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Review Article

Sarcomatoid component and the risk of renal cell carcinoma: a systematic review and meta-analysis

Xingchen Liu[1*], Ping Qi[1*], Jianbin Jin[1*], Robert Svatek[2], Ronald Rodriguez[2], Zhiping Wang[3], Yongsheng Yin[1]

[1]Department of Urology, Gansu Provincial Hospital, Lanzhou 730030, China; [2]Department of Urology, University of Texas Health Science Center San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA; [3]Institute of Urology, Lanzhou University Second Hospital, Lanzhou 730030, China. [*]Equal contributors.

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Abstract: The sarcomatoid component is increasingly reported to be associated with the prognosis of patients with renal cell carcinoma (RCC), but the results remain controversial. We conducted a meta-analysis to quantitatively evaluate the impact of the sarcomatoid component on prognosis of patients with RCC. Systematic detailed searches were performed on PubMed, EBSCO, EMBASE, and the Cochrane Library until to October 31, 2016. Based on a fix-effects model or random-effects model, the pooled hazard ratio (HR) with 95% confidence interval (CI) for overall survival (OS), progression-free survival (PFS), or cancer-specific survival (CSS) were used to evaluate the potential risk. Twenty-three studies met the inclusion criteria for the present study and contained a combined total of 27856 study subjects. The presence of the sarcomatoid component was associated with poor OS (HR = 1.89; 95% CI, 1.50-2.38, p < 0.00001), PFS (HR = 2.04; 95% CI, 1.45-2.87, p < 0.0001) and CSS (HR = 1.87; 95% CI: 1.48-2.37, P < 0.00001) in RCC patients. Additionally, while the presence of the sarcomatoid component was more common in patients with a higher tumor stage (T3-4) and Fuhrman grade (G3-4), there was no correlation between presence of the sarcomatoid component and gender or metastasis status. The results of this meta-analysis suggest that the presence of sarcomatoid component is associated with an increased risk and poorer survival in RCC patients. The sarcomatoid component plays an important role in the carcinogenesis and prognosis of RCC.

Keywords: Renal cell carcinoma, sarcomatoid component, prognostic, meta-analysis

Introduction

Renal cell carcinoma (RCC) accounts for an estimated 3% of all human cancers worldwide. Epidemiologic studies have reported that the incidence of RCC has steadily increased in recent years [1]. With approximately 25%-30% of patients found to have metastatic disease at the time of the initial diagnosis, metastatic RCC is resulting in poor prognosis and a subsequent 5-year survival rate of only 12% [2]. Therefore, more effective preventive strategies to reduce the risk of RCC are needed. Several powerful prognostic factors for RCC have been identified and consist of the pathological tumor TNM stage (pT), the Fuhrman grade, the presence of distant metastases, the lymph node status and the lymphovascular invasion [3-6]. These factors predict disease outcome and contribute to providing an appropriate therapeutic strategy for patients with RCC based on their risk of progression. However, several other recognized factors have been proposed with conflicting results. The sarcomatoid component also represents a controversial risk factor. Tirumani et al. [7] showed that the sarcomatoid transformation was associated with high-grade tumors and that patients had shorter metastasis-free survival and overall survival (OS).

In addition, Cheville and Jiang et al. [8, 9] have also confirmed that the presence of the sarcomatoid component was a protective factor for incidence risk. However, the converse results showed that there was no correlation between the sarcomatoid component and RCC risk. For example, studies have shown an association between the sarcomatoid features and the RCC tumor stage and metastasis status, but this difference did not reach statistical significance [10]. With regard to a specific median survival of 5 to 19 months, Arnoux et al. [11] reported

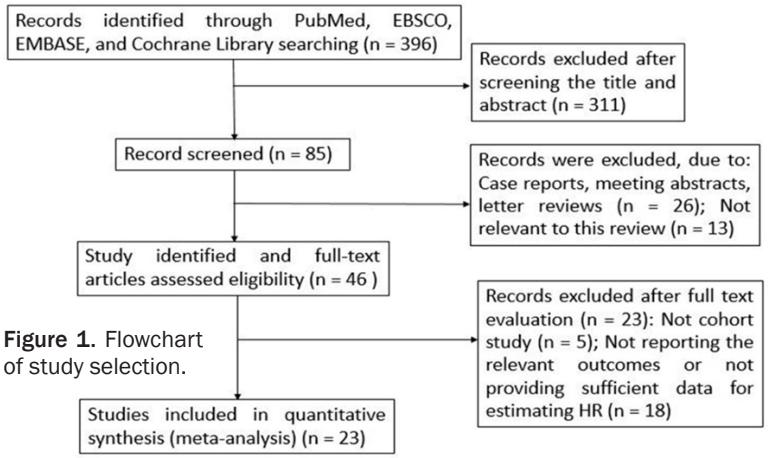

Figure 1. Flowchart of study selection.

that there is no correlation between the sarcomatoid component and RCC survival outcomes. Pal et al. [12] have also demonstrated that there was no significant difference in survival in patients with sarcomatoid predominant disease vs. non-predominant disease.

The discrepancies among these studies may contribute to the relatively small sample size. Therefore, we seek to conduct a meta-analysis to assess the prognostic value of the sarcomatoid component by exploring the associations of the sarcomatoid component with survival features of RCC. This study was performed in compliance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13].

Methods

Search strategy

A literature search for studies published by October 31, 2016 that assessed the effect of the sarcomatoid component in RCC was performed on PubMed, EBSCO, EMBASE, and the Cochrane Library using the following search items through MeSH headings, keywords, and text words: ("renal cancer" or "kidney cancer" or "renal carcinoma" or "renal cell carcinoma") and ("sarcomatoid" or "sarcomatoid component" or "sarcomatoid features" or "sarcomatoid transformation" or "sarcomatoid differentiation" or "sarcomatoid dedifferentiation" or "prognostic or prognosis or outcome") and relevant variants of these search terms. The language of the publications was confined to English. Bibliographies of related papers were reviewed to identify all potential studies.

