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*Original Article*

# Microvascular invasion as a prognostic indicator in renal cell carcinoma: a systematic review and meta-analysis

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**Abstract:** Microvascular invasion (MVI), an omen of potential hematogenous spread of tumor cells, has been identified as an accepted risk factor for poor prognosis in some solid tumors. But its prognostic value in renal cell carcinoma (RCC) remains disputable. In order to address this question rigorously, we performed a systematical review of the published literature on MVI and RCC prognosis. According to the PRISMA statement, we searched PubMed, Web of science, and Cochrane Library database and identified 33 cohort articles that met the eligibility criteria and involved 14,946 patients (48-2596 per study) in this meta-analysis. Using the random effects model, the association between MVI and four generally recognized end points were estimated, including cancer-specific survival (CSS), recurrence-free survival (RFS), metastasis-free survival (MFS) and overall survival (OS). The presence of MVI was detected in 14.4% of the pathological specimens. A higher incidence of MVI was associated with some acknowledged prognostic risk factors such as higher pathological TNM stages and higher tumor grades. Statistical significance of the combined hazard ratio (HR) was detected for CSS (HR, 2.090; 95% CI, 1.530-2.857), RFS (HR = 2.749; 95% CI, 1.974-3.828), MFS (HR = 1.621; 95% CI, 1.095-2.400). However, the association between MVI and worse overall survival did not address statistical significance (HR = 1.371; 95% CI, 0.978-1.923). These findings suggest that the presence of MVI has a detrimental effect on clinicopathological features of RCC and could serve as a poor prognostic factor for patient with RCC.

**Keywords:** Microvascular invasion, renal cell carcinoma, meta-analysis, systematic review, prognosis

## Introduction

There are estimated 63,920 new cases and 13,860 deaths from renal cancer in the United States in 2014 [1]. Renal cell carcinoma (RCC) is one of the most lethal urologic cancers, more than 80-90% of which are histologically diagnosed as clear cell renal cell carcinoma (ccRCC). Tumor TNM stage and nuclear grade are most frequently used in RCC as prognostic factors. However, even with the resection of the localized tumor, up to a third of patients will go on to develop local recurrence or distant metastasis [2], and the worldwide incidence and mortality rates are raising at a rate of 2-3% per decade [3]. One of the major clinician's concerns is therefore how to identify patients at high risk of poor outcome. Recently, with the improved knowledge of pathologic parameters such as sarcomatoid/rhabdoid differentiation, tumor necrosis and microvascular invasion, we can make better prognostic evaluations, for a more comprehensive and effective way.

Considering that RCC is one of the most highly vascularized tumors, it is not surprising that vascular invasion is frequently found in these tumors. And macrovascular invasion into the renal vein and/or the vena cava is one of well recognized prognostic factors in RCC, which has been included in TNM staging of RCC. Microvascular invasion (MVI), another type of vascular invasion, refers to the presence of tumor within microscopic venules or veins with

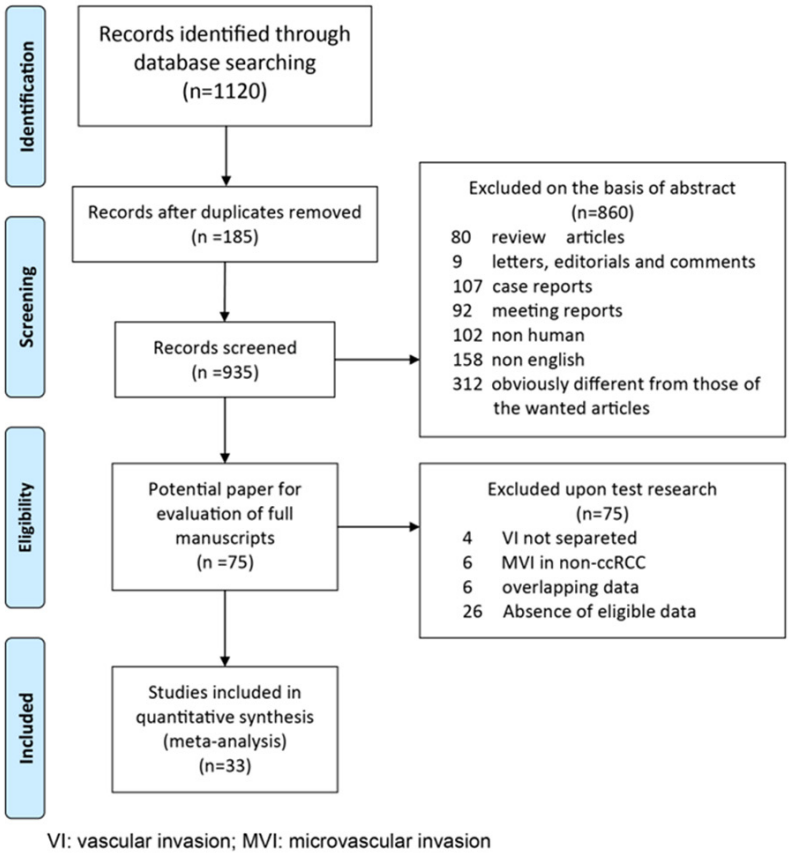


**Figure 1.** The flow diagram of the selection process. Flow diagram illustrating the search strategy used according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement.

a muscular coat or the lymphatic system, or both. It could be considered as an omen of potential hematogenous spread of tumor cells, which has drawn more and more attention and also been identified as an independent risk factor for poor prognosis in many solid tumors [4-8]. Although numerous studies have been performed to evaluate the impact of MVI in RCC on prognosis of RCC, the results remain disputable. The aim of the present systematical review is to assess the prognostic value of MVI in renal cell carcinoma.

## Materials and methods

### *Search strategy*

This meta-analysis was performed and reported following the proposed Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [9] statement. We searched electronic databases including PubMed, web of science, and Cochrane Library for published studies that analyzed the prognostic value of MVI in RCC up to May 31, 2014. The following Medical Subject Headings terms and free text were used: "lymphovascular or lymphatic or microvascular or microvessel or microvenous or microscopic or vascular" AND "invasion or infiltration" AND "renal or kidney" AND "cancer or carcinoma or neoplasm or tumor or mass or tumour" AND "Predict* or prognos* or survival or risk or outcome". The searching strategies and results are shown in Table S1. There was no restriction on population or publication year. Additionally, we conducted a manual search using the bibliographies of all the identified studies, reviews, and editorials to identify references that we may have missed during our primary search.

### *Selection criteria*

*Inclusion criteria:* (1) studies that included the pathologically confirmed diagnosis of RCC; (2) studies that assessed MVI, and other similar or equivalent concepts such as lymphovascular invasion (LVI), microscopic vascular invasion and microscopic venous invasion; (3) studies in which the primary treatment for RCC patients was limited to surgery with or without adjuvant therapy; (4) studies that analyzed the potential association between the prognosis of RCC patients and MVI; and (5) studies that offered a hazard ratio (HR) and 95% confidence interval (CI) categorically or the data presented were available for calculation of the HR and 95% CI.

*Exclusion criteria:* (1) studies that were performed on animal models or renal cancer cell lines; (2) letters, review articles, commentaries, clinical guidelines, or case reports; (3) the language of the studies were not English; (4) studies that only analyzed subtypes of RCC and excluded ccRCC; (5) studies with a sample sizes smaller than 30; and (6) if multiple publi-

**Table 1.** Tumor characteristics of the eligible studies

| Study | Staging system | Grading system | MVI+/MVI- | Stage 1-2/3-4 | Grade1-2/3-4 | Nx-0/N1 | M0/M1 | ccRCC/non-ccRCC |
|---|---|---|---|---|---|---|---|---|
| Belsante [14] | 2010 AJCC | Fuhrman | 60/359 | 333/86 | 288/NA | 411/8 | 419/0 | 419/0 |
| | 2010 AJCC | Fuhrman | 21/312 | 333/0 | 258/NA | 333/0 | 333/0 | 333/0 |
| Eisenberg [15] | 2010 AJCC | Fuhrman | 119/984 | 713/390 | 469/634 | 1106/87 | 971/132 | 1103/0 |
| Shindo [16] | 2009 AJCC | NA | 14/158 | 172/0 | 158/14 | 172/0 | 172/0 | 151/21 |
| Drewniak [17] | 2010 AJCC | Fuhrman | 43/105 | 37/94 | 46/73 | 18/80 | 13/116 | 34/39 |
| Steffens [18] | 2002 AJCC | Fuhrman | 259/1771 | 1301/729 | 1738/292 | 1899/131 | 1780/250 | 1721/309 |
| Betsunoh [19] | 2009 AJCC | Fuhrman | 49/33 | 50/32 | 58/24 | NA | 60/22 | 82/0 |
| Harada [20] | 2009 AJCC | 3 grade system | 48/74 | 74/48 | 99/23 | 122/0 | 122/0 | 104/18 |
| Pichler [21] | 2002 AJCC | Fuhrman | 99/1655 | 1064/690 | 1523/231 | 1732/32 | 1754/0 | 1754/0 |
| Kroeger [22] | 2002 AJCC | Fuhrman | 475/2121 | 1496/1100 | 1614/982 | 1580/1016 | 1902/694 | 2078/518 |
| da Costa [23] | 2002 AJCC | Fuhrman | 26/116 | 89/53 | 91/51 | 127/15 | 123/19 | 99/53 |
| Takayama [24] | 2009 AJCC | 3 grade system | 56/378 | 451/0 | 406/15 | NA | NA | 401/30 |
| Komura [25] | 2002 AJCC | Fuhrman | 58/112 | 140/30 | 140/30 | 170/0 | 170/0 | 131/39 |
| Suzuki [26] | 1997 AJCC | 3 grade system | 32/179 | 166/45 | 187/24 | 211/0 | 211/0 | 211/0 |
| Katz [27] | 2002 AJCC | Fuhrman | 92/749 | 575/194 | 589/252 | NA | 841/0 | 641/200 |
| Kume [28] | 2002 AJCC | Fuhrman | 20/128 | 158/7 | 156/9 | 165/0 | 160/5 | 151/14 |
| Kim [29] | 2002 AJCC | Fuhrman | 6/87 | 93/0 | 52/41 | 93/0 | 93/0 | 79/14 |
| Rey [30] | 2002 AJCC | Fuhrman | 23/116 | 139/30 | 70/69 | 139/0 | 139/0 | 110/29 |
| May [31] | NA | Fuhrman | 70/701 | 642/129 | 531/240 | 758/13 | 771/0 | 605/166 |
| Cho [32] | 2002 AJCC | Fuhrman | 24/275 | 299/0 | 253/46 | 299/0 | 299/0 | 299/0 |
| Zubac [33] | 2002 AJCC | Fuhrman | 7/69 | 76/0 | 65/11 | 76/0 | 76/0 | 76/0 |
| Pflanz [34] | 2002 AJCC | Thoenes grade | 53/554 | 515/92 | 432/75 | NA | NA | 479/128 |
| Horiguchi [35] | 2002 AJCC | 3 grade system | 50/70 | 93/27 | 105/15 | 117/3 | 103/17 | 112/8 |
| Dall'Oglio [36] | NA | Fuhrman | 59/171 | 164/86 | 145/84 | 216/14 | NA | 148/82 |
| Klatte [37] | 2002 AJCC | Fuhrman | 22/497 | 519/0 | 414/92 | 519/0 | 519/0 | 409/110 |
| Madbouly [38] | 1997 AJCC | Fuhrman | 8/40 | 45/3 | 41/7 | 48/0 | 48/0 | 43/5 |
| Komai [39] | 2002 AJCC | 3 grade system | 63/38 | 79/22 | 96/5 | 101/0 | 101/0 | 97/4 |
| Ito [40] | 1997 AJCC | 3 grade system | 78/100 | 127/51 | 162/16 | 165/13 | 150/28 | 140/38 |
| Lee [41] | 1997 AJCC | Fuhrman | 26/456 | 382/103 | 264/221 | NA | NA | 419/66 |
| Goncalves [42] | NA | Fuhrman | 24/71 | 95/0 | 63/32 | 87/8 | 95/0 | 56/39 |
| Lang [43] | 2002 AJCC | Fuhrman | 74/181 | 172/83 | 114/141 | 255/0 | 255/0 | 236/19 |
| Ishimura [44] | 1998 JUA | 3 grade system | 70/87 | 120/37 | 153/4 | 157/0 | 157/0 | 120/37 |
| Griffiths [45] | NA | Fuhrman | 24/152 | NA | 123/53 | 176/0 | 176/0 | 119/57 |
| VanPoppel [46] | 1987 AJCC | Fuhrman | 51/129 | 142/38 | 116/64 | 180/0 | 180/0 | NA |

