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REVIEW

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Neutrophil Percentage-to-Albumin Ratio and Neutrophil-to-Albumin Ratio as novel biomarkers for non-alcoholic fatty liver disease: a systematic review and meta-analysis

Amr Ali Mohamed Abdelgawwad El-Sehrawy[1], Maryam Jafari[2], Ahmed Hussein Zwamel[3,4,5], Pegah Rashidian[6], Suhas Ballal[7], Rishiv Kalia[8], Anima Nanda[9], Laxmidhar Maharana[10], Sepide Javankiani[11], Mohammad Hashemi[12*] and Ehsan Amini-Salehi[6*]

Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is a major global health concern, with rising prevalence linked to obesity, insulin resistance, and metabolic syndrome. Timely and accurate identification of individuals at risk is crucial for improving outcomes. Recently, systemic inflammatory and nutritional markers such as the Neutrophil Percentage-to-Albumin Ratio (NPAR) and the Neutrophil-to-Albumin Ratio (NAR) have emerged as promising non-invasive biomarkers for NAFLD. Both ratios reflect inflammation and hepatic nutritional status, offering potential utility in predicting disease presence and progression. This systematic review and meta-analysis aimed to evaluate the diagnostic value of NPAR and NAR in patients with NAFLD.

Methods A comprehensive search was performed across databases including PubMed, Embase, Scopus, and Web of Science from inception to December 28, 2024. Data extraction was carried out using a standardized form, and the methodological quality of included studies was assessed using the Newcastle-Ottawa Scale. Statistical analyses were performed using STATA version 18, employing a random-effects model.

Results The meta-analysis demonstrated that both the Neutrophil Percentage-to-Albumin Ratio (NPAR) and the Neutrophil-to-Albumin Ratio (NAR) were significantly higher in patients with NAFLD compared to healthy individuals. NPAR showed a standardized mean difference (SMD) of 0.28 (95% CI: 0.22–0.35, $P < 0.01$), while NAR had a higher effect size with an SMD of 0.69 (95% CI: 0.44–0.93, $P < 0.01$). The pooled diagnostic performance of NPAR yielded a sensitivity of 69.5% (95% CI: 56.3–82.6%), specificity of 63.1% (95% CI: 46.6–70.0%), and an area under the curve (AUC) of 76.05% (95% CI: 66.3–85.7%). For NAR, the pooled sensitivity was 65.0% (95% CI: 49.0–82.0%), specificity was 63.0% (95% CI: 47.0–79.0%), and AUC was 69.0% (95% CI: 48.0–89.0%).

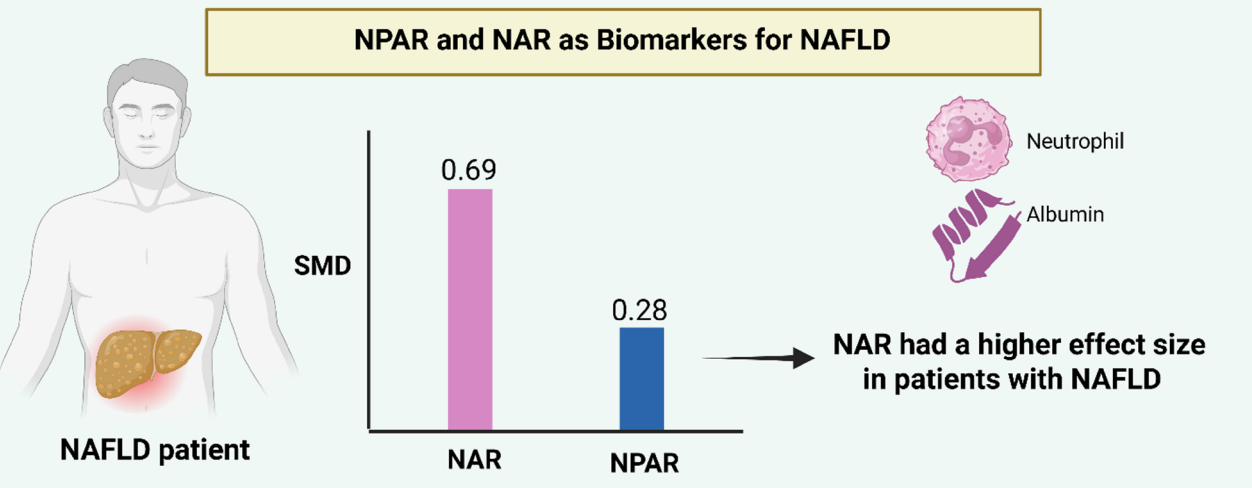
*Correspondence:
Mohammad Hashemi
mohammadhashemi281@gmail.com
Ehsan Amini-Salehi
ehsanaminisalehi1998@gmail.com

