

Prognostic role of pretreatment serum albumin in renal cell carcinoma: a systematic review and meta-analysis

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Abstract: Recently, many studies have shown that pretreatment serum albumin can be closely linked to the prognosis of cancer patients, including those with renal cell carcinoma (RCC). However, not all studies have reached the same conclusion. We therefore conducted a systematic review and meta-analysis to evaluate the prognostic value of pretreatment serum albumin in RCC patients. A total of 17 studies involving 6,447 patients were included in our meta-analysis. Our results indicated that a lower pretreatment serum albumin level yielded a worse overall survival (hazard ratio [HR]=2.46, 95% confidence interval [CI] 1.92–3.13), cancer-specific survival (HR=2.22, 95% CI 1.87–2.64), and relapse-free survival/progression-free survival (HR=1.75, 95% CI 1.28–2.38). Generally, these findings were particularly pronounced when stratified by tumor type, analysis type, cut-off value, and HR-obtaining method. In conclusion, a decreased pretreatment serum albumin level implies a poor prognosis for RCC patients, and can be monitored for risk stratification and individualized treatment in RCC patients.

Keywords: albumin, prognosis, renal cell carcinoma, meta-analysis

Introduction

Renal cell carcinoma (RCC) is one of the most fatal types of urologic oncology and accounts for 2%–3% of adult malignancies. According to an American investigation, 58,000 patients are newly diagnosed with RCC, and nearly 13,000 patients die from this disease every year.¹ Rapid progress has been made in treatment methods, but some RCC patients with local recurrence and distant metastasis do not survive for long.² An effective prognostic model could be used to ascertain the malignant degree of the tumor, as well as to carry out risk stratification and allow individualized treatment for cancer patients. The postoperative tumor–node–metastasis (TNM) staging system is the conventional prognostic model used for RCC patients in clinical practice, but its precision may be unsatisfactory, with outcomes of patients at the same stage being significantly different. Moreover, the TNM staging system can only be evaluated in patients who undergo surgery. Therefore, a new laboratory index to complement the current risk stratification system of RCC patients is urgently required for clinical decision-making.

Serum albumin is synthesized by the liver and is the main serum protein.³ The concentration of normal serum albumin ranges from 3.5–5.0 g/dL for adults; when serum albumin is <3.5 g/dL, it is defined as hypoalbuminemia.⁴ Serum albumin is closely related to the degree of malnutrition, so it is often used for evaluating nutritional status.^{5,6} Furthermore, many studies have indicated that the inflammatory response

also affects the concentration of serum albumin, which can therefore be used as a reliable indicator of inflammation.^{7,8} Cancer is often accompanied by malnutrition and chronic inflammation, which often develop into tumor cachexia and speed up the deterioration of cancer patients.⁹ In recent years, numerous studies have indicated that there is a close correlation between pretreatment serum albumin and tumor prognosis; specifically, the lower the concentration of pretreatment serum albumin, the worse the prognosis of cancer patients.^{10–13} Some of these studies have directly or indirectly elaborated the relationship between pretreatment serum albumin and the prognosis of RCC patients.^{14–28} However, owing to differences in research design, sampling protocols, and other factors, the prognostic value of pretreatment serum albumin in RCC patients is not consistent. Some investigations have shown that pretreatment serum albumin is related to the prognosis of RCC patients, but others have failed to draw similar conclusions. Therefore, a systematic review and meta-analysis are necessary to assess the prognostic value of pretreatment serum albumin in RCC patients.

Materials and methods

Search strategy and selection criteria

This meta-analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses guidelines.²⁹

We searched PubMed, Embase, and Web of Science for published studies that analyzed the prognostic value of pretreatment serum albumin in RCC patients up to November 3, 2015. Search terms used were: “kidney cancer or renal cancer or renal carcinoma or renal cell carcinoma” (all fields) and “albumin or hypoalbuminemia” (all fields) and “prognosis or prognostic or survival or outcome”. We checked the titles and abstracts of the papers retrieved, excluded irrelevant studies, screened the full text for the remaining papers, included satisfactory studies, and extracted the required data. In addition, we manually screened the references of related papers, including all the identified studies, reviews, and editorials, in order to retrieve unpublished but relevant investigations. Considering overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), and progression-free survival (PFS) were the frequently used outcomes of RCC, we chose them as the primary outcomes of the studies that were selected for this meta-analysis. Inclusion criteria: 1) diagnosis of RCC was histopathologically confirmed; 2) treatment was limited to surgery, targeted therapy, or immunotherapy; 3) pretreatment albumin values were measured and their potential association with the prognosis of RCC patients

was analyzed; 4) retrospective or prospective study design; and 5) studies that directly offered the hazard ratio (HR) and 95% confidence interval (CI) or cases in which the presented data were available for reconstruction of HR and 95% CI.