AJCC: American Joint Committee on Cancer; ccRCC: clear cell renal cell carcinoma; non-ccRCC: non clear cell renal cell carcinoma; JUA: Japanese Urological Association.

cations for the same data from the same study group occurred, only the most informative and recent article was recruited into final analysis.

*Data extraction*

Two investigators (H.H. and P.X.W.) conducted the extraction process independently for the following information: (1) publication and methodology data including first author's surname, publication year, location of the study performed, inclusion and exclusion criteria, study design, period of recruitment, definition of survival, definition of MVI, slice staining methods, NO. of observers, interpretation of MVI, staging system, and nuclear grading system; (2) the baseline data including sample size, gender, age, follow-up period and treatment, MVI proportion, pathological TNM stage, nuclear grade, and histological subtypes; and (3) statistical data such as HRs and their 95% CIs. We preferred to gather multivariate analysis data. If they were not available, univariate analysis of survival outcomes was extracted instead. Discrepancies between the reviewers were resolved by a consensus meeting with three senior investigators (G.Y., Y.L., and C.X.G.) who made the final decision regarding inclusion or exclusion of the study.

*End-points*

The outcome measure was the recurrence-free survival (RFS), cancer-specific survival (CSS),

**Table 2.** Main characteristics of the eligible studies

| Study | Year | Country | Recruitment period | No. of patients | Median FU, range (mon) | Study design | Inclusion and exclusion criteria | Definition of survival | Definition of MVI | Staining methods | No. of observers | Interpretation of MVI | Quality scale |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Belsante [14] | 2014 | USA | 1997-2010 | 419 | 26 (0-150) | Retrospective | yes | yes | yes | NA | NA | NA | 5 |
| Eisenberg [15] | 2013 | USA | 2001-2008 | 1103 | 78 (0-121) | Retrospective | yes | NA | yes | HE | 1 | blind | 5 |
| Shindo [16] | 2013 | Japan | 1980-2005 | 172 | 104.5 (8-308) | Retrospective | yes | yes | NA | EVG | 1 | NA | 4 |
| Drewniak [17] | 2013 | Poland | 2000-2007 | 148 | 51 (5-109) | Retrospective | NA | NA | NA | NA | 1 | NA | 5 |
| Steffens [18] | 2013 | Germany | 1990-2011 | 2030 | 66 (30-96) | Retrospective | yes | yes | NA | NA | NA | NA | 4 |
| Betsunoh [19] | 2013 | Japan | 1999-2012 | 82 | 46 (3-112) | Retrospective | yes | yes | NA | NA | 2 | NA | 5 |
| Harada [20] | 2012 | Japan | 1998-2008 | 122 | 44 (8–148) | Retrospective | yes | yes | NA | HE/IHC | 2 | blind | 7 |
| Pichler [21] | 2012 | Austria | 1984-2006 | 1754 | 82 (0-280) | Retrospective | yes | yes | yes | NA | NA | NA | 5 |
| Kroeger [22] | 2012 | Multination | 1981-2009 | 2596 | 22.4 (1-212) | Retrospective | NA | yes | yes | NA | NA | NA | 4 |
| da Costa [23] | 2012 | Brazil | 1992-2009 | 142 | 44 | Retrospective | yes | yes | NA | HE/IHC | 2 | NA | 6 |
| Takayama [24] | 2011 | Japan | 1978-2007 | 431 | 42.3 | Retrospective | yes | yes | NA | NA | NA | NA | 4 |
| Komura [25] | 2011 | Japan | 1996-2004 | 170 | 50 (28-84) | Retrospective | yes | yes | yes | NA | 2 | blind | 7 |
| Suzuki [26] | 2011 | Japan | 1994-2001 | 211 | 81 (4-208) | Retrospective | yes | NA | NA | NA | NA | NA | 3 |
| Katz [27] | 2011 | USA | 1989-2004 | 841 | 61 (1-209) | Retrospective | yes | yes | yes | HE | 1 | blind | 6 |
| Kume [28] | 2010 | Japan | 1983-2009 | 165 | 30.7 (0.4-270.4) | Retrospective | yes | NA | NA | NA | NA | NA | 3 |
| Kim [29] | 2010 | Korea | 1995-2004 | 93 | 63.6 (10-159) | Retrospective | NA | NA | NA | NA | 1 | NA | 2 |
| Rey [30] | 2010 | Spain | 1993-2005 | 139 | 66.2±44.11 | Retrospective | NA | NA | yes | NA | NA | NA | 3 |
| May [31] | 2009 | Germany | 1992-2006 | 771 | 75.7 | Retrospective | yes | yes | yes | HE | NA | NA | 5 |
| Cho [32] | 2009 | Japan | 1986-2004 | 502 | 77.6 (0.4-246.9) | Retrospective | NA | yes | NA | NA | NA | NA | 3 |
| Zubac [33] | 2008 | Norway | 1985-1994 | 76 | 112.8 (1-232.8) | Retrospective | yes | NA | yes | HE/IHC | 2 | blind | 7 |
| Pflanz [34] | 2008 | Germany | 1992-2007 | 607 | 54 | Retrospective | NA | yes | NA | HE | NA | NA | 3 |
| Horiguchi [35] | 2007 | Japan | 1994-2006 | 120 | 24 (2-141) | Retrospective | NA | NA | yes | NA | NA | NA | 3 |
| Dall'Oglio [36] | 2007 | Brazil | 1988-2003 | 230 | 48 (10-130) | Retrospective | NA | NA | yes | NA | 1 | NA | 3 |
| Klatte [37] | 2007 | USA | 1985-2005 | 519 | 49 (1-199) | Retrospective | NA | yes | NA | NA | ≥ 2 | NA | 4 |
| Madbouly [38] | 2007 | Saudi Arabia | 1990-2004 | 48 | 37.7 (12-60) | Retrospective | NA | NA | yes | NA | 1 | NA | 3 |
| Komai [39] | 2007 | Japan | 1986-2004 | 101 | 55 (2-187) | Retrospective | NA | NA | NA | NA | NA | NA | 2 |
| Ito [40] | 2006 | Japan | 1985-2003 | 178 | 44.5 (1-232) | Retrospective | NA | yes | NA | NA | NA | NA | 3 |
| Lee [41] | 2006 | Korea | 1993-2003 | 516 | 50.9 (1-148.6) | Retrospective | yes | yes | NA | NA | NA | NA | 4 |
| Goncalves [42] | 2004 | Brazil | 1989-1999 | 95 | 45 (14-132) | Retrospective | yes | NA | yes | NA | 1 | NA | 4 |
| Lang [43] | 2004 | France | 1980-1990 | 255 | 183 | Retrospective | NA | NA | NA | HE/IHC | NA | NA | 3 |
| Ishimura [44] | 2002 | UK | 1991-1996 | 176 | 44 (25-99) | Retrospective | yes | yes | yes | NA | 2 | blind | 7 |
| Griffiths [45] | 2004 | Japan | 1986-2002 | 157 | 45 (6-162) | Retrospective | yes | NA | yes | HE | 1 | NA | 4 |
| VanPoppel [46] | 1997 | Belgium | 1980-1993 | 180 | 60 (8-88) | Retrospective | yes | NA | yes | HE/PA/Elastin | NA | NA | 4 |

EVG: Elastica van Gieson; HE: Haematoxylin and eosin; IHC: Immunohistochemistry; MVI: Microvascular invasion; PA: Periodic acid. NA: not available. FU: follow-up.

