Hypertension as a prognostic factor in metastatic renal cell carcinoma treated with tyrosine kinase inhibitors: a systematic review and meta-analysis

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Abstract

Background: Conflicting evidence exists regarding the effect of hypertension on the prognosis of metastatic renal cell carcinoma (mRCC) patients treated with tyrosine kinase inhibitors (TKIs). This study aimed to assess the predictive value of TKIs-induced hypertension in patients with mRCC.

Methods: This study was registered in PROSPERO (CRD42019129593). PubMed, Embase, Web of Science and the Cochrane Library database were searched with terms: “renal cell carcinoma”, “hypertension”, “blood pressure”, “tyrosine kinase inhibitor”, “sunitinib”, “axitinib”, “sorafenib” and “pazopanib” until March 21, 2019. Hazard Ratios (HR) and 95% confidence intervals (CI) for progression-free survival (PFS) or overall survival (OS) were extracted and analyzed with Stata 15.0 software. Heterogeneity was assessed using the I^2 value. Meta-regression, subgroup analysis and sensitivity analysis were also performed to explore heterogeneity. Publication bias was assessed with funnel plots and precisely assessed by Egger’s and Begg’s tests. The quality of evidence of outcomes was generated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results: A total of 4661 patients from 22 studies were included in the study. The results showed that the increase of blood pressure was an effective predictor for longer PFS (HR = 0.59, 95% CI: 0.48–0.71, p < 0.001; I^2 = 77.3%) and OS (HR = 0.57, 95% CI: 0.45–0.70, p < 0.001; I^2 = 77.4%) of patients with mRCC. Subgroup analysis revealed that patients receiving sunitinib and pazopanib could have longer PFS and OS.

Conclusions: This study indicated that TKIs-induced hypertension may be a good predictor for better prognosis of patients with mRCC receiving TKIs treatment, especially using sunitinib or pazopanib.

Keywords: Metastatic renal cell carcinoma, Tyrosine kinase inhibitors, Hypertension, Prognosis, Meta-analysis

Background

Renal cell carcinoma (RCC) is the 9th most common cancer in men and 14th most common cancer in women worldwide [1]. Its incidence (3–6/100,000) and mortality (1.2–2.5/100,000) are increasing rapidly, which has a great negative effect on our society [2, 3]. In addition, about 25–30% of patients have evidence of metastasis upon its diagnosis [4]. Now, vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs), like sunitinib, pazopanib, sorafenib or axitinib, are the favored medicine for metastatic RCC (mRCC). Several clinical trials showed that response to TKIs was uncertain (objective response rate was 31–67.4%) [5–8], which indicated the existence of wide inter-individual variation and the lack of reliable factors for predicting the outcomes of mRCC patients. Therefore, a big challenge faced by urologists is how to predict the prognosis of mRCC patients receiving TKIs more precisely.

The occurrence of several adverse events (AEs) during TKIs therapy, such as hypertension, hand-foot syndrome or hypothyroidism, were shown to be correlated with the

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However, others reported insignificant results [14, 15]. In tension may be associated with improved prognosis [12, 13]. with shorter PFS [11]. It indicated that TKIs-induced hyper-tension (a treatment-associated adverse event) than those with shorter PFS [11]. It indicated that TKIs-induced hypertension may be associated with improved prognosis [12, 13]. However, others reported insignificant results [14, 15]. In 2014, a systematic review and meta-analysis reported that the occurrence of hypertension due to sorafenib therapy may be associated with improved prognosis of patients with cancer. However, this study did not specifically focus on the mRCC patients. Thus, the association between TKIs-induced hypertension and prognosis of mRCC is still controversial. In the present study, we attempt to conduct a systematic review and meta-analysis to assess the predictive value of the TKIs-induced hypertension for PFS and OS in patients with mRCC during TKIs therapy.

Methods
Data sources and literature search strategy
We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. This study was registered in PROSPERO (CRD42019129593). A literature search was performed in the following databases: PubMed, Embase, Web of Science and the Cochrane Library database. The latest search was performed on March 21, 2019. The search keywords were (renal cell carcinoma) AND [(tyrosine kinase inhibitor) OR sunitinib OR axitinib OR sorafenib OR pazopanib] AND [hypertension OR (blood pressure). The resulted literatures were further scanned by Endnote X7 (Thomson Corporation, Canada) to exclude duplications followed by title and abstract screening. In addition, we manually searched the references of the literatures for additional eligible studies.

