stages and comorbid conditions is needed to better understand the potential role of LMR in diagnosing and monitoring NAFLD.

Limitations and future research directions

This study has several limitations that should be acknowledged. First, significant heterogeneity was observed across the included studies, which may be attributed to variations in study design and population characteristics. Differences in sample size, inclusion/exclusion criteria, and diagnostic

methods are potential sources of heterogeneity. Additionally, differences in age, ethnicity, and the presence of co-morbid conditions across studies may have influenced the outcomes. Sensitivity analyses and subgroup analyses helped assess how these factors influenced the results, revealing that certain studies, such as Zhao [40], had a substantial impact on the combined effect size in PLR analysis. Excluding this study resulted in a significant reduction in the combined effect size from 97.38 to 85%. In contrast, both the NLR and LMR analyses showed the least amount of variation when any individual study was excluded, suggesting that the heterogeneity observed was not primarily driven by any single study. Our subgroup analyses revealed geographic and study design factors influencing the relationship between NLR, PLR, and NAFLD progression. Geographic differences in diet, lifestyle, and the prevalence of metabolic syndrome can influence biomarker levels and their association with NAFLD progression. For instance, regions with higher rates of obesity and insulin resistance may show stronger associations between NLR and PLR and liver inflammation or fibrosis. Regarding study design, the type of study (retrospective, prospective, or cross-sectional) can impact the strength of associations between biomarkers and liver damage. Retrospective studies may have biases, while prospective studies offer insights into disease progression over time. Cross-sectional studies, though informative, capture only a snapshot of the disease. Although Egger's test and funnel plots suggested no significant publication bias, we recognize the potential impact of small-study effects and selective reporting on the reliability of our findings. Small-study effects can lead to exaggerated estimates of the association due to the tendency of smaller studies to report more extreme outcomes. While our sensitivity analyses did not show significant changes in the pooled estimates after excluding smaller studies, the potential for small-study effects remains a limitation of the analysis.

Another limitation is the overrepresentation of Chinese populations in the studies included in this meta-analysis, which raises concerns about the generalizability of our findings to other populations. Both cultural and genetic factors may influence the levels of NLR, PLR, and LMR, thereby affecting their utility as biomarkers for NAFLD in different regions or populations. For instance, genetic variations related to immune function, platelet activity, or liver metabolism may result in population-specific differences in these biomarkers. Furthermore, cultural differences in dietary habits, lifestyle factors, and environmental exposures may also significantly influence inflammation and biomarker levels. To enhance the robustness of these findings and ensure their global applicability, future studies should include multiethnic cohorts and participants from diverse geographic regions. Such research would be crucial to confirming the diagnostic and prognostic utility of these biomarkers in NAFLD and understanding their broader relevance in diverse populations.

Additionally, while the trends in NLR and PLR are supported by several studies, their predictive value for progression to NASH or fibrosis remains limited. We suggest that combining these biomarkers with other markers, such as FIB-4, the AST/ALT ratio, and APRI, may improve predictive accuracy. A composite score incorporating NLR, PLR, and FIB-4 could provide a more reliable model for assessing NAFLD progression. Furthermore, integrating genetic markers and advanced imaging techniques, such as elastography, may enhance predictive capability. Further validation of these combined approaches through longitudinal studies is necessary to confirm their clinical applicability.

Conclusions

In conclusion, this meta-analysis demonstrates that NLR and PLR are strongly associated with the onset and early development of NAFLD, indicating their potential as useful diagnostic and prognostic markers. However, further research is needed to clarify the protective role of PLR and to explore the involvement of LMR in disease progression, as well as to better understand their underlying mechanisms and clinical relevance.

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Data availability Data will be available to any researcher who contact the corresponding author.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Ethics approval was not required as this was a systematic review of published studies.

Informed consent Not applicable.

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