Tumor necrosis as a prognostic variable for the clinical outcome in patients with renal cell carcinoma: a systematic review and meta-analysis

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Abstract

Background: Tumor necrosis (TN) correlates with adverse outcomes in numerous solid tumors. However, its prognostic value in renal cell carcinoma (RCC) remains unclear. In this study, we performed a meta-analysis to evaluate associations between TN and cancer-specific survival (CSS), overall survival (OS), recurrence-free survival (RFS) and progression-free-survival (PFS) in RCC.

Methods: Electronic searches in PubMed, EMBASE and Web of Science were conducted according to the PRISMA statement. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated to evaluate relationships between TN and RCC. A fixed- or random-effects model was used to calculate pooled HRs and 95%CIs according to heterogeneity.

Results: A total of 34 cohort studies met the eligibility criteria of this meta-analysis. The results showed that TN was significantly predictive of poorer CSS (HR = 1.37, 95% CI: 1.23–1.53, p < 0.001), OS (HR = 1.29, 95% CI: 1.20–1.40, p < 0.001), RFS (HR = 1.55, 95% CI: 1.39–1.72, p < 0.001) and PFS (HR = 1.31, 95% CI: 1.17–1.46, p < 0.001) in patients with RCC. All the findings were robust when stratified by geographical region, pathological type, staging system, number of patients, and median follow-up.

Conclusions: The present study suggests that TN is associated with CSS, OS, RFS and PFS clinical outcomes of RCC patients and may serve as a predictor of poor prognosis in these patients.

Keywords: Renal cell carcinoma, Tumor necrosis, Prognosis, Meta-analysis

Background

Renal cell carcinoma (RCC), the third most common urologic tumor, accounts for 2–3% of all adult malignancies [1], and its incidence has continuously increased over the past few decades [2]. Although most RCC cases are diagnosed at an early stage, approximately 20% of patients undergoing curative nephrectomy will subsequently develop metastasis during the follow-up period [3]. Due to the varying efficacy of adjuvant therapies in RC, it is necessary to define more prognostic factors that will allow identification of patients at high risk of recurrence who may benefit from such treatment.

Currently, TNM stage classification [4] and the Fuhrman grade system [5] are the most important factors affecting the prognosis of patients with RCC. Additionally, several integrated prognostic models and histologic characteristics have been studied for their prognostic impact, including the American Joint Committee on Cancer (AJCC) staging system [6], International Society of Urologic Pathologists (ISUP) [7] and Mayo Clinic Stage, Size, Grade and Necrosis (SSIGN) Score [8], though these parameters are not entirely reliable. Tumor necrosis (TN) is believed to define regions of severe and chronic hypoxia, and there is renewed interest in using TN to predict...
prognosis after tumor resection. However, the prognostic impact of TN in RCC remains controversial, and there is increasing debate on whether TN can provide any additional information beyond grade and stage [9].

Hence, to further clarify the prognostic value of TN in RCC, we performed a systematic review and meta-analysis of the available published literature to evaluate whether the presence of TN has a prognostic impact on cancer-specific survival (CSS), overall survival (OS), recurrence-free survival (RFS) and progression-free-survival (PFS) in RCC patients.

Methods
Literature search strategy
According to the PRISMA guidelines [10], a comprehensive literature search was conducted using the electronic databases of PubMed, EMBASE and Web of Science up to April 2018. The MeSH terms and full text terms adopted were as follows: “kidney neoplasms”, “renal cell cancer”, “renal cell carcinoma”, “necrosis”, “tumor necrosis”, “prognosis”, “prognostic outcome”, “survival outcome”, “oncologic outcome” and their combinations. We also manually searched the reference lists of reviews, meta-analyses, and selected research articles to identify other “gray literature”. The language of the publications was restricted to English.

Inclusion and exclusion criteria
Eligible studies were selected only if they met the following criteria: (i) RCC and TN were pathologically confirmed, with all patients undergoing surgical resection; (ii) the potential prognostic value of TN for CSS, OS, RFS and PFS were reported; (iii) the authors categorically reported hazard ratios (HRs) and 95% confidence intervals (95%CIs), or they could be computed from the given data. Studies were excluded if the following criteria were met: (i) animal models or cancer cell lines were used; (ii) reviews, letters, commentaries, case reports and non-original articles; (iii) TN, clinical features and survival outcome were not analyzed; (iv) lacking sufficient data to acquire HRs and 95%CIs; (v) not in English. Additionally, when duplicate articles were found, only the most informative and recent article was adopted.

