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Chronic Diseases and Translational Medicine

META-ANALYSIS

Prognostic role of C-reactive protein to albumin ratio in lung cancer: An updated systematic review and meta-analysis

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Abstract

Background: C-reactive protein to albumin ratio (CRP/Alb ratio, CAR) has been suggested as a potential prognostic biomarker in lung cancer. This updated systematic review and meta-analysis aimed to assess the association between CAR and lung cancer prognosis in current literature.

Methods: A systematic search of databases was conducted to identify relevant studies published up to April 2023. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to assess the association between CAR and overall survival (OS) and progression-free survival (PFS) and recurrence-free survival (RF) in lung cancer patients.

Results: This meta-analysis includes 16 studies with a total of 5337 patients, indicating a significant association between higher CAR and poorer OS, PFS, and RFS in lung cancer patients, with a pooled HR of 1.78 (95% CI = 1.60–1.99), 1.57 (95% CI = 1.36–1.80), and 1.97 (95% CI = 1.40–2.77), respectively.

Conclusions: This updated meta-analysis provides evidence for the potential prognostic role of CAR in lung cancer, suggesting its utility as an effective and noninvasive biomarker for identifying high-risk patients and informing treatment decisions in a cost-effective manner. However, further large-scale studies will be necessary to establish the optimal cut-off value for CAR in lung cancer and confirm the present findings.

KEYWORDS

C-reactive protein to albumin ratio, inflammation: biomarker, lung cancer, prognosis

Highlights

- Higher C-reactive protein to albumin ratio (CAR) is associated with poorer prognosis in lung cancer patients.
- CAR is a potentially useful prognostic biomarker for lung cancer as it is simple, inexpensive, and widely available.
- CAR may be used to identify high-risk patients who may benefit from more aggressive treatment strategies.
- Further studies are needed to investigate the potential use of CAR as a predictive biomarker for response to therapy and to establish optimal cutoff values for different stages of lung cancer.

1 | INTRODUCTION

Lung cancer is a malignant neoplasm that originates from lung tissue. It is broadly categorized into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), among which NSCLC is the most prevalent. NSCLC can be further divided into lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and lung large cell carcinoma. LUAD, the most frequently occurring subtype, constitutes 60%–70% of all NSCLCs. LUSC accounts for 20%–30% of cases, while large cell carcinoma represents a minority, with only 5%–10%.[1] Lung cancer is the reason for causing the greatest amount of fatalities related to cancer in the United States, with a mortality rate of over 350 individuals. This figure is 2.5 times greater than the number of fatalities attributed to colorectal cancer, which is the second most prevalent malignancy.[2]

Despite notable progress in surgical, radiotherapeutic, chemotherapeutic, and immunotherapeutic interventions, advances in the care and handling of lung cancer persist. Regrettably, the prognosis for individuals diagnosed with lung cancer remains unfavorable,[3] and the 5-year overall survival (OS) rate only was 18.2%.[4] Moreover, a retrospective study conducted in China has revealed that the median time of survival of individuals diagnosed with lung cancer is roughly 1 year.[4] Patients suffering from advanced NSCLC who undergo chemotherapy have a 5-year survival rate of under 5%. Moreover, the risks of chemotherapy toxicity are on the rise in this population.[5] Although immunotherapy is associated with sustained improvements in 5-year OS and progression-free survival (PFS) in patients diagnosed with lung cancer as compared to conventional chemotherapy, the OS rates (median 47.5 vs. 29.1 months) and PFS rates (median 16.9 vs. 5.6 months) were below the 50% threshold in this study cohort.[6] Thus, accurate prognosis assessment of lung cancer patients is crucial in guiding the selection of clinical treatment options.

C-reactive protein (CRP) is synthesized by the liver as an acutely reactive protein. It can activate the innate immune system's complement system,[7] serving as a reliable prognostic marker for monitoring a diverse range of malignant tumors. Examples include pancreatic cancer,[8] urinary system tumors,[9] and hepatocellular carcinoma.[10] Albumin (Alb), synthesized in the liver, is a plasma protein that plays a significant role in regulating fluid balance in the body by maintaining plasma osmolality and facilitating blood volume transport.[11] Various studies have validated that serum CRP levels are predictive of unfavorable survival outcomes for patients diagnosed with lung neoplasm.[12–14] Likewise, serum albumin is also deemed an essential prognostic factor for the survival of NSCLC patients.[15] The utilization of the CRP-to-albumin ratio in evaluating inflammatory response and nutritional status can provide a more inclusive evaluation of lung cancer prognosis. Moreover, CAR has been recognized as an independent prognostic indicator for various types of cancers.[16–18] Prior meta-analyzes have suggested that pretreatment CAR is a potential prognostic marker for NSCLC, specifically excluding small cell lung cancer, with OS and RFS outcomes being the only events studied and PFS being overlooked.[19] Due to the lack of a comprehensive analysis on the reliability and extent of CAR's prognostic significance in lung cancer, this meta-analysis was conducted to further explore this association.

