



Prognostic significance of venous tumor thrombus consistency (solid vs. friable) in patients with renal cell carcinoma: A systematic review and meta-analysis

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Background: To assess the prognostic value of venous tumor thrombus consistency (VTTC) in patients with renal cell carcinoma (RCC), and the association of RCC clinicopathological variables between friable venous tumor thrombus (VTT) and solid VTT.

Methods: Relevant studies were systematically searched from the databases PubMed, EMBASE, Web of Science and the Cochrane Library up to December 1st, 2017. Data was centrally extracted and analyzed from the previous studies by two independent reviewers. The pooled hazard ratio (HR) and its 95% confidence intervals (CI) were calculated to assess the prognostic impact of VTTC on RCC patients. Besides, the associations between VTTC and clinical parameters of RCC were calculated using the pooled odds ratio (OR) with 95% CI.

Results: Overall, friable VTT is an important adverse predictor of OS in patients with RCC using the Fixed-effort model (pooled HR =1.60; 95% CI, 1.13–2.26). Nevertheless, the results showed that friable VTT was not a significant predictor of CSS in patients with RCC (pooled HR =1.32; 95% CI, 0.88–1.99). Besides, this meta-analysis also investigated the association of RCC clinicopathological variables between friable VTT and solid VTT. Of the selected variables, nodal status, perinephric fat invasion, tumor necrosis, Fuhrman grade, pathologic grade and histological subtype were associated with VTTC.

Conclusions: This meta-analysis indicated a friable VTT might significantly affect the prognosis of the RCC patients with VTTC.

Keywords: Venous tumor thrombus consistency; renal cell carcinoma (RCC); prognosis; meta-analysis

Received: 01 March 2018; Accepted: 16 May 2018; Published: 14 June 2018.

doi: 10.21037/amj.2018.05.01

View this article at: <http://dx.doi.org/10.21037/amj.2018.05.01>

Introduction

Renal cell carcinoma (RCC) represents 2–3% of all cancers, with an estimated 63,990 new cases and 14,400 deaths in 2017 in the United States (1). In the newly diagnosed cases, the number of patients with RCC forming a venous tumor thrombus (VTT) and invading the inferior vena cava (IVC) occupied 4–10% (2). RCC tumor thrombus could extend to the renal vein (RV), the IVC, or even the heart, and an RCC tumor thrombus in the IVC was a significant adverse predictive of survival in patients with RCC (3).

Radical nephrectomy with thrombectomy might have revealed an improved prognosis and a better effect of subsequent targeted therapy than other treatments and become a preferred treatment option (4,5). Several different surgery techniques of thrombectomy were applied to the patients, according to different thrombus levels, including open surgery, pure laparoscopy, robotic-assisted laparoscopy (6). However, each kind of surgery can be most appropriate or efficacious only in a subset of patients (7). Therefore, a more precise prognostic prediction might be useful for surgical selection.

Recently, venous tumor thrombus consistency (VTTC) was defined as solid or friable from the morphologic aspect of the tumor thrombus (8). Typically, Bertini *et al.* suggested that the existence of a friable thrombus was an independent prognostic factor of cancer-specific survival (CSS) in the patients with RCC (8). To date, previous studies have investigated the effect of VTTC on the survival of RCC (7,8). However, controversies exist about the effect to the prognosis of RCC. In addition, several prognostic clinicopathological features including TNM classification, Fuhrman grading system, RCC subtypes, microvascular invasion, tumor necrosis and invasion of the collecting system have been considered as an independent predictive factor of RCC (3). Nevertheless, the definite prognostic significance of VTTC in patients with patients with RCC is still unclear (9-12).

Until now, there were five articles discussing about the effect of VTTC on the prognosis of patients with RCC, but the available results remained contradictory (7,8,13-15). Hence, we conducted a meta-analysis including all eligible case-control studies for the first time to investigate whether VTTC was an independent prediction of the patients with RCC.