**Table 3.** Patient characteristics of the eligible studies

| Study | Year | Country | No. of patients | Median age, range (yr) | Gender (m/f) | Adjuvant therapy (+/-) | RN/PN |
|---|---|---|---|---|---|---|---|
| Belsante [14] | 2014 | USA | 419 | 57 (17-85) | 247/172 | NA | 236/183 |
| | | | 333 | 55.9 (17-85) | 194/139 | NA | 153/180 |
| Eisenberg [15] | 2013 | USA | 1103 | 62.3 (19-93) | 710/393 | NA | NA |
| Shindo [16] | 2013 | Japan | 172 | 60 (23-82) | 133/39 | NA | 107/65 |
| Drewniak [17] | 2013 | Poland | 148 | 59.6 (33-79) | 102/46 | NA | NA |
| Steffens [18] | 2013 | Germany | 2030 | 62.3 (20-90) | 1316/714 | NA | 1620/410 |
| Betsunoh [19] | 2013 | Japan | 82 | 63.1 (39-83) | 62/20 | 22/60 | 82/0 |
| Harada [20] | 2012 | Japan | 122 | 65.0 (32-84) | 87/35 | NA | 122/0 |
| Pichler [21] | 2012 | Austria | 1754 | 62.6 (20-89) | 979/775 | NA | NA |
| Kroeger [22] | 2012 | Multination | 2596 | 61 (19-97) | 1685/911 | NA | NA |
| da Costa [23] | 2012 | Brazil | 142 | 54.7 (23-81) | 87/55 | NA | 100/42 |
| Takayama [24] | 2011 | Japan | 431 | 60.3 (15-81) | 312/119 | NA | 377/53 |
| Komura [25] | 2011 | Japan | 170 | 62.4±11.4 | 114/56 | 49/121 | 153/17 |
| Suzuki [26] | 2011 | Japan | 211 | 59 (16-87) | 152/59 | 90/121 | 173/38 |
| Katz [27] | 2011 | USA | 841 | NA | 530/311 | NA | 622/233 |
| Kume [28] | 2010 | Japan | 165 | 59 (23-83) | 127/38 | NA | 81/81 |
| Kim [29] | 2010 | Korea | 93 | 55±11.4 | 64/29 | NA | 63/30 |
| Rey [30] | 2010 | Spain | 139 | 63±11.48 | 85/54 | NA | 127/12 |
| May [31] | 2009 | Germany | 771 | 61.1 (18-84) | 488/283 | NA | 653118 |
| Cho [32] | 2009 | Korea | 299 | 56 (25-86) | 195/104 | NA | 267/32 |
| Zubac [33] | 2008 | Norway | 76 | 67 (39-88) | 36/40 | NA | 76/0 |
| Pflanz [34] | 2008 | Germany | 607 | 61.6 (18-84) | 387/220 | NA | 490/117 |
| Horiguchi [35] | 2007 | Japan | 120 | 64 (36-81) | 83/37 | NA | NA |
| Dall'Oglio [36] | 2007 | Brazil | 230 | 59 (9-90) | 168/62 | NA | 180/47 |
| Klatte [37] | 2007 | USA | 519 | 61 (19-88) | 320/199 | NA | 305/214 |
| Madbouly [38] | 2007 | Saudi Arabia | 48 | 50.7 (20-80) | 22/26 | NA | 48/0 |
| Komai [39] | 2007 | Japan | 101 | 64 (33-84) | 26/75 | NA | NA |
| Ito [40] | 2006 | Japan | 178 | 59.3±0.9 | 127/51 | NA | NA |
| Lee [41] | 2006 | Korea | 516 | 55 (26-81) | 360/125 | NA | NA |
| Goncalves [42] | 2004 | Brazil | 95 | 60 (9-81) | 72/23 | NA | NA |
| Lang [43] | 2004 | France | 255 | 60 (16-87) | 169/86 | NA | 255/0 |
| Ishimura [44] | 2004 | Japan | 157 | 63.4 (20-84) | 99/58 | NA | 140/17 |
| Griffiths [45] | 2002 | UK | 176 | 65 (34-88) | 120/56 | NA | 176/0 |
| VanPoppel [46] | 1997 | Belgium | 180 | 52 (1-180) | 107/73 | NA | 259/6 |

RN: Radical nephrectomy; PN: Partial nephrectomy.

metastasis-free survival (MFS), and overall survival (OS) between patients with or without MVI; the association between microvascular invasion and the clinical outcomes was statistically reflexed by use of hazard ratios (HR).

*Quality assessments*

Three investigators (G.Y., Y.L., and C.X.G.) evaluation for the enrolled studies according to a predefined form modified on the basis of Graeff's [10], knowing that no generally accepted criteria for the assessment of study quality are available at present. Our quality scale consists of nine criteria with 9 as the maximum score (Table S2). A study with a score ≥ 5 was regarded as high quality, and low quality when the score was < 5.

*Statistical analysis*

Categorical features were gathered and arranged with frequency counts. Continuous data were summarized with medians and rang-

es; Comparisons of quality scales and MVI proportion between eligible studies were evaluated using spearman's rank correlations test by SPSS (Version 19; IBM Corp).

We gathered HRs and their 95% CI of each eligible study to conduct the meta-analysis. In case they were not directly provided, we estimated HRs and their 95% CI using the available survival data by means of the accepted method [11]. A pooled HR and 95% CI were computed for the risk allele using Stata (Version 12.0; Stata Corp, College station, TX) by a random-effects model to generate forest plots. If the 95% CI did not overlap with 1 and $P < 0.05$, the influence of MVI on clinical outcomes was identified as statistically significant. Heterogeneity was quantifiably assessed by use of the Higgins I squared statistic [12] and the Cochran's Q statistic [13]. The $I^2$ statistic yielded results ranging between 0 and 100% (0-25%, no heterogeneity; 25-50%, moderate heterogeneity; 50-75%, large heterogeneity; and 75-100%, extreme heterogeneity). $P < 0.10$ was deemed to stand for notable heterogeneity among studies. Publication bias was evaluated by use of egger's linear regression test and Begg's funnel plot.

In view of the heterogeneity between the studies, we conducted subgroup analyses. First we divided the studies into four groups, Group A with data of patients whose stages, grades, and tumor types were not separated, including all stages and all tumor types, ccRCC and non-ccRCC (TanyNanyMany); Group B with data of all RCC types with the emphasis laid on non-metastatic RCCs (TanyN0M0); Group C with data of all RCC types with the emphasis laid on organ-confined RCCs (T1-2N0M0); and Group D with data of ccRCC only (ccRCC). Then other potential sources of heterogeneity were explored, including publication year, median follow-up, and study location, number of patients, study quality score, and analytical results. When overlapping data appeared, we chose the more informative one.

## Results

### *Study selection and characteristics*

Initially, we assembled a total of 1120 articles from the electronic databases, of which 185 duplicate publications were excluded in the first round. Additional 860 articles were excluded after screening the titles and abstracts. Then, we reviewed full texts of the remaining 75 articles, of which 26 were excluded for lacking of sufficient data to estimate the HRs, 4 studies were excluded because they focused on vascular invasion without clear definition. 6 studies were excluded because MVI was assessed for RCC subtypes without including ccRCC, and 6 studies were excluded for the existence of reduplicative data with another study. Finally, 33 studies [14-46] that focused on the association between RCC and MVI were included for meta-analysis, involving a total of 14,946 patients, ranging from 48 to 2,596 per study. A flow diagram of the selection process is showed in **Figure 1**.

The main features of the 33 eligible studies for aggregation are listed in **Tables 1-3**. The publishing time of the studies was between 1997 and 2014. The 33 studies originated from Asia (14), Europe (9), the United States (4), multinational research (1) and other regions (5). The median follow-up duration ranged from 24 months to 183 months. Five of these studies included fewer than 100 patients, and 14 studies enrolled more than 200 patients, and 4 studies involved more than 1000 patients. All the included studies were based on the data of retrospective analysis of survival. Other characteristics including tumor features and pathologic outcomes are presented in **Table 1**. MVI was detected in 14.4% in pathological specimens of the 14,946 patients included in the meta-analysis. And higher frequencies of MVI were found to be associated with higher tumor grades and pathological T stages, distant metastasis and lymph node metastasis in the eligible studies (Table S3). And Eisenberg et al [15] reported a significant correlation between MVI and sarcomatoid differentiation coagulative tumor necrosis, and collecting system invasion. Goncalves et al reported positive association between MVI and perirenal fat invasion [43], in contrast Madbouly et al observed no significant correlation between MVI and perirenal fat invasion [38]. Of the 58 survival analyses, 56 (96.5%) directly provided HRs and their 95% CI for multivariate analysis, and 28 (48.3%) showed no significant correlation between MVI and survival. There was a wide variety of cofactors reported in the multivariate analysis of these studies, among which the most common

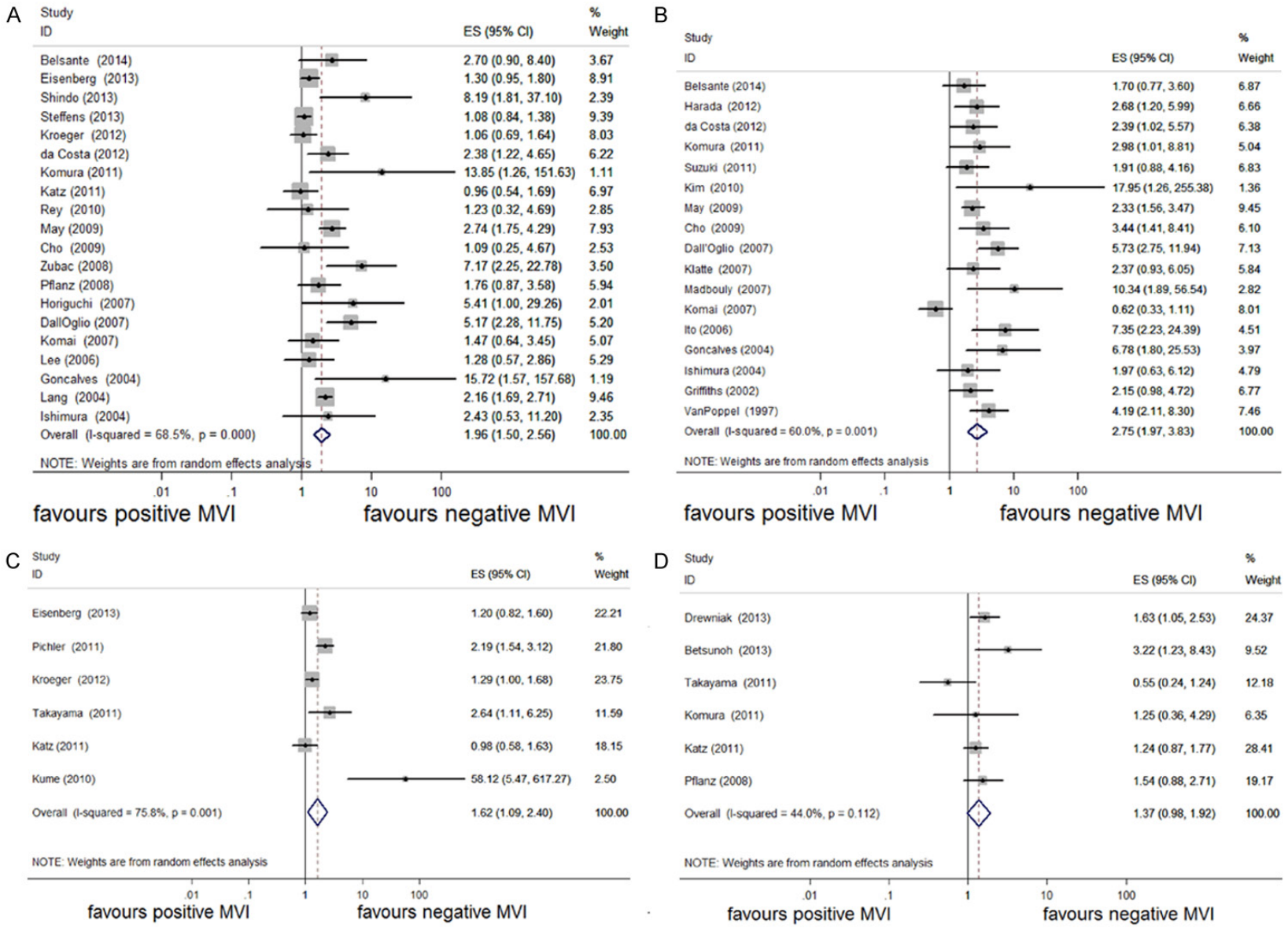


**Figure 2.** Forest plots of prognosis of microvascular invasion. The horizontal lines correspond to the study-specific hazard ration and 95%. A. CSS for all eligible studies. Cancer-specific survival. B. RFS for all eligible studies. Recurrence-free survival. C. MFS for all eligible studies. Metastasis-free survival. D. OS for all eligible studies. Overall survival.