Inclusion and exclusion criteria
Studies were included in our meta-analysis if the following criteria were met: 1) mRCC patients were treated with TKIs; 2) studies compared Hazard Ratios (HR) between patients with or without TKIs-induced hypertension for PFS or OS.

Studies were excluded based on the following criteria: 1) reviews, meta-analysis, letters, comments, case reports or conference abstracts; 2) duplicated studies and repeated analysis; 3) studies lacking sufficient data for HR and their 95% confidence intervals (CI); 4) studies included mRCC patients received different therapeutic regimen, such as TKIs or radiotherapy.

Data synthesis and statistical analysis
Data were extracted and analyzed with Stata 15.0 software (Stata Corporation, College Station, TX, USA). P value<0.05 was considered statistically significant. A merged HR greater than 1 indicated a poorer prognosis for mRCC patients. Heterogeneity was assessed using the $I^2$. We considered $I^2 > 50\%$ as an indicator of substantial heterogeneity. A random effects model and a fixed effects model were applied for $I^2 > 50\%$ and $I^2 < 50\%$, respectively. Then, to determine which factors may contribute to heterogeneity, univariate and multivariate meta-regression analysis were performed. The possible factors were year, sample size, gender, mean age, country, ECOG PS, MSKCC score, histology, prior nephrectomy, Number of disease sites, type of analysis (univariate, multivariate), study design (retrospective, prospective), type of TKIs. Then, subgroup analysis was performed to investigate whether different sample size could explain the heterogeneity and whether relationship between hypertension and PFS or OS still exist in different TKIs subgroups. Factor with $P$ value $< 0.05$ meant that it may be the source of heterogeneity. We did sensitivity analysis to find if some original studies may mainly contribute to the heterogeneity. Publication bias was assessed with funnel plots and precisely assessed by Egger’s and Beggs’s tests.