Methods

Search strategy

This meta-analysis was conducted according to the guideline

of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16). No ethical approval was required due to the fact that all included articles have been published. We searched PubMed, EMBASE, Web of Science and the Cochrane Library electronic databases comprehensively to evaluate the prognostic role of VTTC in patients with RCC, up to December 1st, 2017. The key search words included “tumor thrombus consistency” or “neoplasms thrombosis consistency” “prognosis” or “survival”, and “renal cancer” or “renal cell carcinoma” or “kidney cancer”. In addition to electronic search original papers, references of relevant articles were manually retrieved for potential eligible trials. Moreover, no language limitation existed in this search process.

Selection criteria

Studies were included in this meta-analysis only if they met the following inclusion criteria: (I) RCC patients with VTT confirmed by histopathological examination and underwent nephrectomy with thrombectomy; (II) studies analyzing the prognostic role of VTTC in patients with RCC; (III) outcomes of studies included overall survival (OS) or cancer-specific survival (CSS); (IV) sufficient data from the included studies could be extracted. Accordingly, the exclusive criteria were as follows: (I) case reports or editorials or review articles; (II) studies not related to RCC or VTTC; (III) unavailable information or complete data; (IV) duplicates of previous publication.

Data extraction

Two independent investigators assessed the titles and abstracts of all included articles and guaranteed the eligible studies for next analysis. Data from the included studies were independently extracted with a unified items form. Additionally, any disagreement or uncertainty was brought to a group discussion until it came to a consensus. The following information were recorded: first author's name, publication year, country, sample size, the number of cases with solid VTT and friable VTT respectively, median of patient age, follow-up and survival data including OS or CSS.

Quality assessment

Newcastle Ottawa Scale (NOS) was used to evaluate the quality of the studies, including case-control and cohort

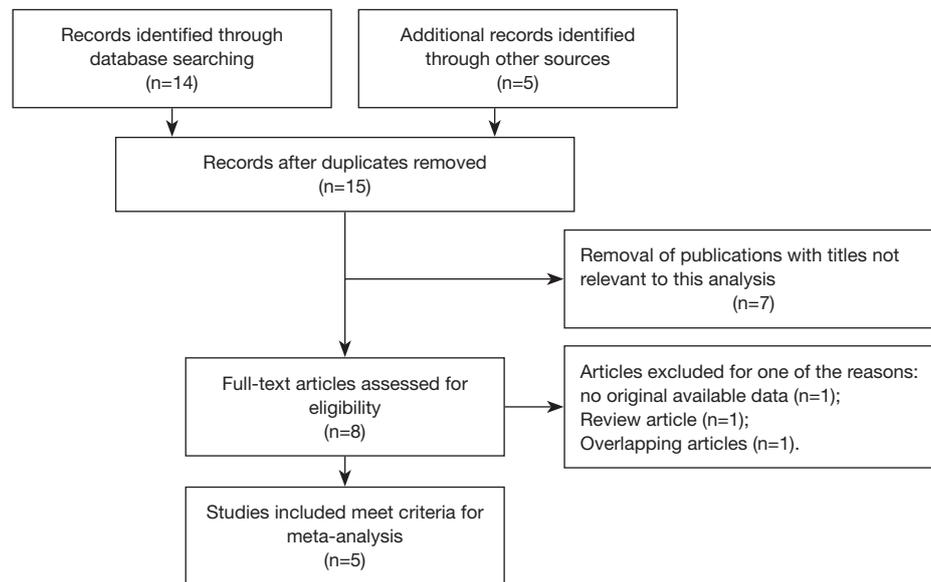


Figure 1 Flow diagram of literature search and selection process.

studies (17). A study could be awarded a maximum of one star for each point within the selection and exposure categories, and a maximum of two stars can be given for comparability. We considered studies with scores of more than 7 as high-quality studies and only high-quality studies were included in our meta-analysis.