Data extraction and quality assessment

Data extraction was independently performed by 2 investigators (MH and FW) and cross-checked. Additionally, any disagreement or uncertainty was resolved by consensus. The extracted data included the following: first author's last name, year of publication, country, number of patients, period of recruitment, age, gender, cut-off value of the sarcomatoid component, follow up, prognostic outcomes, definitions of outcomes, and adjusted factors. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). Next, 0-9 stars were assigned to each study: studies with an NOS score equal to or higher than 6 were deemed as being high quality. If a study provided both the results of multivariate outcomes and univariate outcomes, we chose the former, but if no multivariate outcomes were reported, univariate outcomes were used instead.

Eligibility criteria

All studies should meet the following criteria for the meta-analysis: (1) Articles were published in English; (2) Case-control or cohort study published as an original article; (3) All patients must have a diagnosis of a sarcomatoid component confirmed by pathology, and (4) Authors must offer hazard ratios (HRs) and 95% confidence intervals (CIs) or information that could allow us to calculate these values in the papers.

The papers containing any of the following were excluded: (1) Duplicated literature, or duplicated data presented in conferences; (2) Reviews, no available data, or abstract only; (3) Studies on cancer cell lines and animal models were excluded; (4) Insufficient data to acquire HR and its standard error were excluded. For overlapping articles, only the highest quality or most recent literature was retained.

Statistical analysis

HRs and 95% CIs were used to evaluate the relationships between the sarcomatoid compo-

Table 1. Characteristics of included studies

Study (yr)	Country	Patients	Study period	Age (range), yr	Gender (M/F)	Cut off (absence/high)	FU (range), mon
Kwak C, 2007	Korea	252	1990-2004	Md = 58 (20-79)	99/26	Absence vs. presence	Md = 17.4 (2.4-78.9)
Rodríguez-Covarrubias F, 2010	Mexico	126	1980-2009	Mn = 60.18 ± 13.3	71/55	Absence vs. Presence	Md = 20.5 (2-228)
Ku JH, 2011	Korea	82	1995-2005	Mn = 57.6	67/15	Absence vs. Presence	Md = 9 (0-73)
Shuch B, 2012	USA	104	1989-2009	Mn = 60.1	74/29	< 25% vs. ≥ 75%	Md = 5.9 (4.7-8.9)
Keegan KA, 2012	USA	17605	2000-2005	NA	11177/6428	Absence vs. Presence	Md = 19 (0-71)
Brookman-May S, 2013	Germany	562	1992-2010	Md = 65.0 (IQR: 55.9-71.1)	357/205	Yes vs. No	Md = 36.5 (IQR: 15-82)
Park JY, 2014	Korea	83	2006-2011	Md = 57 (33-80)	60/23	< 10% vs. ≥ 10%	Md = 18 (1-62)
Beuselinck B, 2014	Belgium	117	2005-2013	Mn = 59	77/40	< 25% vs. ≥ 25%	Md = 63 (1-96)
Culp SH, 2014	USA	2478	2005-2010	Md = 60 (IQR: 53-67)	1749/729	Absence vs. Presence	Md = 13 (IQR: 5-27)
Tantravahi SK, 2015	USA	27	2000-2012	Md = 63 (39-74)	18/9	< 20% vs. > 20%	Md = 8.2 (3.8-14.2)
Zhang BY, 2015	USA	204	1970-2009	Mn = 62 (32-88)	139/65	< 30% vs. ≥ 30%	Md = 80.8 (0.1-29.4)
Merrill MM, 2015	USA	77	1986-2011	Md = 63 (38-85)	44/33	1-24% vs. 25-49%	Md = 20.4 (1.0-213.5)
Kyriakopoulo CE, 2015	USA	2286	2008-2013	Mn = 58	NA	Absence vs. Presence	NA
Kim T, 2015	USA	45	1999-2012	Mn = 61	42/13	≤25% vs. > 25%	Mn = 21.5 (0.4-101)
Zhang YS, 2015	China	1326	2002-2012	Md = 54 (45-63)	899/427	Absence vs. Presence	Md = 43.55 (25.47-68.75)
Park I, 2015	Korea	123	2006-2011	Md = 57 (17-85)	88/35	≤40% vs. > 40%	Md = 60.0 (56.3-63.6)
Borregales LD, 2015	USA	61	1992-2012	Md = 56 (IQR: 49-64)	42/19	Absence vs. Presence	Md = 12 (5.25-41.5)
Lee H, 2016	Korea	1511	2006-2013	Md = 58 (IQR: 49-67)	1077/434	Absence vs. Presence	Md = 36 (IQR: 24-57)
Sacré A, 2016	Belgium	108	2006-2015	Md = 59 (30-78)	74/34	< 25% vs. ≥ 25%	Md = 40 (1-64)
Gu LY, 2016	China	103	2004-2015	Md = 56 (16-79)	71/32	≤50% vs. > 50%	Md = 19.9 (IQR: 10.8-35.1)
Fu HC, 2016	China	198	2003-2004	Md = 54 (26-80)	137/61	Absence vs. Presence	Md = 106 (11-120)
Kara O, 2016	USA	264	2005-2013	Mn = 61.6	154/110	< 50% vs. > 50%	Md = 16.8 (IQR: 6-33.6)
Du YJ, 2016	Germany	114	2006-2015	Mn = 62.0 ± 12.1	89/25	Absence vs. Presence	Md = 24.1 (16.5-31.7)

FU: follow-up; IQR, interquartile range; Md: median; Mn: mean; mon: month; NR: not reported; NOS score: Newcastle-Ottawa Scale score; yr: year.