**Table 4.** Summarized hazard ratios (including subgroup analysis)

| Analysis | N | Pooled HR[a] (95% CI) | $I^2$ value (%) | *P*-value* |
|---|---|---|---|---|
| CSS | | | | |
| All studies | 20 | 1.957 (1.498-2.556) | 68.5% | 0.0001 |
| TanyNanyMany | 7 | 1.435 (1.024-2.011) | 74.3% | 0.001 |
| TanyN0M0 | 12 | 1.757 (1.340-2.304) | 47.6% | 0.033 |
| T1-2N0M0 | 5 | 7.645 (3.647-16.025) | 0.0% | 0.776 |
| ccRCC | 5 | 1.954 (0.920-4.149) | 58.5% | 0.047 |
| PY (1997-2009) | 9 | 2.544 (1.720-3.763) | 46.7% | 0.059 |
| PY (2009-2014) | 11 | 1.594 (1.160-2.191) | 65.2% | 0.001 |
| Median FU < 60 months | 12 | 2.154 (1.440-3.222) | 51.1% | 0.021 |
| Median FU ≥ 60 months | 8 | 1.821 (1.243-2.668) | 81.2% | 0.0001 |
| Asian | 7 | 2.326 (1.246-4.342) | 37.6% | 0.142 |
| Other regions | 13 | 1.886 (1.395-2.549) | 76.0% | 0.0001 |
| No. of patients < 200 | 9 | 3.335 (1.929-5.765) | 37.8% | 0.117 |
| No. of patients ≥ 200 | 11 | 1.616 (1.213-2.153) | 74.0% | 0.0001 |
| Quality scale < 5 | 12 | 1.855 (1.295-2.657) | 71.2% | 0.0001 |
| Quality scale ≥ 5 | 8 | 2.196 (1.392-3.463) | 67.5% | 0.003 |
| Not significant | 11 | 1.195 (1.023-1.395) | 0.0% | 0.810 |
| Significant | 9 | 3.462 (2.375-5.044) | 47.7% | 0.054 |
| RFS | | | | |
| All studie | 17 | 2.749 (1.974-3.828) | 60.0% | 0.001 |
| TanyN0M0 | 12 | 2.278 (1.612-3.218) | 58.1% | 0.006 |
| T1-2N0M0 | 6 | 4.365 (2.540-7.499) | 0.0% | 0.527 |
| ccRCC | 3 | 2.152 (1.349-3.431) | 0.0% | 0.469 |
| PY (1997-2009) | 9 | 3.182 (1.668-6.068) | 77.6% | 0.0001 |
| PY (2009-2014) | 8 | 2.391 (1.844-3.101) | 0.0% | 0.759 |
| Median FU < 60 months | 13 | 2.754 (1.782-4.257) | 65.6% | 0.0001 |
| Median FU ≥ 60 months | 4 | 2.779 (1.743-4.432) | 37.3% | 0.188 |
| Asion | 8 | 2.476 (1.311-4.676) | 70.6% | 0.001 |
| Other regions | 9 | 3.005 (2.174-4.154) | 33.7% | 0.148 |
| No. of patients < 200 | 11 | 3.019 (1.754-5.196) | 69.5% | 0.0001 |
| No. of patients ≥ 200 | 6 | 2.613 (1.862-3.666) | 27.8% | 0.226 |
| Quality scale < 5 | 11 | 3.323 (1.905-5.798) | 74.0% | 0.0001 |
| Quality scale ≥ 5 | 6 | 2.292 (1.728-3.042) | 0.0% | 0.960 |
| Not significant | 6 | 1.554 (0.963-2.510) | 52.3% | 0.063 |
| Significant | 11 | 3.330 (2.614-4.243) | 20.4% | 0.249 |
| MFS | | | | |
| All studies | 6 | 1.621 (1.095-2.400) | 75.8% | 0.001 |
| TanyNanyMany | 2 | 1.259 (1.026-1.544) | 0.0% | 0.027 |
| TanyN0M0 | 2 | 1.499 (0.683-3.292) | 84.2% | 0.012 |
| T1-2N0M0 | 2 | 10.098 (0.500-203.84) | 82.8% | 0.016 |
| ccRCC | 3 | 1.409 (0.935-2.124) | 79.7% | 0.007 |
| OS | | | | |
| All studies | 6 | 1.371 (0.978-1.923) | 44.0% | 0.112 |
| TanyNanyMany | 3 | 1.729 (1.248-2.397) | 0.0% | 0.399 |
| TanyN0M0 | 3 | 1.545 (1.139-2.096) | 45.1% | 0.162 |

PY: publication year; FU: follow-ups; HR = hazard ratio; 95% CI = 95% confidence interval; a Pooled hazards ratios were obtained from using a DerSimonian-Laird random effects model, applying the inverse of variance as a weighing factor. **P* values obtained from $\chi^2$-test for heterogeneity.

cofactor applied to evaluate the risk of poor survival was the histological grade (Table S4).

*Assessment of study quality*

The median quality score of the 33 included studies was 4 (mean: 4.13, range: 2-7) (**Table 1**). The score of 5 or more in methodological assessment indicates high quality, which included 12 (36.4%) studies. 16 of 33 studies present a definition of MVI (Table S5). No significant association was found between quality scores and study size (Spearman's r = 0.091, P = 0.605). Also we did not find statistical difference in quality score in accordance with location of the study performed, median follow-up time and publication year.

*Meta-analysis*

According to the conceivable heterogeneity between the studies, we used the random effects model to estimate the combined HR of each study. **Figure 2** displays a forest plot of the individual HRs and pooled results from the meta-analysis. When we pooled 20 eligible studies into the meta-analysis for cancer-specific survival (CSS), there was a significant correlation between MVI and worse CSS, the pooled HR being 1.957 (95% CI, 1.498-2.556), while the test of inconsistency ($I^2$ = 68.5%) failed to eliminate a notable heterogeneity (**Figure 2A**). The meta-analysis performed on 17

studies that evaluated the correlation between MVI and recurrence-free survival (RFS) showed that the pooled HR was 2.749 (95% CI, 1.974-3.828), despite the large heterogeneity between studies ($I^2$ = 60.0%) (**Figure 2B**). Data on MFS was available in six studies, and meta-analysis of MFS suggested that MVI was linked with poor MFS with pooled HR = 1.621 (95% CI, 1.095-2.400). Cochrane Q test ($Chi^2$ = 20.63; P = 0.001) and $I^2$ = 75.8% showed a remarkable heterogeneity (**Figure 2C**). Six studies with data as regards overall survival (OS), the pooled HR from the meta-analysis suggested that the correlation between MVI and worse OS did not address statistical significance (pooled HR = 1.371; 95% CI, 0.978-1.923). And cochrane Q test ($Chi^2$ = 39.96; P = 0.001) with a moderate heterogeneity is shown in the data ($I^2$ = 44.0%) (**Figure 2D**).

*Assessment of heterogeneity*

The meta-analysis of most subgroup again suggested MVI as a prognostic factor despite heterogeneity among some groups (**Table 4**). It should be noted that the combined HR of CSS and RFS in group C (T1-2N0M0) showed statistical significance (CSS: pooled HR = 7.645, 95% CI, 3.647-16.025, $I^2$ = 0.0%; RFS: pooled HR = 4.365, 95% CI, 2.540-7.499, $I^2$ = 0.0%) with no heterogeneity. However, the association between MVI and worse CSS in Group D (ccRCC) was statistically insignificant, with a pooled HR = 1.954 (95% CI, 0.920-4.149; P = 0.047 for heterogeneity test; $I^2$ = 58.5%). Similar results were seen in the MFS where the pooled HR in Group B, C, D did not show statistical significance. And when we pooled the HRs of CSS in the studies with no significance, the pooled HR showed statistical significance instead (pooled HR = 1.195; 95% CI, 1.023-1.395; P = 0.810 for heterogeneity test; $I^2$ = 0.0%). Moreover, compared with the no statistically significant pooled HR of OS in all eligible studies, The pooled HR of OS in Group A and B showed statistical significance (A: pooled HR = 1.729, 95% CI, 1.248-2.397, $I^2$ = 0.0%; B: pooled HR = 1.545, 95% CI, 1.139-2.096, $I^2$ = 0.0%).

*Publication bias*

We used Begg's funnel plot to examine potential publication bias between the studies (**Figure 3**) and found no exact evidence of funnel plot asymmetry. Begg's test showed no evidence of statistical publication bias (all P > 0.05) between the studies in terms of HR of CSS, RFS, OS and MFS, the *p* values being 0.144, 0.064, 1.000 and 0.452, respectively. Egger's test confirmed the conclusion that no significant publication bias was found in the meta-analysis with respect to RFS, OS and MFS with a *p* value of 0.062, 0.964 and 0.174 respectively, except for CSS with a *p* value of 0.045.

## Discussion

Microvascular invasion is defined as the presence of tumor within microscopic veins with a muscular coat, in spite of gross tumor in the renal vein [15], which most probably links with hematogenous spread of tumor cells. Cancer cells intrude into the lymphovascular space, highly proliferate, and then pierce the local vessels or lymphatics to disseminate more extensively [47, 48]. MVI has been identified as a risk factor of lymph node invasion, a recurrence of tumor and distant metastasis in many solid cancers including urothelial tumor [4, 49], lung cancer [5], and hepatocellular carcinoma [7] which has been confirmed in the systematic review studies. And in the liver and testiculars, MVI has been brought into the TNM staging system for improved cancer staging [50, 51]. However, only endometrial/cervical and head and neck cancers consider the presence of MVI as indication for further adjuvant therapy [5]. The prognostic value of MVI has been evaluated in numerous studies, but the results remain equivocal in RCC.

The present meta-analysis consisted of 14,946 RCC patients derived from 33 studies. The individual data were organized according to CSS, DFS, MFS and OS. No statistical difference in quality score was found between the location of the study performed, median follow-up time and publication year. MVI was detected in 14.4% of 14,946 RCC patients. We found a significant correlation between MVI and some acknowledged pathological parameters including pathologic TNM stage and grade.