Full list of author information is available at the end of the article

Conclusion In conclusion, both NPAR and NAR were found to be elevated in individuals with NAFLD, supporting their potential as non-invasive and accessible biomarkers. These ratios reflect key aspects of systemic inflammation and nutritional status, offering clinical value in early detection and risk stratification. However, given the limited number of studies available—particularly for NAR—further research is needed to confirm these findings, establish standardized thresholds, and assess their performance across diverse populations and clinical settings.

Clinical trial number Not applicable.

Graphical Abstract



Biomarker	SMD	AUC	Sensitivity	Specificity
NPAR	0.28 (0.22–0.35, P < 0.01)	76.05%	69.5%	63.1%
NAR	0.69 (0.44–0.93, P < 0.01)	69.0%	65.0%	63.1%

Keywords Biomarkers, Inflammation, Meta-analysis, NAR, NAFLD, Neutrophil Percentage-to-Albumin Ratio

Highlights

1. Both NPAR and NAR were significantly higher in NAFLD patients compared to healthy individuals.
2. NARP is introduced as a novel non-invasive biomarker for NAFLD.
3. Elevated NPAR indicates heightened systemic inflammation combined with reduced albumin levels, reflecting compromised liver function.
4. Future research should target standardized diagnostic thresholds in larger, prospective cohorts.

Introduction

NAFLD represents a highly prevalent hepatic disorder, defined by the excessive accumulation of fat within hepatocytes, independent of alcohol consumption [1–3]. This condition encompasses a continuum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), which may further progress to advanced fibrosis, cirrhosis, or hepatocellular carcinoma [4–7]. Globally, the prevalence of NAFLD is estimated to affect approximately 30% of the population, with a higher incidence observed among individuals with obesity, type 2 diabetes, or metabolic syndrome [8–10]. The growing burden of NAFLD highlights substantial public health

challenges, necessitating the development of precise diagnostic and prognostic approaches [11].

The progression of NAFLD is fundamentally influenced by chronic inflammation, which serves as a critical driving factor [4, 12–14]. Identifying reliable, non-invasive biomarkers to assess inflammation and predict disease progression is crucial for patient management. Two such biomarkers that have garnered attention are the neutrophil-to-albumin ratio (NAR) and the NPAR [15–18]. Both are calculated using components readily obtainable from routine blood tests: NAR is derived from the absolute neutrophil count divided by serum albumin levels, while NPAR is calculated by dividing the neutrophil percentage by serum albumin levels. Both of these novel inflammatory markers have been proposed as a prognostic and diagnostic indicator in different, metabolic, inflammatory, and also autoimmune diseases [19–21]. Elevated values of these ratios may reflect systemic inflammation and nutritional status, both pertinent to NAFLD pathogenesis [22–24].

Given these findings, a comprehensive meta-analysis is warranted to systematically evaluate the possible role of NAR, and NPAR as rapid, cost-effective alternatives to conventional diagnostics by reflecting both systemic inflammation and hepatic nutritional status, thus facilitating early detection and better management of NAFLD.

Methods

This meta-analysis adhered to the methodological framework specified in the *Cochrane Handbook for Systematic Reviews and Meta-Analyses* [25]. The findings were reported following the standards set by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines [26]. The study protocol was preregistered in PROSPERO with the registration number CRD42024627138.

Search strategy

A comprehensive search was performed across electronic databases, including PubMed, Embase, Scopus, and Web of Science, covering the period from their inception to March 7, 2025. The search employed a combination of keywords and Medical Subject Headings (MeSH) terms such as "Non-Alcoholic Fatty Liver Disease," "NAFLD," "Neutrophil-to-Albumin Ratio," and "Neutrophil Percentage-to-Albumin Ratio." Additionally, manual screening of reference lists from pertinent articles was undertaken to identify further studies. Only English-language, peer-reviewed publications were included in the analysis. Detailed search strategies for each database are provided in Table S1.