Exclusion criteria: 1) studies that were not written in English; 2) letters, review papers, meeting records, commentaries, case reports, or clinical guidelines; 3) lack of critical data, such as HR or 95% CI; 4) studies on cancer cells and experimental animal studies; 5) sample sizes smaller than 40; 6) in cases where data overlapped across several different articles, only the study with the largest sample size was reviewed.

Quality assessment

According to the Newcastle–Ottawa quality assessment scale, two researchers independently assessed the quality of each study.³⁰ For quality assessment, scores ranged from 0 (lowest) to 9 (highest), and studies with scores of 6 or more were rated as being of high quality.

Data extraction and conversion

All data were extracted from the literature by two independent reviewers. When divergence appeared in the data-extraction process, a consensus would be reached after discussion. We extracted the following data: 1) basic information on the study: first author’s last name, publication year, country; 2) basic features of the patients, ie, case number, age, TNM staging, pathological grading, follow-up time; 3) cut-off value of pretreatment serum albumin; and 4) HR of albumin for OS, CSS, PFS, or recurrence-free survival (RFS), as well as 95% CI. If both the results of univariate and multivariate analysis were reported, only the result of multivariate analysis was extracted because this is more accurate, as it accounts for confounding factors.

If an article provided HRs and 95% CIs, they were extracted directly. However, if a paper did not provide HR and 95% CI, they were calculated using the data provided in the paper. If only the Kaplan–Meier curves of pretreatment albumin were available, we reconstructed the HRs and 95% CIs from the data extracted from the survival plots. We also sent emails to the corresponding authors to request any additional data needed for our meta-analysis. All the calculation methods mentioned were provided by Parmar et al³¹ and Tierney et al.³²

Statistical analysis

HRs with 95% CIs were used to describe the relationship between pretreatment serum albumin and survival of

RCC patients. An HR >1 suggested a worse prognosis in patients with a low concentration of pretreatment serum albumin, and an HR <1 indicated a better prognosis. We used Cochran's Q test and Higgins I^2 -squared statistic to conduct the test of heterogeneity of the combined HRs. If the P -value was <0.1 and/or I^2 was $>50\%$, the heterogeneity of the combined HRs was considered statistically significant, and a random effects model (the DerSimonian–Laird method) was then applied; otherwise, a fixed effects model (the Mantel–Haenszel method) was applied. The factors contributing to heterogeneity were analyzed by subgroup analysis. By assessing the asymmetry of an inverted funnel plot, publication bias was evaluated. Furthermore, we performed Begg's and Egger's tests to provide quantitative evidence of publication bias. Data analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA). All statistical tests were two-sided, and when $P<0.05$, differences were considered statistically significant.

Results

Search results

The process of searching and screening the literature is shown in Figure 1. We identified a total of 822 publications in accordance with the search method described. When scanning the titles, abstracts, publication types, and full texts of the 822 publications, it was found that only 35 articles mentioned the correlation between pretreatment serum albumin and the outcome of RCC patients. Among these, 18 articles were excluded (three lacked some important data, seven used

continuous or two cutoffs, and eight only reported odds ratios or relative risks). Thus, a total of 17 studies comprising 6,447 cases were included in our meta-analysis.^{14–28}

Characteristics of included studies

The basic information on the studies conforming to the inclusion criteria is collected in Table 1. The 17 included articles were published from 2000 to 2015, and most of them came from Asia ($n=4$), Europe ($n=4$), and North America ($n=8$). Our meta-analysis included a total of 6,447 patients, with a median number of 209 patients per study (range: 70–2,119). Of these studies, nine explored the effect of pretreatment serum albumin on the prognosis of metastatic renal cell carcinoma, three on localized RCC, and four on clear cell renal cell carcinoma. Meanwhile, ten studies were evaluated using multivariate analysis, and seven were evaluated using univariate analysis. OS was evaluated in eleven studies, CSS was reported in eight studies, PFS was reported in two studies, and RFS was reported in one study. Considering there are more studies about OS, we chose OS as the primary outcome of the studies selected for this meta-analysis. HRs were directly reported for 15 studies, and estimated indirectly for the remaining two studies. The cutoff value of pretreatment serum albumin used in most studies was 3.5 g/dL (the lower limit of normal).