Table 2. Quality assessment of studies enrolled using the Newcastle-Ottawa Quality Assessment Scale

Study (author, year)	Selection				Comparability	Outcome			Scores
	1	2	3	4		1	2	3	
Kwak C, 2007	★		★	★	★	★	★	★	7
Rodríguez-Covarrubias F, 2010	★	★	★		★★		★	★	7
Ku JH, 2011	★	★	★	★	★	★		★	7
Shuch B, 2012	★		★	★	★★	★	★	★	8
Keegan KA, 2012	★	★	★	★	★	★		★	7
Brookman-May S, 2013	★	★		★	★	★	★	★	7
Park JY, 2014	★	★		★	★★	★	★	★	8
Beuselinck B, 2014	★	★	★	★	★	★	★	★	8
Culp SH, 2014	★	★	★	★	★★	★		★	8
Tantravahi SK, 2015	★	★		★	★★	★	★	★	8
Zhang BY, 2015	★	★		★	★	★	★	★	7
Merrill MM, 2015	★	★	★	★	★★	★	★	★	9
Kyriakopoulo CE, 2015	★		★	★	★		★	★	6
Kim T, 2015	★	★	★	★	★★	★	★	★	9
Zhang YS, 2015	★	★	★	★	★★	★	★	★	9
Park I, 2015	★	★		★	★	★	★	★	7
Borregales LD, 2015	★	★	★	★	★	★		★	7
Lee H, 2016	★	★		★	★★		★	★	7
Sacré A, 2016	★	★	★	★	★	★	★	★	8
Gu LY, 2016	★	★	★	★	★★	★		★	8
Fu HC, 2016	★		★	★	★	★	★	★	7
Kara O, 2016	★	★	★		★★	★		★	7
Du YJ, 2016	★	★		★	★★	★	★	★	8

nent and OS, progression-free survival (PFS), and cancer-specific survival (CSS). Odds ratios (ORs) with 95% CIs were used to estimate the association between the sarcomatoid component and the clinical characteristics of RCC patients, including gender, tumor stage, Fuhrman grade, and metastasis status. A *p* value of < 0.05 was considered significant. The statistical significance of the pooled HRs and ORs was evaluated using the Z test. Heterogeneity among studies was measured with the Cochran Q test and Higgins I-squared statistic [14]. A random effects model was used when significant heterogeneity was observed ($P < 0.05$ or $I^2 > 50\%$); otherwise, a fixed-effects model was employed in the absence of between-study heterogeneity [15]. The publication bias was tested using Begg's funnel plot and the Egger linear regression test. All statistical calculations were performed by Review Manager 5.3 (Cochrane Collaboration, Copenhagen). Publication bias was detected with the Egger test and was performed in outcomes comprising more than 10 studies by using STATA software (v.14.0, Stata Corp, College Station, TX) [16].

Results

Characteristics of eligible studies

In total, 396 potentially relevant articles were retrieved by the initial search strategy. After screening, 23 articles were included in the qualitative and quantitative synthesis [17-39]. The screening diagram is shown in **Figure 1**. The characteristics of the included studies and the NOS quality assessment are shown in **Tables 1** and **2**, respectively.

Six studies provided original information on the relationships between the sarcomatoid component and the clinicopathological parameters of RCC patients directly [17, 19, 20, 22, 29, 30]. Of the 23 studies, a significant

Table 3. HR values of OS, PFS and CSS of RCC subgroups

	Outcome	Studies (n)	Patients	HR	95% CI	*P* value	Model	Chi², I², *P* value
OS	All study	16	24079	1.91	1.54-2.38	< 0.00001	Random	41.51, 64%, 0.0003
	Asian	7	3473	2.42	1.89-3.10	< 0.001	Fixed	5.51, 0%, 0.48
	Non-Asian	9	20606	1.60	1.18-2.16	0.002	Random	32.11, 75%, < 0.001
	Metastatic	8	4498	1.84	1.21-2.77	0.004	Random	25.78, 73%, 0.0006
	Non-metastatic	2	1588	1.44	0.85-2.43	< 0.001	Fixed	0.06, 0%, 0.17
	Target therapy	6	2831	1.83	1.10-3.03	0.02	Random	22.25, 78%, 0.0005
	Immuntherapy	1	129	2.83	1.48-5.40	0.002	Fixed	-
PFS	All study	9	5765	2.04	1.45-2.87	< 0.0001	Random	32.72, 76%, < 0.0001
	Asian	6	3254	2.31	1.82-2.91	< 0.001	Fixed	6.11, 18%, 0.30
	Non-Asian	3	2511	1.47	0.58-3.73	0.41	Random	17.57, 89%, 0.0002
	Metastatic	6	2846	1.86	1.19-2.89	0.006	Random	23.61, 79%, 0.0003
	Non-metastatic	1	1511	1.57	0.97-2.54	0.067	Fixed	-
CSS	All study	10	22747	1.87	1.48-2.37	< 0.00001	Random	39.22, 77%, < 0.0001
	Asian	2	1593	1.85	1.17-2.92	0.009	Fixed	1.06, 5%, 0.30
	Non-Asian	8	21154	1.96	1.46-2.63	< 0.001	Random	35.58, 83%, < 0.001
	Metastatic	2	2596	2.30	1.97-2.67	< 0.001	Fixed	1.27, 21%, 0.26
	Non-metastatic	3	1783	1.81	1.23-2.64	0.002	Fixed	2.77, 28%, 0.25

CI: confidence interval; CSS: cancer-specific survival; Fixed: fixed, inverse variance model; HR: hazard ratio; I²: *I*-squared; OS: overall survival; PFS, progression-free survival; Random: random, I-V heterogeneity model; RCC: renal cell carcinoma.

