

Prognostic value of C-reactive protein/albumin ratio in renal cell carcinoma: a systematic review and meta-analysis

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Abstract

Background: There are a mass of studies declared the prognostic significance of C-reactive protein/albumin ratio (CRP/Alb) in renal cell carcinoma (RCC). Nevertheless, these works are controversial. In our study, we investigate the expression of CRP/Alb in RCC and its role in prognosis and clinicopathological features. **Methods:** The PubMed, Embase and Cochrane databases were searched systematically for correlative articles published before August 1, 2019. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined according to eligible studies. And we use fixed and random effects models to calculate on the basis of heterogeneity. **Results:** Six relevant studies were identified in this study, 1959 participants included in total. Our results showed that CRP/Alb was related to poor overall survival (HR=1.86, 95% CI: 1.56-2.21). In addition, CRP/Alb was also associated with tumor stage (OR=3.29, 95% CI: 1.66-6.50), lymph node involvement (OR=3.76, 95% CI: 2.57-5.51), metastasis (OR=5.69, 95% CI: 2.40-13.51), Fuhrman nuclear grade (OR=4.21, 95% CI: 3.14-5.64), pTNM (OR=4.34, 95% CI: 1.94-9.70) and tumor size (WMD=2.26, 95% CI: 1.86–2.67). However, CRP/Alb was not associated with necrosis. **Conclusion:** Our study illustrates that the higher CRP/Alb expression was correlated with poorer prognosis and more advanced clinicopathological features in RCC patients. High CRP/Alb expression may act as a valuable predictive biomarker for poor prognosis in RCC patients.

Background

Renal cell carcinoma (RCC) represents 5% and 3% of the malignancies in males and females respectively, is the most common neoplasm of kidney [1-3]. In spite of the development of diagnosis and treatment for RCC, like abdominal ultrasound, computerized tomography, surgical methods improvement, targeted therapy and immunotherapy, the patient's prognosis is still poor in the long-term, given 40% patients will eventually relapse and distal metastasis [3, 4]. Thus, some precise prognostic factors that could predict the outcome of RCC patients is in urgent need.

A great deal of evidences has elucidated the role of inflammation in tumor formation and progression [5, 6]. For instance, neutrophil level, platelet level, CRP, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, some parameters derived from blood tests have been proven to independently predict clinical outcomes of various human cancer types, including RCC [7-16]. A new prognostic index, preoperative C-reactive protein/albumin (CRP/Alb) ratio, together with the systemic inflammation and nutritional status come to researcher's eyes recently. It has also been declared as an independent prognostic marker in RCC. Due to differences in study design, sample size, and other factors, CRP/Alb in RCC patients reported some opposite results. Therefore, it is time to shine a light on performing a systematic meta-analysis to understand the prognostic value of CRP/Alb in patients with RCC.

In our study, we evaluated the prognostic significance of CRP/Alb for overall survival (OS) and clinicopathological value in those with RCC by gathering the available outcome data.

Methods

Search strategy

This study is based on the accepted top-notch report for systematic reviews and meta-analyses, and we chose to use this commonly used protocol for this study [17]. The PubMed, Embase and Cochrane databases were searched systematically for correlative articles published before August 1, 2019. We searched for keywords: “renal cell carcinoma” or “renal cancer” or “kidney cancer” and “C-reactive protein/albumin ratio” and “prognosis” or “survival” or “outcome” in humans. The language of the articles included in this study must be in English, regardless of the language of other languages.

Inclusion and exclusion criteria

We identified articles in this meta-analysis according to the following criteria: 1) the prognostic indicator of CRP/Alb needs to be OS; 2) all patients must undergo a final pathological diagnosis of RCC; 3) hazard ratios (HRs) and the 95% CIs for survival analysis could be gotten.

The exclusion criteria were described below: 1) animal studies, non-English articles; 2) specific paper types such as abstract, case report, review, or letter; 3) duplicate publications; 4) with incomplete data to obtain the HR and 95% CIs.

Data extraction and quality

The data was evaluated by two independent reviewers, and if there were inconsistencies, they were discussed together with the participation of QLC. We assess the quality of selected items on the basis of the Newcastle-Ottawa Scale (NOS) [18]. A high-quality study should get a score of six or higher. We recorded information for each study as follows: first author, time of publication, origins, participant number, cut-off value, the amounts of patients with positive CRP/Alb, HR for survival (OS), and follow-up time.

Statistical analysis

The statistical analysis was conducted on Stata SE14.0 (Stata Corp LP, USA). HRs and 95% CIs were applied to evaluate the relations between CRP/Alb expression and OS. Similarly, ORs (odds ratios) and 95% CIs were used to illustrate the interaction between CRP/Alb expression and clinicopathological features. We use the chi-square test and I^2 statistic ($100\% \times [(Q-df)/Q]$) to evaluate inter-study heterogeneity [19, 20], the value of P (heterogeneity) <0.05 or $I^2 >50\%$ was considered statistically significant. When the value of P (heterogeneity) is >0.05 or $I^2 <50\%$, we choose to use the fixed effect model, otherwise we choose to use the random effect model. We chose to use a funnel chart to measure publication bias. $P < 0.05$ indicates statistical significance.