Quality assessment

According to the Newcastle–Ottawa scale, we assessed the quality of the 17 eligible studies included in our

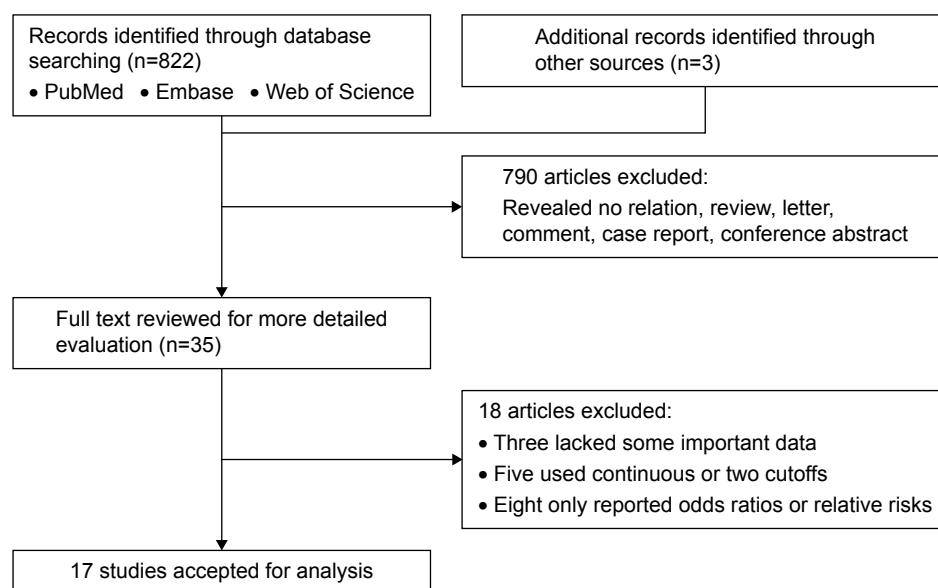


Figure 1 Flow diagram of the study selection process.