Quality of evidence
The quality of evidence of the predictive effect of TKIs-induced hypertension for the outcomes in mRCC patients
| Study | Year | Country | Study design | Sample size | Male/ Female ratio | Mean age | Histology (clear cell%) | Survival analysis | Definition of hypertension | Type of analysis | TKIs | Quality Assessment |
|-------|------|---------|--------------|-------------|-------------------|---------|------------------------|----------------|----------------------------|----------------|------|------------------|
| Rini (a) [10] | 2011 | the USA | R | 534 | 2.3 | 60.6 | 98% | PFS, OS | SBP ≥ 140 mmHg, DBP ≥ 90 mmHg | multivariate | SUN 7 |
| Szmit [12] | 2011 | Poland | R | 111 | 3.0 | 55.9 | 100% | PFS, OS | BP ≥ 140/90 mmHg | univariate | SUN 9 |
| Bono [17] | 2011 | Finland | R | 64 | 1.7 | 64 | 92% | PFS | BP > 150/100 mmHg OR blood pressure requiring intensification of pre-existing anti-hypertensive medication. | multivariate | SUN 7 |
| Fujita [18] | 2012 | Japan | R | 41 | 2.7 | 64 | 100% | PFS | – | univariate | SUN 7 |
| Eechoute [19] | 2012 | Netherlands | R | 158 | 1.7 | 60 | 87% | PFS, OS | SBP > 140 mmHg, DBP > 90 mmHg, MAP > 110 mmHg | multivariate | SUN 7 |
| Rini (b) [13] | 2013 | the USA | R | 168 | 2.5 | 60 | – | PFS, OS | DBP ≥ 90 mmHg | multivariate | AXI 7 |
| Motzer (a) [20] | 2013 | the USA | P | 350 | 2.8 | 61 | 100% | PFS, OS | SBP > 140 mmHg, DBP > 90 mmHg | multivariate | AXI 6 |
| Motzer (b) [20] | 2013 | the USA | P | 336 | 2.5 | 61 | 100% | PFS, OS | SBP > 140 mmHg, DBP > 90 mmHg | multivariate | SOR 6 |
| Hong [21] | 2013 | China | R | 136 | 2.0 | 56 | 93% | OS | Hypertension class III/IV | multivariate | SUN 7 |
| Nakano [22] | 2013 | Japan | R | 36 | 3.5 | 65.8 | 61% | PFS | grade 1–3 (NCI-CTCAE, version 3.0) | multivariate | SUN 7 |
| Fujita [23] | 2014 | Japan | R | 44 | 2.7 | 63.5 | 95% | PFS | – | multivariate | SUN 7 |
| Eto [24] | 2014 | Japan | R | 64 | 2.2 | 63 | 97% | OS | DBP ≥ 90 mmHg | – | AXI 7 |
| Rini (c) [25] | 2015 | the USA | P | 203 | 2.0 | 61.9 | – | PFS | DBP change from baseline ≥10/15 mmHg | – | AXI 7 |
| Zhang (a) [26] | 2015 | China | R | 256 | 2.5 | 58 | 79% | OS | – | multivariate | SOR 7 |
| Kucharz [27] | 2015 | Poland | R | 28 | 2.1 | 65 | – | PFS | office SBP ≥140 and/or DBP ≥90 mmHg; home SBP ≥135 and/or DBP ≥85 mmHg; pre-existing medication-controlled arterial hypertension and required additional antihypertensive medication during treatment | multivariate | SUN 7 |
| Izzedine [28] | 2015 | France | R | 212 | 3.4 | 57.7 | 86% | PFS, OS | – | multivariate | SUN 8 |
| Donskov [29] | 2015 | the USA | R | 770 | 2.6 | 60 | 98% | PFS | SBP ≥ 140 mmHg | multivariate | SUN 7 |
| Zhang (b) [30] | 2016 | China | R | 134 | 2.4 | 59.8 | 77% | OS | – | multivariate | SOR 7 |
| Goldstein (a) [14] | 2016 | Australia | R | 479 | 2.2 | 59.5 | – | PFS, OS | SBP > 140 mm H, DBP > 90 mm H, pre-existing medication-controlled arterial hypertension | univariate | PAZ 9 |
| Goldstein (b) [14] | 2016 | Australia | R | 506 | 2.6187 | 61 | – | PFS, OS | SBP > 140 mm H, DBP > 90 mm H, MAP change from baseline>10 mmHg, SBP change from baseline>10 mmHg | univariate | PAZ 9 |
| Goldstein (c) [14] | 2016 | Australia | R | 475 | 3.3394 | 60.9 | – | PFS, OS | SBP > 140 mm H, DBP > 90 mm H, MAP change from baseline>10 mmHg, SBP change from baseline>10 mmHg | univariate | SUN 9 |
Table 1 Baseline characteristics of eligible studies in the meta-analyses (Continued)

| Study       | Year | Country | Study design | Sample size | Male/ Female ratio | Mean age | Histology (clear cell%) | Survival analysis | Definition of hypertension | Type of analysis | TKIs | Quality Assessment (NOS Score = 9) |
|-------------|------|---------|--------------|-------------|-------------------|----------|------------------------|------------------|---------------------------|-----------------|------|-----------------------------------|
| Cecere [31] | 2016 | Italy   | R            | 38          | 1.375             | 61       | 84.2%                  | OS               | grade ≥ 3 (NCI-CTCAE, version 4.0) | multivariate   | PAZ  | 7                                 |
| Miyake [32] | 2016 | Japan   | R            | 50          | 4.0000            | 64       | 80%                    | PFS              | SBP ≥ 140 or DBP ≥ 90 mmHg       | multivariate   | SUN  | 7                                 |
| Fukuda [15] | 2016 | Japan   | R            | 62          | 2.4444            | 66       | 92%                    | PFS, OS          | –                                  | univariate      | SUN  | 7                                 |
| Matias [33] | 2017 | France  | P            | 106         | 2.3125            | 54       | 90%                    | PFS, OS          | grade ≥ 3 (NCI-CTCAE, version 4.0) | univariate      | AXI   | 7                                 |

R Retrospective, P Prospective, PFS Progression-free survival, OS Overall survival, SBP Systolic blood pressure, DBP Diastolic blood pressure, MAP = 2/3 DBP + 1/3 SBP; SUN Sunitinib, AXI Axitinib, SOR Sorafenib, PAZ Pazopanib, NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events
— The data were not available in this study
was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [16].