Fig. 1 Diagram of the literature search used in this meta-analysis
| Study          | Country | Recruitment period | No. of patients | Age (years) | Gender (m/f) | Follow-up (months) | Study design | Survival analysis | Surgery          |
|---------------|---------|--------------------|----------------|-------------|--------------|-------------------|--------------|-------------------|------------------|
| Xia et al.2017 [12] | China   | 2005–2007          | 293            | Median (range) 55 (15–86) | 90/203       | Median (range) 99.1 (263–120.47) | Retrospective | OS, PFS          | Nephrectomy       |
| Wu et al.2017 [13] | China   | 2004–2012          | 301            | Median (range) 53 (4–83) | 206/95       | Median (range) 51.6 (3–121) | Retrospective | OS               | Nephrectomy       |
| Niu et al.2017 [14] | China   | 2008–2009          | 384            | Mean ± SD 539 ± 149 | 273/111      | Median (range) 73 (42–74) | Retrospective | OS, RFS          | RN and PN         |
| Kim et al.2017 [15] | Korea   | 2006–2012          | 177            | Mean ± SD 62 ± 10.9 | 136/41       | Median (range) 19.2 (02–638) | Retrospective | OS, PFS          | Nephrectomy       |
| Gu et al.2017 [16] | China   | 2006–2014          | 184            | Mean ± SD 543 ± 13 | 142/42       | Mean ± SD 23.3 ± 14.6 | Retrospective | OS, PFS          | Nephrectomy       |
| Gershman et al.2017 [17] | USA    | 1980–2010          | 138            | Mean (range) 63 (54–72) | 91/47        | Median (QOR) 102 (67.2–130.8) | Retrospective | CSS, OS          | RN and PN         |
| Chen et al.2017 [18] | China   | 2006–2015          | 172            | Mean ± SD 55 ± 12.4 | 123/40       | Mean ± SD 34.4 ± 22.9 | Retrospective | CSS, RFS         | RN                |
| Chang1 et al.2016 [19] | China   | 2008–2014          | 233            | Median (QOR) 56 (48–62) | 170/63       | Median (QOR) 68 (41–71) | Retrospective | RFS              | Nephrectomy       |
| Volpe et al.2016 [3] | Italy   | 2000–2010          | 308            | Median (QOR) 65 (57–73) | 110/80       | Median (QOR) 72 (39–108) | Retrospective | CSS              | RN                |
| Khor et al.2016 [20] | USA     | 1985–2003          | 842            | Median (range) 61 (22–89) | 527/315      | Median (range) 73 (2–273.6) | Retrospective | OS               | RN and PN         |
| Nguyen Hoang et al.2016 [21] | China  | 2008–2009          | 392            | Mean ± SD 55 ± 12.1 | 116/276      | Median (range) 73 (39–74) | Retrospective | OS, RFS          | RN and PN         |
| Errarte et al.2016 [22] | Spain   | NA                | 59             | Mean (range) 59 (25–83) | 45/39        | Mean (range) 65 (1–240) | Retrospective | OS               | Nephrectomy       |
| Byun et al.2016 [23] | Korea   | 2000–2014          | 1284           | Mean ± SD 55 ± 12.9 | 913/371      | Mean (QOR) 39 (19–69) | Retrospective | CSS              | RN and PN         |
| Huang et al.2015 [24] | China   | 1991–2011          | 218            | Mean ± SD 58 ± 12.2 | 169/49       | Mean (QOR) 43 (17.8–67.5) | Retrospective | RFS              | RN and PN         |
| Cornejo et al.2015 [25] | USA     | 1984–2010          | 154            | Mean (range) 62.7 (26–86) | 125/29       | Mean (range) 73.9 (013–222) | Retrospective | CSS, OS          | RN and PN         |
| Teng et al.2014 [26] | China   | 2004–2009          | 378            | Mean ± SD 53 ± 12.4 | 272/106      | Mean (range) 60 (2–97) | Retrospective | CSS, RFS         | RN and PN         |
| Park et al.2014 [27] | Korea   | 2006–2011          | 83             | Mean ± SD 563 ± 105 | 60/23        | Median (range) 18 (1–62) | Retrospective | OS, PFS          | RN and PN         |
| Oliveira et al.2014 [28] | Brazil  | 1988–2006          | 94             | Mean ± SD 59 ± 12.3 | 67/27        | Median 11.7         | Retrospective | CSS              | RN and PN         |
| Can et al.2014 [29] | Turkey  | 1995–2012          | 127            | Mean (range) 56 (26–80) | 70/57        | Mean (range) 46 (3–169) | Retrospective | CSS              | RN and PN         |