Table 1 Main characteristics of all studies included in the meta-analysis

Study	Country	Tumor type	Case number	Age (years)	Sex (M/F)	TNM stage (I/II/III/IV)	Fuhrman grade (I/II/III/IV)	Treatment	Follow-up (months)	Survival analysis	Cut-off value	Multivariate analysis	HR
Kim et al ¹⁸ (2003)	USA	RCC	1,046	Mean 59	697/349	290/93/182/397	I/17/446/307/45	Surgery	Median 24.5	CSS	3.6	Yes	Report
Ramsey et al ¹⁴ (2007)	UK	mRCC	119	56/63 (≤ 60 / > 60)	85/35	NR	NR	MT	Median 10	CSS	3.5	No	Report
Kim et al ³⁹ (2004)	USA	IRCC	250	Mean 62.5	43/207	NR	72/141/31/1	Surgery	Median 43	CSS	3.5	No	Report
Ramsey et al ¹⁵ (2008)	UK	IRCC	83	40/43 (≤ 60 / > 60)	50/33	37/11/33/2	10/27/26/14	Surgery	Median 38	CSS/RFS	3.5	No	Report
Wang et al ¹⁶ (2000)	People's Republic of China	RCC	231	93/138 (≤ 60 / > 60)	181/50	158/73 (I-II/III-IV) (T stage)	NR	Surgery	Median 35.6	OS	3.5	No	Report
Kaffenberger et al ¹⁷ (2012)	USA	IRCC	900	437/463 (≤ 60 / > 60)	581/319	474/100/291/34 (T stage)	102/428/230/112	Surgery	Median 28.7	OS/CSS	3.5	Yes	Report
Fox et al ¹⁸ (2013)	Australia	mRCC	362	Median 62	268/94	NR	NR	MT	NR	OS	3.5	No	SC
Atkinson et al ¹⁹ (2014)	USA	mRCC	185	Median 60	138/47	NR	NR	Targeted therapy	NR	OS/PFS	4.0	Yes	Report
Yap et al ²⁰ (2013)	Malaysia	RCC	151	Median 60.7	101/50	66/25/10/50	11/50/24/10	MT	Median 26	CSS	3.5	Yes	Report
Stenman et al ²¹ (2014)	Sweden	mRCC	84	Median 67	57/27	NR	NR	Targeted therapy	NR	OS	3.0	Yes	Report
Furukawa et al ²² (2015)	Japan	mCCRCC	209	Mean 66	161/48	71/138 (I-II/III-IV) (T stage)	NR	MT	Median 36.9	OS/PFS	3.5	Yes	Report
Corcoran et al ²³ (2015)	USA	mRCC	246	124/122 (≤ 60 / > 60)	176/70	174/72 (I-II/III-IV) (T stage)	40/200 (I-II/III-IV)	Surgery	Median 17	OS/CSS	3.5	Yes	Report
Sharma et al ²⁴ (2015)	USA	mRCC	93	Median 61	65/28	22/71 pT1a-pT2b/ \geq pT3c	16/77 (I-II/III-IV)	Surgery	Median 13	OS	3.5	Yes	Report
Chang et al ²⁵ (2015)	People's Republic of China	CCRCC	441	Median 56	318/123	297/30/108/6	72/202/106/61	Surgery	Median 66	OS	4.0	No	SC
Sacre et al ²⁶ (2016)	Belgium	mCCRCC	108	Median 59	74/34	NR	24/78 (I-II/III-IV)	MT	Median 40	OS	3.5	No	Report
Hakimi et al ²⁷ (2013)	USA	CCRCC	2,119	Median 61	1,408/711	1,325/98/506/188	98/1,095/738/170	Surgery	Median 4 years	CSS	4.0	Yes	Report
Malik et al ²⁸ (2014)	USA	mRCC	70	Median 56.5	46/24	NR	NR	MT	Median 10	OS	3.5	Yes	Report

Abbreviations: CCRCC, clear cell renal cell carcinoma; CSS, cancer-specific survival; HR, hazard ratio; IRCC, localized renal cell carcinoma; mCCRCC, metastatic clear cell renal cell carcinoma; mRCC, metastatic renal cell carcinoma; TNM, tumor node metastasis; MT, multiple therapy; NR, not reported; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RFS, relapse-free survival; SC, survival curve.

meta-analysis. The quality scores of the studies varied from 4 to 9, with a mean of 6.5. A higher score showed better methodology. None of the studies mentioned were excluded from subsequent analyses.

Meta-analysis results

Pretreatment serum albumin and survival of RCC patients

The main results of this meta-analysis are shown in Table 2. Considering the similarities between RFS and PFS, we merged them together to conduct this analysis. A decreased pretreatment serum albumin level yielded a worse OS ($I^2=54.7\%$; $P=0.015$, random-effects model; HR=2.46, 95% CI 1.92–3.13, $P<0.001$) (Figure 2A); CSS ($I^2=39.6\%$, $P=0.128$, fixed-effects model; HR=2.22, 95% CI 1.87–2.64, $P<0.001$); and RFS/PFS ($I^2=39.4\%$, $P=0.192$, fixed-effects model; HR=1.75, 95% CI 1.28–2.38, $P<0.001$) (Figure 2B). To explore the heterogeneity between these studies, the significance of pretreatment serum albumin was evaluated further via subgroup analysis based on the main

features, including tumor type, analysis type, cutoff value, and HR-obtaining method. Considering that the number of studies that evaluated RFS and PFS was relatively small, we only conducted subgroup analysis for OS and CSS. In the tumor type subgroup, a decreased pretreatment serum albumin level was closely associated with the poor prognosis of RCC patients, except for OS in the all-stage RCC group (Figure 3). As for the analysis type, cutoff value, and HR-obtaining method subgroups, previous findings were powerful, as shown in Table 2.

Sensitivity analyses

Each single cohort included in our meta-analysis was deleted, in turn, to check if individual studies influenced the results. Results of sensitivity analyses indicated the strength of our findings (data not shown).