2 | METHODS

2.1 | Search strategy and criteria

Relevant literature was collected through computer searches of databases including PubMed, Embase, Cochrane Library, and Web of Science, from the establishment of each database until April 25, 2023. English search terms included "lung," "pulmonary," "cancer," "tumor," "neoplasm," "carcinoma," "C-reactive protein/albumin ratio," "C-reactive protein to albumin ratio," "C-reactive protein in albumin ratio," "CRP/Alb ratio," "CAR," and so forth. The PubMed-specific search strategy was: (lung OR pulmonary) AND (cancer OR tumor OR neoplasm OR carcinoma) AND (C-reactive protein/albumin ratio OR C-reactive protein to albumin ratio OR C-reactive protein in albumin ratio OR CRP/Alb ratio OR CAR). The reference lists of included studies were also searched.

2.2 | Study selection and exclusion

Inclusion criteria: (1) Research type: Observational studies on the relationship between CAR and lung cancer prognosis, which have been published domestically and internationally. (2) Study population: Patients with NSCLC confirmed by pathology. (3) Exposure: Patients were classified into a high CAR or low CAR group based on CAR values reported in the literature. (4) Outcome measures: The main research indicator was OS, and the secondary indicators were RFS and PFS.

Exclusion criteria: (1) Studies on nonprimary lung cancers such as metastatic tumors or recurrent cancers; (2) abstracts, letters, case reports, reviews, or nonclinical studies; (3) studies that did not provide sufficient data or hazard ratio (HR) values with 95% confidence intervals (CI) for the calculation of OS; (4) Newcastle-Ottawa Scale (NOS) scores <7;[20] (5) For duplicate or identical studies, only those with higher methodological quality were retained.

2.3 | Data extraction

According to the search strategy described above, the databases were thoroughly searched, and duplicate

studies were removed. Articles that met the inclusion criteria were chosen determined by their titles and abstracts. Subsequently, the full texts were read to further screen the remaining literature according to the inclusion and exclusion criteria. Articles with missing or duplicate data were excluded, and the remaining articles were included for data extraction. The data extraction process was independently completed by two reviewers, and cross-checking was performed after completion to make final decisions. Discrepancies were discussed and resolved by the two reviewers, and a third reviewer was consulted when necessary. The following information was extracted: first author, year of publication, study time, country, sample size (gender ratio), follow-up time, treatment regimen, age, critical value of CAR, pathological type, TNM stage, outcome measures, HR, and 95% CI.

2.4 | Quality evaluation

All included literature was evaluated for quality based on the NOS,[20] which includes three aspects: the appropriateness of the selection of study cohorts, the comparability between study cohorts, and the evaluation of outcome events in the literature. The included literature was assessed, and a score was assigned based on the three aspects mentioned above. Studies with a score ≥7 were considered to be of high quality.

2.5 | Statistical analysis

All data statistical processing and analysis were performed using Stata 12.0 (64-bit) software. Meta-analysis was used to calculate the pooled HR and corresponding 95% CI of OS to explore the correlation between CAR and prognosis of lung cancer patients, and a forest plot was generated. *Z*-test was used to determine statistical differences, and $p < 0.05$ was considered significant. Heterogeneity was evaluated using the I^2 statistic and *Q*-test.[21] When $I^2 \geq 50\%$ and $p < 0.05$, significant heterogeneity was present, and a random-effects model was used. Otherwise, a fixed-effects model was used ($p \geq 0.05$, $I^2 < 50\%$).[22,23] When significant heterogeneity was observed, sensitivity analysis and subgroup analysis were performed to explore the source of heterogeneity, and the stability of the meta-analysis results was assessed. Begg's test,[23] Egger's test,[24] and funnel plots were used to detect publication bias, and if the Egger's plot was significantly asymmetric or the *p*-value of Egger's test was <0.05, significant publication bias was considered to be present. If there was publication bias, studies used the Trim and Fill method to assess the robustness of the findings. Trim and Fill method is a statistical approach used to evaluate publication bias. It serves to assess and correct the effect of such bias based on trimming unreliable estimates from analysis results and filling in the model. This way, potential distortions in results due to bias can be remedied.