Results

Study selection

The searching process is shown in Additional file 1: Figure S1. A total of 982 studies were searched in the database. We excluded 345 duplicated articles. After screening title and abstract, 26 relevant studies were identified. In addition, three relevant studies were obtained from the references and seven articles were excluded due to lack of HR and 95% CI for PFS or OS. Finally, 22 studies were selected for the meta-analysis.

Study characteristics and quality

The baseline characteristics of these studies were demonstrated in Table 1. All the studies were published between 2011 and 2017. Of them, 3 were prospective and 19 were retrospective. The sample size ranged from 28 to 770 patients. The total number of included patients was 4661 and hypertension occurred in 2932 (62.9%). The male/female ratio included in each study ranged from 1.4 to 3.5%, and the median age of the study patients was between 54 years and 66 years. The histology of most RCC is clear cell (61–100%). Most patients had received nephrectomy, cytokine therapy, targeted therapy or radiation therapy. Among the 22 studies providing HR, four reported univariate HR, which did not adjust for the potential confounding factors. The standard of hypertension or BP increasement during TKIs therapy varied between studies, including systolic blood pressure (SBP) ≥140/135 mmHg, diastolic blood pressure (DBP) ≥90/85 mmHg, mean arterial blood pressure (MAP) > 110 mmHg, an increase in BP (SBP, DBP, MAP) > 10/15 mmHg from baseline, or grades of hypertension according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 or 4.0 [34, 35]. The quality of the studies varied from a NOS score of 6 to 9, most of which were high-quality (Table 2).

| Study (a) | Rini | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (b) | Rini | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (c) | Rini | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (d) | Zhang | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (e) | Kucharz | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (f) | Izzedine | ★★ ★ | – | ★★ | ★ | ★ | 8 |
| Study (g) | Donskov | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (h) | Zhang | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (i) | Goldstein | ★★ ★ | – | ★★ | ★ | ★ | 9 |
| Study (j) | Miyake | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (k) | Fukuda | ★★ ★ | – | ★★ | ★ | ★ | 7 |
| Study (l) | Matias | ★★ ★ | – | ★★ | ★ | ★ | 7 |

Table 2 Newcastle-Ottawa scale score of the reviewed studies

| Study (a) | Selection (4 stars) | Comparability (2 stars) | Outcome (3 stars) | Total score |
|-----------|---------------------|-------------------------|-------------------|-------------|
| Rini (a)  | ★★ ★                 | –                       | ★★ ★             | 7           |
| Szmit     | ★★ ★★                | –                       | ★★ ★             | 9           |
| Bono      | ★★ ★★                | –                       | ★★ ★             | 7           |
| Fujita    | ★★ ★★                | –                       | ★★ ★             | 7           |
| Eechoute  | ★★ ★★                | –                       | ★★ ★             | 7           |
| Rini (b)  | ★★ ★★                | –                       | ★★ ★             | 7           |
| Motzer    | ★★ ★★                | –                       | ★★ ★             | 6           |
| Hong      | ★★ ★★                | –                       | ★★ ★             | 7           |
| Nakano    | ★★ ★★                | –                       | ★★ ★             | 7           |
| Fujita    | ★★ ★★                | –                       | ★★ ★             | 7           |
| Eto       | ★★ ★★                | –                       | ★★ ★             | 7           |
| Rini (c)  | ★★ ★★                | –                       | ★★ ★             | 7           |
| Zhang (a) | ★★ ★★                | –                       | ★★ ★             | 7           |
| Kucharz   | ★★ ★★                | –                       | ★★ ★             | 7           |
| Izzedine  | ★★ ★★                | –                       | ★★ ★             | 8           |
| Donskov   | ★★ ★★                | –                       | ★★ ★             | 7           |
| Zhang (b)| ★★ ★★                | –                       | ★★ ★             | 7           |
| Goldstein | ★★ ★★                | –                       | ★★ ★             | 9           |
| Miyake    | ★★ ★★                | –                       | ★★ ★             | 7           |
| Fukuda    | ★★ ★★                | –                       | ★★ ★             | 7           |
| Matias    | ★★ ★★                | –                       | ★★ ★             | 7           |

—: The data were not available in this study
Relationship between TKIs-induced hypertension and PFS or OS of mRCC patients

HR of PFS and OS were quantitatively synthesized and data were shown in Figs. 1 and 2. Elevated blood pressure was positively correlated with better PFS (HR = 0.59, 95% CI: 0.48–0.71, p < 0.001; I² = 77.3%) and OS (HR = 0.57, 95% CI: 0.45–0.70, p < 0.001; I² = 77.4%). It meant that patients developing hypertension may have a lower mortality risk and live longer without progression of mRCC. The heterogeneity was obvious between studies.

