

The prognostic value of C-reactive protein to albumin ratio in patients with lung cancer

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Abstract

Background: To perform a meta-analysis of retrospective studies exploring the association of C-reactive protein to albumin (CAR) with overall survival (OS) in patients with lung cancer.

Methods: Relevant studies were enrolled by searching databases of PubMed, Cochrane Library, Web of Science, and Embase were searched until July 16, 2017. We combined the hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the correlation between CAR and OS in patients with lung cancer

Results: Four studies involving 1257 participants from several countries were involved in the meta-analysis. In a pooled analysis of all studies, elevated CAR predicted poor OS (HR: 2.13; 95% CI: 1.52–2.97; $P < .05$). Subgroup analysis showed that high level of CAR predicted poor OS in patients with lung cancer though multivariate analyses on 1092 participants (HR: 1.63; 95% CI: 1.24–2.51; $P < .001$) and the heterogeneity decreased to 45.4%. Moreover, a similar trend was observed in patients receiving surgery (HR: 2.64; 95% CI: 2.08–3.35; $P < .001$) and chemotherapy (HR: 1.75; 95% CI: 1.93–2.57; $P = .004$). And the HRs for patients receiving surgery was moderately higher than that for patients receiving chemotherapy.

Conclusion: Our findings indicate that CAR may have a prognostic value in lung cancer as we detected a significant association between elevated CAR and poorer OS. However, further studies are warranted to draw firm conclusions.

Abbreviations: CAR = C-reactive protein to albumin ratio, CIs = confidence intervals, GPS = Glasgow Prognostic Score, HRs = hazard ratios, NLR = neutrophil lymphocyte ratio, NOS = Newcastle-Ottawa quality assessment Scale, NSCLC = nonsmall cell lung cancer, OS = overall survival, PLR = platelet to lymphocyte ratio, SCLC = small cell lung cancer.

Keywords: CAR, lung cancer, prognosis, systemic inflammation

1. Introduction

Lung cancer is one of most common cancers and the leading cause of death in all cancers.^[1] Among people with smoking history, the death rate of lung cancer reduced 16% to 20% though computed tomography.^[2] Although the treatments for lung cancer have improved and the 5-year survival rate has decreased recent years, the ideal method to predict the prognosis of lung cancer remains unavailable.

Mounting evidence supported that high level of systemic inflammation is associated with poor survival in patients by

promoting cancer cell proliferation and survival, angiogenesis, tumor metastasis in many kinds of cancers.^[3,4] Inflammation-based prognostic scores, including neutrophil lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), Glasgow Prognostic Score (GPS) have been reported to have prognosis effect on patients with cancers.^[5–9] Recently, CAR showed its impact on a large variety of tumor types.^[10–18] CAR based on C-reactive protein and albumin, which not only presenting the inflammatory status but also the nutritional status may be a potential prognostic predictor for lung cancer. However, there were few studies regarding the effect of the CAR on prognosis in patients with lung cancer.^[19–23] Therefore, we collected the available publications and conducted a meta-analysis to investigate whether CAR has a prognostic value in patients with lung cancer in this present study.

2. Method

2.1. Search strategy

The databases of PubMed, Cochrane Library, Web of Science, and Embase were searched until July 16, 2017. The key words such as “lung carcinoma,” “Pulmonary Neoplasms,” “Pulmonary Cancer,” “Albumin, serum,” and “C-Reactive Protein” were used in combination. Reviews and reference lists were also manually retrieved for additional publications. The publication language was limited to English. The titles and abstracts were screened to identify related studies, and full texts were evaluated carefully. The published studies were sought with no restrictions of the minimum number of patients. All procedures performed in studies involving human participants were in accordance with the

Editor: Kou Yi.