Results

Study Characteristics

The search strategy of the current meta-analysis identified a total of 617 literature. Overall, 570 records, identified irrelevant by title and abstract screening, were excluded; and the remained 47 records, which investigated the correlation between CRP/Alb reactivity and survival outcomes of patients with RCC, were evaluated in full text. To meet our inclusion and exclusion criteria, six articles of five literatures [21-25] were eligible and eventually included in our study for analysis of the relationship between CRP/Alb and outcomes of the RCC patients. Our work flowchart is shown in Fig. 1. Major characteristics of these studies are summarized in Table 1. The number of cohorts of each study ranged from 108 to 699, for a total of 1959 patients. The cut-off value to distinguish high CRP/Alb reactivity from low CRP/Alb was set from 5% to 11.5%. The median follow-up periods range from 54.5 to 73 months.

Prognostic value of CRP/Alb for OS

The correlation between CRP/Alb and prognosis for OS in patients with RCC were evaluated using pooled HRs and 95% CIs displayed in Table 2 and Fig. 2. All the HRs data were obtained owing to the multivariate analysis and the results implied that CRP/Alb predicted worse OS (HR=1.56, 95% CI: 1.30-1.87, P<0.001).

Evaluation of CRP/Alb and clinicopathological characteristics

The Table 2 and Fig. 3 shows the association between CRP/Alb and clinicopathological features in the RCC patients. CRP/Alb was significantly associated with tumor stage (T3/T4 vs T1/T2, OR=3.29, 95% CI: 1.66-6.50, P=0.001, Fig. 3a), lymph node involvement (N1 vs N0, OR=3.76, 95% CI: 2.57-5.51, P<0.001, Fig. 3b), metastasis (M1 vs M0, OR=5.69, 95% CI: 2.40-13.51, P<0.001, Fig. 3c), Fuhrman nuclear grade (III/IV vs I/II, OR=4.21, 95% CI: 3.14-5.64, P<0.001, Fig. 3d), pTNM (III/IV vs I/II, OR=4.34, 95% CI: 1.94-9.70, P<0.001, Fig. 3e) and size (WMD=2.26, 95% CI: 1.86–2.67, P<0.001, Fig. 3f). However, CRP/Alb do no relationship with necrosis (positive vs negative, OR=2.31, 95% CI: 0.83-6.43, P=0.108).

Publication bias

Funnel plot of meta-analysis for OS (Fig. 4a), tumor stage (Fig. 4b), lymph node involvement (Fig. 4c), metastasis (Fig. 4d), Fuhrman nuclear grade (Fig. 4e), pTNM (Fig. 4f) and size (Fig. 4g) were evaluated for publication bias. The funnel plots for OS and clinical features implied no obvious publication bias.

Sensitivity analysis

We perform a sensitivity analysis to assess the stability of results and to lessen the effect of the individual studies on the final conclusions. The results indicated that for OS, the pooled result would not alter prominently when excluded a certain study (Fig. 5).

Discussion

For RCC, it is well known that the TNM staging system is a commonly used prognostic factor, but it is a postoperative indicator and cannot accurately predict the patient's clinical course. As the research

progressed, we gradually found that many patients at the same stage or level faced completely different results, so we need an preoperative indicator that can predict the clinical course well. In the nineteenth century, Virchow originally found the connection between cancer and inflammation [6]. Gradually, the opinion that inflammation has an important role in carcinogenesis was widely recognized [26-29]. Except the secretion of inflammatory cells, cancer-related inflammation consists of inflammatory cytokines produced by cancer cells themselves and tumor-associated leukocytes during the process of tissue remodeling, tissue repair and angiogenesis [5, 30].

In this study, we evaluated the prognostic significance of CRP/Alb in RCC patients. Given laboratory examination are routinely performed in those patients before treatment, the CRP/Alb is an easily accessible, and convenient measure of the systemic inflammatory response. There are some studies show a relationship between CRP/Alb and prognosis in multiple cancers, RCC included [31-34]. But researchers have not reached a consensus. Hence, we performed this study to investigate the association between CRP/Alb and prognostic value and clinicopathological features in RCC patients.

This meta-analysis was to systematically evaluate the correlation between CRP/Alb and the prognosis of RCC patients. We report a systematic review of 1959 patients included in five literatures. Consistently, the results indicated that the increasing CAR was associated with shorter OS significantly and acted as an independent prognostic factor for RCC patients. According to univariate and multivariate analysis results showed that CRP/Alb predicted worse OS.