Due to apparent heterogeneity of the enrolled studies, we used the random-effects model during pooling data. Meta-analysis of the eligible studies addressed a significant association between MVI and CSS, RFS, and MFS, suggesting that MVI is a significant predictor for poor

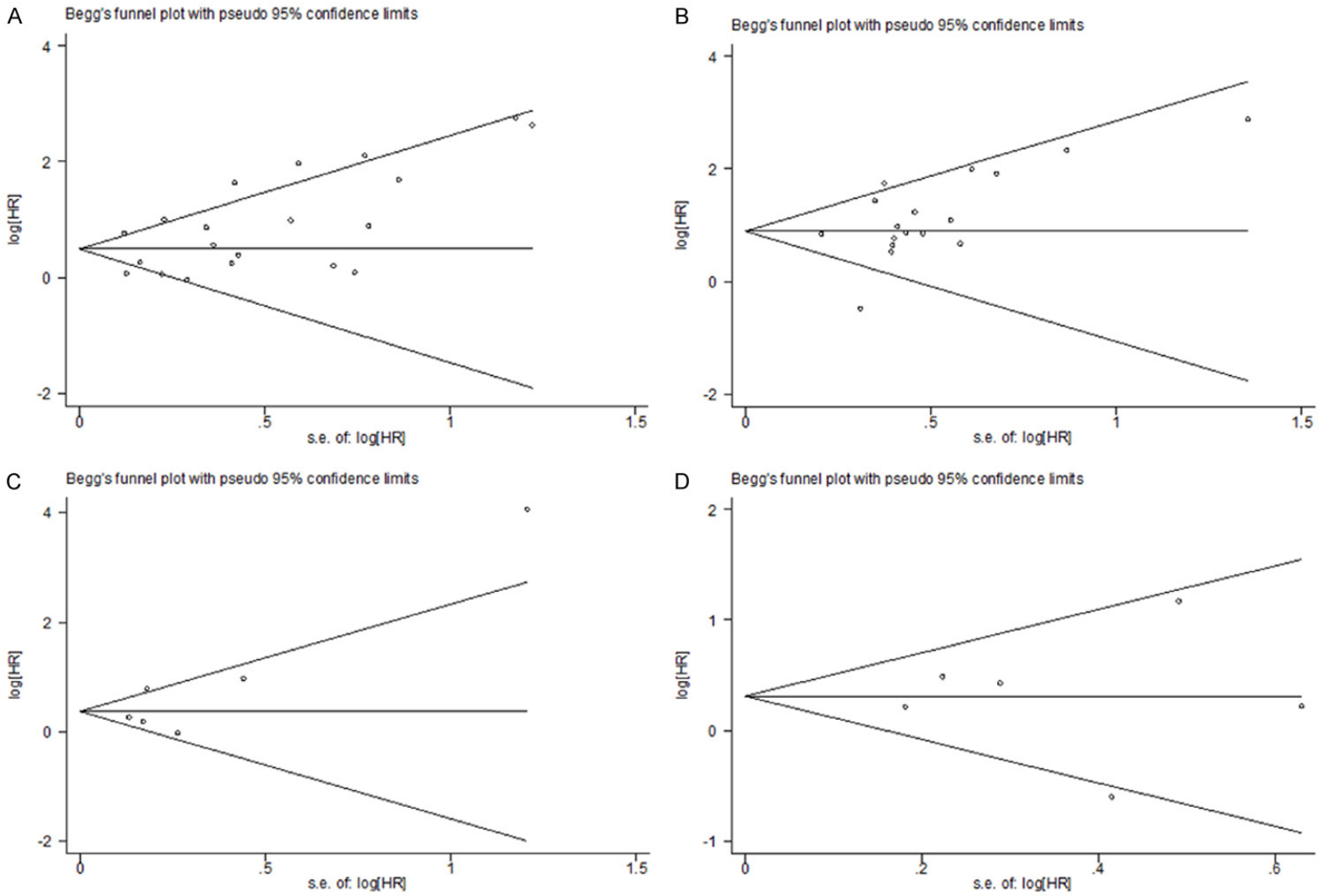


**Figure 3.** Begg's Funnel plots for publication bias test. Each point stands for a separate study for the indicated correlation. The horizontal lines represent the mean effects size. A. Beggs Funnel plots for CSS. Cancer-specific survival. B. Beggs Funnel plots for RFS. Recurrence-free survival. C. Beggs Funnel plots for MFS. Metastasis-free survival. D. Beggs Funnel plots for OS. Overall survival.

survival regarding cancer related events, but the presence of MVI did not seem to have an unfavorable impact on OS. Most of the subgroup analyses demonstrated similar results, wherein the combined analysis in group C (T1-2N0M0) revealed a significant association between MVI and CSS, RFS with no heterogeneity ($I^2$ = 0%), which denoted that the presence of MVI predicts poorer prognosis in RCC patients on early pathological stage. However, there was no statistical significance in linking MVI with poor CSS for patients in Group D (ccRCC). When we combined the HRs of CSS in 10 individual studies with negative results, the pooled HR showed statistical significance with no heterogeneity ($I^2$ = 0%), which further addresses that the prognostic valve of MVI for poor CSS. In addition, compared with the statistically insignificant pooled HR of OS in 6 eligible studies, the pooled HR of OS in Group A (TanyNanyMany) revealed statistical significance with no heterogeneity ($I^2$ = 0%), suggesting that MVI might be a predictor for high risk of mortality. Notably, heterogeneities of data were detected in most of these subgroup analyses. Thus more studies with larger sample sizes of ccRCC patients or focusing on OS and MFS are needed to further estimate the impact of MVI on prognosis.

The results of the present study should be approached with caution in view of its merits and shortcomings. As a systematic review and meta-analysis, it possesses the power of adequate studies and large numbers of patients to provide more exact evaluation of effects and enable more authentic subgroup analyses. In addition, we found no publication bias using Begg's tests and egger's test for the analysis of association between MVI and RFS, MFS and OS, suggesting that this meta-analysis obtained from these studies approximate the actual results. However, with improved precision, there are several inherent limitations, specifically regarding the potential selection bias that results in heterogeneity between studies. Non-English studies, unpublished studies, and studies that did not provide sufficient data in HRs calculated did not contribute to evaluating of the predictive value of MVI for survival. The first defect is the presence of a slight publication bias of the eligible studies on the summary CSS, indicating the pooled HR may overestimate the true effect size. Another weakness of the present study is heterogeneity in term of different baseline characteristics of patients in each study. Although we take into account the heterogeneity in our meta-analysis by using the random-effects model, the conclusion drawn in this study should be considered prudently. In addition, all the included studies were retrospectively designed, and prospective multicenter trials are needed to seek more exact answers. Finally, although we included 33 studies comprising 14,946 cases for this meta-analysis, relatively few studies were categorized for subgroup analysis and several survival subgroup analyses were lacking in data.

Besides, only a few included studies incorporated immunohistochemical (IHC) analysis in cases negative for MVI by examination of H&E stained sections. The reason is that the use of IHC staining is not common for routine clinical practice. Knowing that this added measurement may increase the detection rate of MVI [27], rigorous morphological criteria should be established to standardize the diagnosis of MVI reproducibly, which is crucial for exerting its predictive value in daily clinical settings.

## Conclusions

The results of the present meat-analysis show that estimates of the significance of MVI in RCC patients vary substantially between studies. Our meta-analysis indicates that the presence of MVI has a detrimental effect on survival and clinicopathological features in RCC and therefore could serve as an independent prognostic factor of CSS, RFS, and MFS. It could also be used to predict RCC patients who need further adjuvant therapies.

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## Disclosure of conflict of interest

None.

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## References

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[2] Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am 2003; 30: 843-852.

[3] Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mrcc): a literature review. Cancer Treat Rev 2008; 34: 193-205.

[4] Kim H, Kim M, Kwak C, Kim HH, Ku JH. Prognostic significance of lymphovascular invasion in radical cystectomy on patients with bladder cancer: a systematic review and meta-analysis. PLoS One 2014; 9: e89259.

[5] Mollberg NM, Bennette C, Howell E, Backhus L, Devine B, Ferguson MK. Lymphovascular invasion as a prognostic indicator in stage i non-small cell lung cancer: a systematic review and meta-analysis. Ann Thorac Surg 2014; 97: 965-971.

[6] Heinzelbecker J, Gross-Weege M, Weiss C, Horner C, Trunk MJ, Erben P, Haecker A, Bolenz C. Microvascular invasion of testicular non-seminomatous germ cell tumors: implications of separate evaluation of lymphatic and blood vessels. J Urol 2014; 192: 593-9.

[7] Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol 2013; 20: 325-339.

[8] Grimm M. Prognostic value of clinicopathological parameters and outcome in 484 patients with oral squamous cell carcinoma: microvascular invasion (v+) is an independent prognostic factor for oscc. Clin Transl Oncol 2012; 14: 870-880.

[9] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-41.

[10] de Graeff P, Crijns AP, de Jong S, Boezen M, Post WJ, de Vries EG, van der Zee AG, de Bock GH. Modest effect of p53, egfr and her-2/neu on prognosis in epithelial ovarian cancer: a meta-analysis. Br J Cancer 2009; 101: 149-159.

[11] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

[12] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.

[13] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[14] Belsante M, Darwish O, Youssef R, Bagrodia A, Kapur P, Sagalowsky AI, Lotan Y, Margulis V. Lymphovascular invasion in clear cell renal cell carcinoma--association with disease-free and cancer-specific survival. Urol Oncol 2014; 32: 23-30.

[15] Eisenberg MS, Cheville JC, Thompson RH, Kaushik D, Lohse CM, Boorjian SA, Costello BA, Leibovich BC. Association of microvascular and capillary-lymphatic invasion with outcome in patients with renal cell carcinoma. J Urol 2013; 190: 37-43.

[16] Shindo T, Masumori N, Kobayashi K, Fukuta F, Hirobe M, Tonooka A, Hasegawa T, Kitamura H, Tsukamoto T. Long-term outcome of small, organ-confined renal cell carcinoma (rcc) is not always favourable. BJU Int 2013; 111: 941-945.

[17] Drewniak T, Sandheim M, Jakubowski J, Juszczak K, Stelmach AW. Prognostic factors of overall survival in renal cancer patients-single oncological center study. Cent European J Urol 2013; 66: 283-291.

[18] Steffens S, Ringe KI, Schroeer K, Lehmann R, Rustemeier J, Wegener G, Schrader M, Hofmann R, Kuczyk MA, Schrader AJ. Does overweight influence the prognosis of renal cell carcinoma? Results of a multicenter study. Int J Urol 2013; 20: 585-592.

