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The prognostic value and clinicopathological features of sarcomatoid differentiation in patients with renal cell carcinoma: a systematic review and meta-analysis

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Background and purpose: Numerous studies have demonstrated that sarcomatoid differentiation is linked to the risk of renal cell carcinoma (RCC). However, its actual clinicopathological impact remains inconclusive. Therefore, we undertook a meta-analysis to evaluate the pathologic and prognostic impacts of sarcomatoid differentiation in patients with RCC by assessing cancer-specific survival, overall survival, recurrence-free survival, progression-free survival, and cancer-specific mortality.

Materials and methods: In accordance with the preferred reporting items for systematic reviews and meta-analysis statement, relevant studies were collected systematically from PubMed, Embase, and Web of Science to identify relevant studies published prior to January 2018. The pooled effects (hazard ratios, odds ratios, and standard mean differences) and 95% confidence intervals were calculated to investigate the association of sarcomatoid differentiation with cancer prognosis and clinicopathological features.

Results: Thirty-five studies (N=11,261 patients [n=59–1,437 per study]) on RCC were included in this meta-analysis. Overall, the pooled analysis suggested that sarcomatoid differentiation was significantly associated with unfavorable cancer-specific survival (HR=1.46, 95% CI: 1.26–1.70, $p<0.001$), overall survival (HR=1.59, 95% CI: 1.42–1.78, $p<0.001$), progression-free survival (HR=1.61, 95% CI: 1.35–1.91, $p<0.001$), recurrence-free survival (HR=1.60, 95% CI: 1.29–1.99, $p<0.001$), and cancer-specific mortality (HR=2.36, 95% CI: 1.64–3.41, $p<0.001$) in patients with RCC. Moreover, sarcomatoid differentiation was closely correlated with TNM stage (III/IV vs I/II: OR=1.84, 95% CI: 1.12–3.03, $p=0.017$), Fuhrman grade (III/IV vs I/II: OR=8.37, 95% CI: 2.92–24.00, $p<0.001$), lymph node involvement (N1 vs N0: OR=1.88, 95% CI: 1.08–3.28, $p=0.026$), and pathological types (clear cell RCC-only vs mixed type: OR=0.48, 95% CI: 0.29–0.80, $p=0.005$), but was not related to gender (male vs female, OR=0.86, 95% CI: 0.58–1.28, $p=0.464$) and average age (SMD=−0.02, 95% CI: −0.20–0.17, $p=0.868$).

Conclusion: This study suggests that sarcomatoid differentiation in histopathology is associated with poor clinical outcome and advanced clinicopathological features in RCC and could serve as a poor prognostic factor for RCC patients.

Keywords: sarcomatoid differentiation, renal cell carcinoma, prognosis, meta-analysis

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Introduction

As the 8th most common cancer worldwide, renal cell carcinoma (RCC) accounts for 2–3% of all adult malignancies[1] and causes approximately 140,000 deaths per year.[2] Although most patients with RCC can be cured by surgical resection, more than

25% of patients still experience local recurrence or distant metastasis.[3] Given that clear cell RCC (ccRCC) accounts for approximately 80% of all RCCs,[4] it should be noted that a particular histologic subtype is accompanied by different manifestations and pharmacologic consequences.[5] Therefore, ideally, the clinical significance of a particular prognostic factor should always be independently validated for each histologic subtype.

RCC with sarcomatoid differentiation is a rare variant of RCC that accounts for 1–8% of all RCC histologic subtypes.[6] Histologically, sarcomatoid is a term used to describe morphologic changes within an RCC. Previous research demonstrates that sarcomatoid differentiation is associated with a more aggressive disease and poor outcome after surgical resection or immunotherapy.[7,8] The International Society of Urological Pathology recommended that the presence of sarcomatoid differentiation should be classified as Grade 4 regardless of the histological subtype or nuclear grade.[9] Given small sample sizes and different conditions, minimal evidence is available on the prognostic role of sarcomatoid differentiation for RCC.

To further clarify the prognostic and clinicopathological value of sarcomatoid differentiation in RCC, we conducted a systematic review and meta-analysis to evaluate whether the presence of sarcomatoid differentiation has a prognostic impact on cancer-specific survival (CSS), overall survival (OS), recurrence-free survival (RFS), progression-free survival (PFS), and cancer-specific mortality (CSM).

Materials and methods
Literature search
In accordance with the preferred reporting items for systematic reviews and meta-analysis guideline,[10] we systematically searched for relevant studies in PubMed, Embase, and Web of Science until January 2018. The following terms were included in the search strategy: "sarcomatoid differentiation," "renal cell cancer OR renal cell carcinoma", and "prognostic factor OR oncologic outcome." These terminologies were used in all possible combinations, and the language of publications was restricted to English. Moreover, the reference lists of the included articles were scanned manually for additional potentially relevant studies.

Inclusion and exclusion criteria
Studies eligible for inclusion in our meta-analysis had to meet the following criteria: 1) studies that included RCC and where the expression of sarcomatoid differentiation was pathologically confirmed; 2) studies in which the association between sarcomatoid differentiation and the prognosis of RCC (CSS, OS, RFS, PFS, and CSM) were reported; and 3) studies wherein HRs and their 95% CIs for survival analysis were reported or could be computed from given data. The exclusion criteria were as follows: 1) reviews, case reports, conference records, and comments and non-original articles; 2) studies that did not analyze the sarcomatoid differentiation, clinicopathological features, and survival outcome; 3) studies with insufficient data to estimate the HRs and 95% CIs; and 4) studies that were not published in English. In addition, when multiple reports describing the same population were published, the most recent or most complete report was used.

Data extraction and quality assessments
According to the inclusion and exclusion criteria, 2 investigators independently extracted the following data from eligible studies: first author's name, year of publication, country, period of recruitment, study design, age of patients, gender ratio, number of patients, follow-up time, histology, nuclear grade, pathology tumor (pT) stage, and survival end point. If multivariate and univariate analyses were both conducted in the same study, only the results of multivariate analysis were extracted because this information is more accurate as it accounts for confounding factors. When disagreement occurred, the issue was resolved through discussion among the authors. The quality in prognosis studies[11] tool was used to assess the methodological quality of each included study. Each study can be assessed by 6 important bias domains: study participation, study attrition, prognostic factor measurement, study confounding, outcome measurement, and statistical analysis and reporting. Studies from the analysis that are at high risk for any important bias were defined as low quality.

Statistical analysis
The statistical processes in this meta-analysis were undertaken using Stata 12.0 (StataCorp, College Station, TX, USA). Dichotomous variables were calculated by HRs, and pooled HRs with 95% CIs were used to evaluate the association of sarcomatoid differentiation with RCC prognosis (CSS, OS, RFS, PFS, and CSM). Furthermore, we studied the associations between sarcomatoid differentiation and clinical parameters of RCC. Data about Fuhrman grade (III/IV vs I/II), pT stage (pT3–4 vs pT1–2), lymph node involvement (N1 vs N0), pathological types (ccRCC-only vs mixed type), and gender (male vs female) were continuous variables whereas average age was a dichotomous variable. Comparisons of continuous and dichotomous variables were pooled as standard mean differences (SMDs) and ORs.

Statistical heterogeneity among studies was assessed using Cochran's Q test and Higgins I^2 statistic. When I^2 <50% or $p_{heterogeneity}$ >0.1, which indicates that no obvious heterogeneity existed among studies, the fixed effects (FE) model was applied; otherwise, the random-effects (RE) model was applied. To obtain a more precise evaluation of heterogeneity, subgroup analyses were conducted for CSS, OS, RFS, PFS, and CSM by geographical region, year of publication, pathological types, pT stage, Fuhrman grade, number of patients, and median follow-up. Publication bias was assessed using funnel plots and Egger's linear regression test. In addition, sensitivity analyses were used to estimate the robustness of the results by sequential omission of individual studies. A 2-tailed p-value <0.05 was considered statistically significant.