The correlation between CRP/Alb and clinicopathological characteristics was evaluated at the same time. The result implied that CRP/Alb were associated with primary tumor stage, regional lymph node involvement, distant metastases, Fuhrman nuclear grade, pTNM stage, and size in RCC patients significantly. The higher CRP/Alb was associated with a higher tumor stage Fuhrman nuclear grade and pTNM stage. Our study indicated that the CRP/Alb can be a prognostic factor in N1 and M1 RCC patients. Furthermore, we found that higher CRP/Alb was likely to have a larger tumor size. However, CRP/Alb was not associated with necrosis.

We should and must acknowledge that there are some limitations in this study alone. First, the criteria for determining CRP/Alb positive expression are inconsistent in the different literature we have included, which of course may lead to some heterogeneity. Therefore, we believe that more research is needed in the future to support the establishment of a more unified standard. Second, the number of patients included in some included studies is relatively small. Therefore, there should be some large-scale studies in the future to conceive more reliable results. Finally, although not detected in the present analysis, the publication bias actually could exist because research with positive results have much more possibilities to be published than negative [35].

Conclusions

Our study implies that high CRP/Alb is associated with a poor OS in RCC patients. The results also suggest that high CRP/Alb play a role in more aggressive clinical features in those patients. Therefore, we

might benefit from the detection of CRP/Alb when make clinical decision and evaluate prognosis for RCC patients in the future. To clarify our results, some more prospective and large-scale studies are needed.

Abbreviations

CRP/Alb: C-reactive protein/albumin ratio; RCC: Renal cell carcinoma; HR: Hazard ratios; CI: Confidence interval; NOS: Newcastle-Ottawa Scale; OS: Overall survival

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed in the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

HS designed and drafted the manuscript. SJ collected data. PX and SL performed the analysis. SH and JJ was involved in research design, data interpretation, supervision of the analysis. All authors read and approved the final manuscript.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
2. Petejova N, Martinek A. Renal cell carcinoma: Review of etiology, pathophysiology and risk factors. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2016;160(2):183-94.
3. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol.* 2015;67(5):913-24.
4. Park YH, Baik KD, Lee YJ, Ku JH, Kim HH, Kwak C. Late recurrence of renal cell carcinoma >5 years after surgery: clinicopathological characteristics and prognosis. *BJU Int.* 2012;110(11 Pt B):E553-8.
5. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature.* 2008;454(7203):436-44.
6. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet.* 2001;357(9255):539-45.
7. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol.* 2010;6(1):149-63.
8. Ocana A, Nieto-Jimenez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. *Mol Cancer.* 2017;16(1):137.
9. Faget J, Groeneveld S, Boivin G, Sankar M, Zangger N, Garcia M, et al. Neutrophils and Snail Orchestrate the Establishment of a Pro-tumor Microenvironment in Lung Cancer. *Cell Rep.* 2017;21(11):3190-204.
10. Wojtukiewicz MZ, Sierko E, Hempel D, Tucker SC, Honn KV. Platelets and cancer angiogenesis nexus. *Cancer Metastasis Rev.* 2017;36(2):249-62.
11. Franco AT, Corken A, Ware J. Platelets at the interface of thrombosis, inflammation, and cancer. *Blood.* 2015;126(5):582-8.
12. Ma Z, Qi Z, Shan Z, Li J, Yang J, Xu Z. The role of CRP and ATG9B expression in clear cell renal cell carcinoma. *Biosci Rep.* 2017;37(6).
13. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer-j Iaslc.* 2017;111:176-81.
14. Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2014;106(6):dju124.
15. Prodromidou A, Andreakos P, Kazakos C, Vlachos DE, Perrea D, Pergialiotis V. The diagnostic efficacy of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in ovarian cancer. *Inflamm Res.*

- 2017;66(6):467-75.
16. Yodying H, Matsuda A, Miyashita M, Matsumoto S, Sakurazawa N, Yamada M, et al. Prognostic Significance of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Oncologic Outcomes of Esophageal Cancer: A Systematic Review and Meta-analysis. *Ann Surg Oncol*. 2016;23(2):646-54.
 17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
 18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-5.
 19. Handoll HH. Systematic reviews on rehabilitation interventions. *Arch Phys Med Rehabil*. 2006;87(6):875.
 20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj*. 2003;327(7414):557-60.
 21. Tsujino T, Komura K, Hashimoto T, Muraoka R, Satake N, Matsunaga T, et al. C-reactive protein-albumin ratio as a prognostic factor in renal cell carcinoma - A data from multi-institutional study in Japan. *Urol Oncol*. 2019.
 22. Guo S, He X, Chen Q, Yang G, Yao K, Dong P, et al. The C-reactive protein/albumin ratio, a validated prognostic score, predicts outcome of surgical renal cell carcinoma patients. *BMC Cancer*. 2017;17(1):171.
 23. Chen Z, Shao Y, Fan M, Zhuang Q, Wang K, Cao W, et al. Prognostic significance of preoperative C-reactive protein: albumin ratio in patients with clear cell renal cell carcinoma. *Int J Clin Exp Pathol*. 2015;8(11):14893-900.
 24. Konishi S, Hatakeyama S, Tanaka T, Ikehata Y, Tanaka T, Hamano I, et al. C-reactive protein/albumin ratio is a predictive factor for prognosis in patients with metastatic renal cell carcinoma. *Int J Urol*. 2019.
 25. Gao J, Agizamhan S, Zhao X, Jiang B, Qin H, Chen M, et al. Preoperative C-reactive protein/albumin ratio predicts outcome of surgical papillary renal cell carcinoma. *Future Oncol*. 2019;15(13):1459-68.
 26. Gao F, Liang B, Reddy ST, Farias-Eisner R, Su X. Role of inflammation-associated microenvironment in tumorigenesis and metastasis. *Curr Cancer Drug Targets*. 2014;14(1):30-45.
 27. Bonomi M, Patsias A, Posner M, Sikora A. The role of inflammation in head and neck cancer. *Adv Exp Med Biol*. 2014;816:107-27.
 28. Bishayee A. The role of inflammation and liver cancer. *Adv Exp Med Biol*. 2014;816:401-35.
 29. Mantovani A. Molecular pathways linking inflammation and cancer. *Curr Mol Med*. 2010;10(4):369-73.
 30. Santos J, Fernandes E, Ferreira JA, Lima L, Tavares A, Peixoto A, et al. P53 and Cancer-Associated Sialylated Glycans Are Surrogate Markers of Cancerization of the Bladder Associated with