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The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:50(e13505)

Received: 26 June 2018 / Accepted: 8 November 2018

<http://dx.doi.org/10.1097/MD.00000000000013505>

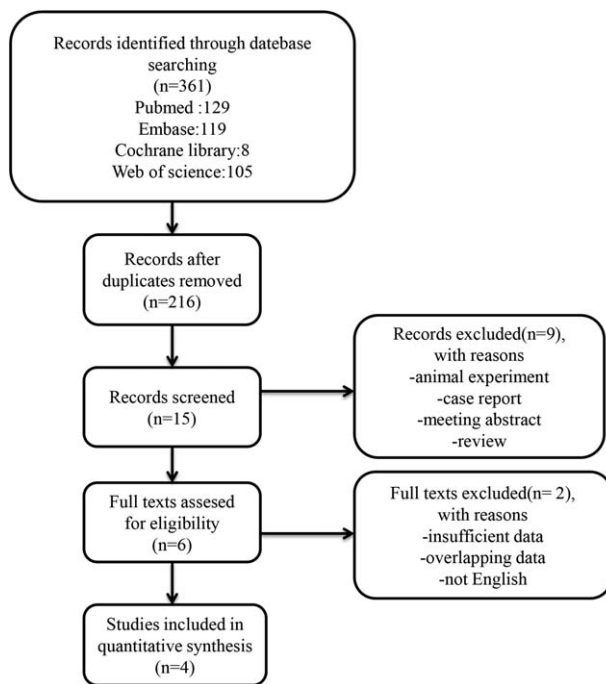


Figure 1. Flow chart of the study selection.

ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendment.

2.2. Eligibility criteria

The following inclusion criteria were used: retrospective or prospective study design; published before July 2017; patients were pathologically diagnosed as lung cancer; CAR was measured based on C-reactive protein and albumin of serum; provision of HRs and 95% CIs for CAR in OS or data necessary to calculate them; full text papers published in English.

The exclusion criteria were as follows: nonhuman studies; review, meeting abstract, and letter, not full text in English; did not present the value for CAR.

If data sets were overlapped or duplicated, only the most recent information was included in this meta-analysis. All identified studies were reviewed by 2 authors independently for eligibility.

2.3. Data extraction

The following information such as the surname of the first author, study country, year of publication, sample size, treatment

methods, and survival data were extracted from the eligible studies by 2 independent reviewers and any disagreement between them was resolved by discussion until consensus was reached.

2.4. Quality assessment

The quality assessment of primary studies was performed according to Newcastle-Ottawa quality assessment Scale (NOS). The full mark is 9 points and studies labeled with more than 6 points were regarded as high-quality researches (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

2.5. Statistical analysis

Statistical analysis was conducted using STATA 14.0 (STATA Corp, College Station, TX).^[18] We used the hazards ratios in univariate models to calculate the pooled HRs. HRs with 95% CIs were directly obtained from the articles or estimated from the K-M curves according to the methods reported by Tierney et al.^[19] Statistical heterogeneity among the studies was evaluated with Q and I^2 statistics, with the significance level set at $P < .05$.^[20] If there was significant heterogeneity among the studies, a random effects model was used to calculate the pooled HRs and 95% CIs.^[21] Sensitivity analyses to rule out overrepresentation of results from a single study in the meta-analysis were performed by excluding each study individually from the meta-analysis. The potential publication bias was evaluated using Begg's test.^[22] $P < .10$ was considered as statistically significant.

3. Result

3.1. The characteristics of included studies

The flow diagram of this study was presented in Fig. 1. A total of 4 studies with 1257 patients were enrolled in the meta-analysis.^[19–22] The sample sizes ranged from 108 to 617. These publications were retrospective studies and were conducted in Asia. Two of them were carried out in China.^[19,22] One of the remaining researches was conducted in Japan^[20] and another one was conducted in Korea.^[21] Seven hundred twenty-five patients from 2 studies,^[19,20] received the treatment of surgery for lung cancer and 532 patients from another 2 researches received the treatment of chemotherapy or other palliative treatment. Only 1 study involved patients with small cell lung cancer (SCLC)^[22] and the remaining studies included patients with nonsmall cell lung cancer (NSCLC). Different studies use the different cut-off value of CAR, which is shown in Table 1. Almost all studies provided the HRs. We calculated them from K-M curve though the method mentioned before if there was no HRs was reported in articles.

Table 1

Characteristics of all included studies.