Statistical analysis

The pooled hazard ratio (HR) and its 95% confidence intervals (CIs) were calculated to assess the prognostic impact of VTTC on RCC patients. Besides, the associations between VTTC and clinical parameters of RCC were calculated using the pooled odds ratio (OR) with 95% CIs. Cochrane Q test and Higgins I^2 statistic were used to evaluate the statistical heterogeneity among included studies. If the heterogeneity was acceptable ($I^2 > 50\%$ suggested obvious heterogeneity), the fixed-effect model (Mantel-Haenszel method) would be adopted. Otherwise, the random-effect model (DerSimonian-Laird method) would be applied. To test the reliability and stability of all the pooled outcomes, sensitivity analysis was performed by sequential omission of individual studies. In addition, publication bias was assessed using Begg's funnel plots and Egger's linear regression test. Stata software (version 12.0; StataCorp LP, College Station, TX) was utilized to dispose all above statistical analyses and a P value < 0.05 was considered statistically significant.

Results

Studies characteristics

Based on the retrieve strategy above, a total of 19 relevant articles were retrieved from the aforementioned databases and other sources. Four duplicated articles were excluded using literature manager software. Then, 7 unrelated articles were excluded after screening titles and abstracts of the remaining articles carefully. Among the remaining 8 articles for full text evaluation, 1 article lacked original available data, 1 article belonged to review articles and 1 article had overlapping data. Finally, 5 articles met the inclusive criteria and were ultimately adopted in the present meta-analysis (Figure 1) (7,8,13-15). The baseline characteristics of these included studies were shown in Table 1. The 5 articles contained 1,018 cases of RCC patients with VTT, which were all diagnosed by histopathological methods. These patients were from three countries (Poland, Germany and Italy) with the follow-up more than 9 months. The relevant prognostic parameters of these included articles contained OS or CSS. Moreover, NOS scores assessing the study quality ranged from 7 to 9, which were considered adequate for the following meta-analysis.

Quantitative synthesis results

Prognostic role of VTTC in patients with RCC

Frangible VTT was an important adverse predictor of OS in

Table 1 Characteristics of individual studies included in the meta-analysis

Author	Year	Country	No of cases	No of cases with friable VTTC	No of cases with solid VTTC	Median (mean)age	Follow-up(months)	Outcome	NOS score
Golabek <i>et al.</i> (14)	2016	Poland	84	46	38	64.5 (26.0–84.0)	9 [1–66]	OS	7
Mager <i>et al.</i> (15)	2016	Germany	413	188	225	61.5 (20.0–84.0)	50 [0–328]	CSS	8
Antonelli <i>et al.</i> (7)	2015	Italy	147	68	79	66.0 (35.5–85.0)	40.5 [1–215]	OS, CSS	8
Weiss <i>et al.</i> (13)	2013	Germany	200	20	130	65.8 (37.0–86.0)	49	OS	7
Bertini <i>et al.</i> (8)	2011	Italy	174	67	107	62.5 (26.0–83.0)	24 [2–220]	CSS	9

VTTC, venous tumor thrombus consistency; OS, overall survival; CSS, cancer-specific survival; NOS, Newcastle-Ottawa Scale.

