INPLASY PROTOCOL

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Conflicts of interest:
The authors declare no conflict of interest.

Diagnostic and Prognostic Value of Circulating Tumor Cells in Renal Cell Cancer: A systematic review and Meta-analysis

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Review question / Objective: **P: Patients diagnosed with renal cell carcinoma clinically and/or pathologically I: Diagnostic accuracy of CTCs in patients with renal cell carcinoma; C: Not applicable. O: Overall sensitivity and specificity; S: Studies included in our meta-analysis were all randomized controlled trials.**

Condition being studied: **At present, the preliminary diagnosis of renal cell carcinoma still relies on imaging examination basically, including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), among which most patients need to undergo renal puncture biopsy to confirm the diagnosis. Meanwhile, there are limited non-invasive diagnostic methods available at present in despite of many non-invasive biomarkers are being explored. Therefore, we urgently need a non-invasive and highly sensitive diagnostic method to diagnose tumors and monitor their prognosis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 September 2020 and was last updated on 02 September 2020 (registration number INPLASY202090007).

INTRODUCTION

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Rationale: **The overall accuracy of the various methods used to detect CTCs in renal cell cancer has not been described,**

and whether CTC-positivity is related to advanced disease has been controversial in the detection of CTCs in renal cell cancer, some studies demonstrated that CTC detection may be associated with higher-stage disease, whereas others failed to show such an association. Hence, we performed a meta-analysis to elucidate the relationship between CTC-positivity.

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METHODS

Search strategy: PubMed/MEDLINE: ((((((Neoplastic Cells, Circulating[MeSH Terms]) OR Neoplastic Cells, Circulating[Title/Abstract]) OR Neoplasm Circulating Cell*[Title/Abstract]) OR Circulating Neoplastic Cell*[Title/Abstract]) OR Circulating Tumor Cell*[Title/Abstract])) AND (((((Carcinoma, Renal Cell[MeSH Terms]) OR Carcinoma, Renal Cell[[Title/Abstract]) OR Renal Cell Carcinoma*[Title/Abstract]) OR Renal Cell Adenocarcinoma*[Title/Abstract]) OR Renal Cell Cancer*[Title/Abstract]). Embase: #1 'circulating tumor cell'/exp OR 'circulating tumor cell*':ti,ab,kw OR 'neoplasm circulating cell*':ti,ab,kw OR 'circulating neoplastic cell*':ti,ab,kw. #2 'renal cell carcinoma'/exp OR 'renal cell carcinoma':ti,ab,kw OR 'renal cell cancer*':ti,ab,kw OR 'renal cell adenocarcinoma*':ti,ab,kw. #1 AND #2. Web of science: #1 TOPIC: (Renal Cell Carcinoma*) OR TOPIC: (Renal Cell Adenocarcinoma*) OR TOPIC: (Renal Cell Cancer*) #2 TOPIC: (Neoplasm Circulating Cell*) OR TOPIC: (Circulating Neoplastic Cell*) OR TOPIC: (Circulating Tumor Cell*) #1 AND #2. Cochrane: #1 (circulating tumor cell*):ti,ab,kw OR (Neoplasm Circulating Cell*):ti,ab,kw OR (Circulating Neoplastic Cell*):ti,ab,kw OR (Neoplastic Cells, Circulating):ti,ab,kw #2 (Carcinoma, Renal Cell):ti,ab,kw OR (Renal Cell Carcinoma*):ti,ab,kw OR (Renal Cell Adenocarcinoma*):ti,ab,kw OR (Renal Cell Cancer*):ti,ab,kw #1 AND #2.

Participant or population: Patients diagnosed with renal cell carcinoma clinically and/or pathologically.

Intervention: Diagnostic accuracy of CTCs in patients with renal cell carcinoma.

Comparator: Not applicable.

Study designs to be included: Studies included in our meta-analysis were all randomized controlled trials.

Eligibility criteria: Studies which met the following inclusion criteria were included in the meta-analysis: (1) The included subjects were patients diagnosed with renal cell carcinoma clinically and/or pathologically; (2) and the number of patients enrolled-in had to be ≥20 patients; (3) Clearly negative control group (healthy volunteers or patients with no history of renal tumor) and/or sufficient data to calculate the odds rate (OR) of CTC-positivity in patients with advanced disease (stage I-II) versus those with organ-confined (stage III-IV) cancer according to the TNM staging classification from the American Joint Committee on Cancer (AJCC), (4) the samples used in these studies should be peripheral blood; and (4) the study language was published in English.

Information sources: A systematic literature search in the Pubmed, Cochrane Database, Embase and Web of science was conducted to identify relevant studies which investigated the presence of CTCs in the peripheral blood of patients with renal cell cancer published up to April 2020.

Main outcome(s): Overall sensitivity and specificity of CTC detection of renal cell cancer.

Additional outcome(s): Overall odds ratio (OR) of CTC positivity in patients with advanced disease (III-IV) versus those with organ-confined(I-II) cancer.

Data management: Two reviewers independently extracted the following data from all eligible studies according to the inclusion and exclusion criteria: first author's name, year of publication, country, number of cases and controls, the stage of cancer the patient is in, diagnostic accuracy, Overall survival and progression-free survival, the time of blood collection(before, during, or after any treatment), blood sample Volume, the number of blood samples per patient, the method of enrichment and detection of CTCs per study, and Molecular markers used in each study.

Quality assessment / Risk of bias analysis: The methodological quality of all included studies was assessed by 2 authors using the QUADAS-2 Scale.

Strategy of data synthesis: The Cochran's Q statistic and I^2 statistic were used to assess the heterogeneity between all eligible studies, and influence analysis would be performed If high heterogeneity(I^2>50) was found. We also used meta-regression to explore the source of heterogeneity. The Deeks' funnel plot was used to evaluate the publication bias in meta-analysis about diagnostic accuracy, and there is no publication bias if the p value obtained by Deeks' test is greater than 0.1 ($p>0.1$). A 2-sided $P<0.05$ was considered statistically significant for all statistical analyses.

Subgroup analysis: Meta regression was performed if the heterogeneity of total sensitivity and specificity was significant, and regression analysis was performed based on the following parameters: 1. The number of research objects;2. Region;3. histologic tumor type, etc.

Sensibility analysis: Sensitivity analysis will be performed by excluding studies with outlier values (e.g., very low or very high procedural costs compared to other studies from the same country and comparable patient setting, outcomes, and procedure) and repeating the primary analysis.

Language: English.

Country(ies) involved: China.

Other relevant information: Not applicable.

Keywords: circulating tumor cells; renal cell cancer; diagnosis; prognosis; meta-analysis.

Dissemination plans: The results of this study will be summarized in English and disseminated by submission for publication in a peer-review journal.

Contributions of each author:
Author 1 - Liang Cao - Data analysis, Manuscript writing/editing.
Author 2 - Dong Lin - Data analysis, Manuscript writing/editing.
Author 3 - Tinghui Hu - Data collection.
Author 4 - Xiaoxi Mou - Data collection.
Author 5 - Hai Liao - Data collection.
Author 6 - Yanjun Chen - Data collection.
Author 7 - Kunpeng Li - Data collection.
Author 8 - Guangqiang Zhu - Data collection.
Author 9 - Shu Cui - Project development, public funding.
Author 10 - Tao Wu - Project development, public funding.