Study	Year	Location	Ethnicity	Follow-up (month)	Sample size	Gender (M/F)	TNM stage	Treatment	Outcomes	HR	Cut-off value	NOS
Zhang et al ^[19]	2017	China	Asian	50 (median)	617	461/410	I–IV	surgery	OS/PFS	R	0.424	9
Miyazaki et al ^[20]	2017	Japan	Asian	33.6 (median)	108	69/39	I–IV	surgery	OS	R	0.028	6
Koh and Lee ^[21]	2017	Korea	Asian	9 (median)	165	115/50	IV	chemotherapy	OS	E	0.195	8
Zhou et al ^[22]	2015	China	Asian	29.4 (median)	367	316/51	I–IV	chemotherapy	OS	E	0.441	7

95% CI = 95% confidence intervals, E = estimated from the K-M curves, HR = hazard ratios, NOS = Newcastle-Ottawa quality assessment Scale, OS = overall survival, PFS = progression-free survival, R = reported in article.

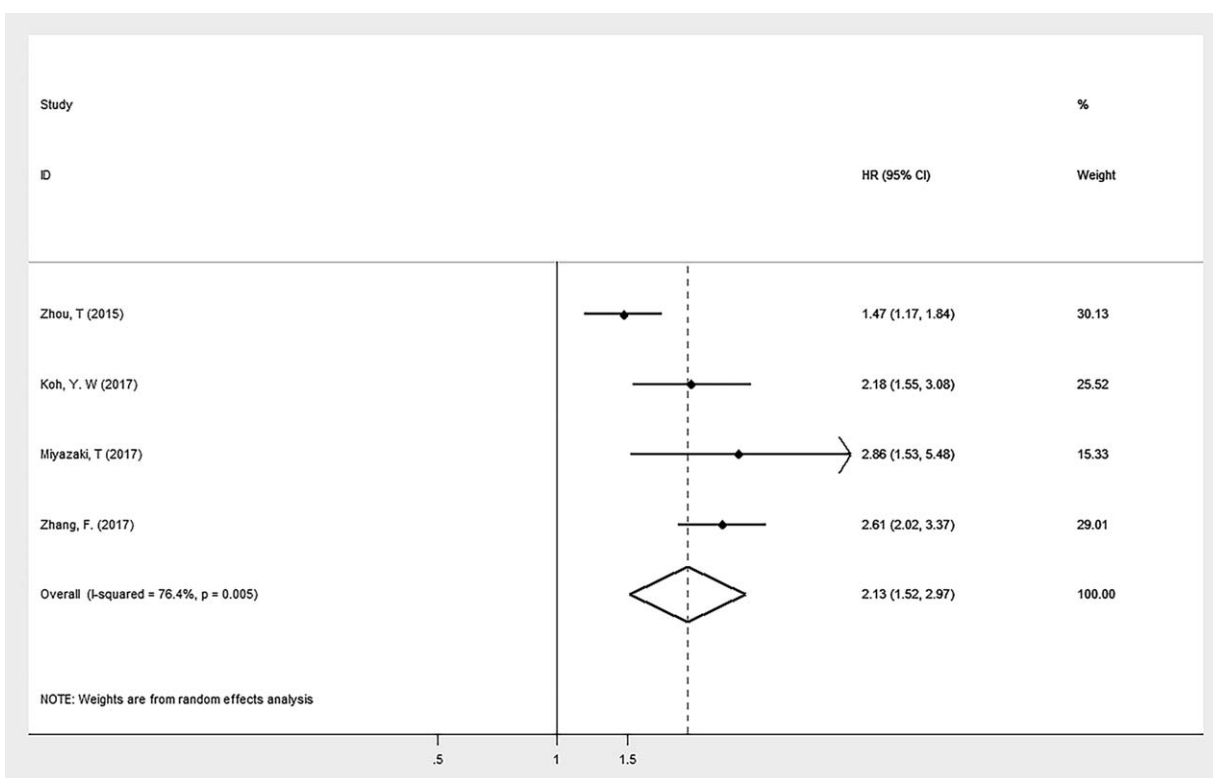


Figure 2. Forest plot of the association between CAR and OS in patients with lung cancer.

Moreover, all studies defined OS as the time from diagnosis to day of death or last follow-up. The researches were published from 2015 to 2017 and the NOS scores of the included studies ranged from 6 to 9. The detail information is provided in Table 1.