Study selection and eligibility criteria

Eligible studies for inclusion in this meta-analysis satisfied specific criteria: they examined the link between NAR or NPAR and NAFLD and provided adequate data to compute effect measures such as odds ratios (OR), relative risks (RR), or mean differences (MD) with 95% confidence intervals (CI), and were designed as observational studies, including cross-sectional, cohort, or case-control approaches. As suggested by Tafik et al. studies were excluded if they lacked sufficient data, were incomplete, or comprised conference abstracts, reviews, case reports, or research on non-human subjects. Two reviewers independently evaluated the titles and abstracts of identified articles to confirm eligibility, followed by a detailed review of full-text articles for potentially relevant studies. Disagreements were addressed through discussions or resolved by consulting a third reviewer [27].

Quality assessment

The methodological quality of the included studies was independently appraised by two reviewers employing the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for observational studies [28–30]. Any discrepancies in assessments were addressed through deliberation or, when required, adjudicated by a third reviewer to reach a consensus.

Data extraction

Data were extracted using a standardized form, capturing study characteristics (author, year, location, design, sample size), population details (age, gender, clinical status), biomarker measurements (NAR, NPAR), and outcome measures (NAFLD diagnosis or severity). Two reviewers independently performed the extraction, resolving discrepancies through discussion or consultation with a third reviewer.

Statistical analysis

In the statistical evaluation, a random-effects model was implemented using Restricted Maximum Likelihood (REML) estimation. To improve the reliability of the results, the Knapp-Hartung correction was applied, which modifies standard errors to better reflect uncertainty in estimating between-study variance [31].

Heterogeneity across studies was examined using multiple measures, including I^2, H^2, and τ^2 statistics, alongside Cochran's Q test. A threshold of I^2 greater than 50% combined with a p-value below 0.1 was interpreted as evidence of substantial heterogeneity [32].

Potential outliers were identified using Galbraith plots, which are effective in detecting studies that contribute disproportionately to heterogeneity. Publication bias was assessed through various methods, including Begg's test, Egger's test, and the trim-and-fill approach, offering a

thorough evaluation of potential bias in the meta-analysis [33].

Additionally, prediction intervals were computed to estimate the range within which the true effect sizes of individual studies are expected to lie, enabling a deeper understanding of variability among studies [34].

Sensitivity analyses were conducted to evaluate the influence of individual studies on the aggregated results, thereby ensuring the reliability of the conclusions [35]. Statistical analyses were carried out using STATA software, version 18.

Results

Study selection

A total of 151 records were initially identified through database searches. After removing 69 duplicate entries, 82 unique records remained for screening. Following the title and abstract review, 67 records were excluded. The remaining 15 full-text articles were assessed for eligibility. Of these, 10 were excluded. Ultimately, 5 studies met the inclusion criteria and were incorporated into the final meta-analysis. The complete study selection process is illustrated in Fig. 1.