Publication bias

Publication bias was assessed for both OS and CSS. The publication bias of all enrolled studies was evaluated using

Table 2 The pooled associations between pretreatment serum albumin and the prognosis of RCC patients

Variables	Outcome	Studies	Patients	HR (95% CI)	P-value	Model	Heterogeneity	
							I^2 (%)	P-value
All	OS	11	2,929	2.46 (1.92, 3.13)	<0.001	Random	54.7	0.015*
	CSS	7	4,664	2.22 (1.87, 2.64)	<0.001	Fixed	39.6	0.128
	PFS/RFS	3	477	1.75 (1.28, 2.38)	<0.001	Fixed	39.4	0.192
Tumor type								
RCC (all-stage)	OS	2	672	1.88 (0.39, 9.11)	0.432	Random	85.6	0.008*
	CSS	3	3,316	2.12 (1.24, 3.62)	0.006	Random	76.0	0.016*
RCC (localized)	OS	1	900	2.27 (1.45, 3.54)	–	–	–	–
	CSS	3	1,233	2.66 (1.58, 4.48)	<0.001	Fixed	27.5	0.252
RCC (metastatic)	OS	8	1,357	2.48 (1.89, 3.25)	<0.001	Random	52.1	0.041*
	CSS	2	365	2.21 (1.56, 3.14)	<0.001	Fixed	0.0	0.602
CCRCC	OS	3	758	3.85 (2.27, 6.53)	<0.001	Random	58.5	0.090
	CSS	1	2,119	2.71 (2.07, 3.54)	–	–	–	–
Analysis type								
Univariate	OS	8	2,581	3.02 (2.33, 3.93)	<0.001	Random	63.7	0.007*
	CSS	7	1,787	3.71 (2.50, 5.51)	<0.001	Random	49.9	0.076
Multivariate	OS	6	1,749	2.06 (1.69, 2.52)	<0.001	Fixed	0.0	0.957
	CSS	5	4,462	2.12 (1.59, 2.84)	<0.001	Random	52.5	0.078
Cutoff value								
≥3.5 g/dL	OS	8	2,219	2.39 (1.77, 3.24)	<0.001	Random	58.7	0.018*
	CSS	6	1,746	2.38 (1.80, 3.15)	<0.001	Fixed	0.0	0.615
Others	OS	3	710	2.62 (1.56, 4.38)	<0.001	Random	60.8	0.078
	CSS	2	3,165	1.97 (1.03, 3.77)	0.039	Random	87.5	0.005*
HR obtaining method								
Reported in text	OS	9	2,126	2.41 (1.75, 3.33)	<0.001	Random	62.8	0.006*
	CSS	8	4,914	2.24 (1.89, 2.66)	<0.001	Fixed	40.9	0.106
Data extrapolated	OS	2	803	2.95 (1.90, 4.57)	<0.001	Random	54.7	0.137
	CSS	0	0	–	–	–	–	–

Note: *Indicates that the difference was statistically significant.

Abbreviations: CCRCC, clear cell renal cell carcinoma; CI, confidence intervals; CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RFS, relapse-free survival.