3.2. Relationship between CAR and OS in lung cancer

Four researches with 1257 enrolled population provide the data of CAR before treatment and OS. The random effects model showed a significant relationship between elevated CAR and OS in patients with lung cancer (HR: 2.13; 95% CI: 1.52–2.97; $P < .05$) with high heterogeneity ($I^2 = 76.4%$, $P < .001$, Fig. 2).

3.3. Subgroup analyses

To detect the potential source of heterogeneity, subgroup analyses stratified by different adjustment, treatment and sample size were conducted (Table 2, Fig. 3). The HRs of 3 studies were adjusted by different confounding factors, such as sex, age, and

so on. As shown in Table 2, multivariate analyses on 1092 participants showed that high level of CAR predicted poor OS in patients with lung cancer (HR: 1.63; 95% CI: 1.24–2.51; $P < .001$) and the heterogeneity was decreased to 45.4%. We also conducted subgroup analysis based on treatment to further explain the results of this meta-analysis. A similar trend was observed in patients receiving chemotherapy and surgery (Table 2). And the HRs for patients receiving surgery was moderately higher than that for patients receiving chemotherapy (HR for surgery vs chemotherapy; 2.64 vs 1.75).

If enrolled patients were more than 200 in study, we defined the study as the one with big sample size. Then we perform subgroup analysis based on different sample size. Almost the same result was observed in studies with big or small sample size (Table 2).

3.4. Sensitivity analysis and publication bias

Significant heterogeneity was discovered among all studies ($I^2 = 76.4%$, $P < .01$). However, heterogeneity decreased after sub-

Table 2
A summary of HR for the overall and subgroup analyses of GPS and lung cancer.

		No. of studies	No. of participants	HR	95% CI	P	I ² (%)
Overall		4	1257	2.13	1.52–2.97	<.05	76.4
Adjustment	Multivariate	3	1092	1.63	1.24–2.51	<.001	45.4
	Univariate	1	165	2.18	1.55–3.08	<.05	—
Sample size	>200	2	984	1.95	1.11–3.43	.02	90.8
	<200	2	273	2.32	1.71–3.14	<.001	0
Treatment	Surgery	2	725	2.64	2.08–3.35	<.001	0
	Chemotherapy	2	532	1.75	1.93–2.57	.004	71.6

95% CI = 95% confidence intervals, HR = hazard ratios.