Schistosoma haematobium Infection. PLoS Neglected Tropical Diseases. 2014;8(12).

31. Mao M, Wei X, Sheng H, Chi P, Liu Y, Huang X, et al. C-reactive protein/albumin and neutrophil/lymphocyte ratios and their combination predict overall survival in patients with gastric cancer. *Oncol Lett.* 2017;14(6):7417-24.
32. Li YJ, Yao K, Lu MX, Zhang WB, Xiao C, Tu CQ. Prognostic value of the C-reactive protein to albumin ratio: a novel inflammation-based prognostic indicator in osteosarcoma. *Onco Targets Ther.* 2017;10:5255-61.
33. Arima K, Yamashita YI, Hashimoto D, Nakagawa S, Umezaki N, Yamao T, et al. Clinical usefulness of postoperative C-reactive protein/albumin ratio in pancreatic ductal adenocarcinoma. *Am J Surg.* 2018;216(1):111-5.
34. Liu Y, Chen S, Zheng C, Ding M, Zhang L, Wang L, et al. The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer. *BMC Cancer.* 2017;17(1):285.
35. Sutton AJ, Song F, Gilbody SM, Abrams KR. Modelling publication bias in meta-analysis: a review. *Stat Methods Med Res.* 2000;9(5):421-45.

Tables

Table 1 Main characteristics of included studies

Year	Country	No. of patients	Mean age	Gender (F/M)	Median follow-up	Cut-off (%)	NOS
2015	China	406	58	253/153	63	<6 vs 6-11.5	7
2015	China	406	58	253/153	63	<6 vs >11.5	7
2017	China	570	51.43	382/188	63.54	8	8
2018	China	108	57	78/30	54.5	9.4	6
2019	Japan	699	61.9	500/199	73	7.3	7
2019	Japan	176	67	129/47	-	5	6

Table 2 Meta-analysis of C-reactive protein/albumin ratio for OS and clinicopathological features in renal cell carcinoma

Group	No. of studies	P (heterogeneity)	I ² (%)	Effect model	OR (95% CI)	P-value
OS	6	0.011	66.6	Random	1.56(1.30-1.87) *	<0.001
T (T3/T4 vs T1/T2)	6	<0.001	81.6	Random	3.29(1.66-6.50)	0.001
N (N1 vs N0)	6	0.083	48.7	Random	3.58(1.98-6.47)	<0.001
M (M1 vs M0)	5	0.014	68.1	Random	5.69(2.40-13.51)	<0.001
Fuhrman (III/IV vs I/II)	3	0.171	43.4	Fixed	4.21(3.14-5.64)	<0.001
pTNM (III/IV vs I/II)	4	0.015	71.4	Random	4.34(1.94-9.70)	<0.001
Necrosis (+ vs -)	3	0.028	72.2	Random	2.31(0.83-6.43)	0.108
Size	2	0.429	0	Fixed	2.26(1.86-2.67)	<0.001

**

Notes: *HR (95% CI), ** WMD (95% CI).