[19] Betsunoh H, Fukuda T, Anzai N, Nishihara D, Mizuno T, Yuki H, Masuda A, Yamaguchi Y, Abe H, Yashi M, Fukabori Y, Yoshida K, Kamai T. Increased expression of system large amino acid transporter (lat)-1 mrna is associated with invasive potential and unfavorable prognosis of human clear cell renal cell carcinoma. BMC Cancer 2013; 13: 509.

[20] Harada K, Miyake H, Kusuda Y, Fujisawa M. Expression of epithelial-mesenchymal transition markers in renal cell carcinoma: impact on prognostic outcomes in patients undergoing

radical nephrectomy. BJU Int 2012; 110: E1131-E1137.
[21] Pichler M, Hutterer GC, Chromecki TF, Jesche J, Groselj-Strele A, Kampel-Kettner K, Pummer K, Zigeuner R. Prognostic value of the leibovich prognosis score supplemented by vascular invasion for clear cell renal cell carcinoma. J Urol 2012; 187: 834-839.
[22] Kroeger N, Rampersaud EN, Patard J, Klatte T, Birkhaeuser FD, Shariat SF, Lang H, Rioux-Leclerq N, Remzi M, Zomorodian N, Kabbinavar FF, Belldegrun AS, Pantuck AJ. Prognostic value of microvascular invasion in predicting the cancer specific survival and risk of metastatic disease in renal cell carcinoma: a multicenter investigation. J Urol 2012; 187: 418-423.
[23] da Costa WH, Rocha RM, da Cunha IW, da Fonseca FP, Guimaraes GC, Zequi SD. Cd133 immunohistochemical expression predicts progression and cancer-related death in renal cell carcinoma. World J Urol 2012; 30: 553-558.
[24] Takayama T, Sugiyama T, Kai F, Suzuki T, Nagata M, Imanishi T, Mizuno T, Sato S, Furuse H, Mugiya S, Ozono S. Characteristics of aggressive variants in t1a renal cell carcinoma. J Cancer Res Clin 2011; 137: 1653-1659.
[25] Komura K, Inamoto T, Black PC, Koyama K, Katsuoka Y, Watsuji T, Azuma H. Prognostic significance of body mass index in asian patients with localized renal cell carcinoma. Nutr Cancer 2011; 63: 908-915.
[26] Suzuki K, Nishiyama T, Hara N, Akazawa K, Takahashi K. Kattan postoperative nomogram for renal cell carcinoma: predictive accuracy in a japanese population. Int J Urol 2011; 18: 194-199.
[27] Katz MD, Serrano MF, Humphrey PA, Grubb RLI, Skolarus TA, Gao F, Kibel AS. The role of lymphovascular space invasion in renal cell carcinoma as a prognostic marker of survival after curative resection. Urol Oncol 2011; 29: 738-744.
[28] Kume H, Suzuki M, Fujimura T, Fukuhara H, Enomoto Y, Nishimatsu H, Homma Y. Distant metastasis of renal cell carcinoma with a diameter of 3 cm or less-which is aggressive cancer? J Urol 2010; 184: 64-68.
[29] Kim JM, Song PH, Kim HT, Park TC. The prognostic factors for patients with pt1a renal cell carcinoma. Korean J Urol 2010; 51: 233-238.
[30] Rey Rey J, Leon Ramirez D, Lopez Garcia S, Fernandez Vazquez P, Benavente Delgado J, Ojea Calvo A. Pathological prognostic indicators in renal cell carcinoma. Actas Urol Esp 2010; 34: 71-77.
[31] May M, Brookman-Amissah S, Kendel F, Knoll N, Roigas J, Hoschke B, Miller K, Gilfrich C, Pflanz S, Gralla O. Validation of a postoperative prognostic model consisting of tumor microvascular invasion, size, and grade to predict disease-free and cancer-specific survival of patients with surgically resected renal cell carcinoma. Int J Urol 2009; 16: 616-621.
[32] Cho HJ, Kim SJ, Ha US, Hong SH, Kim JC, Choi YJ, Hwang TK. Prognostic value of capsular invasion for localized clear-cell renal cell carcinoma. Eur Urol 2009; 56: 1006-1012.
[33] Zubac DP, Bostad L, Kihl B, Eide J, Wentzel-Larsen T, Haukaas A. Organ-confined clear cell renal cell carcinoma: the prognostic impact of microvascular invasion, nuclear grade and tumour size. Apmis 2008; 116: 1027-1033.
[34] Horiguchi A, Asano T, Asano T, Ito K, Sumitomo M, Hayakawa M. Fatty acid synthase over expression is an indicator of tumor aggressiveness and poor prognosis in renal cell carcinoma. J Urol 2008; 180: 1137-1140.
[35] Pflanz S, Brookman-Amissah S, Roigas J, Kendel F, Hoschke B, May M. Impact of macroscopic tumour necrosis to predict survival of patients with surgically resected renal cell carcinoma. Scand J Urol Nephrol 2008; 42: 507-513.
[36] Dall'Oglio MF, Antunes AA, Sarkis AS, Crippa A, Leite KR, Lucon AM, Srougi M. Microvascular tumour invasion in renal cell carcinoma: the most important prognostic factor. BJU Int 2007; 100: 552-555.
[37] Klatte T, Chung J, Leppert JT, Lam JS, Pantuck AJ, Figlin RA, Belldegrun AS. Prognostic relevance of capsular involvement and collecting system invasion in stage I and II renal cell carcinoma. BJU Int 2007; 99: 821-824.
[38] Madbouly K, Al-Qahtani SM, Ghazwani Y, Al-Shaibani S, Mansi MK. Microvascular tumor invasion: prognostic significance in low-stage renal cell carcinoma. Urology 2007; 69: 670-674.
[39] Komai Y, Saito K, Sakai K, Morimoto S. Increased preoperative serum c-reactive protein level predicts a poor prognosis in patients with localized renal cell carcinoma. BJU Int 2007; 99: 77-80.
[40] Ito K, Asano T, Yoshii H, Satoh A, Sumitomo M, Hayakawa M. Impact of thrombocytosis and c-reactive protein elevation on the prognosis for patients with renal cell carcinoma. Int J Urol 2006; 13: 1365-1370.
[41] Lee SE, Byun S, Oh JK, Lee SC, Chang IH, Choe G, Hong SK. Significance of macroscopic tumor necrosis as a prognostic indicator for renal cell carcinoma. J Urology 2006; 176: 1332-1337.
[42] Lang H, Lindner V, Letourneux H, Martin M, Saussine C, Jacqmin D. Prognostic value of microscopic venous invasion in renal cell carcinoma: long-term follow-up. Eur Urol 2004; 46: 331-335.
[43] Goncalves PD, Srougi M, Dall'Oglio MF, Leite K, Ortiz V, Hering F. Low clinical stage renal cell carcinoma: relevance of microvascular tumor

invasion as a prognostic parameter. J Urol 2004; 172: 470-474.
[44] Ishimura T, Sakai I, Hara I, Eto H, Miyake H. Microscopic venous invasion in renal cell carcinoma as a predictor of recurrence after radical surgery. Int J Urol 2004; 11: 264-268.
[45] Griffiths D, Verghese A, Golash A, Kynaston HG, Matthews PN, Hart A, Court JB. Contribution of grade, vascular invasion and age to outcome in clinically localized renal cell carcinoma. BJU Int 2002; 90: 26-31.
[46] VanPoppel H, Vandendriessche H, Boel K, Mertens V, Goethuys H, Haustermans K, VanDamme B, Baert L. Microscopic vascular invasion is the most relevant prognosticator after radical nephrectomy for clinically non-metastatic renal cell carcinoma. J Urol 1997; 158: 45-49.
[47] Alitalo K, Mohla S, Ruoslahti E. Lymphangiogenesis and cancer: meeting report. Cancer Res 2004; 64: 9225-9229.
[48] Padera TP, Kadambi A, di Tomaso E, Carreira CM, Brown EB, Boucher Y, Choi NC, Mathisen D, Wain J, Mark EJ, Munn LL, Jain RK. Lymphatic metastasis in the absence of functional intratumor lymphatics. Science 2002; 296: 1883-1886.
[49] Ku JH, Byun SS, Jeong H, Kwak C, Kim HH, Lee SE. Lymphovascular invasion as a prognostic factor in the upper urinary tract urothelial carcinoma: a systematic review and meta-analysis. Eur J Cancer 2013; 49: 2665-2680.
[50] Albers P, Siener R, Kliesch S, Weissbach L, Krege S, Sparwasser C, Schulze H, Heidenreich A, de Riese W, Loy V, Bierhoff E, Wittekind C, Fimmers R, Hartmann M. Risk factors for relapse in clinical stage i nonseminomatous testicular germ cell tumors: results of the german testicular cancer study group trial. J Clin Oncol 2003; 21: 1505-1512.
[51] Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, Curley SA, Ellis LM, Regimbeau JM, Rashid A, Cleary KR, Nagorney DM. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002; 20: 1527-1536.

**Table S1.** Searching strategies and results

| Database | Date | Search strategy | Results |
|---|---|---|---|
| Pubmed | Up to May 2014 | #1 renal or kidney [all fields] | 846 |
| | | #2 cancer or carcinoma or neoplasm or tumor or mass or tumour [all fields] | |
| | | #3 Predict* or prognos* or survival or risk or outcome [all fields] | |
| | | #4 lymphovascular or Lymphatic or microvascular or microvessel or microvenous or microscopic or vascular [all fields] | |
| | | #5 invasion or infiltration [all fields] | |
| | | #1 AND #2 AND #3 AND #4 AND #5 | |
| Web of science | Up to May 2014 | #1 renal or kidney [topic] | 881 |
| | | #2 cancer or carcinoma or neoplasm or tumor or mass or tumour [topic] | |
| | | #3 Predict* or prognos* or survival or risk or outcome [topic] | |
| | | #4 lymphovascular or Lymphatic or microvascular or microvessel or microvenous or microscopic or vascular [topic] | |
| | | #5 invasion or infiltration [topic] | |
| | | #1 AND #2 AND #3 AND #4 AND #5 | |
| Cochrane library | Up to May 2014 | #1 renal or kidney [title, abstract, key words] | 6 |
| | | #2 cancer or carcinoma or neoplasm or tumor or mass or tumour [title, abstract, key words] | |
| | | #3 Predict* or prognos* or survival or risk or outcome [title, abstract, key words] | |
| | | #4 lymphovascular or Lymphatic or microvascular or microvessel or microvenous or microscopic or vascular [title, abstract, key words] | |
| | | #5 invasion or infiltration [title, abstract, key words] | |
| | | #1 AND #2 AND #3 AND #4 AND #5 | |

**Table S2.** Criteria for quality assessment

| Criterium | Points |
|---|---|
| 1. Is the population under study defined with in- and exclusion criteria? | 1 |
| 2. Were patient data prospectively collected? | 1 |
| 3. Are the main prognostic patient and tumour characteristics presented?[a] | 1 |
| 4. Were the kinds of staining method > 1? | 1 |
| 5. was the definition of MVI available in the studies? | 1 |
| 6. Were stainings evaluated by > 1 observer? | 1 |
| 7. Were the staining results interpreted by pathologists who were blind to the clinicopathological data? | 1 |
| 8. Is the study endpoint defined? | 1 |
| 9. Is the time of follow up specified? | 1 |
| Max | 9 |

[a]: At least four of the following characteristics: age at diagnosis, tumour stage, tumour grade, tumour type.