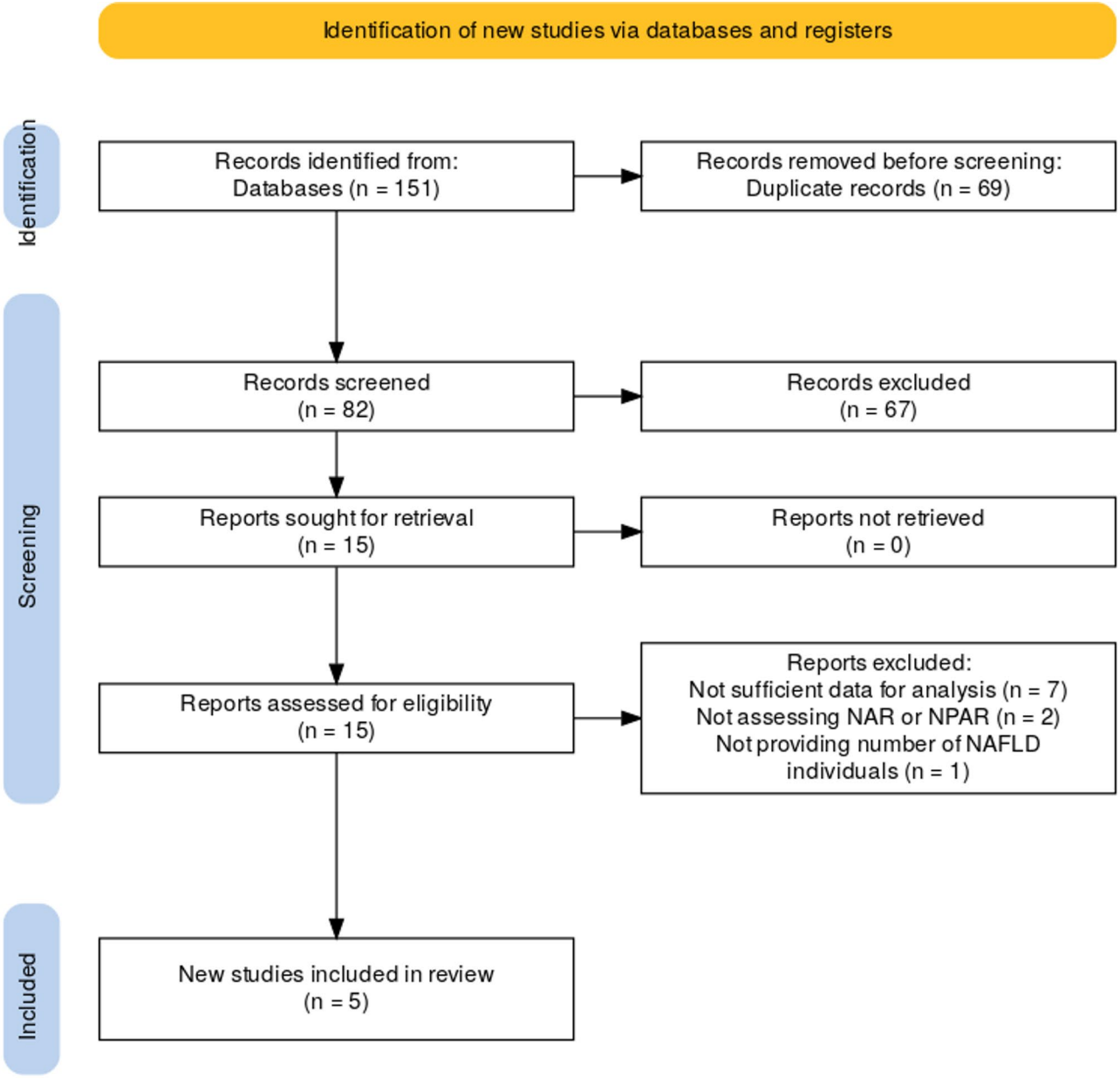


Fig. 1 Study selection process

Table 1 Characteristics of included studies

Author, Year	Country	Journal	Study design	Total sample size	NAFLD/ non-NAFLD sample size	Male/Female	Mean age	Quality
Bao et al., 2024 [15]	China	Frontier in Nutrition	Cross-sectional	11,883	3892/8,011	7529/4354	47.49 ± 15.42	6
Cucoranu et al., 2023 [36]	Romania	Cureus	Cross-sectional	115	72/42	64/51	Not Reported	9
Wang et al., 2024 [37]	China	Frontier in Nutrition	Cross-sectional	14,413	6518/7985	7008/7405	49.76 ± 17.51	7
Liu et al., 2023 [38]	Taiwan	Nutrients	Cross-sectional	3991	1355/2474	1922/3069	45.3 ± 0.7	9
He et al [39].	China	BMC gastroenterology	Cross-sectional	4526	3023/1503	2,088/2,438	44	8