Figures

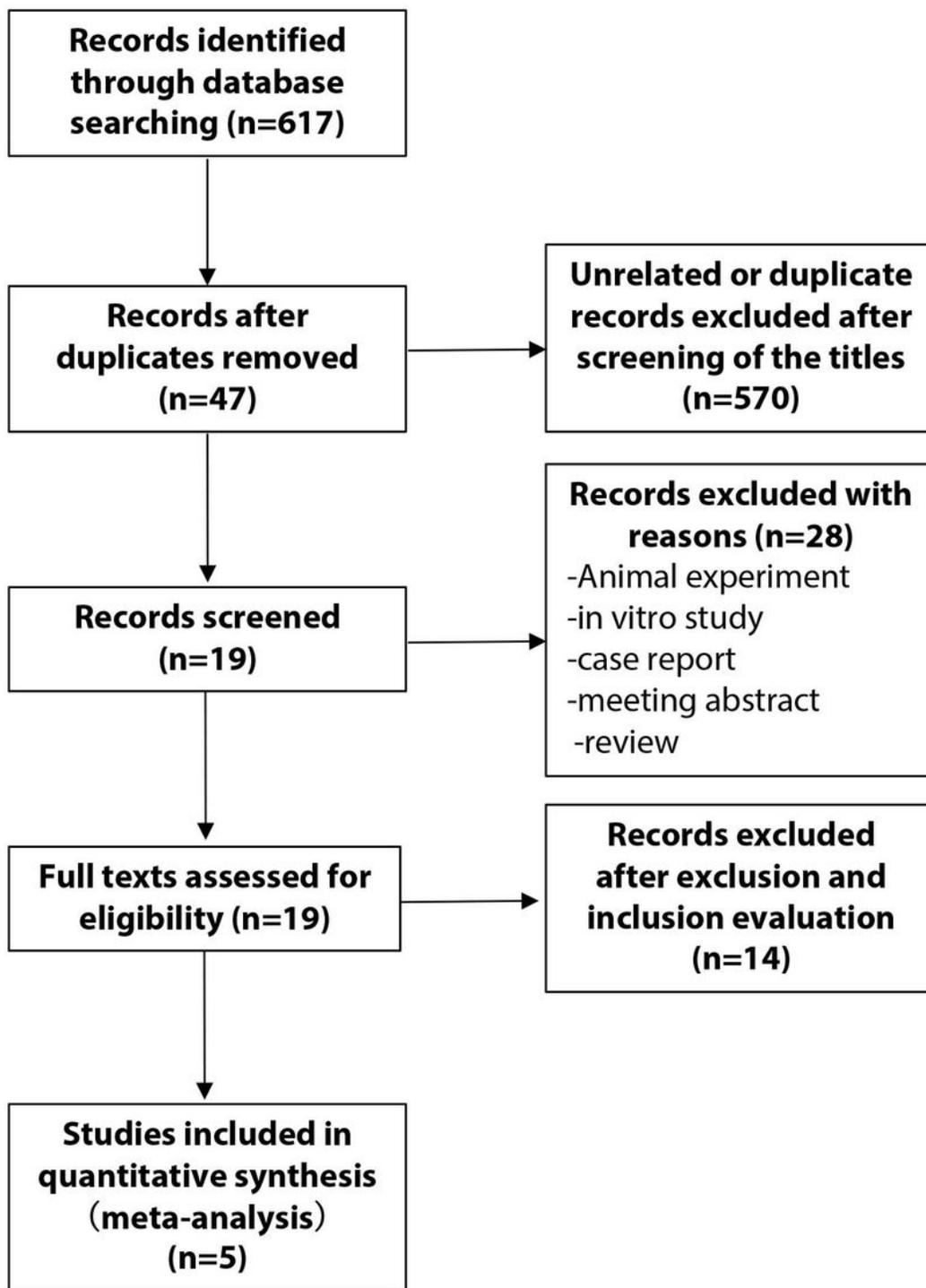


Figure 1

Flow diagram of the study selection process.