| Pichler et al.2013 [30] | Austria | 2000–2010          | 994            | Mean ± SD 599 ± 395 | Mean (range) | Mean (range)         | Retrospective | CSS, OS          | RN and PN         |
| Study            | Country | Recruitment period | No. of patients | Age (years) | Gender (m/f) | Follow-up (months) | Study design | Survival analysis | Surgery            |
|------------------|---------|--------------------|-----------------|-------------|--------------|-------------------|--------------|-------------------|---------------------|
| Kruck et al. 2013 [31] | Germany | 1993–2006          | 278             | 63.2 ± 11.9 | Mean ± SD    | 194/84           | Retrospective | CSS, OS           | RN and PN           |
| Fukatsu et al. 2013 [32] | Japan   | 1986–2008          | 561             | Median (range) 60(21–89) | 442/119     | Retrospective CSS nephrectomy |
| Sukov et al. 2013 [33] | USA     | 1970–2002          | 395             | Median (range) 65(25–89) | 327/68      | Retrospective CSS RN and PN |
| Chang et al. 2011 [34] | China   | 2001–2006          | 328             | Mean (range) 59.2 (23–89) | 216/112     | Retrospective OS RN and PN |
| Leibovich et al. 2010 [35] | USA     | 1970–2003          | 3062            | NA          | 2,016/1002   | Retrospective CSS RN and PN |
| Katz et al. 2010 [36] | USA     | 1989–2004          | 586             | Median 61   | 530/311      | Retrospective CSS OS RN and PN |
| Roos et al. 2009 [37] | Germany | 1990–2006          | 118             | Mean (range) 64.5 (37.8–84.9) | 76/42       | Retrospective CSS PFS nephrectomy |
| Coons et al. 2009 [38] | USA     | 1988–2006          | 128             | Median (range) 64.35–87 | 95/33       | Retrospective CSS, OS, FFS nephrectomy |
| Pflanz et al. 2008 [39] | Germany | 1992–2006          | 607             | Mean (range) 61.6 (18–84) | 387/220     | Retrospective CSS RN and PN |
| Lee et al. 2006 [40] | Korea   | 1993–2003          | 485             | Median (range) 55(26–81) | 360/125     | Retrospective CSS RN and PN |
| Lam et al. 2005 [41] | USA     | 1989–2000          | 311             | Median (range) 62(27–89) | 208/103     | Retrospective CSS nephrectomy |
| Tornberg et al. 2016 [42] | Finland | 2006–2014          | 142             | Median (range) 65(41–89) | 95/47       | Prospective CSS RN and cytoreductive nephrectomy |
| Schiavina et al. 2015 [43] | Italy   | 2000–2013          | 185             | Mean ± SD 63 ± 11.8 | 149/36      | Prospective CSS RN and PN |
| Ramsey et al. 2008 [44] | UK      | 2001–2005          | 83              | NA          | 50/33        | Prospective CSS, FFS nephrectomy |
| Study                  | Staging system | Grading system | TN+/TN- | Stage 1–2/ 3–4 | Grade 1–2/ 3–4 | ccRCC/no-ccRCC | Tumor size (cm) |
|-----------------------|----------------|----------------|---------|----------------|----------------|----------------|-----------------|
| Xia et al. 2017 [12]  | 2010 AJCC      | Furman         | 41/252  | 212/81         | 248/45         | 293/0          | NA              |
| Wu et al. 2017 [13]   | 2010 AJCC      | Furman         | 77/224  | 265/36         | 225/76         | 301/0          | NA              |
| Niu et al. 2017 [14]  | 2010 AJCC      | Furman         | 75/309  | 295/89         | 255/129        | 384/0          | Mean ± SD 4.1 ± 2.1 |
| Kim et al. 2017 [15]  | 2009 AJCC      | Furman         | 46/131  | 60/82          | 44/105         | 159/3          | Median (range) 8 (1–117) |
| Gu et al. 2017 [16]   | 2010 AJCC      | Furman         | 90/94   | NA             | 70/94          | 161/23         | NA              |
| Gershman et al. 2017 [17] | 2010 AJCC  | WHO/ ISUP     | 111/27  | 31/106         | 6/132          | 105/33         | Median (range) 10(8–13) |
| Chen et al. 2017 [18] | 2010 AJCC      | Furman         | 53/110  | 0/163          | 83/55          | 135/8          | Mean ± SD 6.8 ± 3.5 |
| Chang1 et al. 2016 [19]| 2010 AJCC     | Furman         | 182/51  | 169/64         | 135/96         | 233/0          | NA              |