Meta-regression analysis

Univariate meta-regression analysis was performed for PFS and results were showed in Table 3. Among the variables above mentioned, only sample size (Adjusted $R^2 = 27.34\%$, $p = 0.019$) might contribute to the inter-study heterogeneity, while others did not ($p = 0.052$–0.942).

Multivariate meta-regression analysis revealed that $p$ value of sample size changed to 0.025. The overall adjusted $R^2$ was 74.84% ($p = 0.239$), which meant that all these factors together could account for 74.84% of heterogeneity.

Subgroup analysis

Subgroup analysis for PFS revealed that sample size could not change the subgroup heterogeneity significantly ($I^2 = 72.1 \text{ and } 75\%$) (Table 3). In addition, for different TKIs, only patients with TKIs-induced hypertension in sunitinib subgroup (HR = 0.47, 95% CI: 0.34–0.64, p < 0.001) and pazopanib subgroup (HR = 0.79, 95% CI: 0.66–0.94, $p = 0.01$) could have longer PFS. However, development of hypertension in four different TKIs subgroups could all predict longer OS, including sunitinib subgroup (HR = 0.48, 95% CI: 0.30–0.78, $p = 0.003$), pazopanib subgroup (HR = 0.73, 95% CI: 0.55–0.97, $p = 0.032$), axitinib subgroup (HR = 0.62, 95% CI: 0.43–0.88, $p = 0.007$) and sorafenib subgroup (HR = 0.66, 95% CI: 0.48–0.91, $p = 0.010$) (Figs. 1 and 2).

Sensitivity analysis

As shown in Fig. 3, study of “Szmit”, “Motzer (a)” and “Donskov” could affect the heterogeneity for PFS. We excluded these studies and found that $I^2$ decreased to 44.6% ($p = 0.03$), with pooled HR = 0.665
(0.579–0.764, \( P = 0.025 \)). Then, we reviewed these studies carefully to find something they had in common. Interestingly, most of the mRCC patients in these three studies had failed one previous cytokine immunotherapy. Maybe it was the reason for high heterogeneity.

Publication bias
We assessed the publication bias with funnel plot and Egger’s and Begg’s tests (Fig. 4). The shape of funnel plots was not symmetric. The Egger’s and Begg’s tests were further performed. The results indicated significant publication bias for studies, with merged PFS (Begg’s test, \( P = 0.015 \); Egger’s test, \( P = 0.028 \)) and merged OS (Begg’s test, \( P = 0.026 \); Egger’s test, \( P = 0.085 \)).

Evaluation of the quality of evidence according to GRADE system
The assessment of the quality of evidence was performed for PFS and OS which were critical in evaluating the outcome of mRCC patients. The quality of evidence of PFS and OS was both “very low” due to retrospective studies, publication bias and high heterogeneity (Table 4).

Discussion
This meta-analysis and systematic review investigated whether TKIs-induced hypertension can predict the prognosis of patients suffering from mRCC. AEs, like hypothyroidism, though shown to be a good predictor of PFS or OS, was usually diagnosed later than hypertension [17, 36]. Thus, it would be better if we can predict the prognosis of mRCC patients based on the TKIs-induced hypertension. It will help urologists decide whether patients should continue this TKIs therapy or not, which may help patients get more suitable treatments as soon as possible. Based on 22 original studies, our results showed that the occurrence of hypertension during treatment may predict better survival for mRCC, with longer PFS and OS. Additionally, when it comes to different TKIs, sunitinib or pazopanib therapy were both associated with longer PFS and OS.