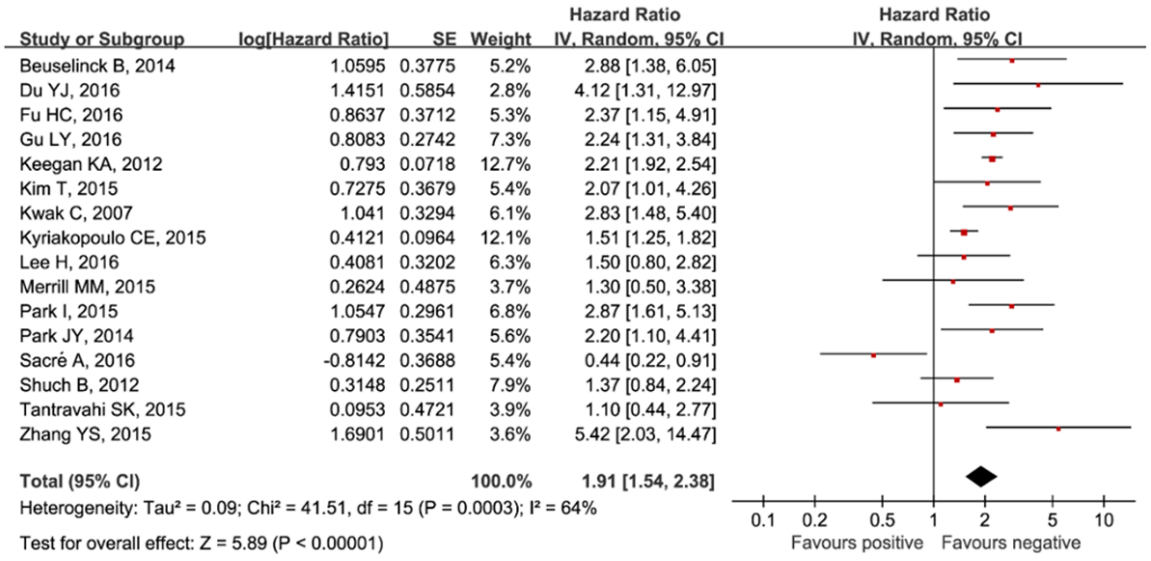

Figure 2. The hazard ratio of the sarcomatoid component associated with overall survival in renal cell carcinoma patients.

association between the presence/high level of the sarcomatoid component and poor OS, PFS and CSS was demonstrated in thirteen [17, 21, 23, 24, 29-32, 34-37, 39], eight [17, 19, 23, 24, 29, 31, 32, 35], and eight studies [18, 19, 21, 25, 27, 33, 38], respectively. Four, one and two studies linking the sarcomatoid component with poor OS [20, 26, 28, 34], PFS [34], and CSS [22, 34], respectively, lacked statistical significance. The follow-up period of the studies ranged from 0 to 213.5 months. The age of the patients ranged from 17 to 88 years. A total of 27856 patients from 6 countries (Korea, Mexico, USA, Germany, Belgium, and China) were included in this meta-analysis. The main characteristics of the 23 studies

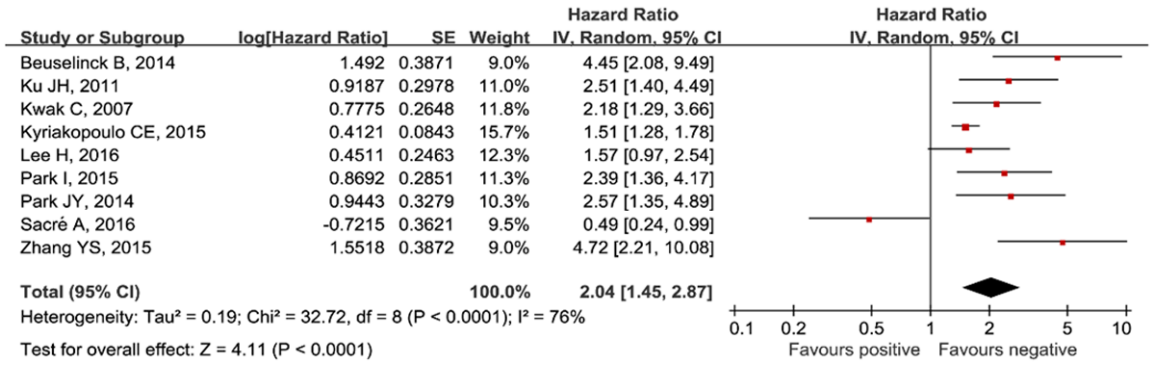

Figure 3. The hazard ratio of the sarcomatoid component associated with progression-free survival in renal cell carcinoma patients.

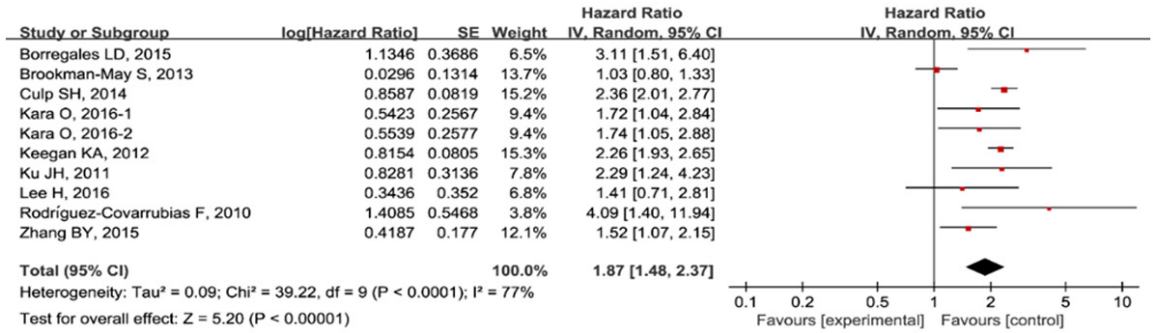

Figure 4. The hazard ratio of the sarcomatoid component associated with cancer-specific survival in renal cell carcinoma patients.