| Volpe et al. 2016 [9] | 2002 AJCC      | Furman         | 60/130  | 190/0          | 155/35         | 156/34         | Median (IQR) 4.9(3.5–7) |
| Khor et al. 2016 [20] | 2010 AJCC      | Furman         | 665/177 | 630/212        | 265/577        | 842/0          | Median (range) 4.2(05–20) |
| Nguyen-Hoang et al. 2016 [21] | 2010 AJCC | Furman         | 78/294  | 292/100        | 259/133        | 392/0          | Mean ± SD 4.3 ± 2.6 |
| Errarte et al. 2016 [22]| 2010 AJCC     | Furman         | 30/29   | 32/27          | 24/35          | 59/0           | Median (range) 7.9(2–19) |
| Byun et al. 2016 [23] | 2002 AJCC      | Furman         | 208/1076| 1105/179       | 664/620        | 1114/170       | Mean ± SD 4.08 ± 2.68 |
| Huang et al. 2015 [24] | 2010 AJCC     | Furman         | 34/184  | 160/58         | 155/63         | 0/218          | Median (IQR) 3.5(2.5–6) |
| Cormejo et al. 2015 [25]| NA            | Fuhrman/ ISUP  | 40/114  | 121/33         | 103/51         | 0/154          | Mean (range) 3.1(04–17) |
| Teng et al. 2014 [26] | 2009 AJCC      | Furman         | 38/340  | 346/32         | 200/178        | 378/0          | Mean ± SD 4.6 ± 2.6 |
| Park et al. 2014 [27] | NA             | Furman         | 37/46   | NA             | 13/70          | 83/0           | NA              |
| Oliveira et al. 2014 [28]| 2010 AJCC     | Furman         | 18/76   | 77/17          | 65/29          | 94/0           | Mean ± SD 4.7 ± 2.6 |
| Can et al. 2014 [29]  | 2010 AJCC      | Furman         | 42/85   | 84/43          | 72/55          | 127/0          | NA              |
| Pichler et al. 2013 [30]| 2010 AJCC     | Furman         | 277/717 | 723/271        | 839            | 804/190        | NA              |
| Kruck et al. 2013 [31] | 2010 AJCC      | Furman         | 114/164 | 169/109        | 234/44         | 278/0          | Mean ± SD 5.26 ± 2.91 |
| Fukatsu et al. 2013 [32]| 2010 AJCC     | Furman         | 57/104  | 508/53         | 341/220        | 561/0          | NA              |
| Sukov et al. 2013 [33] | 2010 AJCC      | Furman         | 186/209 | 346/49         | 247/148        | 0/395          | NA              |
| Chang2 et al. 2011 [34]| 2002 AJCC      | Furman         | 139/189 | 240/88         | 216/112        | 232/96         | NA              |
| Study            | Staging system | Grading system | TN+/TN- | Stage 1–2/ 3–4 | Grade 1–2/ 3–4 | ccRCC/no-ccRCC | Tumor size (cm) |
|-----------------|----------------|---------------|---------|----------------|----------------|----------------|----------------|
| Leibovich et al.2010 [35] | 2002 AJCC       | Furman        | 792/2090 | 1992/1070       | 1649/1413       | 1781/1281       | NA             |
| Katz et al.2010 [36]     | 2002 AJCC       | Furman        | 253/586  | 575/194         | 589/252         | 641/198         | NA             |
| Roos et al.2009 [37]     | 2002 AJCC       | Furman        | 10/108   | 0/118           | 63/55           | 109/16          | Median (range) 8(2.5–20) |
| Coons et al.2009 [38]    | 2002 AJCC       | Furman        | 57/71    | 0/128           | 40/103          | 105/23          | Median (range) 9 (35–21) |
| Pflanz et al.2008 [39]   | 2002 WHO        | Thoenes       | 155/452  | 515/92          | 532/75          | 479/128         | NA             |
| Lee et al.2006 [40]      | 1997 AJCC       | Furman        | 131/354  | 382/103         | 364/221         | 419/66          | NA             |
| Lam et al.2005 [41]      | 1997 AJCC       | Furman        | 168/143  | 157/153         | 186/119         | 270/41          | NA             |
| Tornberg et al.2016 [42] | 2009 AJCC       | Furman        | 84/58    | 0/132           | 38/104          | 129/13          | Mean ± SD 10.3 ± 3.6 |
| Schiavina et al.2015 [43]| 2009 AJCC       | Furman        | 49/136   | 0/185           | 46/139          | 150/35          | Mean ± SD 8.05 ± 2.8 |
| Ramsey et al.2008 [44]   | 1997 AJCC       | Furman        | 55/28    | 48/35           | 37/40           | 33/50           | NA             |