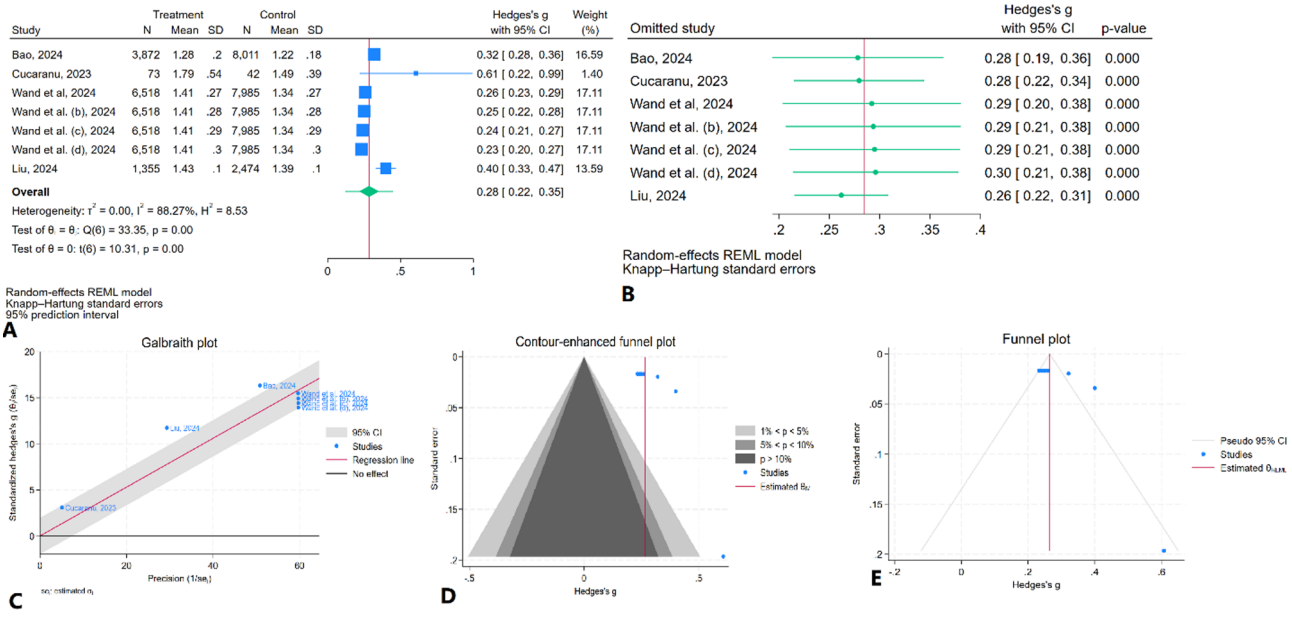


Fig. 2 Meta-analysis of the NPAR status in individuals with NAFLD compared to healthy controls. **A**: Forest plot analysis. **B**: Plot of sensitivity analysis. **C**: Galbraith plot analysis for identifying outlier studies. **D**: Counter enhanced funnel plot. **E**: Trim and fill plot

Study characteristics

The meta-analysis included four cross-sectional studies with a combined total of 34,928 participants, examining the association between the NPAR, NAR and NAFLD. The sample sizes of the studies varied widely, ranging from 115 participants in the smallest study to 14,413 in the largest (Table 1). Geographically, the studies were conducted in China, Taiwan, and Romania. Table S2 presents the quality of the included studies.

Comparison of NPAR in NAFLD and healthy individuals

Seven effect sizes evaluated NPAR, and the overall analysis indicated that NPAR levels were notably higher in individuals with NAFLD compared to those without the condition (Hedges's g = 0.28, 95% CI: 0.22–0.35, $P < 0.01$). These findings were associated with considerable heterogeneity (I^2 = 88.27%). The prediction interval was estimated to range from 0.15 to 0.40 (Fig. 2.A). Sensitivity analysis revealed that no individual study significantly influenced the overall effect size (Fig. 2.B). The Galbraith plot identified Bao (2024) and Liu (2024) as potential outliers (Fig. 2.C). Counter enhanced funnel plot suggested the presence of publication bias (Fig. 2.D). Both Begg's test ($P < 0.01$) and Egger's test ($P < 0.01$) confirmed the presence of substantial publication bias. However, the trim-and-fill method did not identify any further studies for imputation (Fig. 2.E).

Comparison of NAR in NAFLD and healthy individuals

The metanalysis result indicated a significantly higher NAR in the NAFLD group compared to healthy controls (Hedges's g = 0.69, 95% CI: 0.44 to 0.93, $P < 0.01$). Substantial heterogeneity was observed across studies (I^2 = 97.63%, $P < 0.01$) (Fig. 3). Due to the inclusion of only two studies, the calculation of a prediction interval was not suitable, as such intervals require a larger number of studies to provide meaningful estimates. Similarly, conducting sensitivity analyses and assessing publication bias were not feasible with this limited dataset.