3 | RESULTS

3.1 | Characteristics of included studies and quality assessment

According to the search strategy described above, a thorough search of the databases was conducted, and 6158 preliminary research articles were obtained after removing duplicate studies. After preliminary screening, further 6120 articles were excluded, determined by their titles and abstracts, as which did not satisfy the criteria for inclusion. Of the remaining articles, 37 were found to be relevant, and five articles were excluded as they were either reviews or meta-analyzes. Finally, after reading the full texts and excluding 16[25–40] articles with incomplete or duplicate data, a total of 16 articles were included in this meta-analysis. The specific screening process is shown in Figure 1.

This meta-analysis included a complete sum of 5467 lung neoplasm patients from 16 studies conducted in Asian and European countries, including China ($n = 6$), Japan ($n = 7$), Korea ($n = 1$), and Germany ($n = 2$). All studies were retrospective in nature, and 12[25–27,29,31–35,37,38,40] studies reported the HR and 95% CI values for OS, while four studies reported PFS,[30,36,37,40] three studies reported RFS,[28,35,39] and only one study reported DFS.[29] Of the 16 studies, 15 studies focused on NSCLC patients, while two studies included SCLC patients. The CAR cutoff values ranged from 0.014 to 0.830, and the NOS quality scores of all studies ranged from 7 to 9 (Supporting Information: Table S2), indicating high-quality research. The basic characteristics of the included studies are summarized in Supporting Information: Table S1.

3.2 | Correlation between CAR levels and the outcome of individuals diagnosed with lung cancer

A meta-analysis of 12 studies evaluating the association between CAR and OS, four studies assessing the correlation between CAR and PFS, and three studies assessing the correlation between CAR and RFS showed no significant statistical heterogeneity in patients with lung cancer. Using a fixed-effects model, the results indicate a notable correlation between high CAR and poor OS (HR = 1.78, 95% CI = 1.60–1.99, $p < 0.001$; Figure 2), PFS (HR = 1.57, 95% CI = 1.36–1.80, $p < 0.001$; Figure 3), and RFS (HR = 1.97, 95% CI = 1.40–2.77, $p < 0.001$; Figure 3). Subgroup analyzes based on country, pathology type, TNM, and treatment modality