Total numbers rows: 36; TN+/TN tumor necrosis positive/ tumor necrosis negative, SD standard deviation, NA data not applicable, ccRCC/no-ccRCC clear cell renal cell carcinoma/non-clear cell renal cell carcinoma.
Data extraction and quality assessments

Two investigators independently extracted data of eligible studies using a standardized form for the following information: author identification, year of publication, country, period of recruitment, study design, age of patients, gender ratio, sample size, follow-up time, study design, interpretation of TN, histology and survival end point. For HRs and 95% CIs, multivariate analysis data were preferentially adopted. If these data were not available, then univariate analysis of survival outcomes was extracted instead. All discrepancies between the investigators reached a consensus through discussion. The methodological quality of the included cohort studies was assessed using the Newcastle-Ottawa scale (NOS) [11]. Each study was assessed using 8 methodology items in 3 domains with a score ranging from 0 to 9. High scores indicated high quality, a study with a score ≥ 6 was regarded as high quality, a score < 6 was regarded as low quality.

Statistical analysis

Statistical analyses were performed using Stata 12.0 software (Stat Corp, College Station, TX, USA). Dichotomous variables were calculated using HRs, and pooled HRs with 95% CI were used to evaluate the association of TN with RCC prognosis (CSS, OS, RFS and PFS). A heterogeneity test of the pooled HR was conducted using a Chi-square-based Q test and Higgins $I^2$ statistic. When $I^2 < 50\%$ or $P_{\text{heterogeneity}} > 0.1$, no obvious heterogeneity existed among the studies, and the fixed-effects (FE) model would be applied; otherwise, the random-effects (RE) model was applied. To obtain a more precise evaluation of heterogeneity, subgroup analysis was performed for CSS, OS and RFS based on geographical region, pathological types, staging system, No. of patients and median follow-up. Publication bias was examined using funnel plots and Egger’s linear regression test. Additionally, sensitivity analysis was used to estimate the robustness of

![Fig. 2](image_url)
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 |
|------------------------------|---------------|---------------------|---------------|------------------|---------|
|                              |               | $I^2$ (%)           | $P_{\text{heterogeneity}}$ |                 |         |
| CSS                          |               |                     |               |                  |         |
| Overall                      | 22            | 76.5                | < 0.001       | Random           | 1.37(1.23,1.53) | < 0.001 |
| Geographical region          |               |                     |               |                  |         |
| Asian                        | 7             | 51.7                | 0.053         | Random           | 1.34(1.12,1.59) | 0.001   |
| Other regions                | 15            | 80.8                | < 0.001       | Random           | 1.40(1.22,1.60) | < 0.001 |
| Pathological types           |               |                     |               |                  |         |
| ccRCC                        | 6             | 0                   | 0.775         | Fixed            | 1.34(1.15,1.55) | < 0.001 |
| Other types                  | 16            | 81.7                | < 0.001       | Random           | 1.38(1.22,1.58) | < 0.001 |
| Staging system               |               |                     |               |                  |         |
| 2010 AJCC                    | 8             | 0                   | 0.981         | Fixed            | 1.30(1.17,1.44) | < 0.001 |
| Other system                 | 14            | 82.3                | < 0.001       | Random           | 1.42(1.23,1.64) | < 0.001 |
| No. of patients              |               |                     |               |                  |         |
| $\geq$ 300                   | 13            | 82                  | < 0.001       | Random           | 1.39(1.21,1.61) | < 0.001 |
| < 300                        | 9             | 15.4                | 0.301         | Fixed            | 1.33(1.16,1.51) | < 0.001 |
| Median follow-up             |               |                     |               |                  |         |
| $\geq$ 40 months             | 12            | 83.3                | < 0.001       | Random           | 1.36(1.16,1.60) | < 0.001 |
| < 40 months                  | 9             | 30.2                | 0.177         | Fixed            | 1.33(1.16,1.51) | < 0.001 |
| OS                           |               |                     |               |                  |         |
| Overall                      | 17            | 57.6                | 0.002         | Random           | 1.29(1.20,1.40) | < 0.001 |
| Geographical region          |               |                     |               |                  |         |
| Asian                        | 9             | 30.2                | 0.177         | Fixed            | 1.38(1.25,1.51) | < 0.001 |
| Other regions                | 8             | 58.6                | 0.017         | Random           | 1.20(1.09,1.34) | < 0.001 |
| Pathological types           |               |                     |               |                  |         |
| ccRCC                        | 8             | 48.8                | 0.057         | Random           | 1.33(1.19,1.49) | < 0.001 |
| Other types                  | 9             | 62.7                | 0.006         | Random           | 1.26(1.13,1.41) | < 0.001 |
| Staging system               |               |                     |               |                  |         |
| 2010 AJCC                    | 10            | 63.6                | 0.003         | Random           | 1.30(1.17,1.44) | < 0.001 |
| Other system                 | 7             | 53.1                | 0.046         | Random           | 1.30(1.14,1.47) | < 0.001 |
| No. of patients              |               |                     |               |                  |         |
| $\geq$ 300                   | 8             | 67.5                | 0.003         | Random           | 1.25(1.12,1.39) | < 0.001 |
| < 300                        | 9             | 29.2                | 0.185         | Fixed            | 1.35(1.22,1.49) | < 0.001 |
| Median follow-up             |               |                     |               |                  |         |
| $\geq$ 40 months             | 13            | 62.6                | 0.001         | Random           | 1.27(1.16,1.39) | < 0.001 |
| < 40 months                  | 4             | 0                   | 0.412         | Fixed            | 1.37(1.20,1.56) | < 0.001 |
| RFS                          |               |                     |               |                  |         |
| Overall                      | 9             | 35.6                | 0.133         | Fixed            | 1.55(1.39,1.72) | < 0.001 |
| Geographical region          |               |                     |               |                  |         |
| Asian                        | 6             | 42.7                | 0.12          | Fixed            | 1.48(1.31,1.66) | < 0.001 |
| Other regions                | 3             | 0                   | 0.684         | Fixed            | 1.87(1.41,2.37) | < 0.001 |
| Pathological types           |               |                     |               |                  |         |
| ccRCC                        | 4             | 0                   | 0.541         | Fixed            | 1.61(1.40,1.86) | < 0.001 |
| Other types                  | 5             | 57.5                | 0.051         | Random           | 1.46(1.25,1.71) | < 0.001 |
the results via sequential omission of individual studies. A p value of < 0.05 was considered to indicate significance.