Results
Literature search
The flowchart depicting the study selection procedure in this meta-analysis is shown in Figure 1. After the initial search of relevant databases, 5,848 potentially relevant citations were retrieved. In total, 4,906 studies were excluded by reviewing the title and abstract, including 2,783 duplicate reports, 1,770 irrelevant studies, and 353 non-research articles (non-human studies, letters, case reports, meeting records, and reviews). The full-texts of the 942 remaining articles were assessed, and 907 papers were excluded due to insufficient survival information or duplicated cohorts. Finally, in accordance with the inclusion criteria, 35 articles published from 2004 to 2017 about the association of sarcomatoid differentiation and RCC survival were eligible for the meta-analysis.
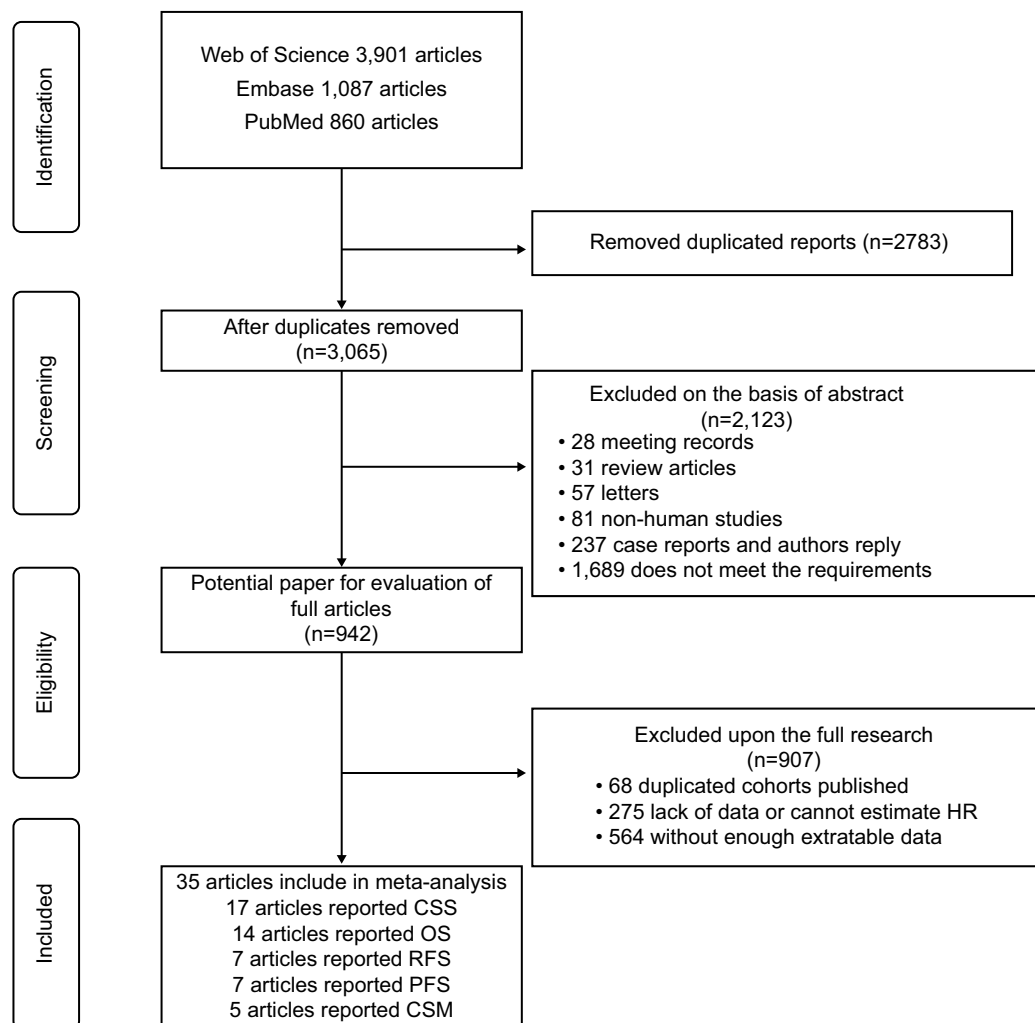

Figure 1 Flow chart of literature search and selection process.
Abbreviations: CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CSM, cancer-specific mortality.

Study characteristics

The characteristics of the 35 eligible studies[12–46] are presented in Table 1. These studies enrolled 11,261 patients (59–1,437 per study), with a median follow-up ranging from 12.6 to 102 months. Most of the included studies had a retrospective design. Among the included studies, 10 were conducted in America, 7 in China, 6 in Korea, 5 in Europe, 4 at multiple centers, 1 in Mexico, 1 in Egypt, and 1 in Japan. CSS was evaluated in 17 studies, and OS was reported in 14 studies. Both PFS and RFS were reported in 7 studies, and CSM was reported in 5 studies. The characteristics, including tumor features and pathologic outcomes, are summarized in Table 2. Sarcomatoid differentiation was detected in (792/11,261) 7.03% of pathological specimens of the included patients. Ten of the included studies were limited to ccRCC, whereas 25 studies involved various tumor types, including ccRCC, papillary RCC, chromophobe RCC, and unclassified variants. The quality in prognosis studies tool was applied to assess the methodological quality of the included studies, demonstrating that all studies were of high quality (Table S1).

Meta-analysis results

Our meta-analysis demonstrated that sarcomatoid differentiation expression in RCC was associated with poor CSS (RE model, HR=1.46, 95% CI: 1.26–1.70; $p<0.001$; I^2=75.2%; Figure 2A), OS (RE model, HR=1.59, 95% CI: 1.42–1.78, $p<0.001$; I^2=46.5%; Figure 2B), PFS (RE model, HR=1.61, 95% CI: 1.35–1.91; $p<0.001$; I^2=57.6%; Figure 2C), RFS (RE model, HR=1.60, 95% CI: 1.29–1.99, $p<0.001$; I^2= 58.6%; Figure 2D), and CSM (RE model, HR=2.36, 95% CI: 1.64–3.41; $p<0.001$; I^2=81.9%; Figure 2E). To explore the heterogeneity between these studies, the significance of sarcomatoid differentiation was evaluated further via subgroup analysis based on the main features, including geographical region, year of publication, pathological types, pT stage, Fuhrman grade, number of patients, and median follow-up (Table 3). The results of subgroup analysis suggested sarcomatoid differentiation as a prognostic factor despite heterogeneity among some groups. Of note, heterogeneity decreased significantly in some models, such as geographical region in non-Asian (CSS, OS, and RFS), year of publication before 2013 (CSS, OS, RFS, and CSM), number of patients <250 (CSS, OS, RFS, and CSM), (pT3–4) % ≥50 (CSS, OS, PFS, and CSM), median follow-up <40 months (CSS, OS, RFS, and CSM), and mixed type pathology (OS and RFS).

To explore the significance of sarcomatoid differentiation in pathologic diagnosis, we evaluated the relationship between the expression of sarcomatoid differentiation and clinicopathological features. As shown in Table 4, sarcomatoid differentiation was significantly related to TNM stage (III/IV vs I/II: OR=1.84, 95% CI: 1.12–3.03, p=0.017, Figure S1A), Fuhrman grade (III/IV vs I/II: OR=8.37, 95% CI: 2.92–24.00, $p<0.001$, Figure S1B), lymph node involvement (N1 vs N0: OR=1.88, 95% CI: 1.08–3.28, p=0.026, Figure S1C), and pathological type (ccRCC-only vs mixed type: OR=0.48, 95% CI: 0.29–0.80, p=0.005, Figure S1D), However, no significant correlations were observed with regard to gender (male vs female, OR=0.86, 95% CI: 0.58–1.28, p=0.464, Figure S1E) and average age (SMD=−0.02, 95% CI: −0.20–0.17, p=0.868, Figure S1F). No significant heterogeneity was observed in those groups.

Sensitivity analysis

In sensitivity analysis by sequential omission of individual studies, the pooled HR for CSS ranged from 1.37 (95% CI: 1.22–1.54) to 1.49 (95% CI: 1.28–1.74) (Figure S2A). Similarly, the pooled HR for OS ranged from 1.54 (95% CI: 1.37–1.72) to 1.62 (95% CI: 1.46–1.80) (Figure S2B), for PFS from 1.53 (95% CI:1.31–1.79) to 1.68 (95% CI: 1.41–2.00) (Figure S2C), for RFS from 1.47 (95% CI: 1.23–1.75) to 1.73 (95% CI: 1.39–2.16) (Figure S2D), and for CSM from 2.06 (95% CI: 1.48–2.87) to 2.72 (95% CI: 1.83–4.04) (Figure S2E). These results indicated that the findings were reliable and robust.

Publication bias

Egger's tests and funnel plots were conducted to estimate publication bias in the present meta-analysis. As shown in Figure 3, the funnel plots indicated that the included studies (CSS, OS, RFS, and PFS) had no evident asymmetry. The p-values of the Egger's tests were all greater than 0.05 in CSS (p-Egger=0.723, Figure 3A), OS (p-Egger=0.925, Figure 3B), PFS (p-Egger=0.443, Figure 3C), and RFS (p-Egger=0.108, Figure 3D). However, a statistically significant publication bias was founded in CSM (p-Egger=0.003, Figure 3E).