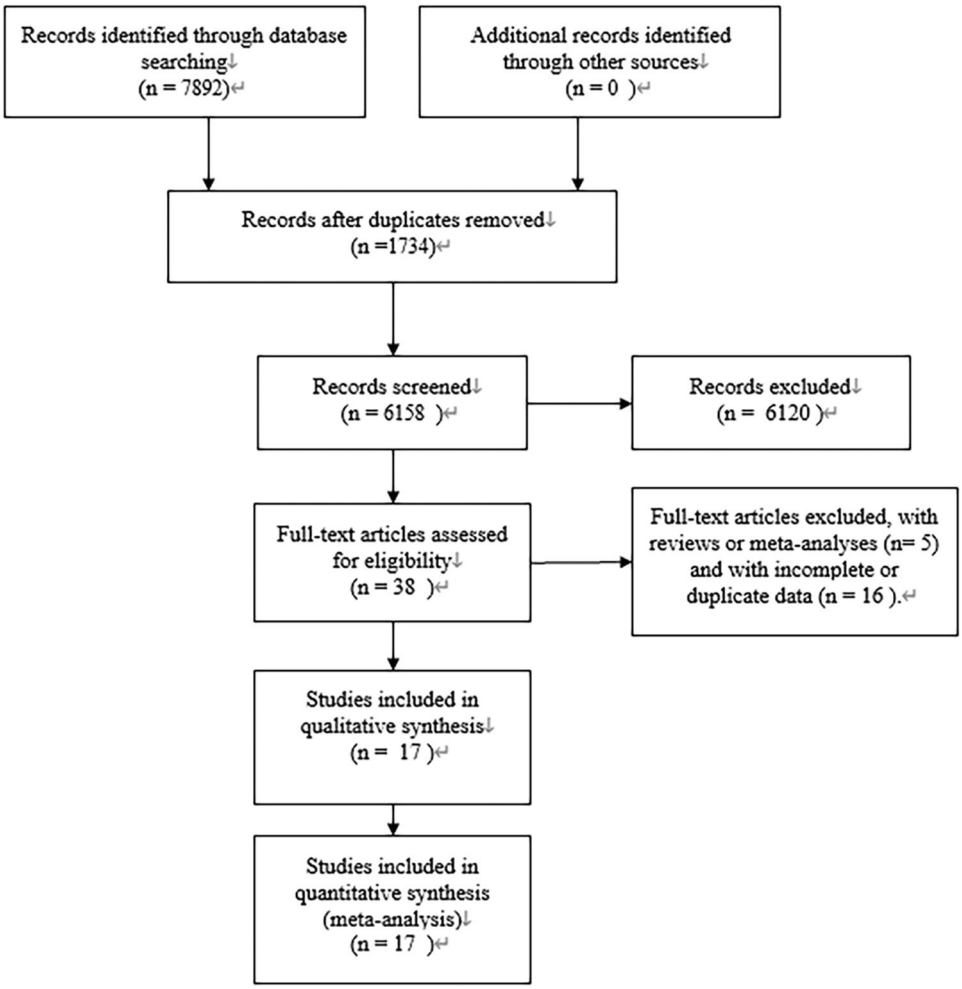

FIGURE 1 Document screening process and results.

revealed that pretreatment CAR is a reliable predictor of prognosis in lung cancer patients. There was no significant statistical heterogeneity among studies conducted in China ($I^2 = 19.8\%$, $p = 0.289$), on III–IV ($I^2 = 0$, $p = 0.964$), on NSCLC ($I^2 = 0$, $p = 0.994$), or on surgery as a treatment modality ($I^2 = 0$, $p = 0.986$). Detailed results are presented in Table 1 and Supporting Information: Figure S1A–D.

3.3 | Sensitivity analyzes and publication bias

To investigate the main source of I^2 in the regional subgroup of China ($I^2 = 19.8\%$, $p = 0.289$) in the subgroup analysis, and in CAR versus PFS in lung cancer patients ($I^2 = 31.0\%$, $p = 0.226$), sensitivity analysis was conducted by removing one study at a time, evaluating the change in values and heterogeneity after the final combination. If removing any study did not significantly affect the combined effect, the meta-analysis would provide reliable results. The results are presented in Figure 4A,B. Funnel plots and Egger's plots were also used to qualitatively and quantitatively detect publication bias of the included articles in the OS, PFS, and RFS studies. Figure S2A–C.

Begg's method and Egger's method were used to investigate publication bias in the articles included in the exploration of OS, PFS, and RFS. The results were as follows: OS (Begg's test, $z = 1.03$, $p = 0.304 > 0.05$; Egger's test, $t = 2.52$, $p = 0.03 < 0.05$), PFS (Begg's test, $z = 1.70$, $p = 0.089 > 0.05$; Egger's test, $t = 3.58$, $p = 0.07 > 0.05$), and RFS (Begg's test, $z = 0$, $p = 1 > 0.05$; Egger's test, $t = 4.25$, $p = 0.147 > 0.05$). As a result, there was no evidence of publication bias among the studies included in the analysis of the secondary outcomes PFS and RFS. However, for the articles included for the primary outcome OS, despite the $p > 0.05$ measured by Begg's method, it was necessary to use the Trim and Fill method to assess the stability of the pooled results due to the $p < 0.05$ obtained by the Egger's method.

The Trim and Fill method was used to evaluate publication bias in a meta-analysis. First, the results from the fixed-effect model and random-effect model were