Table 4. HR values of OS of RCC subgroups depended on cutoff value

Cutoff Value (%)	Studies	HR	95% CI	*P* value	Model	Chi², I², *P* value
< 20	n=1	2.20	1.10-4.41	0.03	Fixed	-
≥ 20	n=6	2.18	1.64-2.90	< 0.00001	Fixed	4.54, 0%, 0.47
< 25	n=2	1.73	0.99-3.04	0.05	Fixed	1.33, 25%, 0.25
≥ 25	n=5	2.33	1.73-3.14	0.0002	Fixed	2.37, 0%, 0.67
< 50	n=5	1.95	1.37-2.78	0.0002	Fixed	3.31, 0%, 0.51
≥ 50	n=2	2.51	1.69-3.73	< 0.00001	Fixed	0.37, 0%, 0.54

Fixed: Fixed, Inverse Variance model; HR: hazard ratio; I^2: I-squared.

included in our meta-analysis are shown in **Table 3**.

The presence/high percentage of the sarcomatoid component was defined by a pathologist. The sarcomatoid component that was present or at a high percentage was considered to be positive and those that were absent or at a low percentage were considered to be negative. The cut-off value to distinguish a high percentage of the sarcomatoid component from a low percentage of the sarcomatoid component was set from 10% to 50%.

Correlation of the sarcomatoid component with OS, PFS, and CSS in RCC

Of the 16 studies investigating the association between the sarcomatoid component and OS, 7 involved Asian patients (n = 3473) and 9 involved non-Asian patients (n = 20606). The overall HR and 95% CI for RCC patients was 1.91 (95% CI 1.54-2.38, P < 0.00001, n = 24079), with significant heterogeneity (I^2 = 64%, P = 0.0003; **Table 3** and **Figure 2**). Subgroup analyses demonstrated that a significant association in both Asian and non-Asian patients (HR = 2.42, 95% CI 1.89-3.10, P < 0.00001 and HR = 1.60, 95% CI 1.18-2.16, P = 0.002, respectively). Next, subgroup analyses also showed that the risk was also significant in both metastatic and non-metastatic patients (HR = 1.84, 95% CI 1.21-2.77, P = 0.004 and HR = 1.44, 95% CI 0.85-

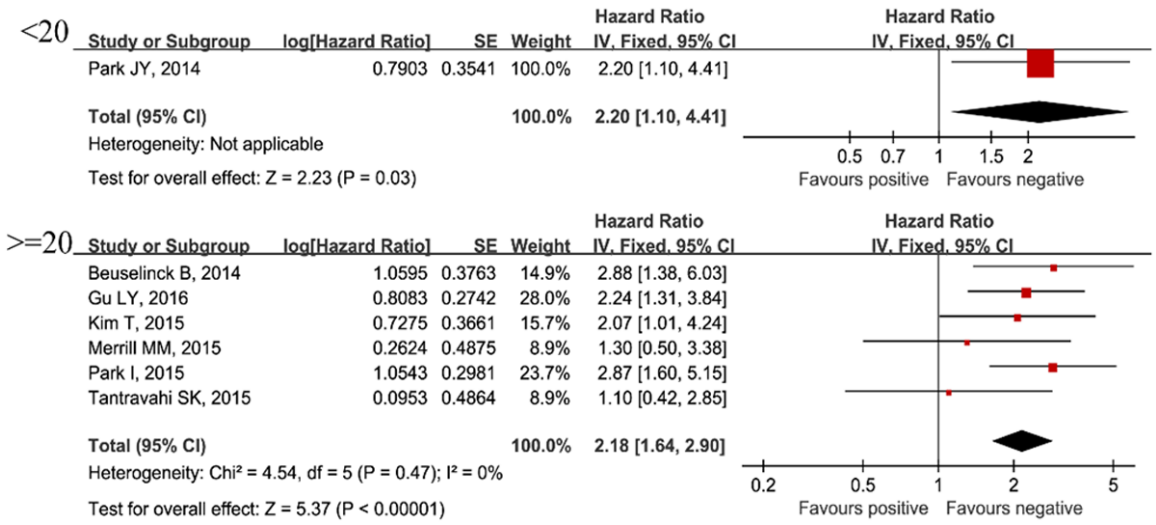

Figure 5. Cutoff value ≥ 20% and cutoff value < 20%. The hazard ratio of the sarcomatoid component associated with overall survival in all renal cell carcinoma patients subgroup.

2.43, P < 0.00001, respectively). Moreover, our analyses revealed that the sarcomatoid component was an independent prognostic factor for RCC treated with target therapy and immunotherapy (HR = 1.83, 95% CI 1.10-3.03, P = 0.02; and HR = 2.83, 95% CI 1.48-5.40, P = 0.002, respectively).

The pooled HR and 95% CI for PFS provided in nine studies was 2.04, 95% CI 1.45-2.87, P < 0.00001, with heterogeneity (I^2 = 76%, P < 0.00001; **Table 3** and **Figure 3**). Subgroup analyses indicated that the risk was significant in Asian patients (HR = 2.31, 95% CI 1.82-2.91, P < 0.00001) with heterogeneity (I^2 = 18%, P = 0.30), but not in non-Asian patients (HR = 1.47, 95% CI 0.58-3.73, P = 0.41), with significant heterogeneity (I^2 = 89%, P = 0.0002). Further subgroup analysis indicated that the risk was significant in metastatic patients (HR = 1.86, 95% CI 1.19-2.89, P = 0.006) with heterogeneity (I^2 = 79%, P = 0.0003), but not in non-metastatic patients (HR = 1.57, 95% CI 0.97-2.54, P = 0.067).