Discussion

The rate of incidence of RCC has rapidly increased by approximately 2% worldwide during the last decade.[47] Although significant advancements have been made in

Table 1 Main characteristics of the eligible studies

Author	Year	Country	Recruitment period	No. of patients	Age (years)	Gender (m/f)	Follow-up (months)	Study design	Survival analysis
Zhang et al[12]	2017	China	2008–2009	602	Mean±SD 55±12.3	422/180	Median (range) 67 (39–74)	Retrospective	OS, RFS
Xie et al[13]	2017	China	2006–2015	209	Mean±SD 47.7±12.0	96/113	Median (range) 48.4 (10.7–129.9)	Retrospective	PFS
Wu et al[14]	2017	China	2004–2012	301	Median (range) 53 (4–831)	206/95	Median (range) 54.6 (3–121)	Retrospective	OS
Gu et al[15]	2017	China	2006–2014	184	Mean±SD 54.3±13.0	142/42	Mean±SD 23.3±14.6	Retrospective	OS, PFS
Gershman et al[16]	2017	USA	1980–2010	138	Mean (range) 63 (54–72)	91/47	Median (IQR) 102 (67.2–130.8)	Retrospective	CSM
Chipollini et al[17]	2017	Multi-center	2000–2015	293	Median (IQR) 61 (54.7–70.3)	NA	Median (IQR) 12.6 (4.47–30.3)	Retrospective	CSS
NguyenHoang et al[18]	2016	China	2008–2009	392	Mean±SD 55.2±12.1	116/276	Median (range) 73 (39–74)	Retrospective	OS, RFS
Khor et al[19]	2016	USA	1985–2003	842	Median (range) 61.5 (22.4–89)	527/315	Median (range) 73.2 (0.12–273.6)	Retrospective	OS
Lee et al[20]	2016	Korea	2006–2013	1,511	Median (range) 57.6 (19–86)	1,077/434	Median (IQR) 36 (24–57)	Retrospective	CSS
Kara et al[21]	2016	USA	2005–2013	264	NA	175/89	Median (IQR) 16.8 (24–57)	Retrospective	CSS
Jeon et al[22]	2016	Korea	1994–2008	1,437	Mean±SD 54.2±11.7	1,011/426	Mean (range) 68.6 (1.2–212.6)	Retrospective	OS, CSS
Errarte et al[23]	2016	Spain	NA	59	Mean (range) 59 (25–83)	45/14	Mean (range) 65 (1–240)	Retrospective	OS
Yu et al[24]	2015	China	2007–2014	140	Mean (range) 57.3 (17–79)	101/39	Median 32	Retrospective	OS, PFS
Schiavina et al[25]	2015	Italy	2000–2013	185	Mean±SD 63.3±11.8	149/36	Median (IQR) 32 (18–62)	prospective	CSM
Psutka et al[26]	2015	USA	1994–2008	283	Median (IQR) 67 (60–72)	195/88	Median (IQR) 97.2 (69.6–116.4)	Retrospective	CSM
Lee et al[27]	2015	Korea	1994–2013	440	Median (range) 56 (18–82)	286/154	Median (IQR) 69 (30–134)	Retrospective	PFS, CSS
Kim et al[28]	2015	USA	1999–2012	55	Mean±SD 61.2±11.1	42/13	Mean (range) 21.5 (10.4–101)	Retrospective	OS
Weiss et al[29]	2014	Germany	1994–2011	200	Median (range) 67 (37–86)	129/71	Median 49	Retrospective	OS
Teng et al[30]	2014	China	2004–2009	378	Mean±SD 53.4±12.4	272/106	Median (range) 60 (2–97)	Retrospective	CSS, RFS
Haddad et al[31]	2014	Multi-center	2000–2013	166	Median (range) 62 (24–84)	108/58	Median (range) 27.8 (1–148)	Retrospective	RFS, CSS, OS
El-Mokadem et al[32]	2014	UK	2001–2005	98	Mean±SD 62.9±11.6	61/37	Median (IQR) 95 (40.5–115.5)	Retrospective	RFS, CSS
Tosco et al[33]	2013	Multi-center	1988–2011	109	Median (range) 62 (25–82)	71/38	Median (range) 52.7 (1.37–283)	Retrospective	CSS
Kruck et al[34]	2013	Germany	1993–2006	278	Mean±SD 62.2±12.5	194/84	Median (IQR) 65 (20–100)	Retrospective	CSS, OS
Kondo et al[35]	2013	Japan	1985–2011	68	Median (range) 63 (19–79)	48/20	Median (range) 19 (0.1–144)	Retrospective	CSS
Volpe et al[36]	2012	Multi-center	1995–2007	291	Mean±SD 59.9±13.8	NA	Median (IQR) 44(24–73)	Retrospective	CSM
Sukov et al[37]	2012	USA	1970–2002	395	Median (range) 65 (25–89)	327/68	Median (range) 33.6 (0–198)	Retrospective	CSM
Sameh et al[38]	2012	Egypt	2000–2010	112	Mean (range) 59 (22–87)	77/35	Median (range) 24 (3–125)	Retrospective	RFS

(Continued)

Table 1 (*Continued*)

Author	Year	Country	Recruitment period	No. of patients	Age (years)	Gender (m/f)	Follow-up (months)	Study design	Survival analysis
Ku et al[39]	2011	Korea	1995–2005	82	Mean 57	67/15	Median (range) 9 (0–73)	Retrospective	PFS, CSS
Rodríguez-Covarrubias et al[40]	2010	Mexico	1980–2009	126	Mean±SD 60.1±13.3	71/55	Median (range) 20.5 (2–228)	Retrospective	PFS
Poon et al[41]	2009	USA	1988–2007	230	Median (IQR) 64.5 (55.7–72.5)	149/81	Median (IQR) 24 (9–48)	Retrospective	CSS
Klatte et al[42]	2009	USA	2001–2007	343	Mean (range) 60.7 (24–85)	240/103	Median (range) 21 (2–67)	Retrospective	CSS
Coons et al[43]	2009	USA	1988–2006	128	Median (range) 64 (35–87)	95/33	Median (range) 25.2 (0–124)	Retrospective	CSS, OS, RFS
Kwak et al[44]	2007	Korea	1990–2004	186	Median (range) 58 (20–79)	151/35	Median (IQR) 17.4 (24–78.9)	Retrospective	PFS, OS
Lee et al[45]	2006	Korea	1993–2003	485	Median (range) 55 (26–81)	360/125	Median (range) 26.9 (4–96.9)	Retrospective	CSS
Sanchez-Ortiz et al[46]	2004	USA	1992–2002	251	NA	165/86	NA	Retrospective	CSS

Abbreviations: m/f, male/female; NA, data not applicable; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CSM, cancer-specific mortality.

Table 2 Tumor characteristics of the eligible studies

Study	Staging system	Grading system	Sarcomatoid + / sarcomatoid -	Stages 1–2/3–4	Grades 1–2/3–4	ccRCC/ no-ccRCC	Tumor size (cm)
Zhang et al[12]	NA	Fuhrman	26/576	450/152	337/265	602/0	Mean±SD 4.0±2.55
Xie et al[13]	2010 AJCC	Fuhrman	13/196	189/20	196/13	0/209	Mean±SD 5.3±3.6
Wu et al[14]	2010 AJCC	WHO	13/288	265/36	225/76	301/0	NA
Gu et al[15]	2010 AJCC	Fuhrman	53/110	0/163	83/55	135/8	Mean±SD 6.8±3.5
Gershman et al[16]	2010 AJCC	WHO/ ISUP	30/108	31/107	6/132	105/33	Median (IQR) 10 (8–13)
Chipollini et al[17]	2016AJCC	Fuhrman	56/236	0/293	30/263	261/32	NA
NguyenHoang et al[18]	2010 AJCC	Fuhrman	5/201	292/100	259/133	392/0	Mean±SD 4.3±2.6
Khor et al[19]	2010 AJCC	Fuhrman	20/822	630/212	265/577	842/0	Median (range) 4.2 (0.6–20)
Lee et al[20]	2010 AJCC	Fuhrman	48/1,463	1,305/206	825/686	1,260/251	Median (range) 4.33 (0.5–16)
Kara et al[21]	2010 AJCC	Fuhrman	159/109	33/231	0/264	223/41	NA
Jeon et al[22]	2010 AJCC	Fuhrman	28/1,409	1,228/209	686/751	1,236/201	Mean±SD 5.1±3.3
Errarte et al[23]	2010 AJCC	Fuhrman	4/55	32/27	24/35	59/0	Median (range) 7.9 (2–19)
Yu et al[24]	2010 AJCC	Fuhrman	9/131	0/140	NA	125/15	NA
Schiavina et al[25]	2009 AJCC	Fuhrman	17/168	0/185	46/139	150/35	Mean±SD 8.05±2.8
Psutka et al[26]	2009 AJCC	Fuhrman	7/276	214/69	151/132	233/50	Median (IQR) 5 (3–7.5)
Lee et al[27]	2009 AJCC	Fuhrman	17/433	188/152	165/266	335/65	Median (range) 6.5 (1.2–32)
Kim et al[28]	2002 AJCC	WHO	20/35	19/36	NA	41/14	Mean±SD 9.9±4.4

