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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

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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.

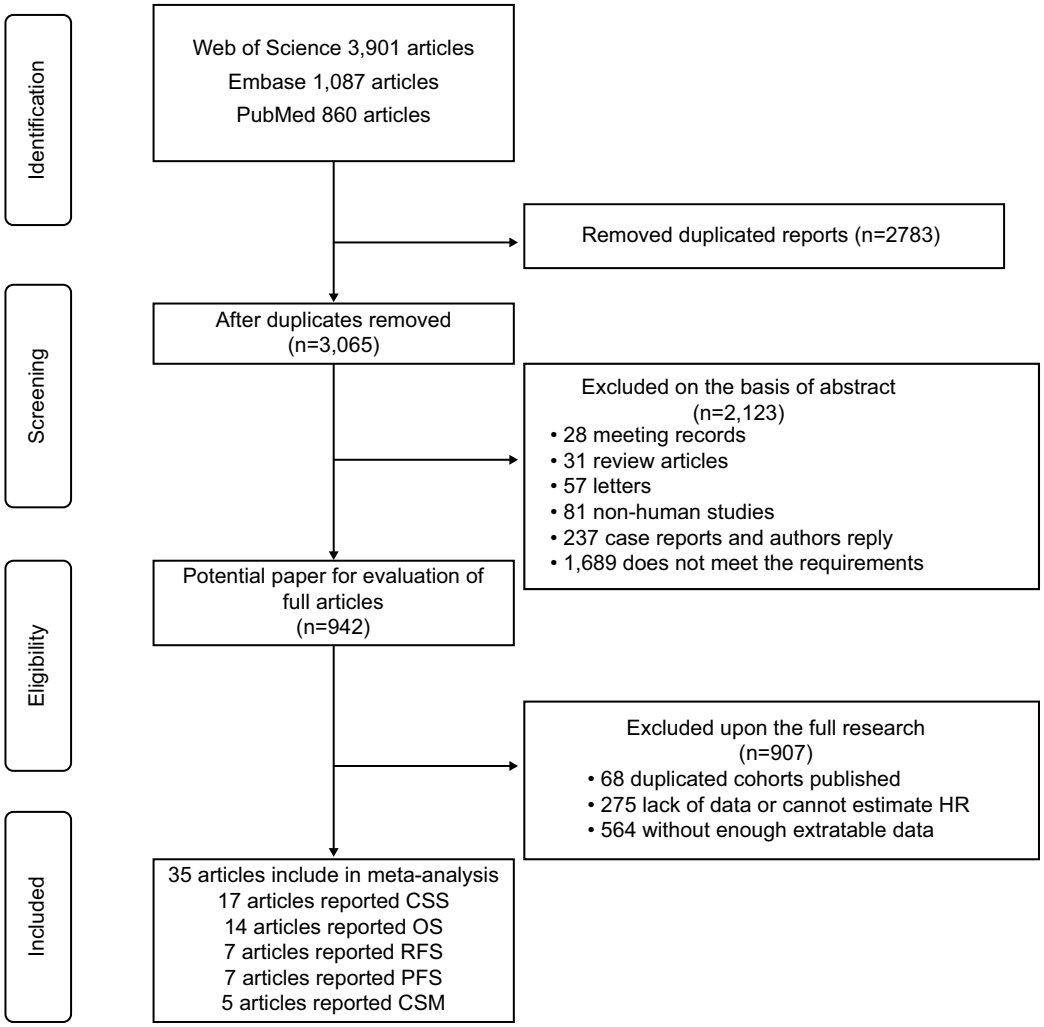


**Figure 1** Flow chart of literature search and selection process.
**Abbreviations:** CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CSM, cancer-specific mortality.