The pooled HR and 95% CI for CSS provided in ten studies was 1.87, 95% CI 1.48-2.37, P < 0.00001, with significant heterogeneity (I^2 = 77%, P < 0.00001; **Table 3** and **Figure 4**). Subgroup analyses demonstrated that the significant statistical differences in both Asian and non-Asian patients (HR = 1.63, 95% CI 1.24-2.15, P = 0.0005 and HR = 1.96, 95% CI 1.46-2.63, P < 0.00001, respectively). Another subgroup analysis showed that the risk was also significant in both metastatic and non-metastatic patients (HR = 2.30, 95% CI 1.97-2.67, P < 0.00001 and HR = 1.81, 95% CI 1.23-2.64, P = 0.002, respectively).

Correlation of the sarcomatoid component with OS in RCC using different cut-off values

Subgroup analysis demonstrated that the risks between the sarcomatoid component and OS were not significant using different sarcomatoid component cut-off values (20%, 25%, 50%). The pooled HRs and 95% CIs were as follows: 2.20 (95% CI 1.10-4.41) vs. 2.18 (95% CI 1.64-2.90) for a cut-off value of 10%, 1.73 (95% CI 0.99-3.04) vs. 2.33 (95% CI 1.73-3.14) for a cut-off value of 25%, and 1.95 (95% CI 1.37-2.78) vs. 2.51 (95% CI 1.69-3.73) for a cut-off value of 50% with significant heterogeneities (**Table 4** and **Figures 5-7**).

Association between a high level of the sarcomatoid component and the clinicopathological characteristics of RCC

In this meta-analysis, clinicopathological features such as gender, tumor stage, Fuhrman grade, and metastatic status, as impacted by the presence of the sarcomatoid component, were compared on the basis of the 23 studies. The results of the meta-analysis showed significant associations between the sarcomatoid component and higher tumor stage (T3-4) and Fuhrman grade (G3-4); the combined ORs and 95% CIs were as follows: OR = 2.09, 95% CI

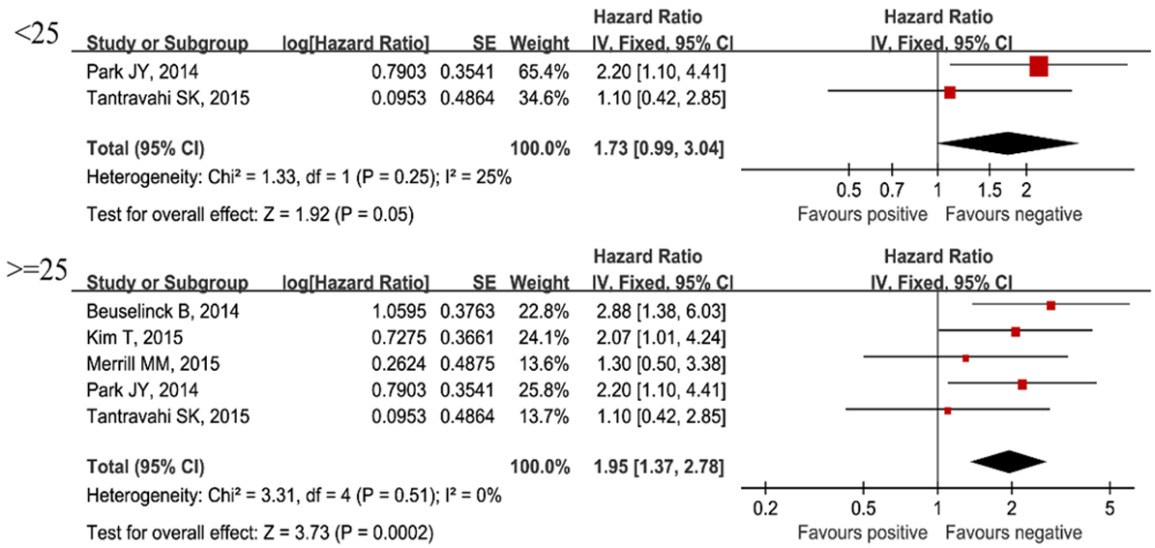

Figure 6. Cutoff value ≥ 25% and cutoff value < 25%. The hazard ratio of the sarcomatoid component associated with overall survival in all renal cell carcinoma patients subgroup.