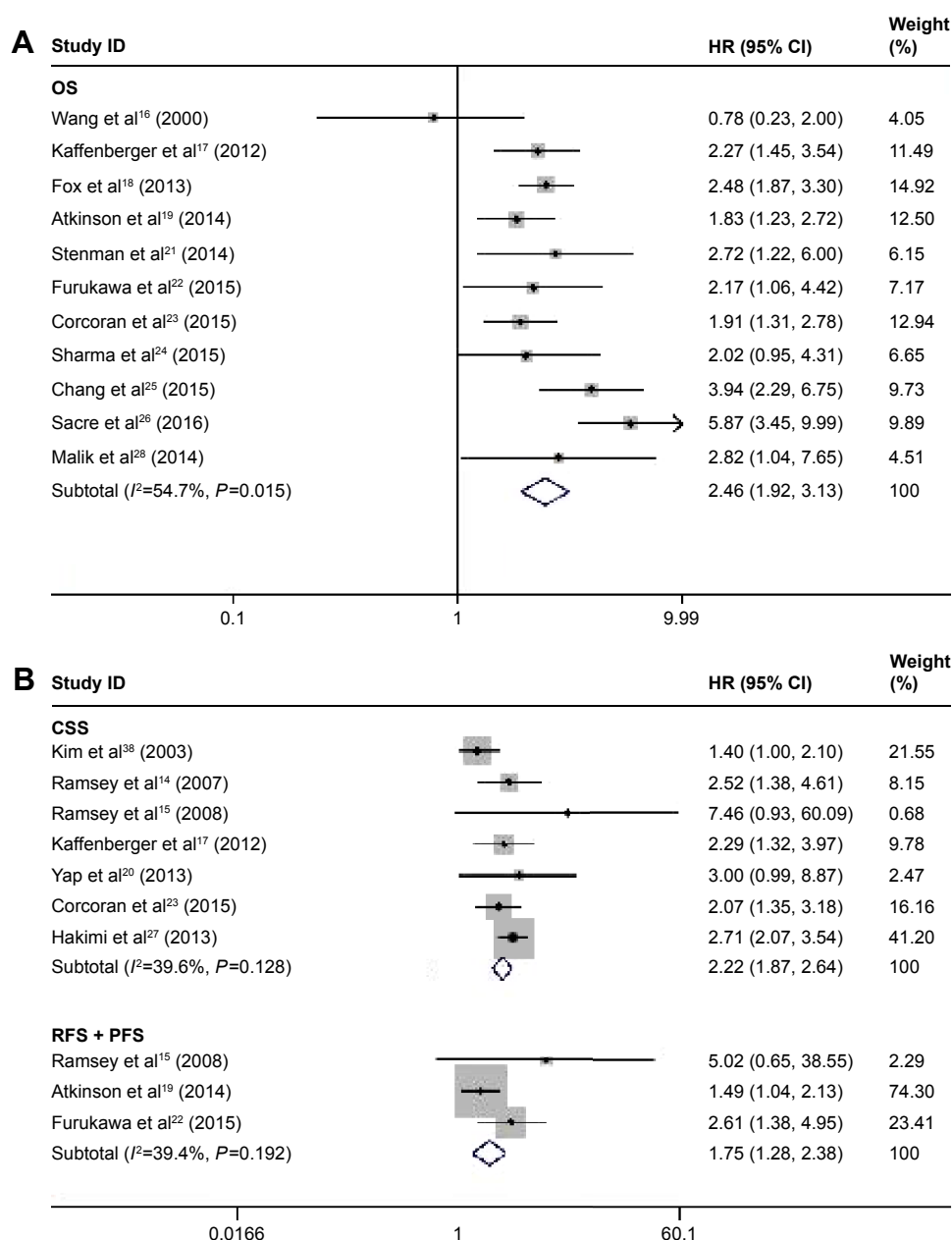


Figure 2 Forest plots of studies evaluating hazard ratios of decreased serum albumin levels for all renal cell carcinomas RCC.

Notes: (A) A decreased serum albumin level was associated with a shorter overall survival in RCC. (B) A decreased serum albumin level was associated with shorter cancer-specific survival and shorter progression-free survival/relapse-free survival in RCC. Weights are from random effects analysis.

Abbreviations: CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival; RCC, renal cell carcinoma.

funnel plots, and Egger's and Begg's tests. The funnel plots were almost symmetrical (Figure 4). The P -values of the Egger's and Begg's tests were all greater than 0.05 (OS, $P=0.938$ for the Begg's test, $P=0.967$ for the Egger's test; CSS, $P=0.230$ for the Begg's test, $P=0.620$ for the Egger's test). Therefore, there was no significant publication bias in our meta-analysis.

Discussion

To the best of our knowledge, the present meta-analysis is the first and most comprehensive study to systematically analyze

the prognostic value of pretreatment serum albumin in RCC patients. It is also the first meta-analysis to expound the relationship between serum albumin and the prognosis of patients with solid tumors. According to our final results, there was a significant correlation of low pretreatment serum albumin levels with poor survival of RCC patients, with a combined HR of 2.46 (95% CI 1.92–3.13) for OS, 2.22 (95% CI 1.87–2.64) for CSS, and 1.75 (95% CI 1.28–2.38) for RFS/PFS. Generally, in the subgroup analysis, decreased pretreatment serum albumin was an important prognostic marker in RCC