(*Continued*)

Table 2 (*Continued*)

Study	Staging system	Grading system	Sarcomatoid + / Sarcomatoid -	Stages 1–2/3–4	Grades 1–2/3–4	ccRCC/ no-ccRCC	Tumor size (cm)
Weiss et al[29]	2009 AJCC	Fuhrman	5/195	0/200	142/58	180/20	MA
Teng et al[30]	2009 AJCC	Fuhrman	4/378	346/32	200/178	378/0	Mean±SD 4.6±2.6
Haddad et al[31]	2009AJCC	Fuhrman	21/145	0/166	13/153	149/17	Median (range) 10.5 (2.2–29)
El-Mokadem et al[32]	2009 AJCC	Fuhrman	6/74	50/30	31/49	80/0	NA
Tosco et al[33]	2009 AJCC	Fuhrman	5/104	49/60	40/69	88/21	Median (range) 7.5 (2–21)
Kruck et al[34]	2010 AJCC	Fuhrman	19/258	169/109	234/44	278/0	Mean±SD 5.26±2.91
Kondo et al[35]	2009 AJCC	Fuhrman	17/51	0/68	33/35	0/68	Median (range) 10 (3.5–20)
Volpe et al[36]	2009 AJCC	Fuhrman	5/286	245/46	175/116	0/291	Median (IQR) 4.6 (3.4–7)
Sukov et al[37]	2009 AJCC	Fuhrman	4/391	357/38	247/148	109/16	Median (range) 8 (2.5–20)
Sameh et al[38]	2009 AJCC	Fuhrman	9/103	0/112	45/51	96/16	Median (range) 8.1 (4–16)
Ku et al[39]	2002 AJCC	Fuhrman	24/58	26/56	17/65	82/0	NA
Rodríguez-Covarrubias et al[40]	2002 AJCC	Fuhrman	11/115	2/124	62/60	102/24	Mean±SD 9.03±5.2
Poon et al[41]	2002 AJCC	Fuhrman	7/223	0/230	138/92	153/77	NA
Klatte et al[42]	2002 AJCC	Fuhrman	27/316	198/145	181/162	343/0	Mean (range) 7.1 (0.8–25)
Coons et al[43]	2002 AJCC	Fuhrman	18/110	0/128	40/103	105/23	Median (range) 9.9 (3.5–21)
Kwak et al[44]	2002 AJCC	Fuhrman	42/144	86/100	55/131	152/34	NA
Lee et al[45]	1997 AJCC	Fuhrman	10/466	382/103	264/221	419/66	NA
Sanchez-Ortiz et al[46]	1997 AJCC	Fuhrman	33/218	184/67	85/166	203/48	Mean 7.9

Abbreviations: NA, data not applicable; AJCC, American Joint Committee on Cancer classification; WHO/ISUP, World Health Organization/International Society of Urological Pathology classification; ccRCC, clear cell renal cell carcinoma.

managing renal masses, long-term survival remains unsatisfactory, and the vast majority of patients with RCC still die of their disease. Therefore, RCC patients should be closely followed up, and reliable prognostic biomarkers that evaluate postoperative risks and allow individualized treatment for RCC patients are necessary. In recent years, numerous studies have investigated a wide variety of prognostic factors, such as TNM stage,[13] Fuhrman's grade, and tumor size.[48] However, these prognostic variables cannot always make accurate predictions due to the limitation of significant tumor heterogeneity in RCC patients.[14] Therefore, novel biomarkers that can distinguish high-risk RCC patients and improve clinical outcomes are desperately needed.

An RCC with sarcomatoid differentiation is a distinct subtype that is defined by the presence of atypical spindle cells and is similar to all forms of sarcoma.[49] The reported incidence of sarcomatoid differentiation is between 0.7% and 13.2% of all RCCs,[50] which is consistent with our result of 7.03% (792/11,261). Clinically, sarcomatoid differentiation in RCC is associated with more aggressive tumor biology, increased rates of recurrence, and poor survival.[28] Furthermore, RCC with sarcomatoid differentiation demonstrates unfavorable responses to targeted therapy.[8] According to the 2016 World Health Organization Classification, RCC with sarcomatoid differentiation should not recognized as a separate and distinct entity, indicating that the sarcomatoid component could occur in all types of RCC.[51]

To date, several studies have examined the prognostic value of sarcomatoid differentiation for RCC patients. However, these results were not consistent. Gu et al[15] demonstrated
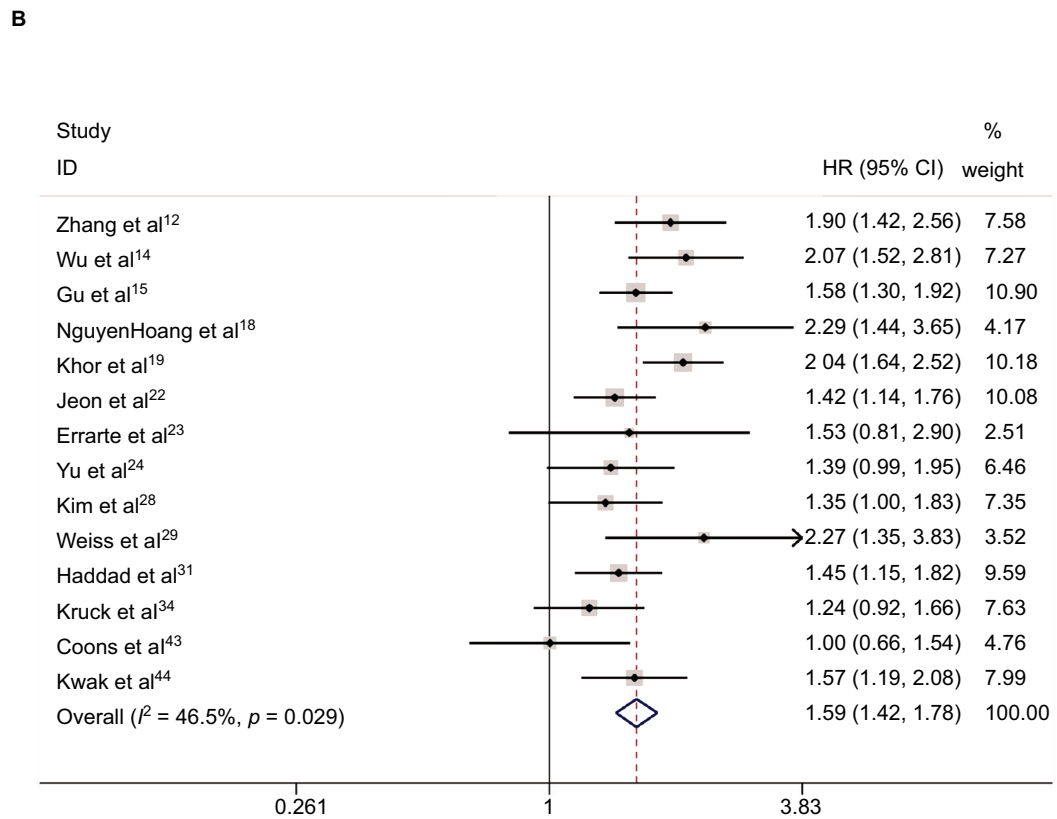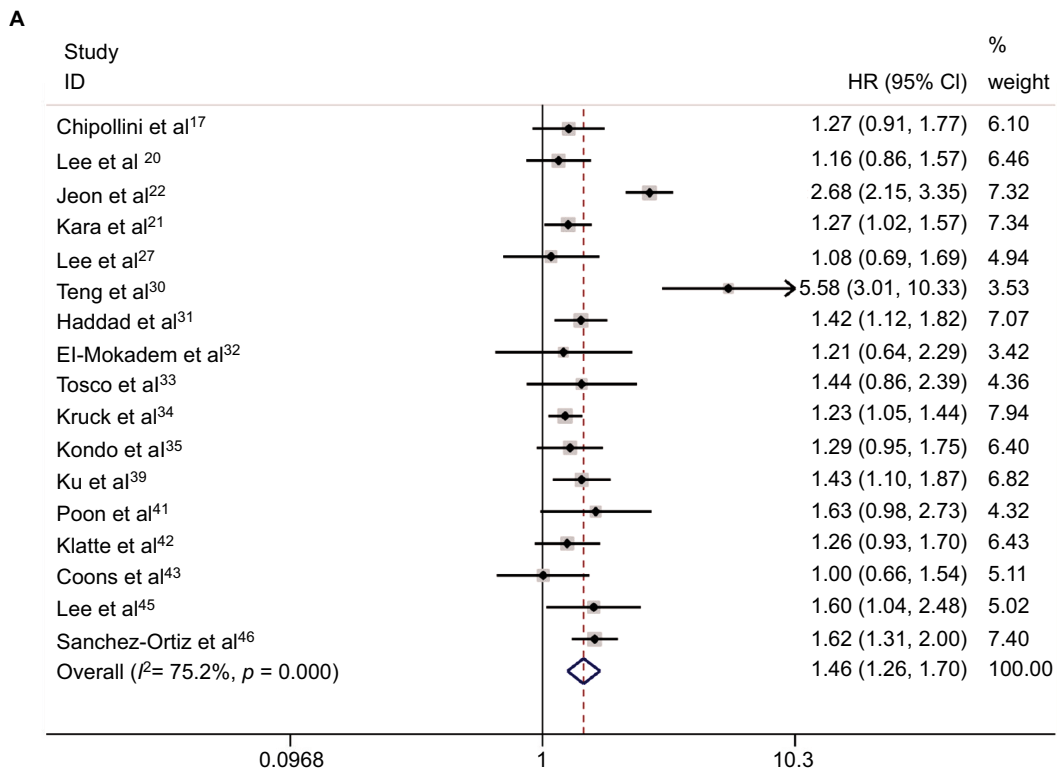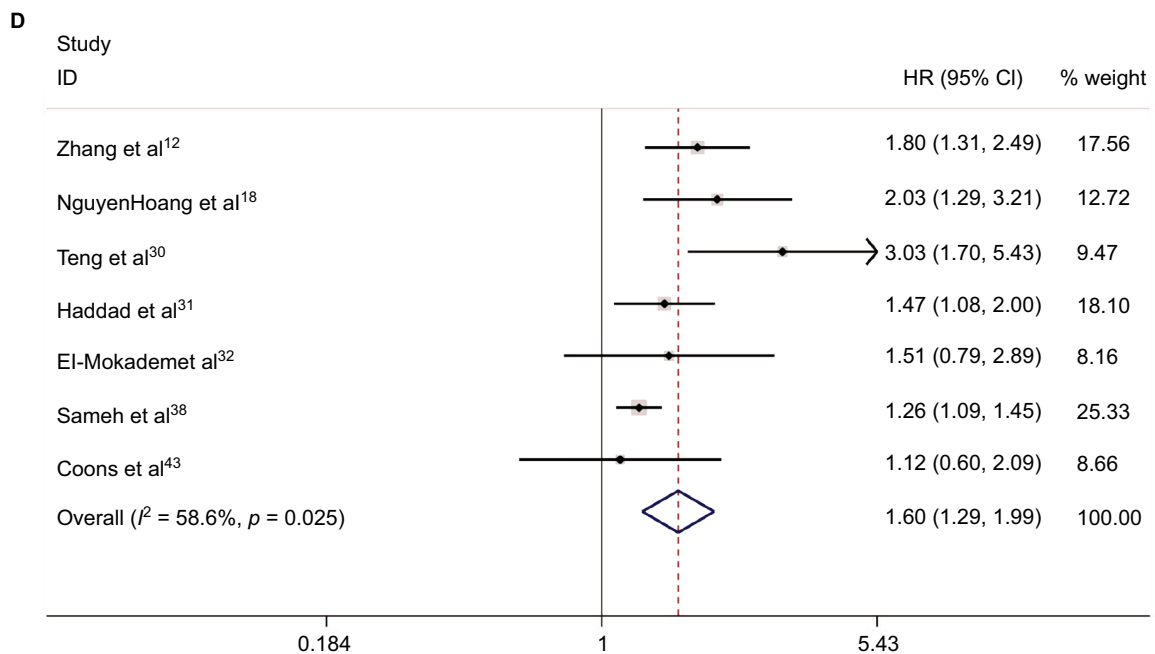
A