Results

Search and eligible studies
A diagram of the selection process is shown in Fig. 1. According to the search strategy, 2715 articles were retrieved from the electronic databases. By excluding 1563 duplicate reports, 1152 articles were considered potentially relevant based on screening of the titles and abstracts. The remaining articles were further excluded upon full-text review for several reasons, such as a lack of sufficient data to estimate HRs or duplicate publication in repeated cohorts. Ultimately, 34 studies [3, 12–44] that focused on the association between RCC and TN were included for meta-analysis. The outcomes were CSS in 22 studies, OS in 17 studies, RFS in 9 studies and PFS in 5 studies.

Characteristics of the included studies
The main characteristics of the 34 eligible studies are listed in Table 1. All of the studies were published between 2005 and 2017, with a mean duration of follow-up varying from 11.7 to 102 months. The present meta-analysis was based on a total sample size of 14,084 patients, ranging from 59 to 3062 patients. The NOS was applied to assess the methodological quality of the included studies, and the results showed that all studies were of high quality (Additional file 1: Table S1). All of the included studies were based on data for retrospective analyses of survival (CSS, OS, RFS, PFS). The characteristics, including tumor features and pathologic outcomes, are summarized in Table 2. TN was detected in 31.6% (4452/14,084) of the pathological specimens from the included patients. A total of 13 of the included studies were limited to clear cell renal cell carcinoma (ccRCC), whereas 21 studies involved various tumor types, including ccRCC, papillary renal cell carcinoma, chromophobe renal cell carcinoma and unclassified tumor.

Prognostic value of TN for survival outcome
The present meta-analysis demonstrated that TN in RCC is associated with poor CSS (RE HR = 1.37, 95% CI: 1.23–1.53, p < 0.001, I² = 76.5%, Pheterogeneity < 0.001; Fig. 2a), OS (RE HR = 1.29, 95% CI: 1.20–1.40, p < 0.001, I² = 57.6%, Pheterogeneity = 0.02; Fig. 2b), RFS (FE HR = 1.55, 95% CI: 1.39–1.72, p < 0.001, I² = 35.6%, Pheterogeneity = 0.133; Fig. 2c) and PFS (FE HR = 1.31, 95% CI: 1.17–1.46, p < 0.001, I² = 32.9%, Pheterogeneity = 0.202; Fig. 2d). To explore the source of heterogeneity for CSS, OS and RFS, subgroup analysis was conducted according to geographical region (Asia vs. other regions), pathological type (ccRCC vs. other types), staging system (2010 AJCC vs. other system), No. of patients (≥300 vs. <300) and median follow-up (≥40 months vs. <40 months). The results of this subgroup analysis again suggested that TN is a prognostic factor, despite heterogeneity among some groups (Table 3). Notably, heterogeneity for CSS, OS and RFS was significantly decreased in some models, such as geographical region in Asia, ccRCC pathological type, 2010 AJCC staging system and ≥300 cases.