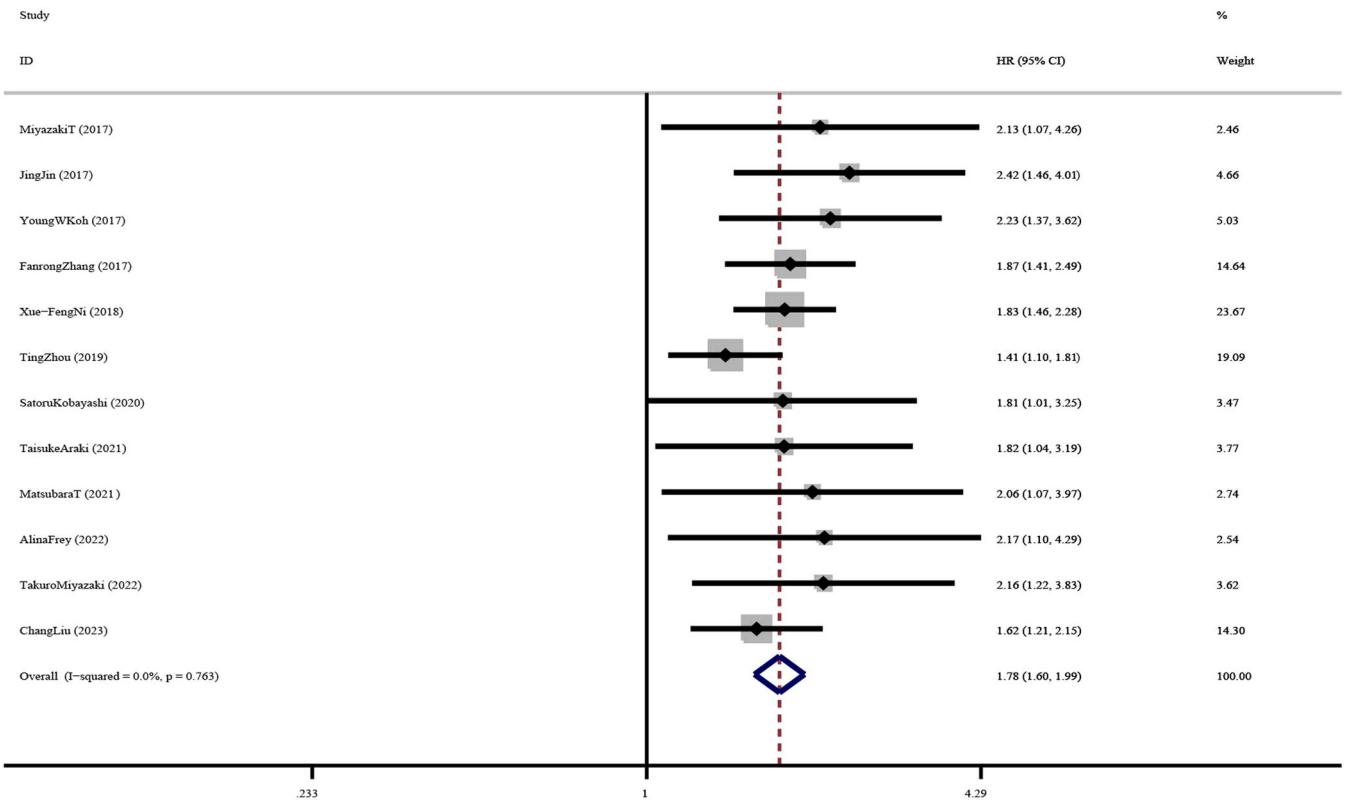

FIGURE 2 Forest plot of OS comparison results in lung cancer patients with higher CAR versus lower CAR. CAR, C-reactive protein to albumin ratio; OS, overall survival.