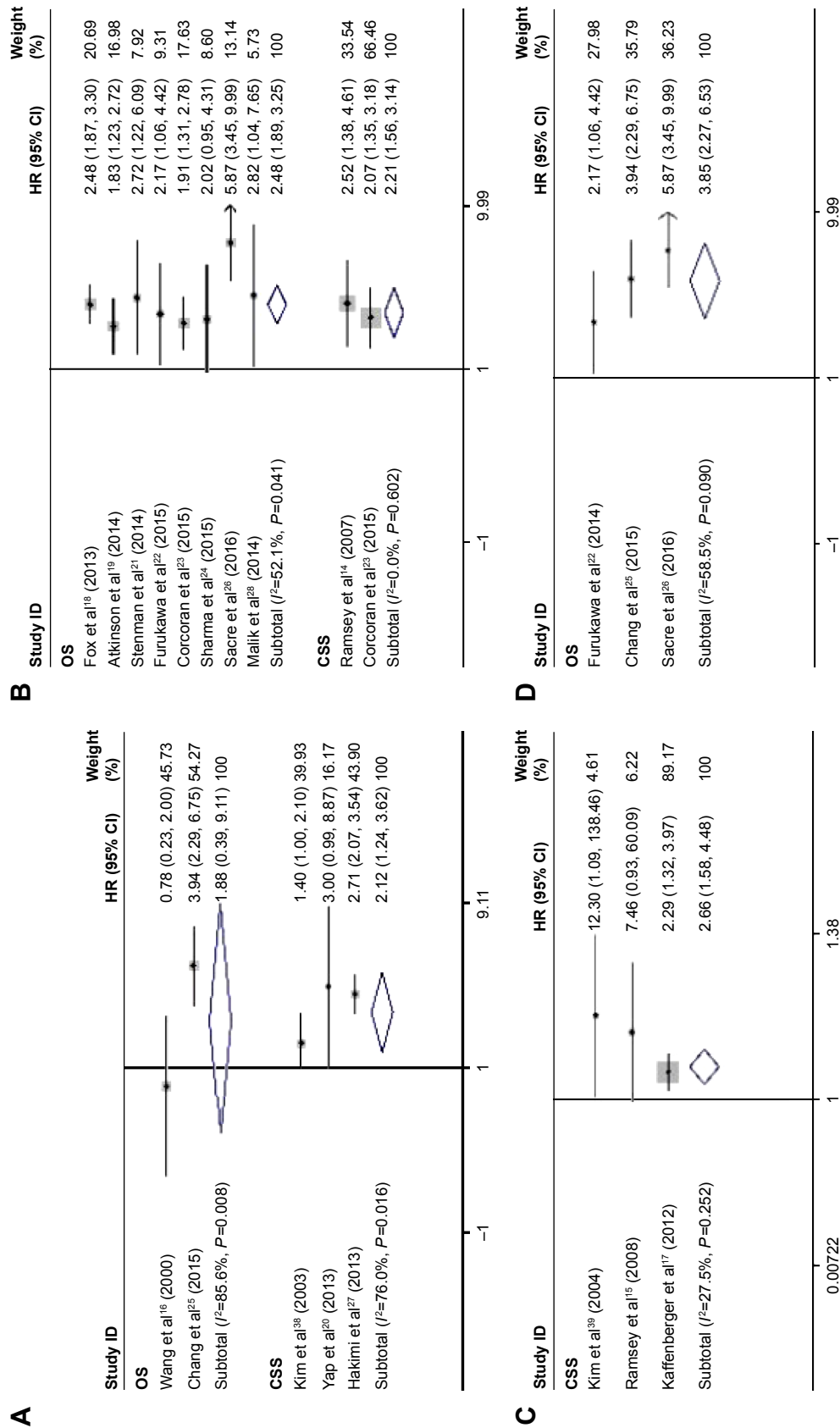


Figure 3 Forest plots of studies evaluating hazard ratios of decreased serum albumin levels for different tumor types. **Notes:** (A) All-stage group. (B) Metastatic group. (C) Localized group. (D) Clear cell renal cell carcinoma. Weights are from random effects analysis. **Abbreviations:** CSS, cancer-specific survival; HR, hazard ratio; OS, overall survival.