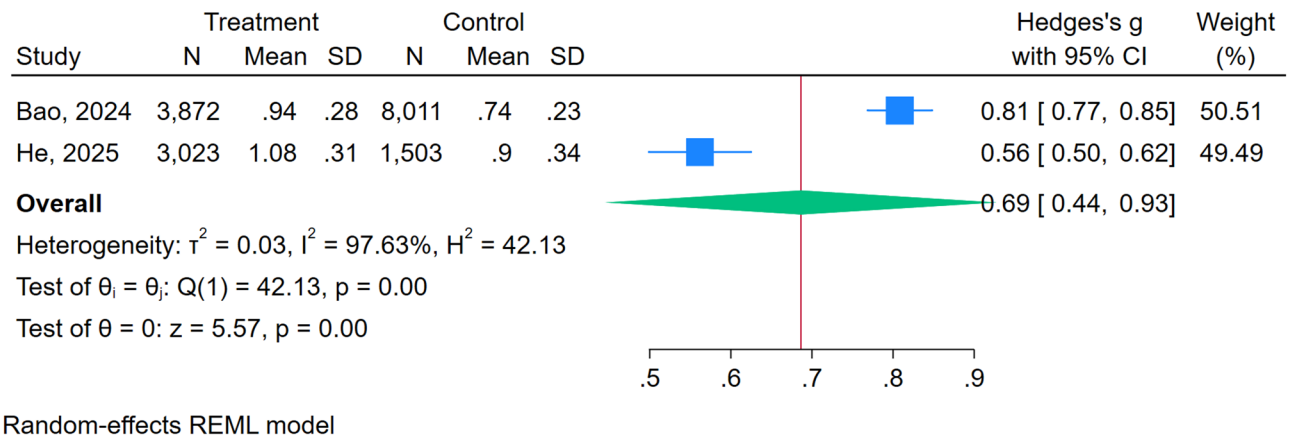


Fig. 3 Forest plot analysis of the NAR status in individuals with NAFLD compared to healthy controls

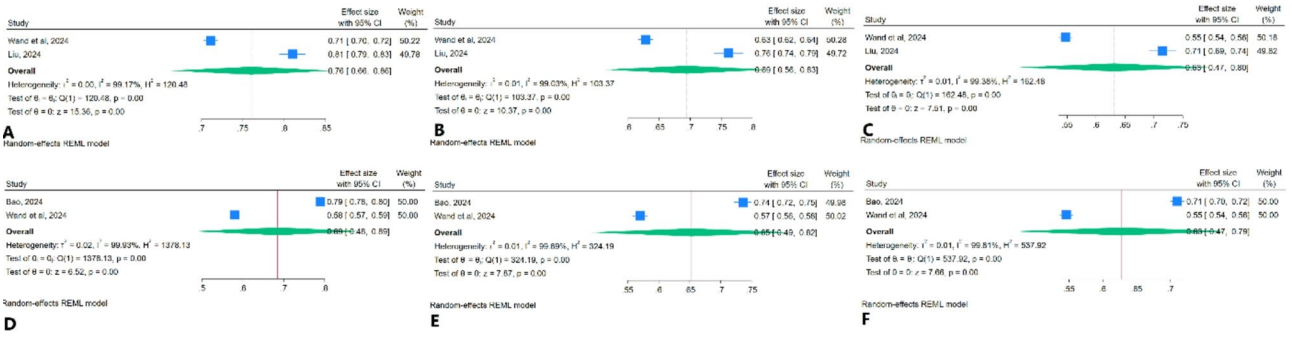


Fig. 4 Forest plot analyses of the diagnostic performance of NPAR and NAR in identifying NAFLD. (**A**) Pooled AUC for NPAR. (**B**) Pooled sensitivity for NPAR. (**C**) Pooled specificity for NPAR. (**D**) Pooled AUC for NAR. (**E**) Pooled sensitivity for NAR. (**F**) Pooled specificity for NAR

Sensitivity and specificity of NPAR and NAR

Only two studies assessed the sensitivity, specificity, and AUC of NPAR and NAR in identifying individuals with NAFLD. The results of the meta-analysis for NPAR demonstrated that the pooled AUC was 76.0% (95% CI: 66.0–86.0%) with substantial heterogeneity (I^2 = 99.17%) (Fig. 4.A). The pooled sensitivity was 69.0% (95% CI: 56.0–83.0%; I^2 = 99.03%) (Fig. 4.B), and the pooled specificity was 63.0% (95% CI: 47.0–80.0%; I^2 = 99.38%) (Fig. 4.C).

Similarly, for NAR, the pooled AUC was 69.0% (95% CI: 48.0–89.0%) with high heterogeneity (I^2 = 99.93%) (Fig. 4.D). The pooled sensitivity was 65.0% (95% CI: 49.0–82.0%; I^2 = 99.69%) (Fig. 4.E), while the pooled specificity was 63.0% (95% CI: 47.0–79.0%; I^2 = 99.81%) (Fig. 4.F).

Discussion

This meta-analysis and systematic review investigated the relationship between NPAR and NAFLD, emphasizing its potential as a non-invasive indicator for early diagnosis and disease prognosis. The results demonstrated that NPAR values were notably elevated in individuals with NAFLD compared to healthy counterparts, with a combined SMD of 0.28 (95% CI: 0.22–0.35). NPAR integrates two key physiological parameters: neutrophil percentage, reflecting systemic inflammation, and serum albumin, indicative of nutritional and hepatic status. Elevated neutrophil levels suggest immune activation in response to hepatic injury, while reduced albumin levels may indicate compromised liver function or systemic inflammation.