Table 3 Summary and subgroup analysis for the eligible studies (Continued)

| Analysis specification | No. of studies | Study heterogeneity | Effects model | Pooled HR(95% CI) | p-Value |
|------------------------|----------------|---------------------|---------------|------------------|--------|
| 2010 AJCC              | 5              | 54                  | Random        | 1.48(1.31,1.69)  | < 0.001|
| Other system           | 4              | 0                   | Fixed         | 1.69(1.40,2.04)  | < 0.001|
| No. of patients        |                |                     |               |                  |        |
| ≥300                   | 4              | 0                   | Fixed         | 1.57(1.35,1.83)  | < 0.001|
| <300                   | 5              | 63.4                | Fixed         | 1.52(1.32,1.76)  | < 0.001|
| Median follow-up       |                |                     |               |                  |        |
| ≥40 months             | 6              | 0                   | Fixed         | 1.62(1.43,1.84)  | < 0.001|
| <40 months             | 3              | 75.3                | Random        | 1.39(1.16,1.68)  | 0.001  |
| PFS                    |                |                     |               |                  |        |
| Overall                | 5              | 32.9                | Fixed         | 1.31(1.17,1.46)  | < 0.001|
| Pathological types     |                |                     |               |                  |        |
| ccRCC                  | 2              | 67.8                | Random        | 1.44(1.20,1.71)  | < 0.001|
| Other types            | 3              | 0                   | Fixed         | 1.23(1.07,1.41)  | 0.004  |
| Staging system         |                |                     |               |                  |        |
| 2010 AJCC              | 2              | 76.3                | Random        | 1.35(1.18,1.54)  | < 0.001|
| Other system           | 3              | 0                   | Fixed         | 1.22(1.01,1.48)  | 0.036  |
Sensitivity analyses and publication bias

In sensitivity analysis excluding one study at a time, the pooled HR for CSS ranged from 1.29 (95% CI: 1.19–1.39) to 1.37 (95% CI: 1.22–1.54) (Additional file 2: Figure S1). Similarly, the pooled HR for OS ranged from 1.27 (95% CI: 1.17–1.37) to 1.31 (95% CI: 1.21–1.42) (Additional file 3: Figure S2), that for RFS from 1.52 (95% CI: 1.32–1.76) to 1.66 (95% CI: 1.47–1.86) (Additional file 4: Figure S3), and that for PFS from 1.21 (95% CI: 1.07–1.38) to 1.35 (95% CI: 1.12–1.63) (Additional file 5: Figure S4). These results indicate that the findings were reliable and robust. Although no statistical evidence of publication bias was observed for RFS (p-Egger = 0.135, Fig. 3c) and PFS (p-Egger = 0.932, Fig. 3d), publication bias was observed for CSS (p-Egger = 0.006, Fig. 3a) and OS (p-Egger = 0.001, Fig. 3b).

Discussion

RCC is the most common solid lesion of the kidney, and more than 40% of patients die from this type of cancer [2]. Despite significant improvements in systemic therapy for RCC, the prognosis of patients with RCC and treatment response rates have not substantially increased [17, 42, 44]. Although several pathologic parameters, including lymphatic vessel invasion [45], tumor fat invasion [26] and primary tumor size [43], provide independent prognostic information, the likely outcome for an individual patient remains uncertain. The TNM stage and Fuhrman grade system are the most widely used approaches for RCC; however, there have been many recent suggestions for modifications based on survival trends in large case series [46]. Additionally, RCC is a highly heterogeneous disease with different clinical presentations and characteristics that remain somewhat unpredictable [47]. Therefore, it is essential to optimize the treatment and prognosis of RCC and to provide better counseling for each RCC patient.

The presence of TN in pathologic specimens may reflect the tumor biology and may also provide additional useful prognostic information. As TN results from rapid tumor proliferation and consequent outgrowth of the blood supply [41], histologic TN has been proposed to
be a sign of tumor aggressiveness that generally leads to poor clinical outcomes [48]. Previous studies have investigated the association of TN with various solid tumors, including breast cancer [49], colorectal cancer [50] and lung cancer [51]. Indeed, there is renewed interest in using TN, which can be assessed in every routine pathological examination without additional costs, to more accurately predict the clinical outcome of RCC. For example, Khor et al. [20] and Ito et al. [48] reported that TN is strongly associated with poor survival and should serve as an independent prognostic factor for patients with RCC. Nonetheless, some studies have shown that the presence of any TN is a negative predictor of survival in RCC [52, 53].