## 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

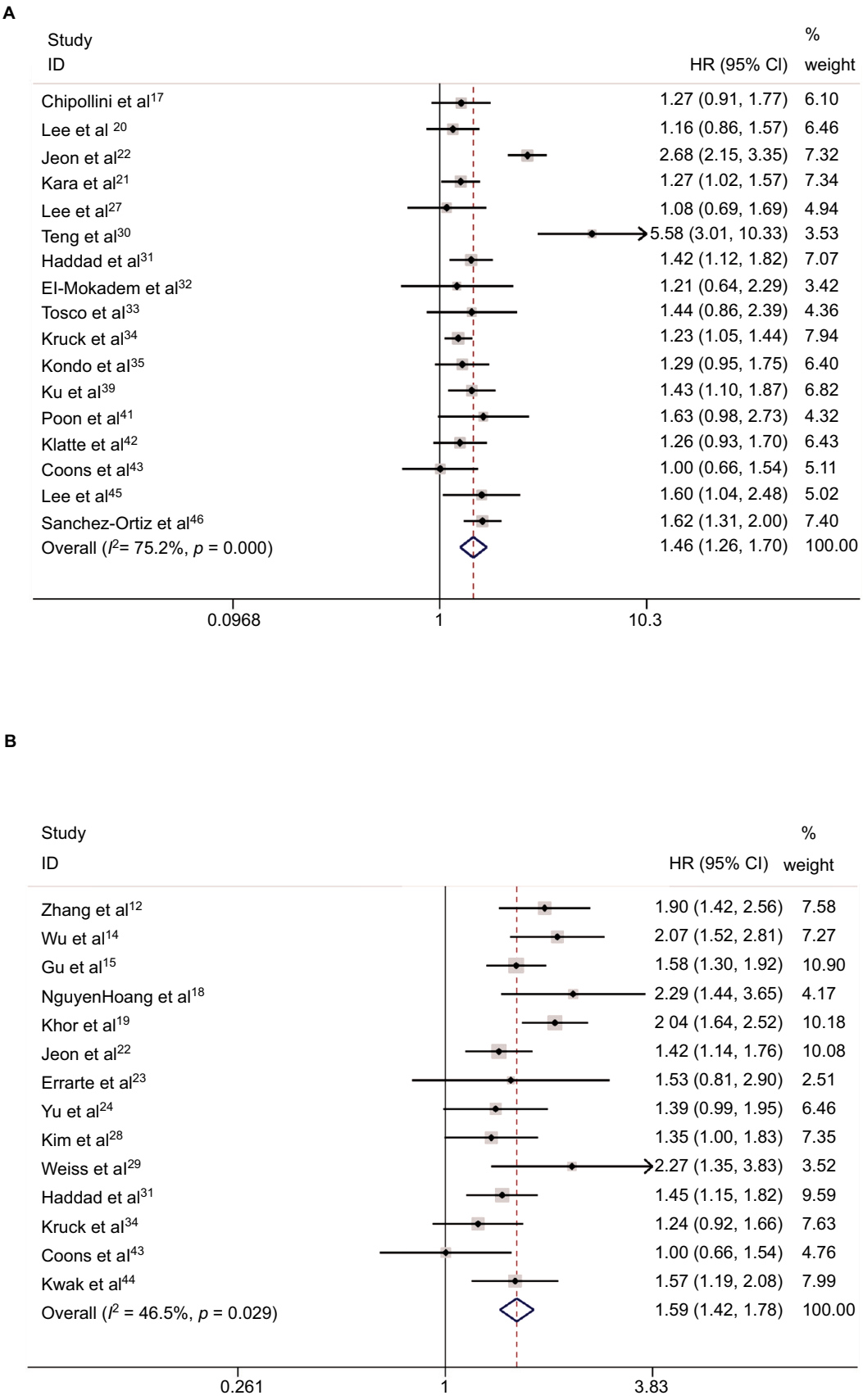


**Figure 2** (*Continued*)

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