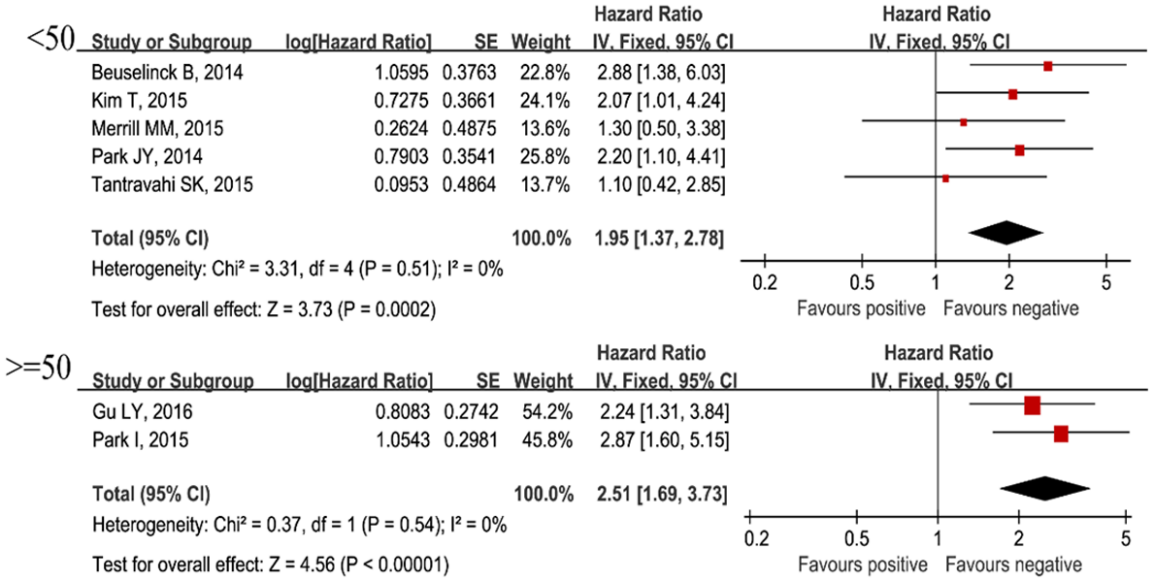

Figure 7. Cutoff value ≥ 50% and cutoff value < 50%. The hazard ratio of the sarcomatoid component associated with overall survival in all renal cell carcinoma patients subgroup.

1.30-3.37, P = 0.002; OR = 9.31, 95% CI 5.30-16.35, P < 0.00001, respectively (**Table 5**).

There was no significant association between the sarcomatoid component and gender (male vs. female) or metastatic status (metastatic vs. non-metastatic); the combined ORs and 95% CIs were OR = 0.86, 95% CI 0.64-1.16, P = 0.32 and OR = 1.02, 95% CI 0.73-1.43, P = 0.89, respectively (**Table 5**).

Publication bias

Publication bias detection was conducted by performing the Egger test and the Begg test in OS. The results show that no significant publication bias was observed. The funnel plot is shown in **Figure 8** (Pbegg = 0.692, Pegger = 0.939), which indicated that the results of our OS analyses were relatively stable and credible.

Table 5. OR values for the RCC subgroups according to clinical characteristics

Outcome of interest	Studies (n)	Patients	OR	95% CI	*P* value	Model	Heterogeneity
							Chi^2, I^2, *P* value
Gender (Male vs. Female)	4	885	0.86	0.64-1.16	0.32	Fixed	0.69, 0%, 0.88
T1-2 vs. T3-4	4	427	2.09	1.30-3.37	0.002	Fixed	3.65, 18%, 0.30
G1-2 vs. G3-4	3	1903	9.31	5.30-16.35	< 0.001	Fixed	2.33, 14%, < 0.001
Metastatic vs. Non-metastatic	4	793	1.02	0.73-1.43	0.89	Fixed	0.79, 0%, 0.85

CI: confidence interval; Fixed: fixed, inverse variance model; I^2: *I*-squared; OR: odds ratio; RCC: renal cell carcinoma.

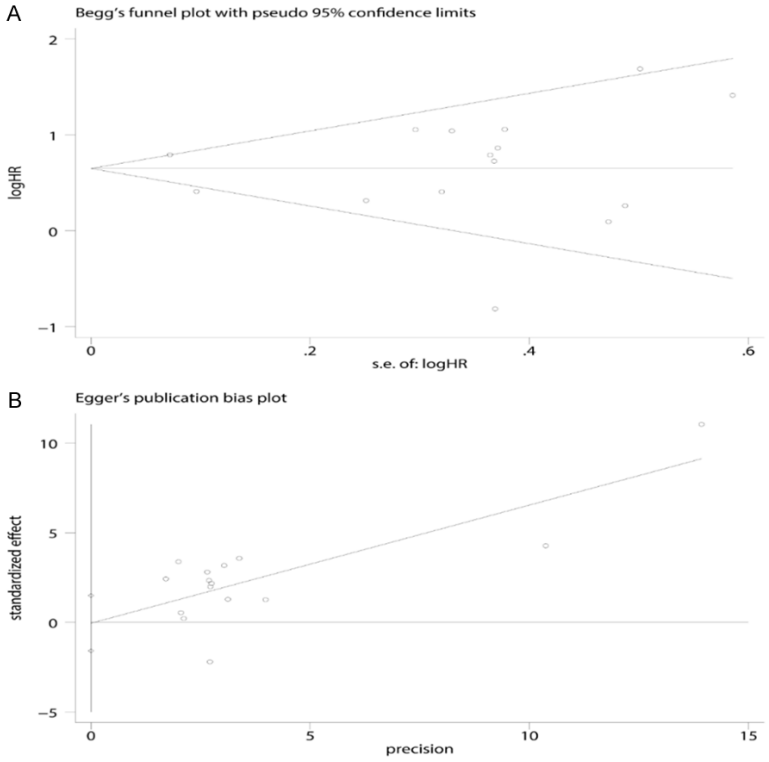

Figure 8. Funnel plots were used to evaluate publication bias on overall survival. A. Begg's test was not significant intending no significant bias was observed on overall survival. B. It showed no publication bias on overall survival in Egger's test.

Discussion

Numerous researchers have reported various results relating the sarcomatoid component to RCC. However, to date, no meta-analysis had been performed for the studies evaluating the sarcomatoid component as a prognostic marker in RCC.

In this meta-analysis, our results have several important implications. First, RCC patients with the sarcomatoid component had a lower survival rate. Second, the sarcomatoid component was strongly associated with the tumor stage and Fuhrman grade in RCC patients. Third, high-risk patients, especially those with the sarcomatoid component, should receive targeted therapy or immunotherapy. Four, the adverse effect of the sarcomatoid component on OS showed similar results using these three recommended cut-off values. Our analysis helps to elucidate the results of individual studies that are related to the hypothesis that the sarcomatoid component is a prognostic factor for RCC, in addition to the identification of high-risk subgroups of patients for whom specific or adjuvant-therapy may be beneficial.