The mechanisms of hypertension induced by TKIs are complicated. First, activation of VEGF receptor-2 via
| Subgroup                          | Meta-regression | Pooled HR of PFS | Heterogeneity |
|----------------------------------|-----------------|------------------|---------------|
|                                  | No. of studies  | Coefficient      | Standard error| T value | P value | Tau² | Adjusted R² | HR (95% CI) | P value | I² | P value |
| Year                             | 20              | 0.060            | 0.228         | 0.26    | 0.795   | 0.182 | -8.86%      | 0.56 (0.40–0.77) | <0.001 | 83.00% | <0.001 |
| 2011–2014                        | 20              | 0.56 (0.40–0.77) | <0.001        | 73.60%  | <0.001 |
| 2015–2017                        | 20              | 0.43 (0.30–0.61) | <0.001        | 72.10%  | <0.001 |
| Sample size                      | 20              | 0.61 (0.48–0.77) | <0.001        | 74.50%  | 0.025  |
| <200                             | 20              | 0.56 (0.40–0.74) | <0.001        | 84.70%  | <0.001 |
| ≥200                             | 20              | 0.73 (0.60–0.89) | 0.002         | 75%     | <0.001 |
| Gender (male/female ratio)       | 20              | -0.117           | 0.228         | -0.51   | 0.614   | 0.177 | -5.64%      | 0.66 (0.53–0.82) | <0.001 | 54.50% | 0.025 |
| <2.5                             | 20              | 0.55 (0.40–0.74) | <0.001        | 84.70%  | <0.001 |
| ≥2.5                             | 20              | 0.73 (0.60–0.89) | 0.002         | 75%     | <0.001 |
| Mean age                         | 20              | 0.44 (0.23–0.86) | 0.015         | 89.40%  | <0.001 |
| <60                              | 20              | 0.66 (0.53–0.78) | <0.001        | 84.70%  | <0.001 |
| ≥60                              | 20              | 0.66 (0.53–0.78) | <0.001        | 84.70%  | <0.001 |
| Country                          | 20              | 0.35 (0.14–0.89) | 0.028         | 87.20%  | <0.001 |
| the USA, Europe                  | 20              | 0.43 (0.21–0.87) | 0.019         | 76%     | 0.002  |
| Asia                             | 20              | 0.35 (0.14–0.89) | 0.028         | 87.20%  | <0.001 |
| ECOG PS (grade 0%)               | 20              | 0.51 (0.31–0.83) | 0.006         | 39.50%  | 0.158  |
| <0.5                             | 20              | 0.60 (0.49–0.74) | <0.001        | 81.40%  | <0.001 |
| ≥0.5                             | 20              | 0.60 (0.49–0.74) | <0.001        | 81.40%  | <0.001 |
| MSKCC score (favorable%)         | 20              | 0.52 (0.33–0.79) | <0.001        | 89.90%  | <0.001 |
| <0.25                            | 20              | 0.43 (0.21–0.87) | 0.019         | 76%     | 0.002  |
| ≥0.25                            | 20              | 0.43 (0.21–0.87) | 0.019         | 76%     | 0.002  |
| Histology (clear cell%)          | 20              | 0.53 (0.39–0.71) | <0.001        | 29.30%  | 0.226  |
| <0.9                             | 20              | 0.53 (0.39–0.71) | <0.001        | 29.30%  | 0.226  |
| ≥0.9                             | 20              | 0.53 (0.39–0.71) | <0.001        | 29.30%  | 0.226  |
| Prior nephrectomy (%)            | 20              | 0.52 (0.40–0.67) | 0.026         | 17.50%  | <0.001 |
| <0.9                             | 20              | 0.52 (0.40–0.67) | 0.026         | 17.50%  | <0.001 |
| ≥0.9                             | 20              | 0.52 (0.40–0.67) | 0.026         | 17.50%  | <0.001 |
| No. of disease sites (1%)        | 20              | 0.52 (0.33–0.81) | <0.001        | 89.90%  | <0.001 |
| <0.2                             | 20              | 0.52 (0.33–0.81) | <0.001        | 89.90%  | <0.001 |
| ≥0.2                             | 20              | 0.52 (0.33–0.81) | <0.001        | 89.90%  | <0.001 |
| Type of analysis                 | 20              | 0.41 (0.28–0.60) | <0.001        | 62.40%  | 0.047  |
| Univariate                       | 20              | 0.52 (0.37–0.74) | <0.001        | 0       | 0.594  |
| Multivariate                     | 20              | 0.59 (0.42–0.82) | 0.002         | 82.70%  | <0.001 |
| Study design                     | 20              | 0.58 (0.46–0.75) | <0.001        | 74.50%  | <0.001 |
| Retrospective                    | 20              | 0.54 (0.44–0.67) | <0.001        | 74.90%  | <0.001 |
| Prospective                      | 20              | 0.77 (0.53–1.12) | 0.175         | 76.20%  | 0.006  |
| Type of TKs                      | 20              | 0.70 (0.48–1.03) | 0.07          | 80.90%  | 0.001  |
| Axitinib                         | 20              | 0.70 (0.48–1.03) | 0.07          | 80.90%  | 0.001  |
| Sorafenib                        | 20              | 0.86 (0.65–1.13) | 0.277         | 0       | 0.339  |
| Sunitinib                        | 20              | 0.47 (0.34–0.64) | <0.001        | 77.90%  | <0.001 |
| Pazopanib                        | 20              | 0.79 (0.66–0.94) | 0.010         | 0       | 1.000  |