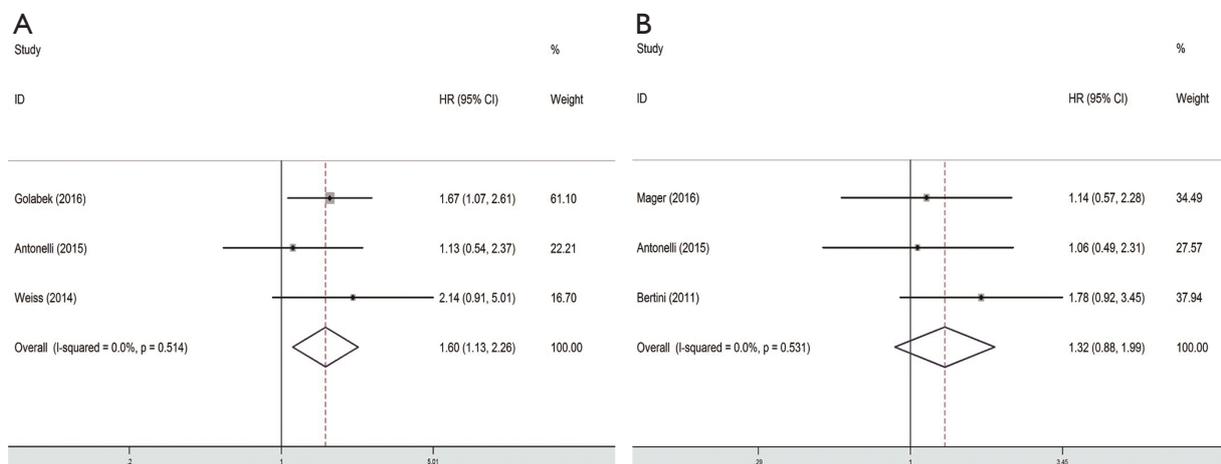


Figure 2 Forest plots for merged analyses of overall survival (OS) and cancer-special survival (CSS) in renal cell carcinoma (RCC) patients with venous tumor thrombus consistency (VTTC). (A) Forest plots of overall analyses of OS; (B) Forest plots of overall analyses of CSS.

patients with RCC (pooled HR =1.60; 95% CI, 1.13–2.26) (*Figure 2A*). There was no prominent heterogeneity ($P=0.514$) in eligible studies, and the pooled HR for OS was performed using the fixed-effect model. Nevertheless, the results showed that friable VTT was not a significant predictor of CSS in patients with RCC (pooled HR =1.32; 95% CI, 0.88–1.99) (*Figure 2B*).

Association of RCC clinicopathological variables between friable VTT and solid VTT

To further investigate the association of RCC clinicopathological variables between friable VTT and solid VTT, we selected some confirmed clinicopathological parameters as independent predictive factors of RCC, such as distant metastases, nodal status, perinephric fat invasion, Fuhrman grade, pathologic stage, histological subtype and so on. The results about the associations on clinicopathologic features between Friable VTTC and Solid

VTTC with RCC were shown in *Table 2*. Of the selected variables, nodal status (pN+ *vs.* pN0/cN0) (OR =1.48; 95% CI, 1.10–2.01; $P=0.214$), perinephric fat invasion (yes *vs.* no) (OR =1.49; 95% CI, 1.14–1.97; $P=0.301$), tumor necrosis (yes *vs.* no; OR =2.75; 95% CI, 1.88–4.01; $P=0.135$), Fuhrman grade (≥ 3 *vs.* <3 ; OR =1.58; 95% CI, 1.12–2.21; $P=0.153$), pathologic grade (>3 *vs.* ≤ 3 ; OR =3.19; 95% CI, 1.92–5.29; $P=0.393$) and histological subtype (clear cell RCC *vs.* others; OR =2.71; 95% CI, 1.01–7.26; $P=0.015$) were associated with VTTC. However, outcomes showed that there were no significant differences between friable VTT and solid VTT in clinicopathological variables of RCC, including distant metastases, sarcomatoid differentiation, venous wall invasion and pathologic stage.