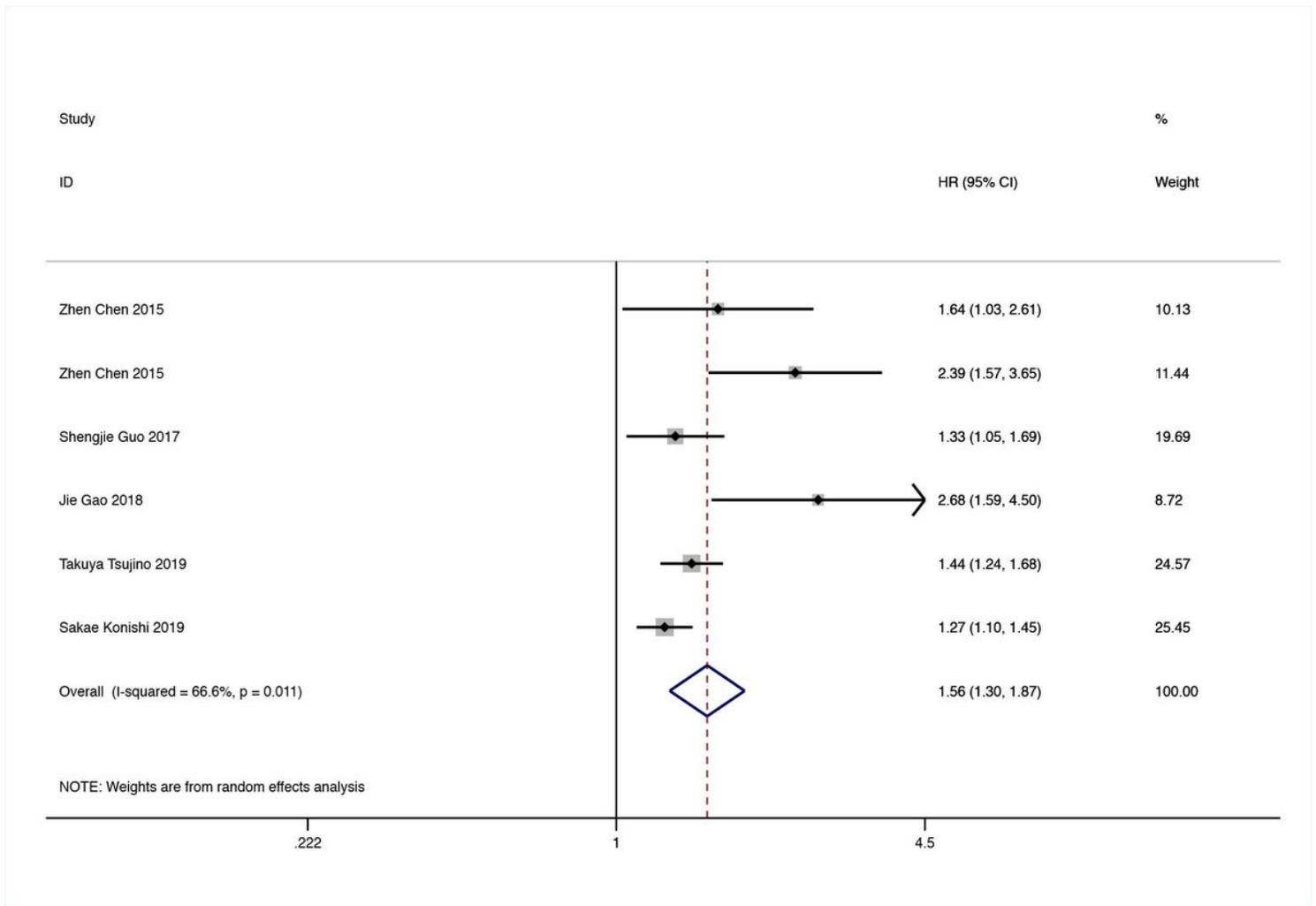
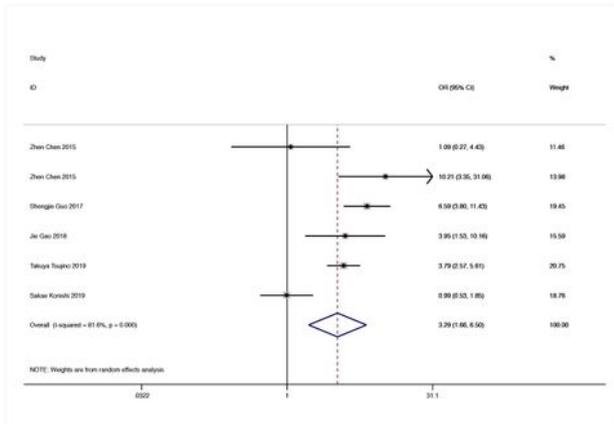


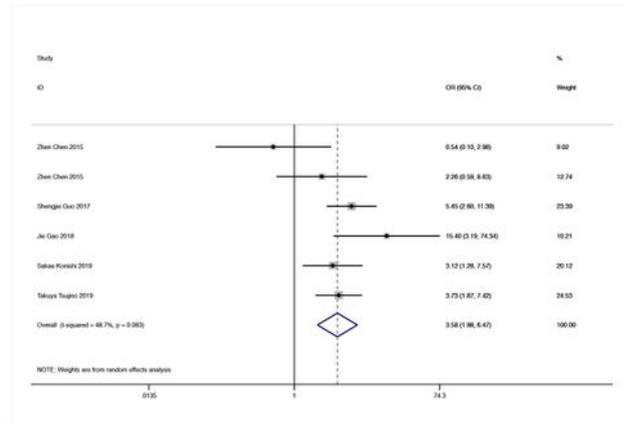
Figure 2

Forest plot HR for the correlation between C-reactive protein/albumin ratio and OS in RCC patients based on univariate, multivariate and overall analysis.