No. number, HR hazard ratio, PFS progression-free survival, ECOG PS Eastern Cooperative Oncology Group performance status, MSKCC score Memorial Sloan Kettering Cancer Center score.
phosphoinositide 3-kinase and its downstream serine protein kinase Akt can stimulate endothelium-derived nitric oxide synthase, leading to the production of nitric oxide (NO). Therefore, the inhibition of VEGF receptor might lead to a decrease in NO bioavailability, followed by vasoconstriction and increased blood pressure (BP) [17, 37–39]. Second, plasma vasoconstrictor endothelin-1, a vasoconstrictor produced by the endothelium, also increased in patients or rats receiving sunitinib [40–42]. Third, NO is also involved in the control of renal and glomerular hemodynamics, tubuloglomerular feedback response, release of renin and sympathetic transmitters, tubular ion transport. As a result, reduction of NO can also result in renal water and sodium retention, leading to hypertension [43]. TKIs may also directly cause renal injury and proteinuria, which could play a role in long-lasting hypertension [44]. Finally, hypertension may also result from structural or functional vascular rarefaction [45–47]. VEGF is also crucial in the maintenance of endothelial viability [48, 49]. Therefore, the inhibition of VEGF and PDGF receptors can induce endothelial cell apoptosis, reduction in capillary density, vascular diameter and microvascular flow, and thus increase the blood pressure.

The reason why TKIs-induced hypertension might be a prognostic factor in patients with mRCC is still
Table 4  Evaluation of the quality of evidence according to GRADE system

| No of studies | Design          | Risk of bias      | Inconsistency | Indirectness | Imprecision | Other considerations | No. of patients | Hazard Ratios (95% CI) | Quality | Importance |
|----------------|----------------|-------------------|---------------|--------------|-------------|----------------------|----------------|--------------------------|---------|------------|
|                | TKI-induced hypertension | Control |
| Progression-free survival |
| (follow-up median 5.6–43.2 years; measured with: follow-up) | | | | | | | | | | |
| 20   | observational studies | no serious risk of bias | serious¹ | no serious indirectness | no serious imprecision | reporting bias² | 3021 | 1327 | 0.59 (0.48–0.71) | Very low | Critical |
| Overall survival (follow-up median 5.2–61.8 months; measured with: follow-up) | | | | | | | | | | |
| 17   | observational studies | no serious risk of bias | serious¹ | no serious indirectness | no serious imprecision | reporting bias³ | 2313 | 1804 | 0.57 (0.45–0.70) | Very low | Critical |

¹The heterogeneity of this outcome was obvious between studies
²The shape of funnel plots was not symmetric. The Egger’s and Begg’s tests were further performed. The results indicated significant publication bias for studies, with merged PFS (Begg’s test, \( P = 0.015 \); Egger’s test, \( P = 0.028 \)).
³The shape of funnel plots was not symmetric. The Egger’s and Begg’s tests were further performed. The results indicated significant publication bias for studies, with merged OS (Begg’s test, \( P = 0.026 \); Egger’s test, \( P = 0.085 \)).
not quite clear. The anticarcinogenic effect of TKIs relies on the block of VEGF receptor, which may also lead to hypertension as above mentioned. Thus, when TKIs inhibit the progress of mRCC and prolong the PFS or OS of patients, hypertension may occur at the same time. It may be the reason why the rise of blood pressure could indicate a better prognosis in mRCC patients.