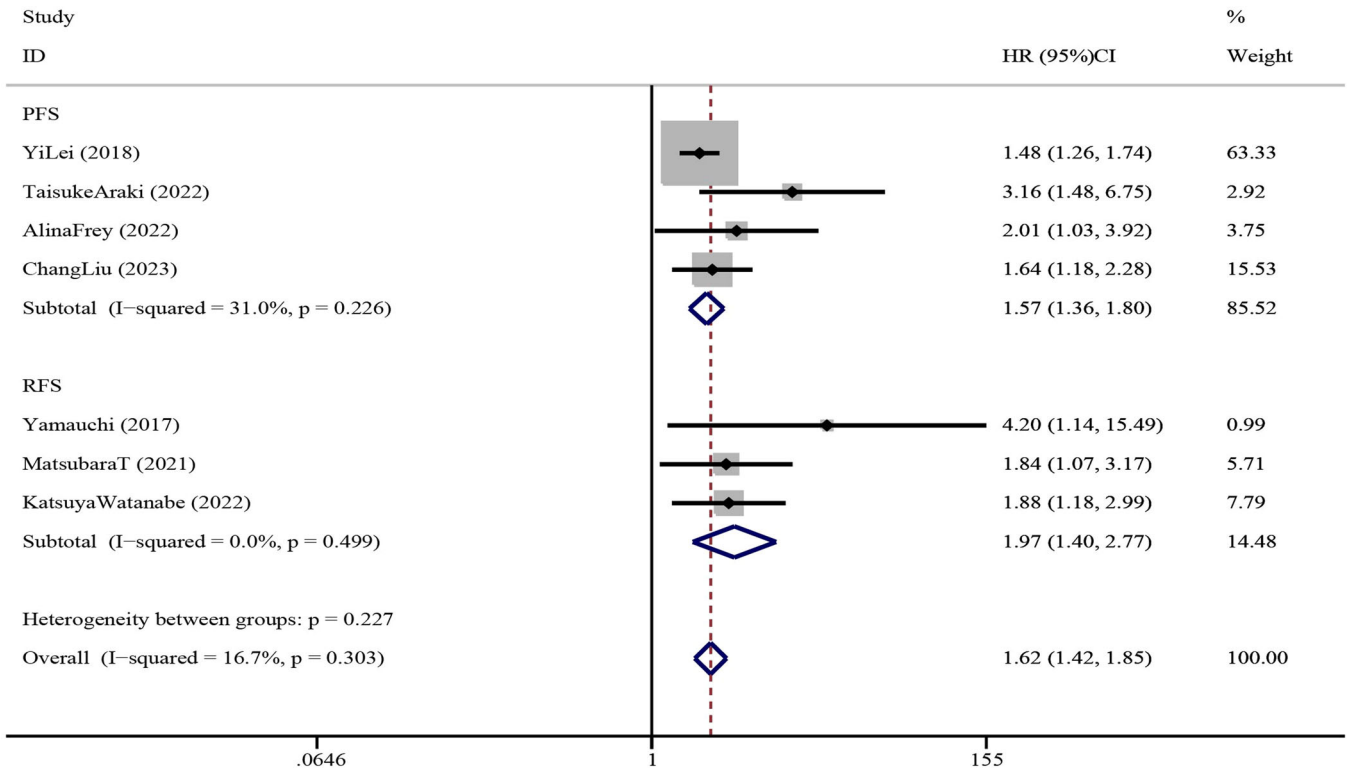

FIGURE 3 Forest plot of PFS and RFS comparison results in lung cancer patients with higher CAR versus lower CAR. CAR, C-reactive protein to albumin ratio; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RFS, recurrence-free survival.

TABLE 1 Results of the OS subgroup analysis of the primary outcome.

		Heterogeneity			Meta-analysis		
Subgroup	***N***	***p***	***I*²** **(%)**	**Effect model**	**HR**	**95% CI**	***p*** **(*z* test)**
Total	12	0.763	0	Fixed-effect model	1.78	1.60–1.99	**
Study regions							
China	5	0.289	19.8	Fixed-effect model	1.71	1.51–1.94	**
non-China	7	0.997	0	Fixed-effect model	2.05	1.64–2.56	**
Treatment							
Surgery	5	0.986	0	Fixed-effect model	1.94	1.57–2.39	**
non-Surgery	3	0.857	0	Fixed-effect model	2.07	1.50–2.86	**
TNM							
I–III	4	0.964	0	Fixed-effect model	1.88	1.55–2.28	**
III–IV	3	0.760	0	Fixed-effect model	1.92	1.54–2.40	**
Type							
NSCLC	10	0.994	0	Fixed-effect model	1.95	1.71–2.23	**
SCLC	2	0.484	0	Fixed-effect model	1.49	1.24–1.80	**

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; SCLC, small cell lung cancer.
**$p < 0.01$.