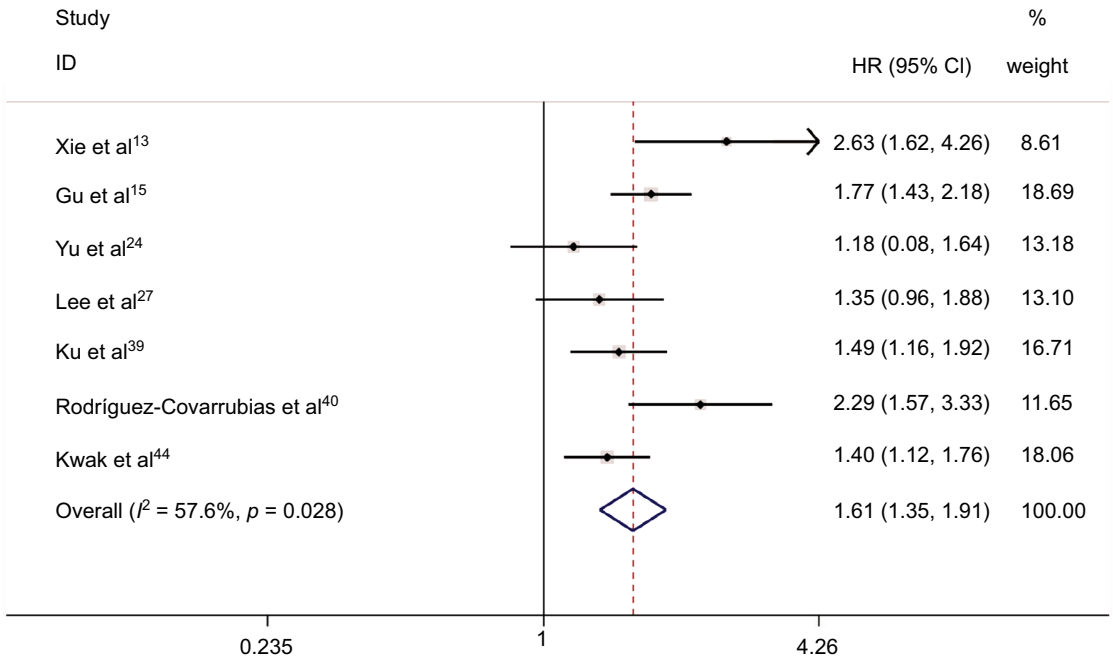


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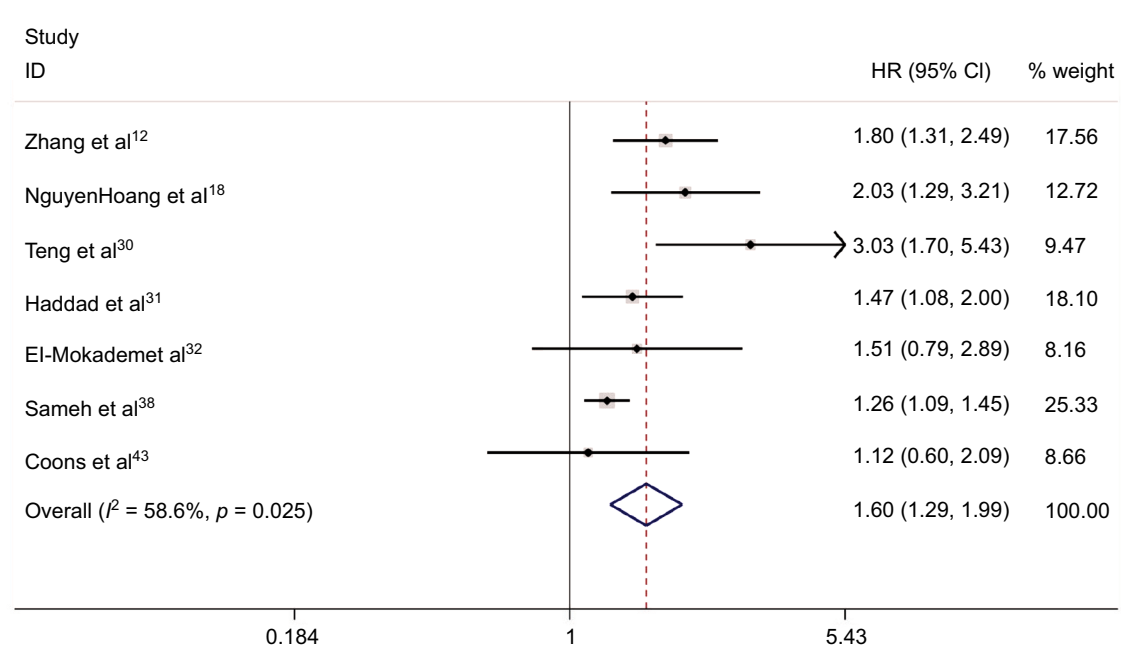