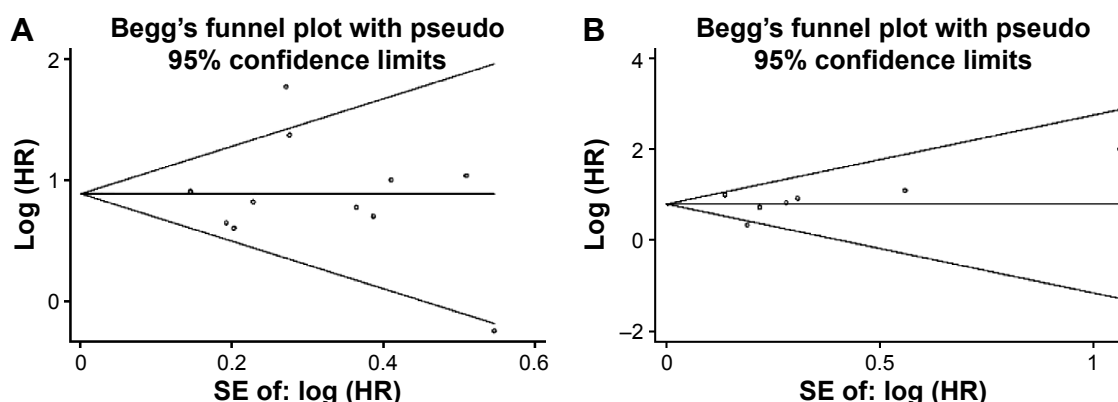


Figure 4 Funnel plots for the evaluation of potential publication bias.

Notes: (A) Overall survival for all renal cell carcinomas. (B) Cancer-specific survival for all renal cell carcinomas.

Abbreviation: HR, hazard ratio.

patients, regardless of tumor type, analysis type, cutoff value, and HR-obtaining method, except for OS in all-stage RCC. Considering the lower sample size of the only subgroup with a different result (two studies involving 672 patients), we can ignore the inconsistent result to some extent.

Pretreatment serum albumin is closely related to the prognosis of RCC and other malignant tumors; the underlying reasons for this are still speculative, but explanations involving nutrition and inflammation have been widely recognized. The initiation and progression of cancer are often accompanied by malnutrition and chronic inflammation, which often develop into tumor cachexia and accelerate the deterioration of cancer patients. Malnutrition in cancer patients is usually caused by loss of appetite and malignant tumor depletion, which is reflected in hypoalbuminemia and pitting edema. The systematic inflammatory response in cancer patients also alters the concentration of serum albumin. Under inflammatory conditions, activated proinflammatory cytokines, including tumor necrosis factor, and interleukin-1, -6, and -8, inhibit the ability of liver cells to generate albumin.^{8,33,34} In addition, the TNF generated by cancer cells increases the permeability of capillaries, which results in the direct loss of albumin from the circulatory system.³⁵ Furthermore, with the malignant progress of the tumor, development of micrometastases in the liver impairs liver function and reduces the synthesis of albumin.^{8,36} Therefore, the lower the level of serum albumin, the worse the prognosis of cancer patients, and consequently, pretreatment serum albumin is an effective prognostic indicator for cancer patients.

Serum albumin is a convenient and economic prognostic indicator for RCC patients; the concentration of serum albumin can be easily monitored by biochemical examination at any time. The reduction of serum albumin concentration in cancer patients not only demonstrates the

deterioration of their nutritional condition, but also indicates a poor prognosis. Therefore, clinical personnel can conduct risk stratification on cancer patients on the basis of the concentration of pretreatment serum albumin, in order to individualize treatment. However, as a prognostic indicator in RCC patients, serum albumin does have some limitations. For example, in the overhydrated state or with other disease processes, serum albumin may not indicate the true nutritional status, so its prognostic value in RCC patients will be disturbed.³⁷ Meanwhile, the level of serum albumin is a blood index, which may be slightly affected by diet and other nontumor-related factors. Nevertheless, without the interference of these factors, pretreatment serum albumin is of great prognostic value in RCC patients.

There were several limitations in this study; first, only 17 studies and 6,447 patients were included in our meta-analysis, ie, there was a relatively small sample size. Second, there was heterogeneity between the studies that may have been caused by differences in research design, basic features of the patients, cutoff values for pretreatment serum albumin, therapeutic methods, and follow-up periods. Moreover, owing to the lack of sufficient data, the associations between pretreatment serum albumin and other important clinical characteristics were not explored.

Conclusion

In conclusion, this meta-analysis clarified that a decreased pretreatment serum albumin level implied a poor prognosis for RCC patients. The level of pretreatment serum albumin is a convenient and economic prognostic indicator, and can be monitored for risk stratification and treatment individualization in RCC patients. Considering the limitation of the present analysis, further prospective multicenter studies should be carried out to confirm our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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