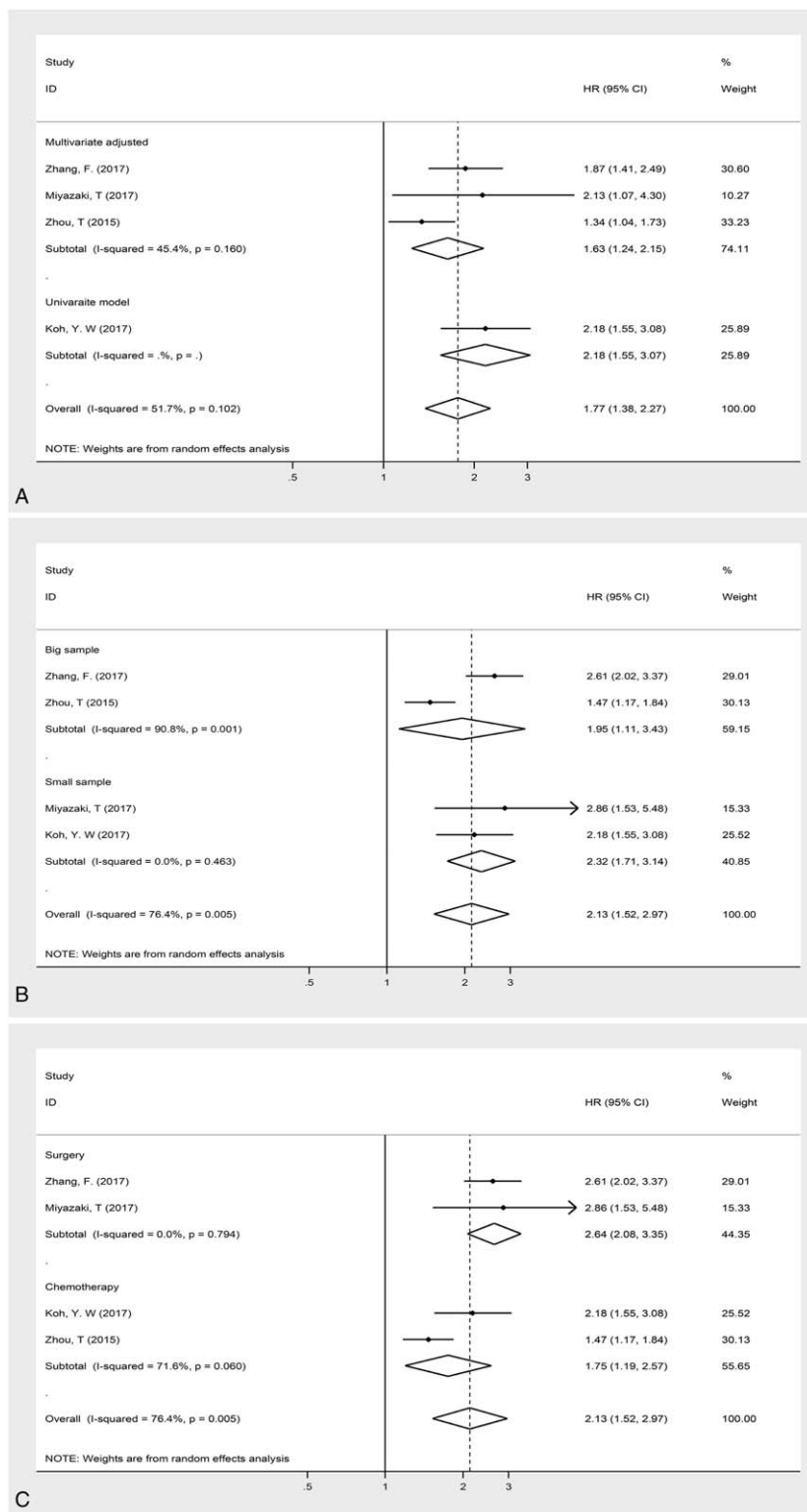


Figure 3. Forest plot of the association between CAR and OS in patients with lung cancer stratified by adjustment, sample size, and treatment.

group analysis. The influence of each single study was evaluated by excluding each study individually from the meta-analysis. The results showed that the pooled HRs for OS were robust in our study (Fig. 4). Moreover, Begg’s test and the funnel plot showed no evidence of obvious publication bias ($P = .500$) (Fig. 5).

4. Discussion

In this study, we investigated utility of CAR as prognostic factors in lung cancer by meta-analysis of 1257 patients. We found that elevated level of CAR was significantly correlated with poor OS before treatment. Moreover, when we conducted subgroup based

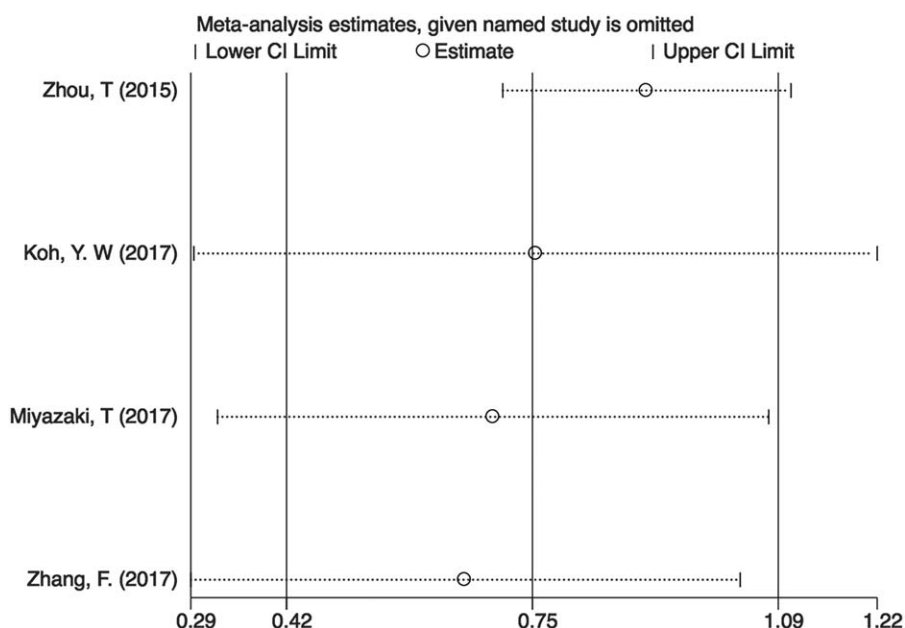


Figure 4. Sensitivity analysis on the relationship between CAR and OS in lung cancer.