B

Figure 2 (*Continued*)

C

Study ID	HR (95% CI)	% weight
Xie et al[13]	2.63 (1.62, 4.26)	8.61
Gu et al[15]	1.77 (1.43, 2.18)	18.69
Yu et al[24]	1.18 (0.08, 1.64)	13.18
Lee et al[27]	1.35 (0.96, 1.88)	13.10
Ku et al[39]	1.49 (1.16, 1.92)	16.71
Rodríguez-Covarrubias et al[40]	2.29 (1.57, 3.33)	11.65
Kwak et al[44]	1.40 (1.12, 1.76)	18.06
Overall (I^2 = 57.6%, p = 0.028)	1.61 (1.35, 1.91)	100.00

0.235   1   4.26

D

Study ID	HR (95% CI)	% weight
Zhang et al[12]	1.80 (1.31, 2.49)	17.56
NguyenHoang et al[18]	2.03 (1.29, 3.21)	12.72
Teng et al[30]	3.03 (1.70, 5.43)	9.47
Haddad et al[31]	1.47 (1.08, 2.00)	18.10
El-Mokademet al[32]	1.51 (0.79, 2.89)	8.16
Sameh et al[38]	1.26 (1.09, 1.45)	25.33
Coons et al[43]	1.12 (0.60, 2.09)	8.66
Overall (I^2 = 58.6%, p = 0.025)	1.60 (1.29, 1.99)	100.00

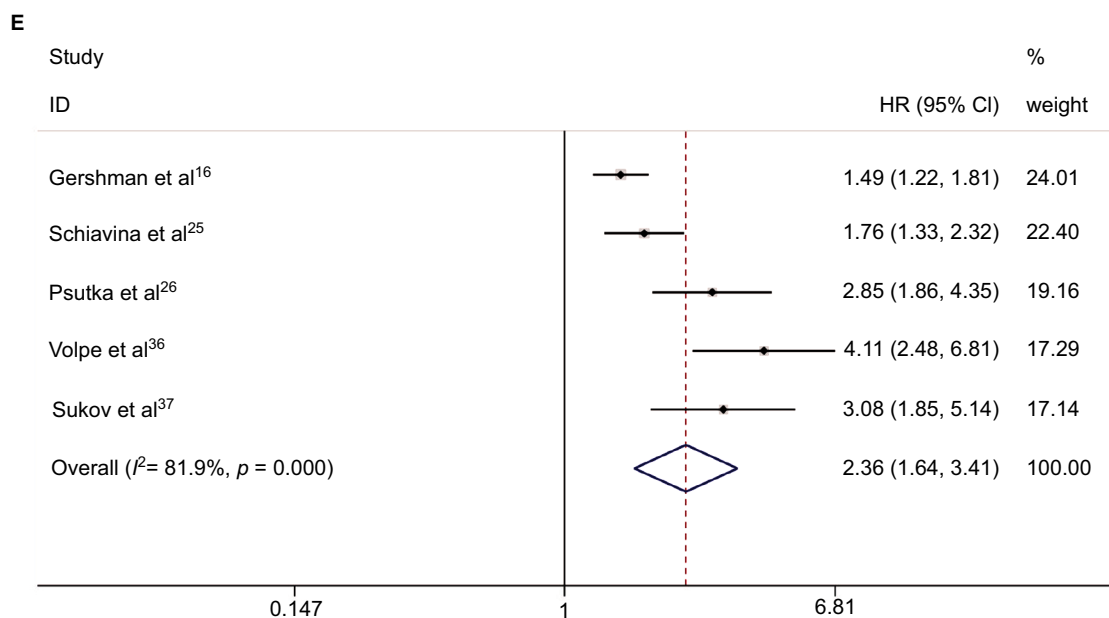0.184   1   5.43

Figure 2 (*Continued*)

Figure 2 Forest plots of studies evaluating the association between sarcomatoid differentiation and clinical outcome of patients with RCC: (**A**) CSS, (**B**) OS, (**C**) PFS, (**D**) RFS, and (**E**) CSM.
Note: Weights are from random-effects analysis.
Abbreviations: CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CSM, cancer-specific mortality; RCC, renal cell carcinoma.

that the presence of sarcomatoid differentiation was significantly associated with poor oncologic outcomes (OS and PFS) for surgically treated RCC patients. Furthermore, Keegan et al[5] confirmed that the sarcomatoid component was associated with poor survival even when encountered in low-stage disease. However, a study by Tosco et al[33] found that sarcomatoid differentiation failed to independently predict CSM in surgically treated RCC patients. Similarly, Chen et al[48] found that the sarcomatoid feature is not a prognostic factor of pT3 RCC for PFS and CSS. Zhang et al[49] demonstrate that the presence of rhabdoid differentiation does not confer an increased risk of death from the largest study, to date, of patients with Grade 4 RCC. Although sarcomatoid differentiation is commonly recognized by clinicians as being associated with poor outcomes, no commonly accepted prognostic system for sarcomatoid RCC is currently available due to the low morbidity and lack of study data. With this objective in mind, we first sought to confirm that sarcomatoid differentiation is an independent prognostic feature for RCC patients.