Sensitivity analysis

Sensitivity analysis was utilized to detect the influence

Table 2 Meta-analysis of the association on clinicopathologic features between friable VTTC and solid VTTC with renal cell cancer

Variables	No. of studies	No. of cases with Friable VTTC	No of cases with solid VTTC	Effectsmodel	OR (95% CI)*	P [§]	I-squared (%)
Distant metastases (yes vs. no)	5	389	579	Random	1.25 (0.95–1.65)	0.010	69.6
Nodal status (pN+ vs. pN0/cNo)	5	389	579	Fixed	1.48 (1.10–2.01)	0.214	31.1
Perinephric fat invasion (yes vs. no)	5	389	579	Fixed	1.49 (1.14–1.97)	0.301	17.9
Sarcomatoid differentiation (yes vs. no)	4	201	354	Fixed	0.91 (0.50–1.67)	0.795	0.0
Tumour necrosis (yes vs. no)	4	201	354	Fixed	2.75 (1.88–4.01)	0.135	46.0
Venous wall invasion (yes vs. no)	2	234	263	Fixed	1.23 (0.84–1.80)	0.444	0.0
Fuhrman grade (≥3 vs. < 3)	3	254	393	Fixed	1.58 (1.12–2.21)	0.153	46.7
Pathologic stage (>T3 vs. ≤T3)	4	321	500	Fixed	1.61 (0.97–2.68)	0.164	41.3
Pathologic grade (>3 vs. ≤3)	2	135	186	Fixed	3.19 (1.92–5.29)	0.393	0.0
Histological subtype (clear cell RCC vs. others)	4	322	472	Random	2.71 (1.01–7.26)	0.015	71.4

*, random-effects model was used when P value for heterogeneity test <0.1; otherwise, fixed-effects model was used. [§], P value of Q test for heterogeneity. VTTC, venous tumor thrombus consistency; OR, odds ratio; CI, confidence interval; RCC, renal cell carcinoma.

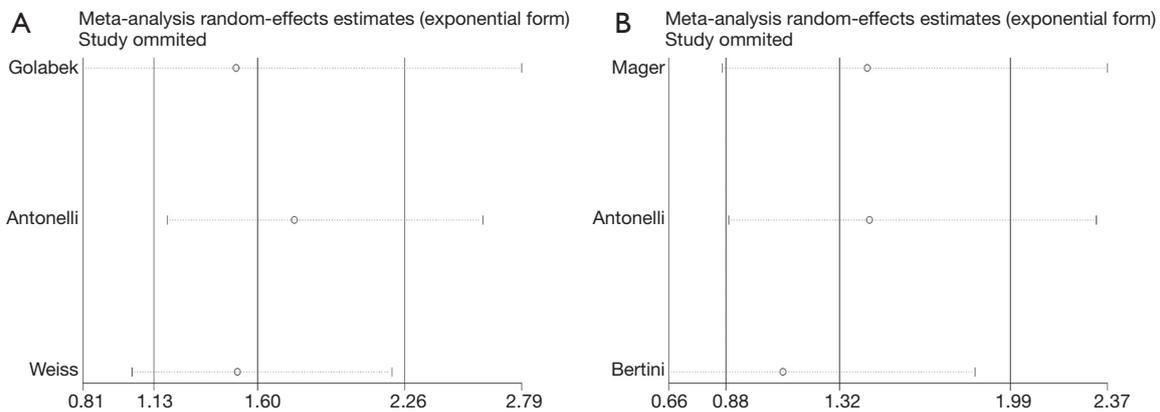


Figure 3 Sensitivity analysis. (A) Pooled HR for OS under Fixed-effort model; (B) Pooled HR for CSS under Fixed-effort model. HR, hazards ratio; OS, overall survival; CSS, cancer-specific survival.

of each study on the pooled HR by repeating the meta-analysis, while omitting one single study each time. The sensitivity analysis for friable VTT and solid VTT in the patients with RCC was shown in *Figure 3*, demonstrating that no individual study significantly affected the pooled HR. Thus, sensitivity analysis showed that our results were reliable.

Publication bias

The Begg’s funnel plot was applied to assess the publication bias of the literature, and the shapes of them seemed no

evidence of obviously asymmetrical, indicating no significant publication bias, which was also confirmed according to funnel plot (OS: Begg’s test, P=0.602; Egger’s test, P=0.604. CSS: Begg’s test, P=0.117; Egger’s test, P=0.383; *Figure 4*). Therefore, the overall outcomes indicated that our results were statistically robust.