Of note, the intention of therapy is not to drive all patients into a hypertensive state. On the contrary, when hypertension occurs, patients should receive antihypertensive therapy as soon as possible. Additionally, despite the PFS and OS of mRCC patients have prolonged because of TKIs therapy, few comparable benefits have been described in terms of the quality of life [50, 51]. An innovative study that compared sunitinib with pazopanib to evaluate patient preferences suggested that the toxicity profile may have an impact on quality of life and the choice of treatment when two comparable options are on offer [52]. In addition, sunitinib-induced hypertension may be associated with cardiotoxicity or reversible posterior leukoencephalopathy [53–55]. Thus, the panel of National Cancer Institute of the USA had several recommendations for mRCC patients received TKIs [56]. First, urologists should recognize the preexisting hypertension prior to therapy or actively monitor BP throughout treatment. Early use of antihypertensive medication is necessary when high blood pressure occurs, and it is critical for maintaining dose intensity and improving a patient’s quality of life simultaneously [56]. If possible, the goal of management is to reduce BP below 140/90 mmHg. It was also suggested that there was no need to reduce the dose of antihypertensive medication because it did not compromise efficacy of TKIs [57]. Some evidence indicated that using Angiotensin receptor blockers (ARBs) or angiotensin-I-converting enzyme inhibitors may even protect against cancer [58–60]. ARBs were shown to induce apoptosis and inhibit the proliferation of RCC cells in vitro [28]. Thus, some randomized prospective studies could be carried out to see if it is better to use more than one drugs with different antihypertensive mechanisms, which may improve the prognosis [12]. Second, doctors should assess the risk of potential cardiovascular complications.

Several underlying limitations of the study should be presented. First, most eligible studies were retrospective, though with high NOS scores. Second, the reciprocal correlation between the hypertension and other AEs should be noted. Patients with more than one adverse event of any grade had longer PFS and OS [61]. Thus, further studies are needed to analyze the relationship between several adverse events and mRCC. Third, obvious inter-study heterogeneity was observed in this meta-analysis, which may be due to different therapies mRCC patients had received before, such as cytokine immunotherapy. In addition, a publication bias was detected in this study. The potential reason may be that studies with non-significant results were not published. High heterogeneity and publication bias weakened the quality of evidence, which may be improved by more randomized prospective trials.

However, our analysis also has some advantages. First, we conducted this review with enough data available for extraction by a comprehensive and robust search strategy. Second, we applied a rigorous inclusion/exclusion criterion. Additionally, most of the studies operated multivariable analysis, which could eliminate the co-factors affecting the PFS and OS of mRCC patients.

Conclusions
In summary, our analysis of currently available clinical evidence suggests that TKIs-induced hypertension may predict longer PFS and OS in patients with mRCC during TKIs therapy, especially using sunitinib or pazopanib.

Additional file

Additional file 1: Figure S1. Flow chart showing literature searching process of meta-analysis. The search keywords are (renal cell carcinoma) AND (tyrosine kinase inhibitor) OR sunitinib OR axitinib OR sorafenib OR pazopanib) AND (hypertension OR (blood pressure). (DOCX 140 kb)

Abbreviations
AEs: Adverse events; BP: Blood pressure; CI: Confidence intervals; DBP: Diastolic blood pressure; ECOG PS: Eastern Cooperative Oncology Group performance status; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: Hazard Ratios; MAP: Mean arterial blood pressure; mRCC: Metastatic renal cell carcinoma; MSKCC: Memorial Sloan Kettering Cancer Center; NO: Nitric oxide; NOS: Newcastle-Ottawa Scale; OS: Overall survival; PFS: Progression-free survival; RCC: Renal cell carcinoma; SBP: Systolic blood pressure; TKIs: Tyrosine kinase inhibitors

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Authors’ contributions
LY was mainly responsible for the design of the work, the acquisition and analysis of data and manuscript writing. ZL carried out the acquisition of data. CYT and YDH participated in the analysis of data. LBH, WKJ and LH revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.
Ethics approval and consent to participate
All analyses were based on previous published studies. Thus, no ethical approval and patient consent are required.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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