Using the largest sample size to date, this meta-analysis is the most comprehensive study to systematically analyze

the prognostic power of sarcomatoid differentiation in patients with RCC. We found that sarcomatoid differentiation was significantly associated with CSS (HR=1.46, $p<0.001$), OS (HR=1.59, $p<0.001$), PFS (HR=1.61, $p<0.001$), RFS (HR=1.60, $p<0.001$), and CSM (HR=2.36, $p<0.001$) in RCC patients. In addition, subgroup analyses demonstrated that sarcomatoid differentiation remained a good biomarker regardless of the background of ethnic background, pT stage, nuclear grade, and tumor type. Given the lower sample size of the subgroup (PFS and median follow-up ≥40 months) with a different result (2 studies involving 1,720 patients), we can ignore the inconsistent result to some extent.

Our findings, furthermore, demonstrated that RCC cases exhibiting sarcomatoid differentiation are prone to experiencing a higher nuclear grade (OR=8.37, $p<0.001$), increased pathological T stage (OR=1.84, $p=0.017$), lymph node involvement (OR=1.88, $p=0.026$), and mixed histologic types (OR=0.48, $p=0.005$). However, sarcomatoid differentiation is not associated with gender (OR=0.86, $p=0.464$) and average age (SMD= −0.02, $p=0.868$). Interestingly, although RCCs differ among histological subtypes,

Table 3 Summary and subgroup analysis for the eligible studies

Analysis specification	No. of studies	Study heterogeneity		Effects model	Pooled HR (95% CI)	p-value
		I^2 (%)	$p_{heterogeneity}$			
CSS						
Overall	17	75.2	<0.001	Random	1.46 (1.26,1.70)	<0.001
Geographical region						
Asia	7	86.9	<0.001	Random	1.72 (1.21,2.43)	0.002
Non-Asian	10	0	0.6	Fixed	1.33 (1.22,1.45)	<0.001
Year of publication						
≥2013	8	86.6	<0.001	Random	1.60 (1.17,2.18)	0.003
<2013	9	0	0.47	Fixed	1.35 (1.23,1.48)	<0.001
No. of patients						
≥250	10	85.1	<0.001	Random	1.55 (1.24,1.95)	<0.001
<250	7	0	0.807	Fixed	1.36 (1.19,1.55)	<0.001
Stage (T_3+T_4, %)						
≥50	7	0	0.804	Fixed	1.35 (1.19,1.53)	<0.001
<50	10	85	<0.001	Random	1.56 (1.23,1.97)	0.001
Grade (G_3+G_4, %)						
≥50	11	73.5	<0.001	Random	1.42 (1.19,1.70)	<0.001
<50	6	79.1	<0.001	Random	1.58 (1.17,2.13)	0.003
Median follow-up						
≥40 months	6	90.3	<0.001	Random	1.78 (1.14,2.78)	0.011
<40 months	10	0	0.855	Fixed	1.31 (1.19,1.44)	<0.001
Pathological types						
ccRCC-only	5	82	<0.001	Random	1.59 (1.13,2.23)	0.008
mixed type	12	72.7	<0.001	Random	1.43 (1.20,1.70)	<0.001
OS						
Overall	14	46.5	0.029	Random	1.59 (1.42,1.78)	<0.001
Geographical region						
Asia	8	38.1	0.126	Fixed	1.72 (1.52,1.94)	<0.001
Non-Asian	6	22.5	0.264	Fixed	1.37 (1.17,1.62)	<0.001
Year of publication						
≥2013	9	39.7	0.103	Fixed	1.68 (1.53,1.84)	<0.001
<2013	5	43.1	0.134	Fixed	1.42 (1.23,1.53)	<0.001
No. of patients						
≥250	8	52.6	0.039	Random	1.77 (1.49,2.09)	<0.001
<250	6	0	0.516	Fixed	1.45 (1.30,1.62)	<0.001
Stage (T_3+T_4, %)						
≥50	7	13.6	0.326	Fixed	1.47 (1.31,1.66)	<0.001
<50	7	56.3	0.033	Random	1.73 (1.45,2.07)	<0.001
Grade (G_3+G_4, %)						
≥50	6	55.3	0.048	Random	1.52 (1.27,1.81)	<0.001
<50	6	49.6	0.078	Random	1.76 (1.47,2.12)	<0.001
Median follow-up						
≥40 months	8	52.6	0.039	Random	1.77 (1.49,2.09)	<0.001
< 40 months	6	0	0.516	Fixed	1.45 (1.30,1.62)	<0.001
Pathological types						
ccRCC-only	6	48.4	0.085	Random	1.82 (1.51,2.19)	<0.001
mixed type	8	1	0.422	Fixed	1.47 (1.33,1.62)	<0.001
PFS						
Overall	7	57.6	0.028	Random	1.61 (1.35,1.91)	<0.001
Year of publication						
≥2013	4	67.2	0.028	Random	1.60 (1.20,2.13)	0.001
<2013	3	59.6	0.094	Random	1.62 (1.26,52.08)	<0.001

(*Continued*)

Table 3 (*Continued*)

Analysis specification	No. of studies	Study heterogeneity		Effects model	Pooled HR (95% CI)	*p*-value
		*I*² (%)	*P*ₕₑₜₑᵣₒgₑₙₑᵢₜy			
No. of patients						
≥250	2	0	0.843	Fixed	1.38 (1.15,1.67)	0.001
<250	5	64.6	0.023	Random	1.73 (1.37,2.19)	<0.001
Median follow-up						
≥40 months	2	79.8	0.026	Random	1.84 (0.95,3.53)	0.068
<40 months	5	55.5	0.061	Random	1.57 (1.31,1.88)	<0.001
Stage (T₃+T₄, %)						
≥50	5	55.5	0.061	Random	1.57 (1.31,1.88)	<0.001
<50	2	79.8	0.026	Random	1.84 (0.95,3.53)	0.068
Grade (G₃+G₄, %)						
≥50	4	45.8	0.137	Random	1.55 (1.27,1.88)	<0.001
<50	2	54.1	0.140	Random	2.02 (1.40,2.93)	<0.001
RFS						
Overall	7	58.6	0.025	Random	1.60 (1.29,1.99)	<0.001
Geographical region						
Asia	3	15.1	0.308	Fixed	2.06 (1.58,2.70)	<0.001
non-Asian	4	0	0.747	Fixed	1.29 (1.14,1.46)	<0.001
Year of publication						
≥2013	5	24.2	0.260	Fixed	1.81 (1.46,2.25)	<0.001
<2013	2	0	0.720	Fixed	1.25 (1.09,1.44)	0.001
No. of patients						
≥250	3	15.1	0.308	Fixed	2.06 (1.58,2.70)	<0.001
<250	4	0	0.747	Fixed	1.29 (1.14,1.46)	<0.001
Stage (T₃+T₄, %)						
≥50	3	0	0.608	Fixed	1.29 (1.13,1.46)	<0.001
<50	4	2.4	0.380	Fixed	1.97 (1.56,2.47)	<0.001
Grade (G₃+G₄, %)						
≥50	4	0	0.747	Fixed	1.29 (1.14,1.46)	<0.001
<50	3	15.1	0.308	Fixed	2.06 (1.58,2.70)	<0.001
Median follow-up						
≥40 months	3	34.3	0.218	Fixed	1.99 (1.40,2.82)	<0.001
<40 months	4	34.9	0.203	Fixed	1.39 (1.14,1.69)	0.001
Pathological types						
ccRCC-only	4	2.4	0.380	Fixed	1.97 (1.56,2.47)	<0.001
mixed type	3	0	0.608	Fixed	1.29 (1.13,1.46)	<0.001
CSM						
Overall	5	81.9	<0.001	Random	2.36 (1.64,3.41)	<0.001
Year of publication						
≥2013	3	73.3	0.024	Random	1.86 (1.35,2.57)	<0.001
<2013	2	0	0.432	Fixed	3.56 (2.49,5.11)	<0.001
No. of patients						
≥250	3	0	0.537	Fixed	3.24 (2.47,4.27)	<0.001
<250	2	0	0.343	Fixed	1.57 (1.34,1.85)	<0.001
Median follow-up						
≥40 months	3	0	0.537	Fixed	3.24 (2.47,4.27)	<0.001
<40 months	2	0	0.343	Fixed	1.57 (1.34,1.85)	<0.001
Stage (T₃+T₄, %)						
≥50	2	0	0.343	Fixed	1.57 (1.34,1.85)	<0.001
<50	3	0	0.537	Fixed	3.24 (2.47,4.27)	<0.001
Grade (G₃+G₄, %)						
≥50	2	0	0.343	Fixed	1.57 (1.34,1.85)	<0.001
<50	3	0	0.537	Fixed	3.24 (2.47,4.27)	<0.001

Abbreviations: CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CSM, cancer-specific mortality; ccRCC, clear cell renal cell carcinoma.

we observed no differences on comparing the positive expression of sarcomatoid differentiation between ccRCC and mixed type (CSS, OS, and RFS). In other words, sarcomatoid differentiation may be independently validated as a prognostic factor for each histologic subtype, and this information reflects the risk stratification in the clinical treatment of RCC.