Discussion

Advanced RCC with VTT is considered as a grave disease with an unfavorable prognosis and the treatment of this disease remains challenging and controversial (3). Several

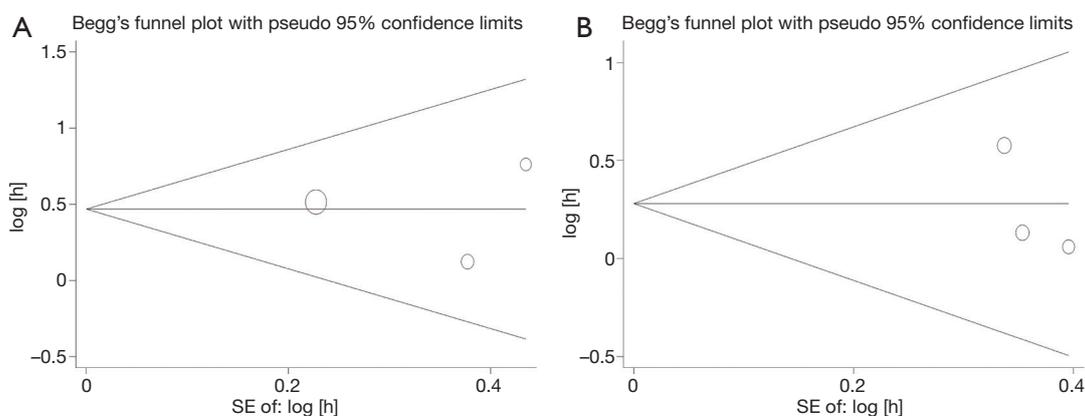


Figure 4 Begg's funnel plot of publication bias test about the prognostic value of VTTC in patients with RCC. (A) Pooled HR for OS under fixed-effort model; (B) pooled HR for CSS under Fixed-effort model. VTTC, venous tumor thrombus consistency; RCC, renal cell carcinoma; HR, hazards ratio; OS, overall survival; CSS, cancer-specific survival.

series articles reported a 5-year survival rate ranging from 25% to 57% (11,18,19). Complete surgical resection was still regarded as the most effective and standard therapeutic approach in general because of the barely satisfactory effect of targeted therapy on the treatment of RCC (4,5,20-22). In addition, the classification method for VTT was not abundant and only Mayo classification was accepted widely (15). Recently, Bertini *et al.* tried to standardise the pathologic definition of VTTC as a solid thrombus or a friable thrombus and reported the presence of a friable thrombus significantly affected patient prognosis (8). Since then, the prognostic significance of VTTC (solid *vs.* friable) in patients with RCC has attracted extensive attention and several studies have been conducted to explore it (8,13,14). However, the results were still unclear and even controversial. Therefore, we conducted a comprehensive meta-analysis to clarify the prognostic value of VTTC in patients with RCC for the first time. Meanwhile, we also further investigated the association between RCC clinicopathological variables and VTTC.

Meta-analysis, as a powerful tool, could provide more reliable results than a single study especially in explaining controversial conclusions. As a consequence, we took advantage of meta-analysis to clarify the accurate results about the prognostic value of VTTC in RCC. This meta-analysis demonstrated friable VTT was an adverse predictor of OS in patients with RCC, which was consistent with the result reported by Weiss *et al.* (13) However, in subsequent analysis, our results indicated that friable VTT was not a significant predictor of CSS in patients with RCC, which were inconsistent with the study conducted by Bertini

et al. (8) The possible reasons about such different results were as follows. On the one hand, marked differences in the number of patients with friable VTT versus solid VTT were observed among the studies. The various proportions of VTTC might interfere with the potential correct results. On the other hand, inhomogeneous distribution of clinicopathologic features might have an effect on the patients' survival, such as nodal status, perinephric fat invasion, tumor necrosis, Fuhrman grade, histological subtype and so on (3). Up to now, the impact of VTTC on the prognosis of RCC patients was still uncertain. Therefore, more high-quality and multicentric studies with larger sample sizes were needed to investigate the association between VTTC and the survival of RCC patients.