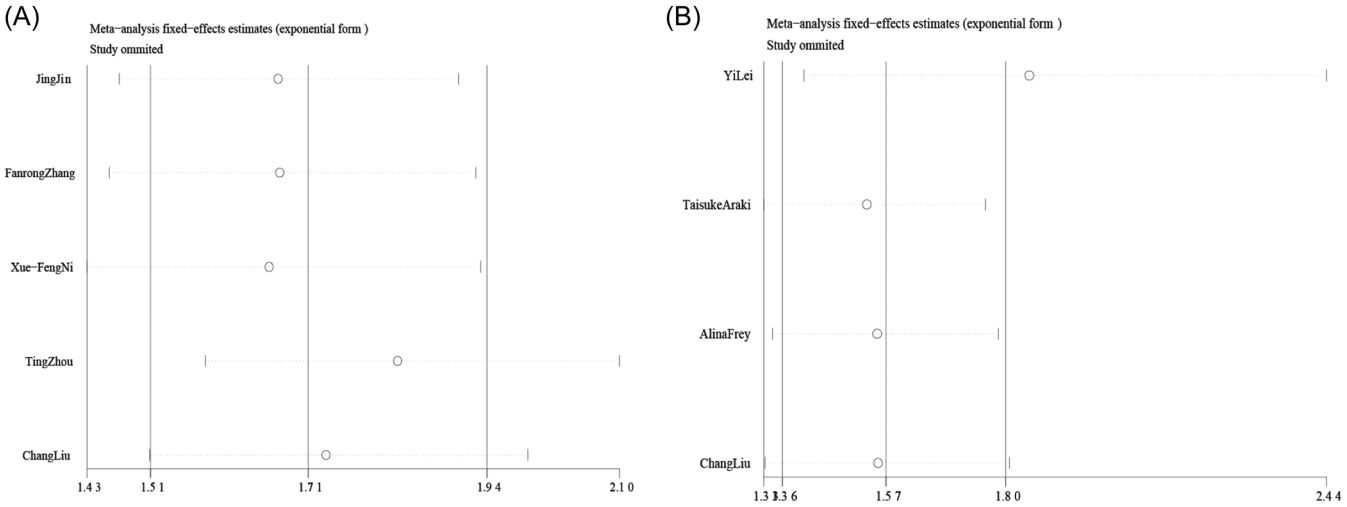

FIGURE 4 Sensitivity analyzes were performed for heterogeneity in the presence of countries (A) and PFS (B). PFS, progression-free survival.

reported, including a heterogeneity test, with $Q = 7.431$ and $p = 0.763$, adopting the fixed-effect model, resulting in a combined effect of HR = 0.579 with a 95% CI of (0.47–0.69). Then, the linear method was used to estimate the missing number of studies, which was calculated as six after four iterations. Finally, the data from the six virtual studies were added to the meta-analysis, and the overall results were re-analyzed. The heterogeneity test showed a Q value of 13.841 and $p = 0.678$, and the fixed-effect model was employed, resulting in a combined effect of HR = 1.684 with a 95% CI of (1.53–1.86). The final result indicated that $p < 0.05$, meaning that the addition of the six studies led to a reversal of the results. Therefore, there might be some instability in the OS estimate (Figure 5). Therefore, starting with subgroup analysis, Begg's test and Egger's test were conducted to explore potential sources of publication bias in studies on OS in both Chinese and non-Chinese populations. The results showed that there was no publication bias in the Chinese studies on OS (Begg's test, $z = 0.24$, $p = 0.806 > 0.05$; Egger's test, $t = 1.15$, $p = 0.334 > 0.05$). Similarly, there was no publication bias in the non-Chinese studies on OS (Begg's test, $z = 0$, $p = 1 > 0.05$; Egger's test, $t = -0.12$, $p = 0.910 > 0.05$). Thus, based on the initial OS (Begg's test, $z = 1.03$, $p = 0.304 > 0.05$; Egger's test,

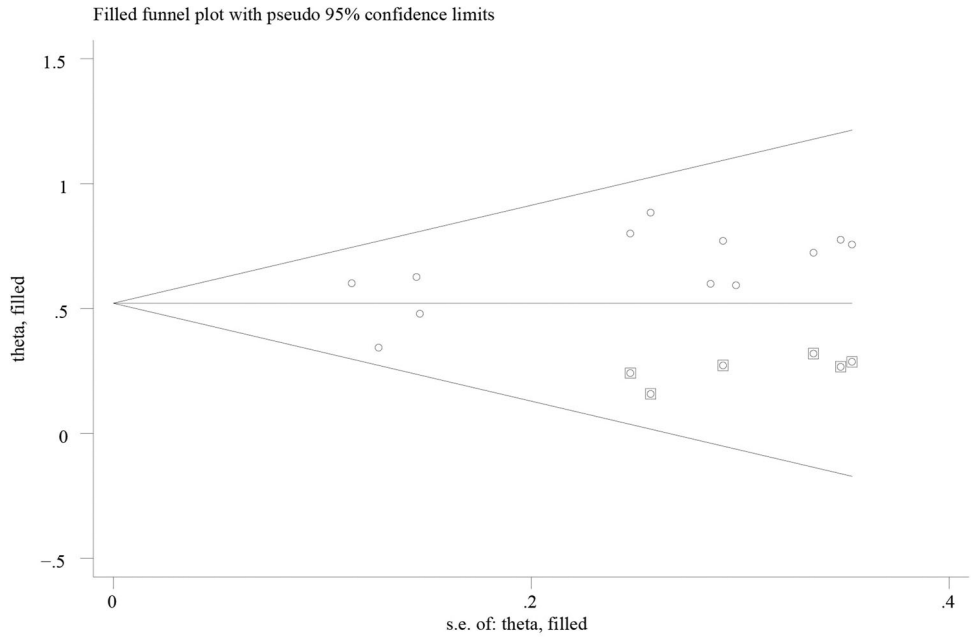

FIGURE 5 Using Trim and Fill method to detect the stability of the conclusion.

$t = 2.52$, $p = 0.03 < 0.05$) and results of bias detection published between subgroups, it can still be argued that the high CAR is still significantly associated with a poorer prognosis for lung cancer, at least based on both Chinese and non-Chinese studies. For a more definitive conclusion, further research may be required to provide additional support.