However, several limitations of this study need to be acknowledged. First, significant heterogeneity was detected for several parameters. Although we selected random-effect or fixed-effect models based on heterogeneity, it still existed

due to the differences in the included studies. Second, although a comprehensive search strategy was applied to determine eligible studies, it is possible that some eligible studies were not included, which may cause selection bias. Third, the criteria for the presence of sarcomatoid differentiation in pathologic specimens were inconsistent, which may potentially contribute to potential bias. Thus, rigorous morphological criteria should be conducted to standardize the diagnosis of sarcomatoid differentiation. Additionally, a publication bias existed in CSM, thus inflating the estimate for the association of sarcomatoid differentiation with CSM risk.

Table 4 Meta-analysis of the association between sarcomatoid differentiation and clinicopathological features of RCC

Variables	Studies	Pooled OR/SMD	95% CI	p-value	Model	Heterogeneity I^2 (%)	$p_{heterogeneity}$ value
TNM stage (III/IV vs I/II)	4	1.84	1.12–3.03	0.017	FE	0	0.896
Fuhrman grade (III/IV vs I/II)	3	8.37	2.92–24.00	<0.001	FE	0	0.457
Lymph node involvement (N1 vs N0)	2	1.88	1.08–3.28	0.026	FE	21.3	0.26
Pathological types (ccRCC-only vs mixed type)	4	0.48	0.29–0.80	0.005	FE	29.8	0.234
Gender (male vs female)	5	0.86	0.58–1.28	0.464	FE	0	0.67
Average age	4	−0.02	−0.20–0.17	0.868	FE	0	0.908

Abbreviations: RCC, renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; SMD, standard mean difference.
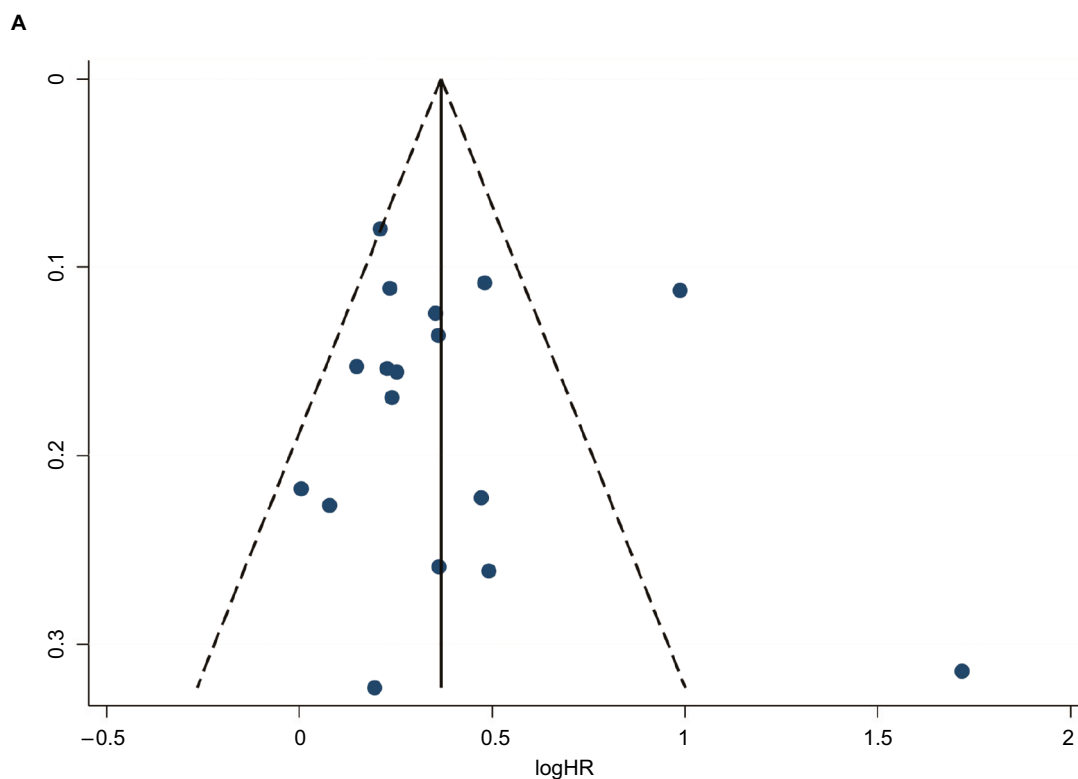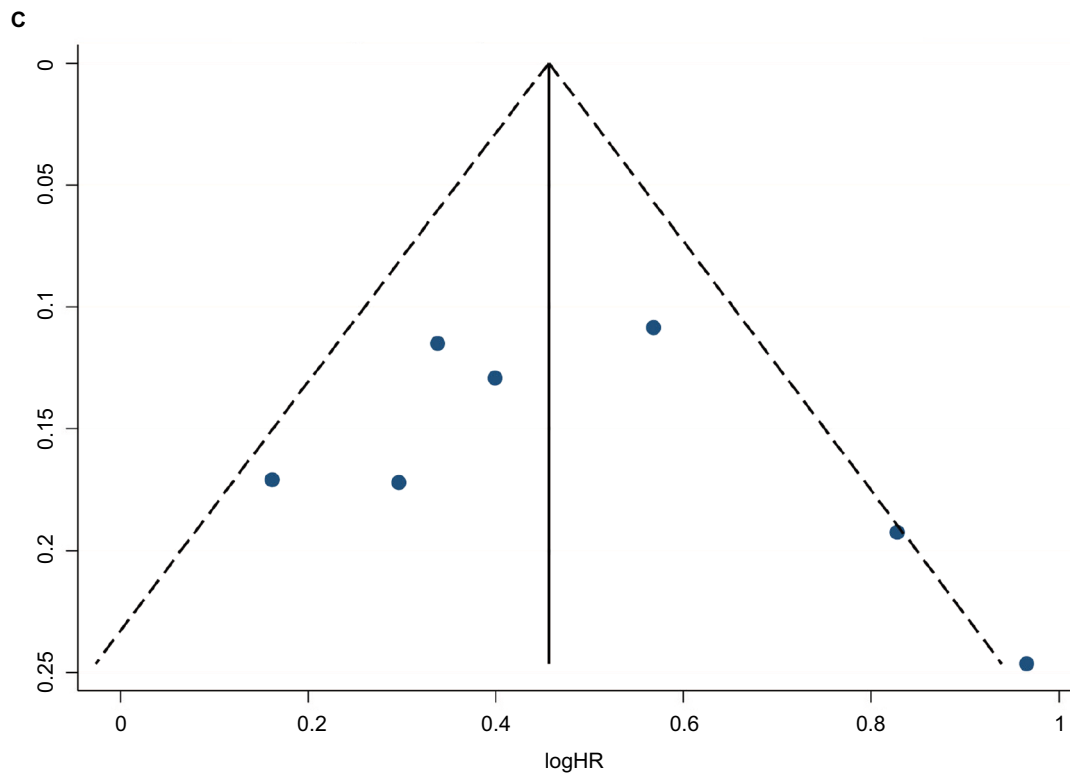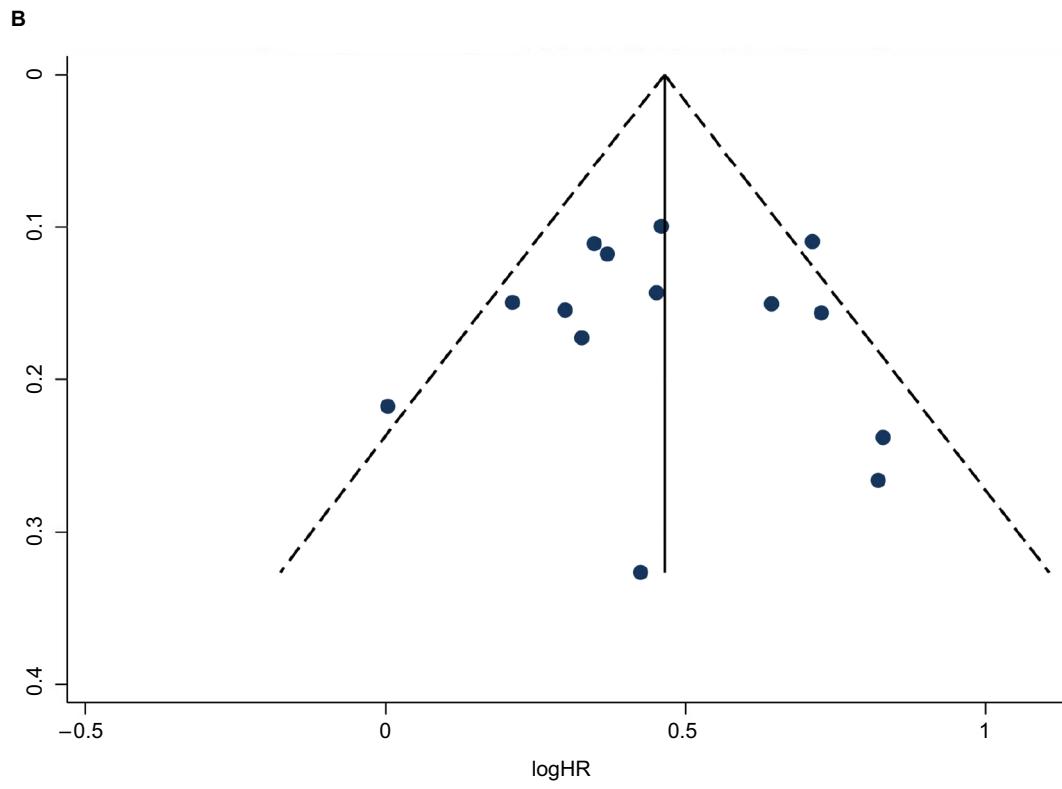
A