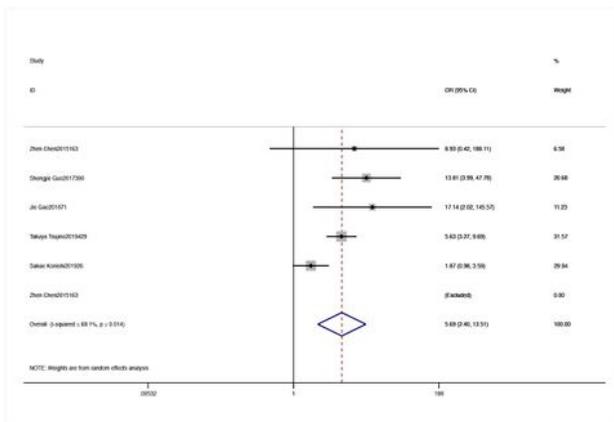
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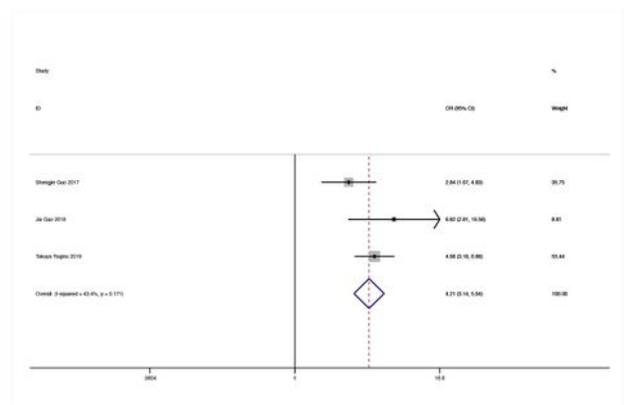
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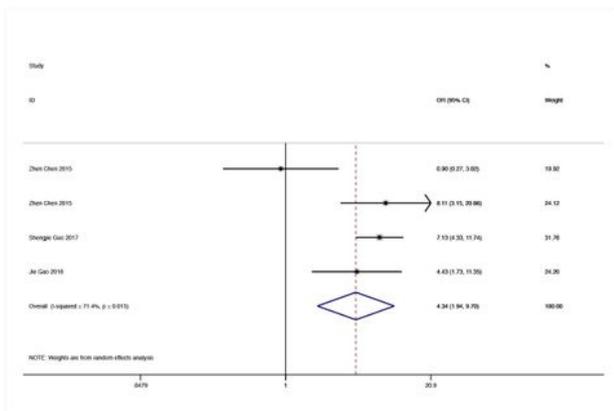
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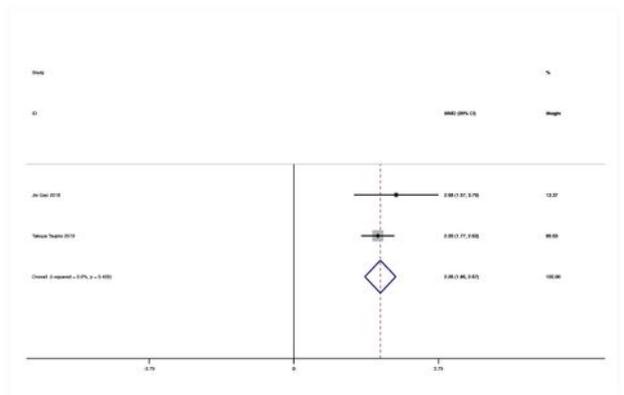


Figure 3

Association between C-reactive protein/albumin ratio and tumor stage (a); lymph node involvement (b); metastasis (c); Fuhrman nuclear grade (d); pTNM (e); tumor size (f).