**Figure 2** (*Continued*)

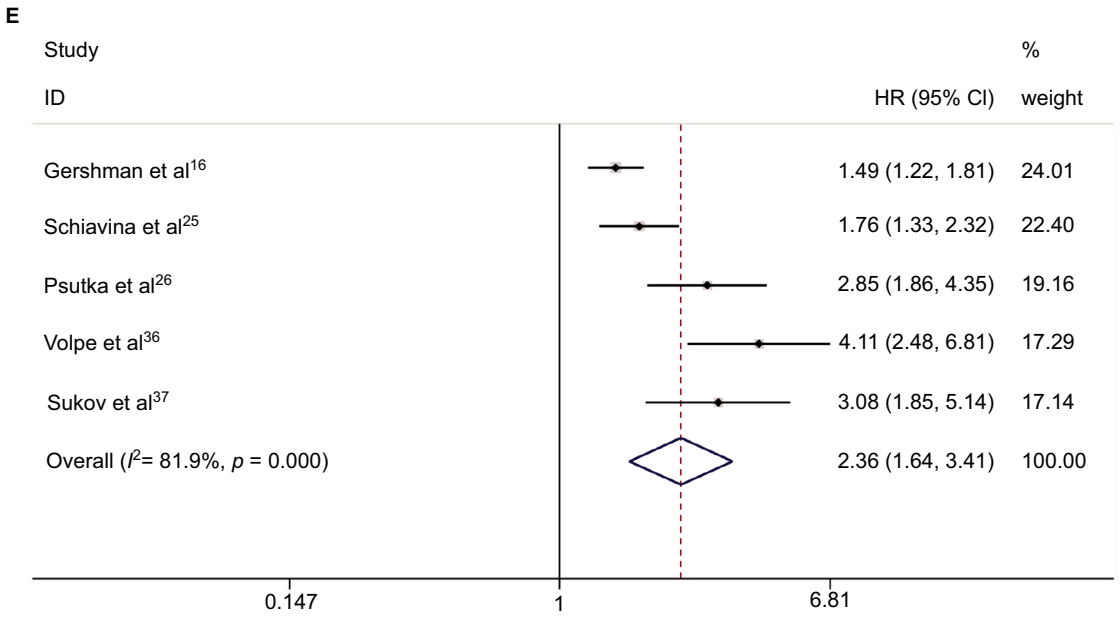



**Figure 2** Forest plots of studies evaluating the association between sarcomatoid differentiation and clinical outcome of patients with RCC: (**A**) CSS, (**B**) OS, (**C**) PFS, (**D**) RFS, and (**E**) CSM.
**Note:** Weights are from random-effects analysis.
**Abbreviations:** CSS, cancer-specific 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 ($T_3$+$T_4$, %) | | | | | | |
| ≥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 ($G_3$+$G_4$, %) | | | | | | |
| ≥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 (1.141.46) | <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 (1.141.46) | <0.001 |
| Stage ($T_3$+$T_4$, %) | | | | | | |
| ≥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 ($G_3$+$G_4$, %) | | | | | | |
| ≥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 ($T_3$+$T_4$, %) | | | | | | |
| ≥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 ($G_3$+$G_4$, %) | | | | | | |
| ≥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.