**Table S3.** MVI proportion in the eligible studies

| Study | Tumor feature | MVI (+/-) | Stage | | | Fuhrman grade | | | Regional lymph node involvement | | | Distant metastases | | | Histologic subtype | | | | | | PFI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | pT1-2 | pT3-4 | P | 1-2 | 3-4 | P | pNx/N0 | pN1 | P | M0 | M1 | P | cc | p | c | cd | s | u | |
| Belsante [14] | ccRCCpTanyNanyM0 | 60/359 | 21/312 | 39/47 | < 0.001 | 20/268 | 40/91 | < 0.001 | NA | NA | | NA | NA | | NA | NA | NA | NA | NA | NA | NA |
| Eisenberg [15] | ccRCCpTanyNanyMany | 119/954 | 19/694 | 100/289 | < 0.001 | 11/458 | 108/526 | < 0.001 | 94/922 | 62/25 | < 0.001 | 95/876 | 24/108 | 0.004 | 119/984 | 5/214 | 1/85 | 1/45 | NA | 3/17 | NA |
| Kroeger [22] | pTanyNanyMany | 475/2121 | 97/1399 | 378/722 | < 0.001 | 170/1444 | 305/677 | < 0.001 | 387/1193 | 42/58 | < 0.001 | 192/1710 | 283/411 | < 0.001 | 412/1666 | 47/309 | 14/135 | 2/11 | NA | NA | NA |
| Katz [27] | pTanyNanyM0 | 91/750 | 23/552 | 68/126 | < 0.001 | 274/562 | 65/187 | 0.036 | NA | NA | | NA | NA | | 67/574 | 6/127 | 2/26 | NA | NA | 17/20 | NA |
| Rey [30] | pTanyN0M0 | 23/153 | 11/135 | 12/18 | < 0.001 | 4/66 | 19/50 | < 0.001 | NA | NA | | NA | NA | | NA | NA | NA | NA | NA | NA | NA |
| Dall'Oglio [37] | pTanyNanyMany | 59/171 | 26/138 | 33/33 | < 0.001 | 12/134 | 47/37 | < 0.001 | NA | NA | | NA | NA | | 39/109 | 8/37 | 2/21 | NA | 9/4 | NA | NA |
| Madbouly [39] | pT1-2N0M0 | 8/40 | 6/39 | 2/1 | < 0.001 | 6/35 | 2/5 | < 0.001 | NA | NA | | NA | NA | | 8/35 | 0/1 | 0/4 | NA | NA | NA | 2/1 |
| Goncalves [43] | pT1-2NanyM0 | 24/71 | 24/71 | NA | | 3/60 | 21/11 | < 0.001 | 16/71 | 8/0 | < 0.001 | NA | NA | | 10/46 | NA | 2/8 | NA | 7/1 | NA | 14/4 |
| Ishimura [45] | pTanyN0M0 | 70/87 | 36/84 | 34/3 | < 0.001 | 65/83 | 2/2 | < 0.001 | NA | NA | | NA | NA | | 59/61 | 4/4 | 5/10 | 0/1 | NA | NA | NA |
| Lang [44] | pTanyN0M0 | 74/181 | NA | NA | | 13/101 | 61/80 | < 0.001 | NA | NA | | NA | NA | | NA | NA | NA | NA | NA | NA | NA |
| VanPoppel [47] | pTanyN0M0 | 51/129 | 31/111 | 20/39 | < 0.001 | 25/90 | 26/38 | < 0.001 | NA | NA | | NA | NA | | NA | NA | NA | NA | NA | NA | NA |

cc: clear cell; p: papillary; c: chromophobe; cd: collecting duct; s: Sarcomatous; u: unclassified; PFI: perirenal fat invasion; NA: not available.

**Table S4.** Estimation of the hazard ratio

| Study | Tumor charateristics | Survival | HR | 95% CI | | co-factors | Analysis results |
|---|---|---|---|---|---|---|---|
| | | | | lower | upper | | |
| Belsante [14] | ccRCCTanyNanyM0 | CSS | 2.7 | 0.9 | 8.4 | MVI, tumor stage, grade | not |
| Belsante [14] | ccRCCTanyNanyM0 | DFS | 1.70 | 0.77 | 3.60 | MVI, tumor stage, grade | not |
| Belsante [14] | ccRCCpT1-2N0M0 | CSS | 12.7 | 1.7 | 92.7 | MVI, tumor stage, grade | Significant |
| Belsante [14] | ccRCCpT1-2N0M0 | DFS | 4.00 | 1.20 | 13.7 | MVI, tumor stage, grade | Significant |
| Eisenberg [15] | ccRCCpTanyNanyMany | MFS | 1.20 | 0.82 | 1.60 | primary tumor, regional lymph node, distant metastases classifications, tumor size, nuclear grade, coagulative tumor necrosis, MVI | not |
| Eisenberg [15] | ccRCCpTanyNanyMany | CSS | 1.30 | 0.95 | 1.80 | primary tumor, regional lymph node, and distant metastases classifications, tumor size, nuclear grade, coagulative tumor necrosis, MVI | not |
| Shindo [16] | pT1aN0M0 | CSS | 8.191 | 1.808 | 37.098 | interferon, histologic subtype, grade, tumor size, MVI | Significant |
| Drewniak [17] | pTanyNanyMany | OS | 1.628 | 1.049 | 2.525 | performance status, smoking history, hemoglobin concentration, AJCC anatomical staging, tumor grade, and presence of microvascular invasion | Significant |
| Steffens [18] | pTanyNanyMany | CSS | 1.08 | 0.84 | 1.38 | age and sex, tumor stage, differentiation grade, histopathological subtype, lymphogenous/visceral metastasis, and MVI | not |
| Betsunoh [19] | ccRCCpTanyNanyMany | OS | 3.222 | 1.231 | 8.434 | histological grade, pT stage, microscopic vascular invasion, metastasis, and LAT1 mRNA expression | Significant |
| Harada [20] | pTanyN0M0 | RFS | 2.680 | 1.200 | 5.987 | Mode of presentation, Karnofsky performance status, C-reactive protein level, Pathological stage, Grade, MVI, Histological subtype, E-cadherin, N-cadherin, β-catenin, γ-catenin, Clusterin, Slug, Snail, Twist, Vimentin, ZEB1, ZEB2 | Significant |
| Pichler [21] | ccRCCpTanyN0M0 | 10y MFS | 2.19 | 1.54 | 3.12 | T stage, N stage, grade, tumor size, tumor necrosis, MVI | Significant |
| Kroeger [22] | pTanyNanyMany | MFS | 1.295 | 1.000 | 1.677 | gender, ECOG PS, Fuhrman grade, size, pT stage, N stage, M stage, MAVI, MVI | Significant |
| Kroeger [22] | ccRCCpTanyNanyMany | MFS | 1.097 | 0.832 | 1.446 | gender, ECOG PS, Fuhrman grade, size, pT stage, N stage, M stage, MAVI, MVI | not |
| Kroeger [22] | pTanyNanyM0 | CSS | 1.061 | 0.686 | 1.642 | gender, ECOG PS, Fuhrman grade, size, pT stage, N stage, M stage, MAVI, MVI | not |
| Kroeger [22] | pTanyNanyMany | CSS | 0.901 | 0.730 | 1.113 | gender, ECOG PS, Fuhrman grade, size, pT stage, N stage, M stage, MAVI, MVI | not |
| Kroeger [22] | ccRCCpTanyNanyM0 | CSS | 0.548 | 0.043 | 6.980 | gender, ECOG PS, Fuhrman grade, size, pT stage, N stage, M stage, MAVI, MVI | not |
| da Costa [23] | pTanyN0M0 | 5y PFS | 2.387 | 1.023 | 5.570 | T stage, tumor size, grade, MVI, necrosis, metastasis, ECOG PS, CD133 | Significant |
| da Costa [23] | pTanyN0M0 | 5y CSS | 2.382 | 1.219 | 4.653 | T stage, tumor size, grade, MVI, necrosis, metastasis, ECOG PS, CD133 | Significant |
| Takayama [24] | pT1aNanyMany | OS | 2.058 | 0.244 | 1.244 | symptom, CRP, size, histological grade, sarcomatoid component, MVI | not |
| Takayama [24] | pT1aNanyMany | MFS | 2.636 | 1.111 | 6.253 | age, sex, side, symptom, CRP, size, histological grade, nephrectomy, histology, sarcomatoid component, MVI | Significant |
| Komura [25] | pTanyN0M0 | OS | 1.248 | 0.363 | 4.292 | mode of presentation, BMI, ECOG performance status, serum level of C-reactive protein (CRP), microvascular invasion, pathological stage, histologic subtype, nuclear grade, adjuvant cytokine therapy, MVI | not |
| Komura [25] | pTanyN0M0 | CSS | 13.845 | 1.264 | 151.63 | mode of presentation, BMI, ECOG performance status, serum level of C-reactive protein (CRP), microvascular invasion, pathological stage, histologic subtype, nuclear grade, adjuvant cytokine therapy, MVI | Significant |
| Komura [25] | pTanyN0M0 | RFS | 2.978 | 1.007 | 8.809 | mode of presentation, BMI, ECOG performance status, serum level of C-reactive protein (CRP), microvascular invasion, pathological stage, histologic subtype, nuclear grade, adjuvant cytokine therapy, MVI | Significant |
| Suzuki [26] | ccRCCpTanyN0M0 | 5y RFS | 1.913 | 0.879 | 4.163 | age, sex, symptoms, T stage, tumor size, grade, MVI | not |
| Katz [27] | pTanyNanyM0 | MFS | 0.98 | 0.58 | 1.63 | LVI, Fuhrman grade, stage, subtype, tumor, size | not |
| Katz [27] | pTanyNanyM0 | DSS | 0.96 | 0.54 | 1.69 | LVI, Fuhrman grade, stage, subtype, tumor, size | not |
| Katz [27] | pTanyNanyM0 | OS | 1.24 | 0.87 | 1.77 | LVI, Fuhrman grade, stage, subtype, tumor, size | not |
| Kume [28] | pT1aN0M0 | MFS | 58.121 | 5.47 | 617.27 | age, sex, side, symptom, size, histology, grade, treatment, sarcomatoid component, MVI | Significant |
| Kim [29] | pT1aN0M0 | RFS | 17.947 | 1.261 | 255.376 | Fuhrman's nuclear grade, MVI, necrosis in tumor | Significant |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rey [30] | pTanyN0M0 | CSS | 1.225 | 0.32 | 4.691 | stage, fuhrman's grade, tumor size, necrosis, MVI, sinus invasion | not |
| May [31] | pTanyNanyM0 | DFS | 2.33 | 1.56 | 3.47 | grade, MVI, tumor size | Significant |
| May [31] | pTanyNanyM0 | CSS | 2.74 | 1.75 | 4.29 | grade, MVI, tumor size | Significant |
| Cho [32] | ccRCCpTanyN0M0 | RFS | 3.444 | 1.411 | 8.409 | univariate analysis | Significant |
| Cho [32] | ccRCCpTanyN0M0 | CSS | 1.091 | 0.254 | 4.673 | univariate analysis | not |
| Zubac [33] | ccRCCpT1-2N0M0 | CSS | 7.17 | 2.25 | 22.78 | tumor size, nuclear grade, MVI, age | Significant |
| Pflanz [34] | pTanyNanyMany | CSS | 1.762 | 0.867 | 3.578 | T stage, N stage, M stage, thoenes grade, tumor size, tumor necrosis, MVI, platelet count | not |
| Pflanz [34] | pTanyNanyMany | OS | 1.541 | 0.875 | 2.714 | T stage, N stage, M stage, thoenes grade, tumor size, tumor necrosis, MVI, platelet count | not |
| Horiguchi [35] | pTanyNanyMany | CSS | 5.415 | 1.002 | 29.259 | stage, grade, regional lymph node metastasis, distant metastasis, MVI, FAS expression | Significant |
| Dall'Oglio [36] | pTanyNanyMany | CSS | 5.169 | 2.275 | 11.75 | Presentation, tumor size, MVI | Significant |
| Dall'Oglio [36] | pTanyNanyMany | DFS | 5.733 | 2.753 | 11.94 | Presentation, grade, MVI | Significant |
| Klatte [37] | pT1-2N0M0 | RFS | 2.37 | 0.93 | 6.05 | tumour size and the categorical variables capsular involvement, collecting-system invasion, microvascular invasion, ECOG PS, Fuhrman grade, and histological type | not |
| Madbouly [38] | pT1-2N0M0 | DFS | 10.34 | 1.891 | 56.54 | MVI, stage, grade, cell type, perirenal fat invasion, tumor size, and patient age | Significant |
| Komai [39] | pTanyN0M0 | DSS | 1.47 | 0.64 | 3.45 | CRP, anaemia, pT stage, grade, histological cell type, MVI | not |
| Komai [39] | pTanyN0M0 | RFS | 0.62 | 0.33 | 1.11 | CRP, anaemia, pT stage, grade, histological cell type, MVI | not |
| Ito [40] | pTanyN0M0 | DFS | 7.353 | 2.227 | 24.39 | age, sex, tumor side, T stage, tumor size, grade, MVI, THC (thrombocytosis), CRP (C-reactive protein) | Significant |
| Lee [41] | pTanyNanyMany | CSS | 1.28 | 0.57 | 2.86 | presence of metastasis, T stage, grade, MVI, tumor size, sarcomatoid differentiation, tumor necrosis | not |
| Lee [41] | pTanyNanyM0 | CSS | 1.67 | 0.91 | 3.05 | T stage, grade, MVI, tumor size, sarcomatoid differentiation, tumor necrosis | not |
| Goncalves [42] | pT1-2NanyM0 | RFS | 6.78 | 1.80 | 25.53 | MVI, perirenal fat infiltration, nuclear grade, tumor diameter, macrovascular involvement, lymph node metastasis, sarcomatous elements | Significant |
| Goncalves [42] | pT1-2NanyM0 | CSS | 15.72 | 1.57 | 157.68 | MVI, perirenal fat infiltration, nuclear grade, tumor diameter, macrovascular involvement, lymph node metastasis, sarcomatous elements | Significant |
| Lang [43] | pTanyN0M0 | CSS | 2.16 | 1.69 | 2.71 | tumor size, nuclear grade, MVI, age, sex | Significant |
| Lang [43] | pTanyN0M0 | OS | 1.82 | 1.5 | 2.22 | tumor size, nuclear grade, MVI, age, sex | Significant |
| Ishimura [44] | pTanyN0M0 | RFS | 1.965 | 0.632 | 6.116 | age, sex, tumor size, pathological stage, grade, histological type, MVI | not |
| Ishimura [44] | pTanyN0M0 | CSS | 2.432 | 0.528 | 11.201 | age, sex, tumor size, pathological stage, grade, histological type, MVI | not |
| Ishimura [44] | pT1-2N0M0 | RFS | 4.41 | 1.115 | 16.918 | age, sex, tumor size, pathological stage, grade, histological type, MVI | Significant |
| Ishimura [44] | pT1-2N0M0 | CSS | 2.284 | 0.248 | 21.056 | age, sex, tumor size, pathological stage, grade, histological type, MVI | not |
| Griffiths [45] | pTanyN0M0 | DFS | 2.15 | 0.98 | 4.72 | MVI, inferior vena cava invasion, renal vein invasion, grade, age, tumor size, histological type | not |
| VanPoppel [46] | pTanyN0M0 | DFS | 4.19 | 2.11 | 8.30 | age, stage, grade, size, MVI | Significant |