To our knowledge, the present study is the first meta-analysis on the association between TN and clinical outcomes of different types of RCC. In this analysis, 14,084 RCC patients were included from 34 cohort studies, and TN was detected in 31.6% of 4452 RCC patients. Robust evidence obtained from sensitivity analysis demonstrated that the presence of TN was associated with poor outcomes in terms of CSS (HR = 1.37, \( p < 0.001 \)), OS (HR = 1.29, \( p < 0.01 \)), RFS (HR = 1.55, \( p < 0.001 \)) and PFS (HR = 1.31, \( p < 0.001 \)) in patients with RCC. These findings were consistently independent of geographical region, pathological type, staging system, No. of patients and median follow-up. Although there was no evidence of heterogeneity in terms of CSS or PFS, significant heterogeneity was detected in analyses of OS and RFS models. To further explore the source of heterogeneity in OS and RFS, subgroup analysis was conducted, and the data showed that significant variations were reduced in OS and RFS within some items.

Notably, the present study has several limitations. First, all the included studies were retrospective cohort studies, and data extracted from those studies may have led to inherent potential bias. Second, the criteria for determining the presence of TN in a pathologic specimen were inconsistent in the included studies, which may contribute to heterogeneity. Thus, rigorous morphological criteria should be used to standardize the diagnosis of TN. Third, we only included published studies written in English, and the lack of “gray literature” may cause selection bias. Fourth, substantial heterogeneity was observed in meta-analysis of CSS and OS, and although we selected the RE model according to heterogeneity, this diversity remained. Using subgroup analysis, we propose that the heterogeneity likely reflected differences in factors, such as patient and tumor characteristics. Fifth, a statistical publication bias was observed for CSS and OS according to Egger’s test. In general, studies with negative results tend not to be submitted or published; therefore, a certain degree of publication bias was observed in the present study. Finally, it should be noted that factors, including age, sex, histology type and surgical method, that may affect survival outcomes were adequately controlled.

Nevertheless, the present study has several key strengths. First, the meta-analysis included 34 studies with large sample sizes, with the ability to detect more stable associations between TN and clinical outcomes of RCC patients. Second, with strict inclusion and exclusion criteria, we extracted available data from relevant studies. Furthermore, through subgroup and sensitivity analyses, the results were reliable and robust. Therefore, TN determination, with excellent accessibility and low costs, warrants wider application in patients with RCC for risk stratification and decision-making of individualized treatment.

Conclusions
In conclusion, the results of the present meta-analysis demonstrate that TN in histopathology is associated with poor CSS, OS, RFS and PFS in patients with RCC. Due to the limitations of the present study, large-scale, multicenter prospective studies with long-term follow-up are needed to verify these results.

Additional files

Additional file 1: Table S1. Quality assessment of cohort studies included in this meta-analysis. (DOCX 15 kb)
Additional file 2: Figure S1. Sensitivity analysis of the association between TN and CSS outcomes in RCC patients. (TIF 302 kb)
Additional file 3: Figure S2. Sensitivity analysis of the association between TN and OS outcomes in RCC patients. (TIF 255 kb)
Additional file 4: Figure S3. Sensitivity analysis of the association between TN and RFS outcomes in RCC patients. (TIF 157 kb)
Additional file 5: Figure S4. Sensitivity analysis of the association between TN and PFS outcomes in RCC patients. (TIF 115 kb)

Abbreviations
AJCC: American Joint Committee on Cancer; ccRCC: Clear cell renal cell carcinoma; CIs: Corresponding 95% confidence intervals; CSS: Cancer-specific survival; FE: Fixed-effects; HRs: Hazard ratios; ISUP: International Society of Urologic Pathologists; NOS: Newcastle Ottawa scale; OS: Overall survival; PFS: Progression-free survival; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta- Analyses; RCC: Renal cell carcinoma; RE: Random-effects; RFS: Recurrence-free survival; SSIGN: Mayo Clinic Stage; Size, Grade and Necrosis; TN: Tumor necrosis

Availability of data and materials
All data generated or analyzed during the present study are included in this published article (and its additional files).

Authors’ contributions
LJZ and BW designed the research. ZLZ, WQ and HZ performed the literature search. JY and YJF analyzed the data and interpreted the results. LJZ drafted the manuscript. All authors approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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