4 | DISCUSSION

This study conducted a meta-analysis of 16 articles to investigate the prognostic value of high levels of CAR in lung cancer patients in terms of OS, PFS, and RFS. Heterogeneity among the studies was examined and a fixed-effects model was used for the analysis, which revealed a significant association between high CAR levels and poor prognosis for all outcome measures, with HRs of 1.78 (95% CI = 1.60–1.99, $p < 0.001$) for OS, 1.57 (95% CI = 1.36–1.80, $p < 0.001$) for PFS and 1.97 (95% CI = 1.40–2.77, $p < 0.001$) for RFS. This result is consistent with the results of previous articles on the meta-analysis of CAR in patients with NSCLC.[41] Subgroup analyzes were performed for OS, which included country, pathology type, and treatment method, all of which confirmed the correlation between high CAR levels and poor prognosis in lung cancer patients. The study also investigated the prognostic value of high CAR levels in SCLC patients, finding that it may predict poor prognosis, similar to NSCLC. Sensitivity analyzes were performed for Chinese studies due to heterogeneity, and further investigation was conducted to identify its possible causes.

Chronic inflammation has emerged as a significant field of interest in cancer research due to its potential carcinogenic effects and its association with tumor progression.[42,43] The chronic inflammatory state promotes tumor development by producing inflammatory cytokines that affect the extracellular matrix and contribute significantly to cancer progression.[44,45] CRP, a significant inflammatory factor, can serve as a prognostic marker for various malignant tumors, including lung cancer, with decreased patient survival rates. Additionally, the association between low levels of albumin and poor prognosis has also been established.[7,15] However, limitations currently exist when using albumin and CRP as individual prognostic factors. For instance, heightened levels of these biomarkers may not solely be attributed to tumors, but rather to other diseases or conditions such as inflammation, infection, liver cirrhosis, myocardial infarction, surgery, trauma, and physiological stress. Additionally, there is interindividual variability in baseline CRP levels, making it challenging to determine significant increases. To continuously monitor CRP levels during the treatment process, measurement time and interval should be accurately determined while interpreting the results. Albumin's longer half-life of 2–3 weeks limits its ability to reflect short-term disease progression or treatment effects. When used as a single prognostic marker, albumin's predictive effect is weak. The use of CAR as a prognostic marker combination offers several advantages over individual biomarkers. CRP and albumin, which are synthesized in the liver, reflect the body's inflammatory and nutritional metabolic status. Advantages of CAR include: (1) greater specificity in reflecting abnormal conditions of inflammation and nutritional metabolism,

avoiding issues of misdiagnosis and missed diagnosis associated with individual biomarkers; (2) improved performance in predicting and assessing disease progression and treatment efficacy by more significantly demonstrating the body's conditions and functions; and (3) improved prognostic effect by more significantly reflecting the body's condition and function, enabling better prediction and assessment of disease progression and treatment efficacy. Therefore, CAR as a prognostic marker combination provides an improved evaluation of the body's nutritional metabolic status and inflammatory response, enhancing the accuracy of prediction and judgment, facilitating effective clinical treatment, and having a promising clinical application prospect.

This study had certain limitations, including: (1) all the included studies were retrospective, increasing the likelihood of bias. (2) Since there are relatively few studies related to the prognosis of CAR and SCLC, and only two of the present articles included are related to SCLC, further validation of the prognostic role of CAR in SCLC through meta-analysis in larger research data is required. (3) Also, most of the included articles are from East Asia (China, South Korea, Japan), with only two from Germany, thereby necessitating further evidence to establish the value of CAR in the prognosis of lung cancer patients in countries and regions outside these areas.

5 | CONCLUSION

This meta-analysis offers proof for the promising use of CAR as a prognostic tool in lung cancer, indicating it could be a valuable and noninvasive biomarker for identifying patients at high risk and guiding treatment in a cost-effective manner. Nevertheless, more extensive studies will be required to determine the best threshold value for CAR in lung cancer and validate these findings.

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AUTHOR CONTRIBUTIONS

Jinghui Wang and Zhendong Lu conceived and designed the study. Zhendong Lu, Siyun Fu, Xiang Gao, and Wei Li collected data. Zhendong Lu wrote the manuscript. All authors read and approved the final manuscript as submitted.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This meta-analysis study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All data used in this study were abstracted from published research articles and publicly available data sources, and the study did not involve any direct patient contact or intervention. Therefore, ethical approval was not required for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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