NAFLD, a manifestation of metabolic syndrome, is closely linked to obesity, type 2 diabetes, dyslipidemia, and endothelial dysfunction, underscoring the importance of early identification for disease management [40, 41]. While liver biopsy remains the gold standard for diagnosing hepatic steatosis and fibrosis, its invasive nature and sampling limitations make non-invasive biomarkers such as NPAR invaluable in clinical practice [42–44]. The NLR has also been shown to be elevated in both NAFLD and alcoholic liver cirrhosis, emphasizing the role of neutrophils in liver disease progression [45, 46]. Inflammatory cytokines such as IL-1β, IL-6, and TNF-α disrupt insulin signaling and exacerbate hepatic damage, further highlighting the inflammatory milieu of NAFLD [47, 48]. Hypoalbuminemia, another component of NPAR, is often seen in advanced liver disease and reflects both reduced hepatic synthesis and structural alterations that impair albumin's anti-inflammatory and antioxidative functions [49–52]. Furthermore,

studies have identified albumin levels below 3.5 g/dL and low platelet counts as predictors of poor prognosis in NAFLD, with patients meeting these criteria exhibiting significantly reduced 10-year survival rates [53]. Elevated NPAR in NAFLD patients as a unique composite biomarker, bridges the gap between inflammation (progression of hepatic steatosis towards steatohepatitis) and nutritional status (hypoalbuminemia).

by combining increased neutrophil-driven inflammatory activity Non-invasive scoring systems such as the NAFLD fibrosis score (NFS), which incorporates serum albumin, have shown effectiveness in identifying patients at higher risk of liver-related complications, while the inclusion of albumin in updated models like MELD 3.0 highlights its critical role in predicting short-term survival in end-stage liver disease [43, 44, 54].

Our results demonstrated that NPAR exhibited a pooled sensitivity of 69.5%, a specificity of 63.1%, and an area under the curve (AUC) of 76.05%, reflecting moderate diagnostic accuracy. Although these values fall short of the precision offered by advanced imaging techniques or liver biopsy [42, 55–57], These findings underscore the potential of NPAR as a promising initial screening marker for NAFLD. Beyond NPAR, other systemic immune-inflammatory indicators, such as the NLR, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, have also been explored for their diagnostic and prognostic significance in NAFLD [58–60]. Additionally, the systemic immune-inflammatory index (SII), an emerging biomarker, captures the interplay between localized immune activity and systemic inflammatory processes [61]. These markers, particularly NLR, have shown strong associations with NAFLD risk, emphasizing their potential in assessing the inflammatory environment [60]. NLR, in particular, has been suggested as a promising biomarker for predicting and preventing NASH and fibrosis in NAFLD patients [62]. Furthermore, while imaging techniques and biopsies provide comprehensive evaluations of hepatic steatosis and fibrosis, they are limited by cost and accessibility [63, 64]. In addition to the accessibility and reducing costs in resource-limited settings, the possibility of measuring NPAR over time could provide insight into disease progression in different stages of the disease [63]. These applications underscore the potential for NPAR to enhance decision-making in NAFLD management by guiding tailored treatment strategies and frequent reassessment in high-risk individuals.

This study has several strengths, notably its comprehensive evaluation of the NPAR as a potential biomarker for NAFLD. By pooling data from multiple studies, we provide a robust analysis of NPAR's diagnostic potential, demonstrating its moderate sensitivity and specificity. These findings position NPAR as a promising, non-invasive biomarker for early NAFLD detection, especially given its ability to integrate both inflammatory and nutritional markers, which offers a unique advantage over traditional liver biomarkers. The systematic approach used in data extraction and statistical analysis, including random-effects models and sensitivity testing, ensures the reliability of our conclusions. However, several limitations must be considered. The studies analyzed in this meta-analysis demonstrated substantial heterogeneity (I^2 = 88.27%), which could restrict the broader applicability of the findings. Variability in patient characteristics, study designs, and methodological approaches may contribute to this heterogeneity. While the sensitivity and specificity of NPAR derived from the two studies were moderate, these values were lower than those of advanced imaging techniques and liver biopsy, suggesting the need for further refinement of NPAR thresholds. The limited number of studies included, alongside the potential for publication bias, may also impact the robustness of the conclusions. Future research should focus on validating NPAR in larger, longitudinal cohorts, establishing standardized cut-off points, and exploring its combined use with other biomarkers and imaging techniques to enhance diagnostic accuracy and prognostic capabilities. This would provide a clearer understanding of NPAR's role in the clinical management of NAFLD.