In addition, subgroup analysis in this study showed that the presence/high level of the sarcomatoid component indicated a poorer outcome in Asian RCC patients compared with non-Asian patients (HR = 2.42, 95% CI 1.89-3.10 vs. HR = 1.60, 95% CI 1.18-2.16 for OS). However, the other subgroup analysis in this study showed that the presence/high level of the sarcomatoid component indicated a better outcome in Asian RCC patients compared with non-Asian patients (HR = 1.63, 95% CI 1.24-2.15 vs. HR = 1.96, 95% CI 1.46-2.63 for CSS). Furthermore, subgroup analyses indicated that the risk was significant in Asian patients (HR = 2.31, 95% CI 1.82-2.91, P < 0.00001) but not in non-Asian patients (HR = 1.47, 95% CI 0.58-3.73, P = 0.41). To date, there has been no consensus regarding the significance of the sarcomatoid component in Asian versus non-Asian

RCC patients. Although future validation and investigations are needed, these data may provide new insights into the biological aggressiveness of RCC in Asian versus non-Asian patients. With regard to the metastasis status, subgroup analyses indicated that the risk was significant in metastatic patients (HR = 1.86, 95% CI 1.19-2.89, P = 0.006) but not in non-metastatic patients (HR = 1.57, 95% CI 0.97-2.54, P = 0.067). Furthermore, subgroup analysis in this study showed that the presence/high level of the sarcomatoid component indicated a poorer outcome in metastatic RCC patients compared with non-metastatic RCC patients (HR = 1.84, 95% CI 1.21-2.77 vs. HR = 1.44, 95% CI 0.85-2.43 for OS and HR = 2.30, 95% CI 1.97-2.67 vs. HR = 1.81, 95% CI 1.23-2.64 for CSS). A hypothesis to explain this result at least partially may be that metastatic RCC is more likely to have the sarcomatoid component.

The biological mechanism of the sarcomatoid component can explain its prognostic significance in RCC. Sarcomatoid components are observed in 5% of tumor in RCC but only among individuals who develop stage IV disease that have sarcomatoid histologic features; the sarcomatoid component can be observed in 15% of tumor [40, 41]. Sarcomatoid is a term that is used to describe morphologic alterations within an RCC tumor similar to sarcomas with features such as elongated, spindle mesenchymal cells, high cellularity and pleomorphism and that can be recognized in association with various histologic types of RCC [40, 42]. Recently, the epithelial-mesenchymal transition (EMT) has been proposed as a potential mechanism for the development of the sarcomatoid component in RCC. Once EMT is established, the loss of E-cadherin, the release of β-catenin into the cytoplasm, and the increased expression of snail and secreted protein acidic rich in cysteine (SPARC) occurred in the sarcomatoid components. It is proposed that the acquisition of the mesenchymal function such as increased motility enables sarcomatoid renal cell carcinomas (SRCC) to be present at higher stages of diagnosis, implying a more aggressive phenotype [43-45]. Some evidence suggests that NF2 (19.2%), CDKN2A (26.9%), VHL (34.6%), and TP53 (42.3%) were the most frequently altered genes in SRCC. A comparison of SRCC and non-SRCC cohorts identified an increased frequency of TP53 and NF2 mutations in the SRCC cohort [46]. TP53 mutations may link EMT and sarcomatoid transformation because loss of p53 can decrease the expression of miR-200c, which contributes to EMT [47]. In addition, (SET domain containing 2) SETD2, polybromo 1 (PBRM1), (phosphatase and tensin homolog) PTEN, AT-rich interaction domain 1A (ARID1A), and BRCA1 associated protein 1 (BAP1) were the most frequently altered genes in the SRCC. Deficiency of BAP1 and ARID1A has been associated with higher tumour grade, poorer prognosis, and a higher incidence of sarcomatoid histology [48-50].

Mutations in other members of the FAT family, including FAT1 and FAT3, were also found in SRCC. FAT proteins are shown to play multiple roles in cancer cell proliferation, motility, signalling, polarity, and adhesion, and mutations are involved in many cancers [50-52]. FAT1 loss can promote WNT signalling, a critical regulator of EMT [53]. Finally, studies suggest that PD-1 and PDL-1 have also been found to exhibit greater expression in RCC with the sarcomatoid component, raising the possibility that RCC may exhibit poor responses to immunotherapy [54].

Several limitations of this study need to be acknowledged. The cut-off values for the percentage of the sarcomatoid component also differed. Moreover, variations among the studies in other clinical factors, such as race, age, and treatment methods, might have led to bias. Non-English studies, unpublished studies, and studies that did not provide sufficient data to calculate HRs did not contribute to assessing the predictive value of the sarcomatoid component for survival. These approaches may have produced errors because of possible inaccurate reading. Finally, of the 23 selected studies including 27856 cases in this meta-analysis, only some were used in the subgroup analysis of survival, but several lacked data and could not be used. Therefore, better-designed and large-scale trials should be performed to confirm these findings.

Conclusions

To our knowledge, this is the first study to find that the sarcomatoid component can risk stratify patients with RCC using formal statistical methodology. Our meta-analysis has demonstrated that the sarcomatoid component has a

detrimental effect on survival and clinicopathological features in RCC and could serve as an independent prognostic factor of OS, PFS, and CSS. Therefore, it may also be used to identify RCC patients who need further adjuvant therapies.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yongsheng Yin, Department of Urology, Gansu Provincial Hospital, Lanzhou 730030, China. Tel: +86-0931-8281955; E-mail: yinys2014@163.com

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