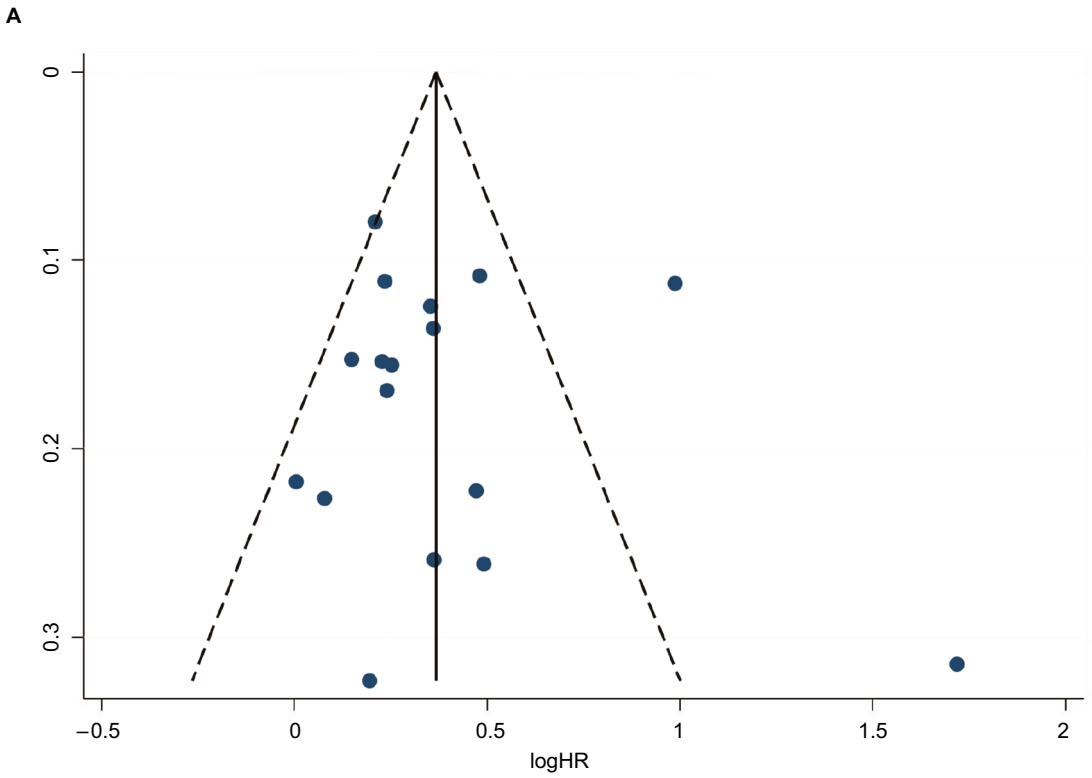
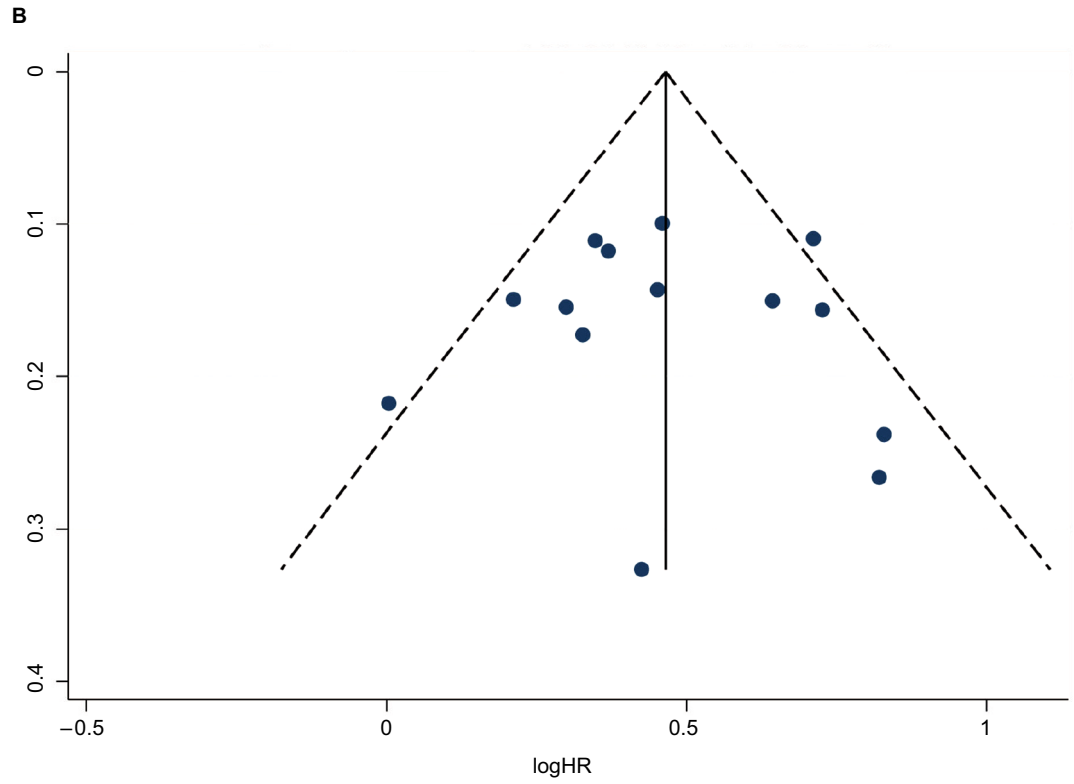