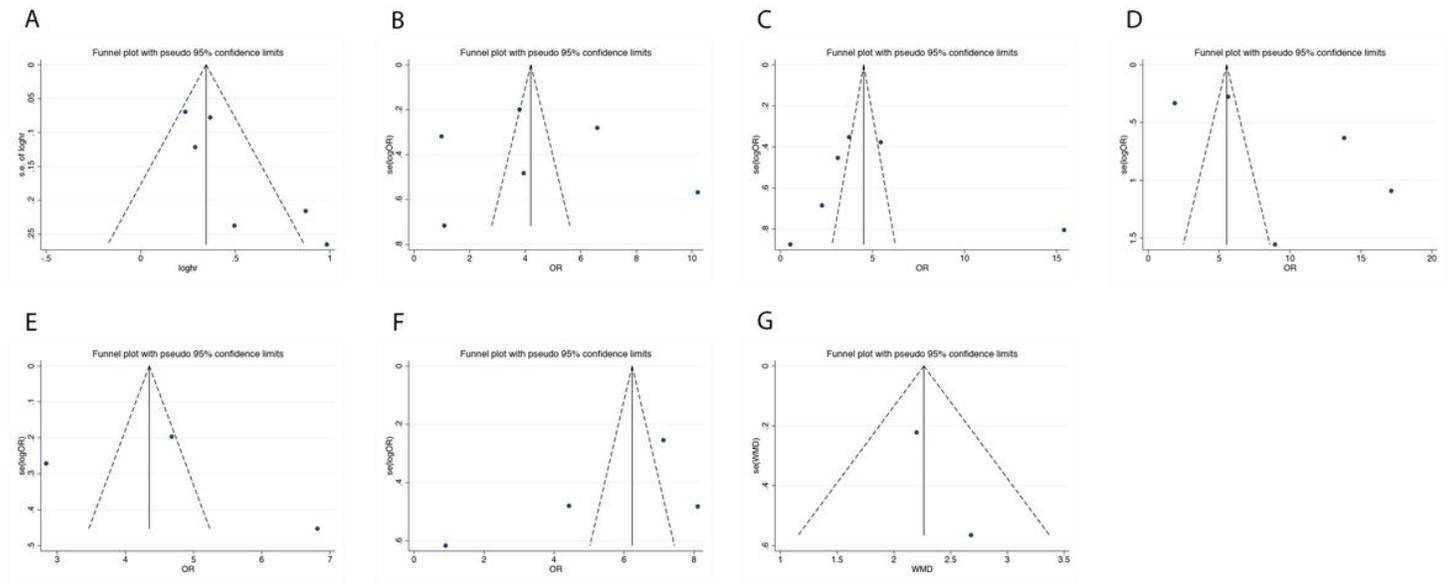


Figure 4

Funnel plot of meta-analysis for OS (a), tumor stage (b), lymph node involvement (c), metastasis (d), Fuhrman nuclear grade (e), pTNM (f) and tumor size (g).

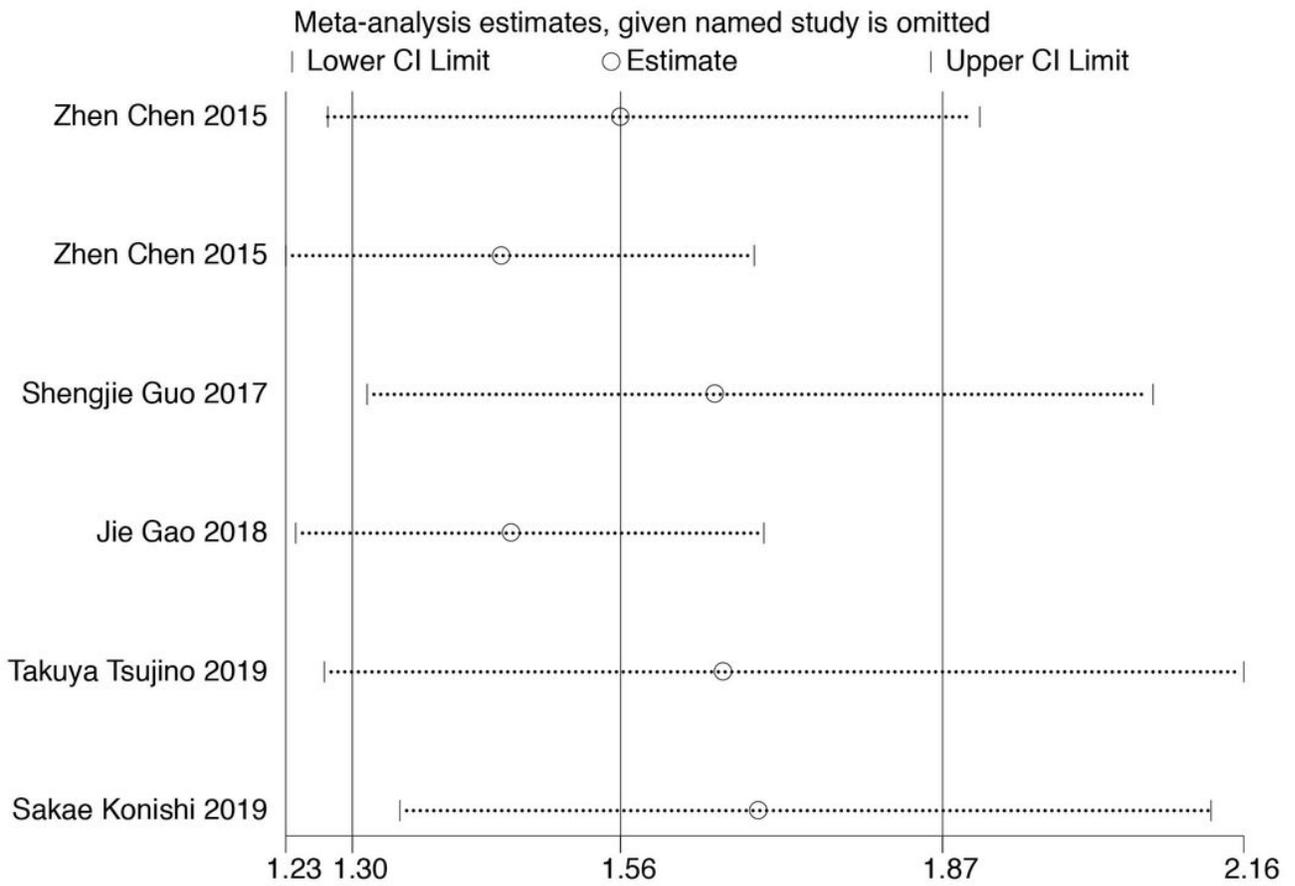


Figure 5

Sensitivity analysis for OS in this meta-analysis.