Figure 3 (*Continued*)

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Figure 3 (*Continued*)
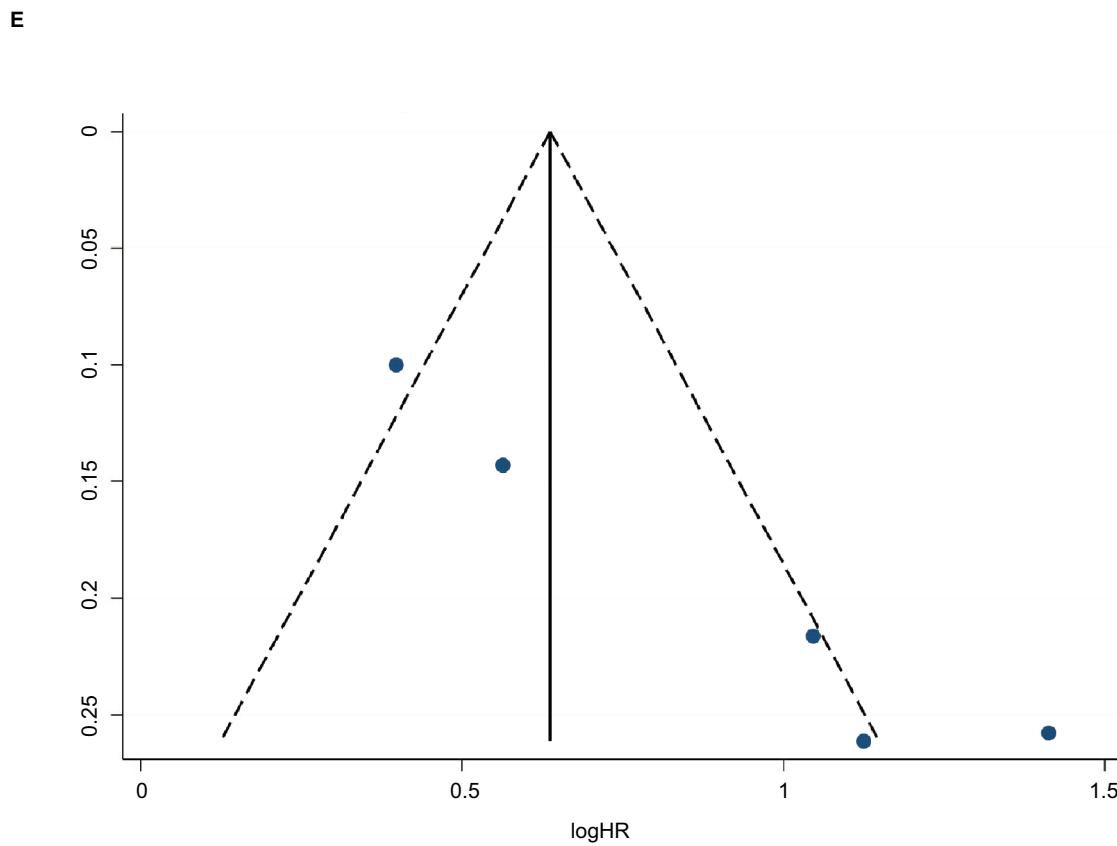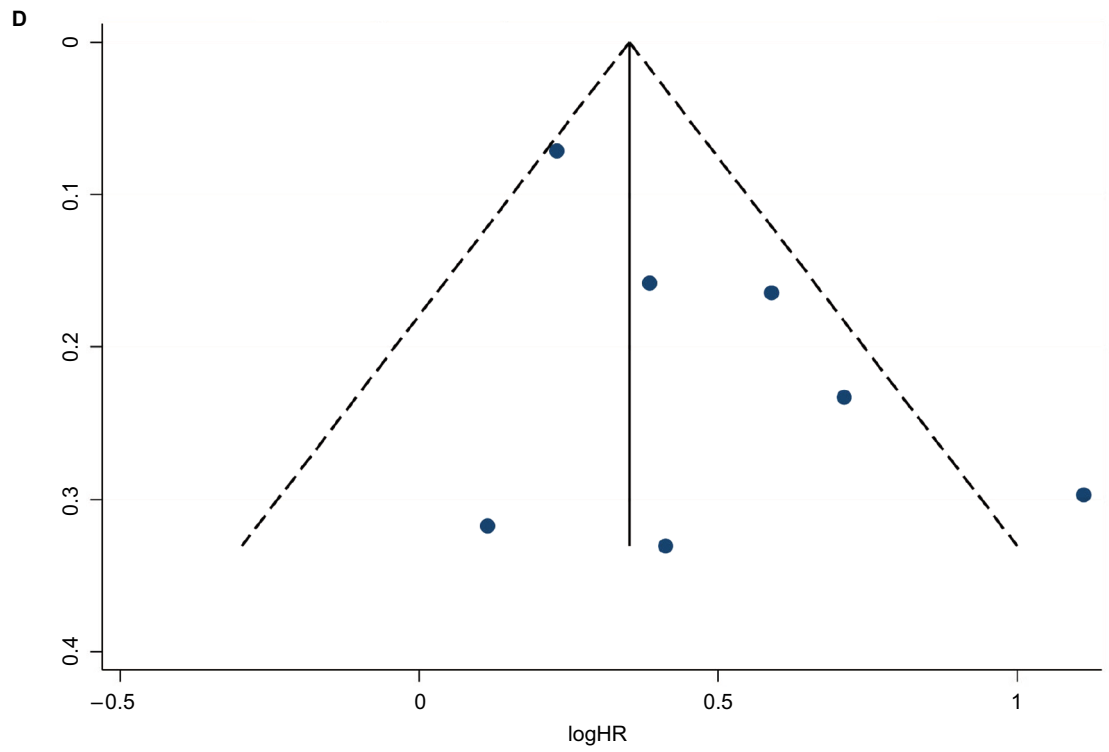
Figure 3 Funnel plots of Egger evaluating possible publication bias for: (**A**) CSS, (**B**) OS, (**C**) PFS, (**D**) RFS, and (**E**) CSM.
Abbreviations: CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CSM, cancer-specific mortality.

Conclusion

Our results demonstrated that sarcomatoid differentiation expression was associated with poor pathological features and prognosis. These findings indicate that sarcomatoid differentiation is a potential adverse prognostic marker that could be utilized to divide risk stratification and formulate individualized treatments for patients with RCC. Considering the limitations of the present analysis, larger studies using standardized methods and criteria are required to verify the prognostic roles of sarcomatoid differentiation expression in RCC.

Author contributions

LJZ and BW designed the research. ZLZ and HZ undertook the literature search. HZ and YJF analyzed the data and interpreted the results. LJZ wrote the paper. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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