Limitations

First, the included studies were exclusively cross-sectional in design, which restricts the ability to infer causality between elevated NPAR or NAR levels and the presence of NAFLD.

Second, the relatively small number of eligible studies — particularly only two studies assessing NAR — restricts the statistical power, robustness, and generalizability of our findings. This limitation reflects the current state of the literature, as NPAR and NAR are relatively novel biomarkers, and more research is still emerging in this area. Third, substantial heterogeneity was observed across most analyses, including diagnostic performance metrics. We explored potential sources of heterogeneity using sensitivity analyses and Galbraith plots, and visually illustrated them in the figures. However, due to the limited number of studies, performing meta-regression analyses or formal subgroup analyses was not statistically feasible. This variability may limit the generalizability of the findings to broader populations. Fourth, demographic and geographic diversity was limited, as most studies were conducted in Asian (China, Taiwan) and Eastern European (Romania) populations. This geographic concentration may affect the applicability and generalizability of our findings to other ethnic groups and regions. Finally, publication bias was detected using Begg's and Egger's tests for NPAR. However, given the small number of included studies (less than ten),

these tests are less reliable, and the results must be interpreted with caution. Although the trim-and-fill analysis did not impute any missing studies, publication bias cannot be entirely excluded and remains a limitation of this meta-analysis.

Given these limitations, future research should focus on conducting large-scale, multicenter, prospective studies with diverse populations. Future meta-analyses should aim to perform meta-regression analyses based on factors such as age, body mass index (BMI), and disease duration. Furthermore, subgroup analyses should be conducted based on sex, NAFLD grade, and diagnostic modality to better clarify the sources of heterogeneity and improve the generalizability and precision of findings related to NPAR and NAR as biomarkers for NAFLD.

Conclusion

In conclusion, NPAR and NAR demonstrate significant promise as non-invasive biomarkers for NAFLD, highlighting their potential in early detection and risk stratification. These biomarkers integrate key aspects of systemic inflammation and nutritional status, which are crucial in NAFLD pathogenesis. While both biomarkers showed acceptable diagnostic accuracy, the limited number of studies, substantial heterogeneity, and evidence of publication bias warrant cautious interpretation of the findings. The clinical implications of these biomarkers are promising, yet further research is necessary to validate their utility and establish standardized thresholds for use in clinical practice. To enhance the applicability and precision of these biomarkers, future studies should focus on large-scale, multicenter, prospective studies across diverse populations. Additionally, meta-regression and subgroup analyses based on sex, NAFLD grade, diagnostic modality, and other relevant factors should be conducted to address sources of heterogeneity and further establish the clinical relevance of NPAR and NAR in the management of NAFLD. Moreover, optimal cutoff values for both biomarkers should be discovered to facilitate their accurate application in clinical settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41043-025-00926-y.

Supplementary Material 1

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Author contributions
Conceptualization (developing the research idea) was carried out by E.AS, P.R, and M.H. The study design (planning the methods used to achieve the results) was handled by M.J, P.R, and A.A.M.A.E.S. Supervision (oversight, coordination, and manuscript preparation) was provided by E.AS, S.B, and A.N. Data collection/processing (conducting experiments, managing patients, organizing, or reporting data) and data analysis/interpretation (statistical analysis, evaluation, and presentation of findings) were undertaken by M.J, L.M, R.K, and S.B. All authors contributed substantially to drafting the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Internal Medicine, Diabetes, Endocrinology and Metabolism, Mansoura University, Mansoura, Egypt
[2]Student Research Committee, Anzali International Campus, Guilan University of Medical Sciences, Rasht, Iran
[3]Department of Medical Analysis, Medical Laboratory Technique College, The Islamic University of Al Diwaniyah, Al Diwaniyah, Iraq
[4]Department of Medical Analysis, Medical Laboratory Technique College, The Islamic University of Najaf, Najaf, Iraq
[5]Department of Medical Analysis, Medical Laboratory Technique College,, Al Diwaniyah, , The Islamic University of Babylon, Babylon, Iraq
[6]Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran
[7]Department of Chemistry and Biochemistry, School of Sciences, JAIN, Bangalore, Karnataka, India
[8]Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, Punjab, India
[9]Department of Biomedical, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India
[10]Department of Pharmaceutical Sciences, Siksha 'O' Anusandhan, Bhubaneswar, Odisha, India
[11]General Surgery Department, Tehran University of Medical Sciences, Tehran, Iran
[12]Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

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