DSS: disease special survival; CSS: cancer special survival; RFS: recurrence free survival; DFS: disease free survival; PFS: progression free survival; MFS: metastasis free survival; OSS: overall survival; MVI: microvascular invasion/microscopic vascular invasion; MAVI: macrovascular invasion; LVI: lymphovascular invasion; ECOG PS: Eastern Cooperative Oncology Group performance status.

**Table S5.** The definition of MVI in the eligible studies

| Study | Year | Research object | Definition |
|---|---|---|---|
| Belsante [14] | 2014 | Lymphovascular invasion | LVI was defined as the presence of the invasion of cancer cells into blood vessels or the lymphatic system (excluding the renal vein and its muscle containing segmental branches and the inferior vena cava). |
| Eisenberg [15] | 2013 | Microvascular invasion/Capillary-Lymphatic Invasion | MVI was defined as the presence of tumor within microscopic veins or venules with a muscular coat, regardless of gross tumor in the renal vein. The term CLI was specifically used to define the presence of tumor within a microscopic capillary or lymphatic channel, vessels lacking a muscular coat. |
| Shindo [16] | 2013 | Microvascular invasion | NA |
| Drewniak [17] | 2013 | Microvascular invasion | NA |
| Steffens [18] | 2013 | Microscopic vascular invasion | NA |
| Betsunoh [19] | 2013 | Microscopic vascular invasion | NA |
| Harada [20] | 2012 | Microvascular invasion | NA |
| Pichler [21] | 2012 | Microscopic vascular invasion/Macroscopic vascular invasion | MVI was defined as microscopic detection of neoplastic cells invading the vessel wall or neoplastic emboli in the vessel lumen. |
| Kroeger [22] | 2012 | Microvascular invasion | MVI was defined as invasion of neoplastic cells in microscopic vessels or tumor emboli in the intratumor microscopic vessels. |
| da Costa [23] | 2012 | Microvascular invasion | NA |
| Takayama [24] | 2011 | Microvascular invasion | NA |
| Komura [25] | 2011 | Microvascular invasion | MVI was defined as tumor cells in an endothelium-lined space by routine light microscopy in whole-mounted RCC specimens. |
| Suzuki [26] | 2011 | Microvascular invasion | NA |
| Katz [27] | 2011 | Lymphovascular invasion | LVI was considered present if any tumor cells were seen with in the luminal space lined by endothelial cells by visual inspection on H and E stained slides from each tumor. |
| Kume [28] | 2010 | Microvascular invasion | NA |
| Kim [29] | 2010 | Microvascular invasion | NA |
| Rey [30] | 2010 | Microscopic vascular invasion | MVI was defined as the presence of tumor cells in the vascular lumen of the analyzed specimens, which also includes lymphatic vessel invasion. |
| May [31] | 2009 | Microvascular invasion | MVI was defined as the unequivocal presence of tumor cells in an endothelium lined space without underlying muscular walls. |
| Cho [32] | 2009 | Microvascular invasion | NA |
| Zubac [33] | 2008 | Microvascular invasion | MVI was diagnosed only when tumour cell aggregates were seen within lumina covered with CD31-positive cells or when tumour cells penetrated a vessel wall. A group of tumour cells invaginated a vessel wall without real invasion. Both sinusoidal and muscular vessels within and close to the tumour were assessed. |
| Pflanz [34] | 2008 | Microvascular invasion | NA |
| Horiguchi [35] | 2007 | Microvascular invasion | MVI was considered to have occurred when routine pathological examination revealed neoplastic cells in at least 1 endothelium lined space. |
| Dall'Oglio [36] | 2007 | Microvascular invasion | The presence of MVI was evaluated and defined as positive when there were neoplastic cells in an endothelium-lined space and/or in the intratumoral microcirculation of the tunica media. |
| Klatte [37] | 2007 | Microvascular invasion | NA |
| Madbouly [38] | 2007 | Microvascular tumor invasion | MVI was defined as the microscopic detection of neoplastic cells invading the vessel wall or neoplastic emboli in the vessel lumen. |
| Komai [39] | 2007 | Microvascular invasion | NA |
| Ito [40] | 2006 | Microvascular invasion | NA |
| Lee [41] | 2006 | Microvascular invasion | NA |
| Goncalves [42] | 2004 | Microvascular tumor invasion | MVI was indicated by neoplastic cells invading the vessel walls or by neoplastic emboli in the vessel lumen. |
| Lang [43] | 2004 | Microscopic venous invasion | NA |
| Ishimura [44] | 2004 | Microscopic venous invasion | MVI was defined by the presence of a cancer cell in blood vessels based on the examination of hematoxylin-eosin stained specimens. |
| Griffiths [45] | 2002 | Inferior vena cava invasion/Renal vein invasion/Microscopic vascular invasion | Vascular invasion was classified into three categories, i.e. (i) inferior vena cava invasion(IVCI), (ii) invasion into the major hilar vessels, designated RVI and (iii) vascular invasion seen microscopically but not in the IVC or major hilar vessels, designated MVI. |
| VanPoppel [46] | 1997 | Microvascular invasion | MVI was considered present when tumor was seen in a vessel that is at least 1 or more endothelial cells or the tunica media of the vessel were recognized to surround a neoplastic cell group. |