In this meta-analysis, we used both OS and CSS as the endpoint of our study. As the cause of death could not have been determined reliably in all patients, CSS would have been likely affected and thus OS was a more robust measure than CSS. Hence, it should be noted that OS was the gold standard for cancer clinical research and was considered as the most preferred and reliable cancer endpoint according to the US Food and Drug Administration, which should be used in preference to CSS (23). Thus, the findings of our current meta-analysis suggested that the presence of a friable VTT might significantly affect the prognosis of the patients with RCC.

With regard to the clinicopathological features, we found that nodal status, perinephric fat invasion, tumor necrosis, Fuhrman grade, pathologic grade and histological subtype were associated with VTTC in the patients with RCC (3,24).

Our results showed that patients with friable VTT were correlated with nodal status (pN+), perinephric fat invasion and tumor necrosis rather than distant metastases. One possible reason for these discrepancies was that the studies included in the meta-analysis about distant metastases existed significant heterogeneity ($P=0.010$, $I^2=69.6\%$), which might have a pronounced effect on the results. Interestingly, as for histological subtype, we found that a friable VTT was most commonly associated with a clear cell histological subtype. However, Weiss *et al.* suggested that papillary RCC was more frequent in patients with friable VTT than these with solid VTT (13). Furthermore, we showed that friable VTT was significantly associated with a higher pathologic grade. With regard to Fuhrman grade, patients with friable VTT were correlated with Fuhrman grade III or IV. Similarly, Martínez-Salamanca *et al.* reported that Fuhrman grade is an independent predictor of CSS in both univariate and multivariate analysis and Fuhrman grade III or IV were the strongest predictors of worse survival (25). The latest version of the TNM classification was published in 2010 and has been proved to be the most reliable prognostic factor in both single- and multi-institutional studies (3,26). Since lacking data about tumor classification, we could not study it in depth. Thus, further studies needed to clarify this point. In this study, our analysis indicated that the clinicopathological variables of RCC were closely associated with VTTC (solid *vs.* friable).

To a certain extent, several limitations in our meta-analysis should be taken into consideration when interpreting the data. Firstly, most of the included articles were retrospective studies, and the relatively small sample size and short-term follow-up also rendered the power of our conclusion less reliable, which might be subject to the bias and limitations inherent to this type of study. Thus, the data used in the analyses should be also obtained from a prospectively maintained database, which reduced the risk of errors and/or omissions. Secondly, only 5 studies were adopted in this meta-analysis, which might inevitably increase the risk of random error. Therefore, more high-quality and multicentric studies were required to explore the prognostic role of VTTC in patients with RCC. Thirdly, most of studies included could have been influenced by involvement of multiple surgeons and different therapies after disease recurrence, which might contribute to biases of this meta-analysis. In addition, the additional targeted therapy of patients with RCC during the study period might also lead to a bias when analysing survival data.

Conclusions

The results of the present meta-analysis indicated that the presence of a friable VTT could be an adverse prognostic factor of patients with RCC. Taking into account the limited the number of articles, more high-quality and multicentric studies with larger sample sizes were needed to investigate the association between VTTC and the prognosis of RCC patients.

Acknowledgements

Funding: None.

Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2018.05.01>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. No ethical approval was required due to the fact that all included articles have been published.

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doi: 10.21037/amj.2018.05.01

Cite this article as: Qin Z, Li R, Qin Y, Han P, Tang J, Zhang L, Wang F, Qi X, Zhang W. Prognostic significance of venous tumor thrombus consistency (solid vs. friable) in patients with renal cell carcinoma: A systematic review and meta-analysis. AME Med J 2018;3:67.