on treatment and different adjustment, the heterogeneity decreased and for patients receiving surgery, the poor OS was more closely associated with elevated CAR than those receiving chemotherapy. The results of different subgroup still showed that elevated CAR was a prognostic factor for OS in lung cancer.

More and more researches revealed that the host systemic inflammatory response plays a critical role in the development and progression of many cancers.^[24,25] However, the mechanism by which inflammatory factors may impact prognosis remains unclear. As a biomarker of system inflammation, C-reactive protein (CRP) is a kind of acute reactive protein synthesized by liver cells, which is caused by microbial invasion and tissue injury.^[26] And its prognostic value in patients with various types of cancer was investigated in many researches.^[27-33] The CAR was primarily used to predict 90-day mortality in sepsis by Ranzani et al.^[34] Then its prognostic value was explored in various of cancers.^[10-16,18,22] More recently, Kinoshita et al^[35] and Chen et al^[10] found that CAR has better performance in predicting

prognosis than other inflammation-based factors in renal and hepatocellular carcinoma. Then, CAR that not only indicate the inflammatory status but also the nutritional status showed its potential prognostic value for lung cancer in some researches^[19-22] and we assessed this in our study. Our result showed that elevated CAR indicated a worse outcome in patients receiving surgery and chemotherapy though multivariate and univariate analyses, which was in accordance with the previous studies.^[19,20,22]

There were some limitations in our study. First, only 4 retrospective studies were included in this current meta-analysis and high heterogeneity existed in this meta-analysis, even after subgroup analyses. Though there was no significant bias after careful evaluation and our result remained stable. Second, participants from enrolled studies were at different clinical stages. Four hundred ninety patients with advanced stages (III and IV) and 767 patients with early stages (I and II) were involved in this meta-analysis, but we were not able to perform a subgroup analysis according to different clinical stages due to the insufficient data we can get from the article. Besides, we were not able to conduct a subgroup analysis according the pathological type of lung cancer, also due to the insufficient data. Finally, different studies use different cut-off value for CAR, which may be an important factor affecting the outcome.

To sum up, our study was the first to demonstrate the prognostic role of increased CAR for poor OS, and for patients receiving surgery, the poor OS was more closely associated with elevated CAR than those receiving chemotherapy. However, given the limitations mentioned above, these findings should be treated with caution when applied to clinical practice. More prospective cohort studies are warranted to test our results.

Author contributions

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Formal analysis: Tai-Bing Deng, Jing Zhang.

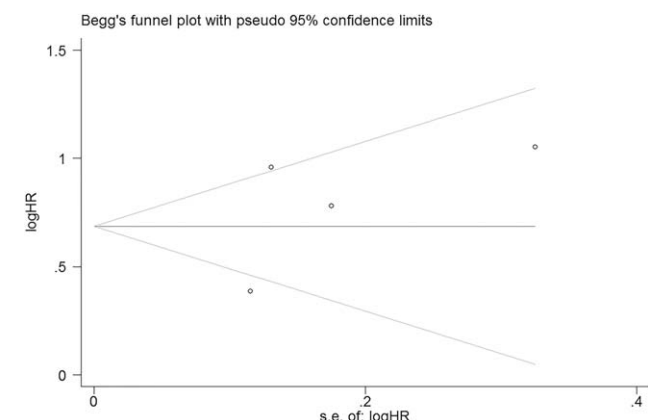


Figure 5. Begg's funnel plot of publication bias test for CAR and OS in lung cancer.

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Project administration: Jing Zhang.

Resources: Jing Zhang.

Software: Jing Zhang.

Writing – original draft: Tai-Bing Deng, Jing Zhang, Yong-Zhao Zhou, Weimin Li.

Writing – review & editing: Tai-Bing Deng, Jing Zhang, Yong-Zhao Zhou, Weimin Li.

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