**Figure 3** (*Continued*)



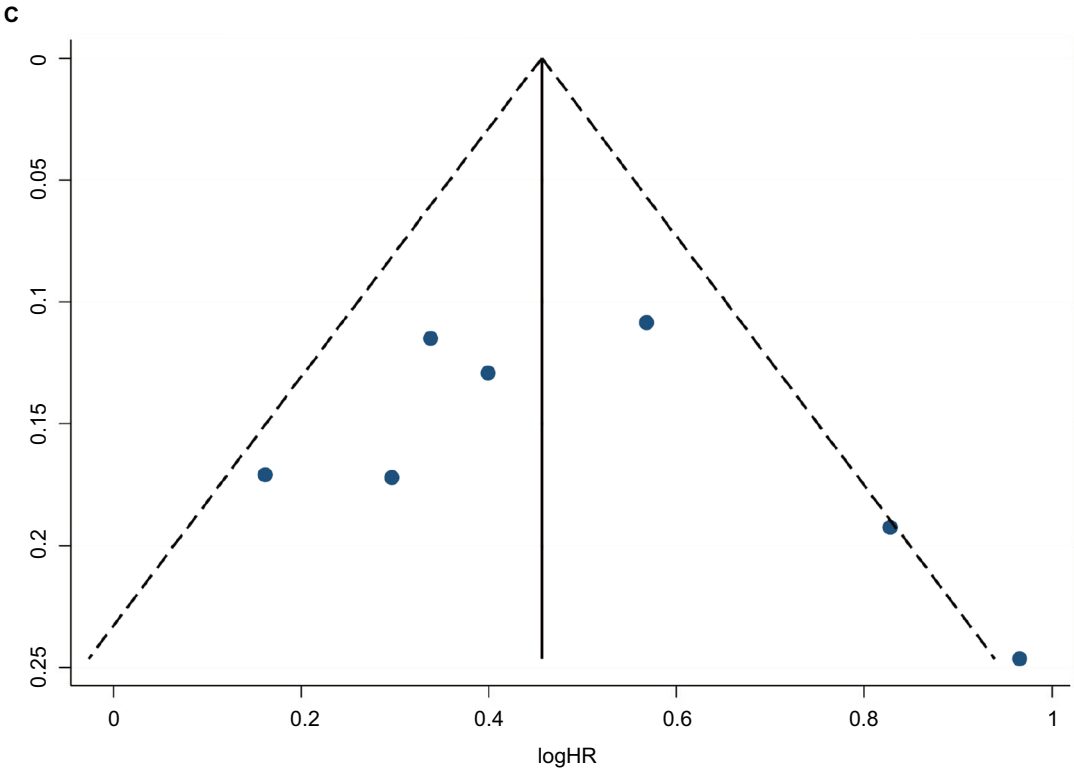




**Figure 3** (*Continued*)

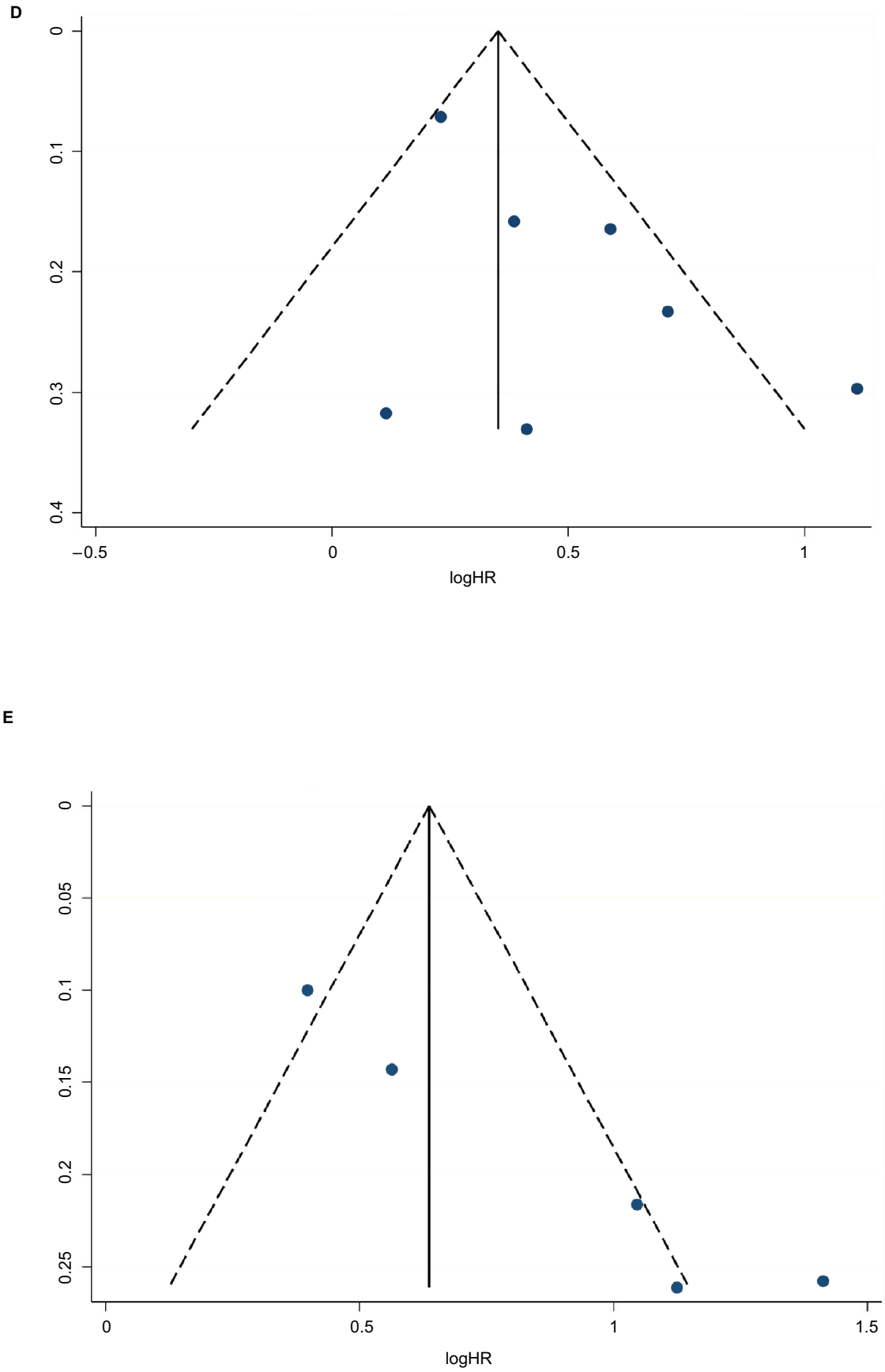



**Figure 3** Funnel plots of Egger evaluating possible publication bias for: (**A**) CSS, (**B**) OS, (**C**) PFS, (**D**) RFS, and (**E**) CSM.
**Abbreviations:** CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; PFS, progression-free survival; CSM, cancer-specific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