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ORIGINAL RESEARCH

Clinicopathological impacts of c-Met overexpression in bladder cancer: evidence from 1,336 cases

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Background: The clinicopathological impacts of c-Met overexpression in bladder cancer have been investigated in several studies with conflicting results. We performed this systematic review and meta-analysis to assess the pathologic and prognostic roles of c-Met status in bladder cancer patients.

Methods: Eligible studies were searched and identified from the PubMed and China National Knowledge Infrastructure (CNKI) databases (up until October 4, 2018). The DerSimonian-Laird random-effects model was used to calculate the pooled risk estimates.

Results: Eight studies including 1,336 bladder cancer cases were eventually included in this meta-analysis. We detected a significantly increased risk of poor overall survival (OS) associated with the high expression of c-Met (HR=2.42, 95% CI 1.36–4.32). There was no association between c-Met status and nuclear grade (OR=0.82, 95% CI 0.29–2.31) or tumor stage (OR=1.42, 95% CI 0.41–4.89).

Conclusion: This study shows that the overexpression of c-Met in primary cancer tissues is associated with a worse OS in human bladder cancer. However, larger studies using standardized methods and criteria are warranted to verify these findings.

Keywords: bladder cancer, c-Met, overall survival, meta-analysis

Introduction

Bladder cancer is the ninth most common cancer worldwide and the thirteenth leading cause of global cancer mortality.[1] Emerging studies have revealed that various human genes, including dysregulated lncRNAs and circRNAs, participate in the genesis and progression of bladder cancer.[2,3] Although multiple and diverse therapeutic strategies have been utilized in recent years,[4] radical cystectomy remains the standard curative treatment for muscle-invasive bladder cancer; this treatment has a 5-year overall survival (OS) rate of 45.9% when combined with chemotherapy.[5] Therefore, the development of novel biomarkers is urgent to improve bladder cancer management and personalized therapy.[6]

The tyrosine kinase c-Met, which is encoded by the proto-oncogene MET located on chromosome 7, is the receptor for hepatocyte growth factor (HGF). c-Met participates in various cellular processes, including differentiation, proliferation, invasion and angiogenesis, by regulating PI3K/AKT, Ras/MAPK, JAK/STAT, SRC and Wnt/β-catenin signaling.[7,8] Agents targeting HGF/c-MET signaling have been tested in various human cancers and have shown promising results in advanced non-small

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cell lung cancer and hepatocellular carcinoma.[9] The role of c-Met in bladder cancer has also been investigated in many studies, and the results have been conflicting. Certain studies reported either a favorable association[10] or an unfavorable association,[11] while others showed no association[12] between c-Met overexpression and the clinicopathological features of bladder cancer. Therefore, we performed this systematic review and meta-analysis to comprehensively assess the pathologic and prognostic roles of c-Met status in bladder cancer patients.

Methods

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] Studies focusing on the clinicopathological impacts of c-Met expression in bladder cancer were identified from the PubMed and China National Knowledge Infrastructure (CNKI) databases (up until October 4, 2018) using the following keywords: "bladder cancer or bladder carcinoma or bladder neoplasm or bladder tumor" and "c-Met or hepatocyte growth factor receptor or HGFR". To expand our search, cited references of the identified articles and reviews were manually searched to identify additional relevant studies. The titles and abstracts of the retrieved studies were initially reviewed to exclude obviously unrelated papers. Then, the full texts of the potentially relevant studies were reviewed. The eligible articles were selected by two independent reviewers (XX and GZ), and controversial articles were discussed with a third reviewer (LH). The complete full search strategy used is provided in Supplementary material.

Inclusion criteria

Eligible studies met all the following criteria: 1) study population was bladder cancer patients; 2) pathological features or OS were analyzed according to c-Met expression status; 3) adequate data were provided to calculate odds ratios (ORs) or hazard ratios (HRs) and their 95% confidence intervals (CIs) and 4) articles were published in English or Chinese. For overlapped studies, the study with the largest sample size or most complete information was included in this meta-analysis. Several potentially eligible studies did not provide enough data to calculate risk estimates. We attempted to contact the corresponding authors of these papers; however, the response rate was very low, and the majority of these articles had to be excluded.

Data extraction

The following information was extracted from each eligible study independently by two reviewers (XX and GZ): first author's surname, publication year, country, sample size, age of patients, nuclear grade, tumor stage, methods used to analyze c-Met expression, cut-off value and clinicopathologic data. Any discrepancies were solved by consensus.

Quality assessment

The quality of each study was assessed by two independent reviewers (XX and GZ) using the Newcastle-Ottawa Scale (NOS) with reasonable modifications. NOS is an eight-item instrument that is used for assessment of the study population, study comparability, follow-up and outcome of interest. We assigned scores of <7 and ≥ 7 for low- and high-quality studies, respectively.

Statistical methods

The impact of c-Met expression on clinicopathologic characteristics was quantified by the pooled ORs or HRs and their 95% CIs. Data on the pathological features were extracted from studies in which the ORs were available. Values that were calculated with the multivariate Cox proportional hazard model were used for OS. If not directly available, these values were calculated using the methods described by Parmar et al.[14]. The DerSimonian-Laird random-effects model[15] was used to calculate the pooled risk estimates. The impact of c-Met expression on the pathology and prognosis was considered statistically significant if the 95% CI did not exceed 1.

Statistical heterogeneity across studies was tested using the Q statistic and I^2 statistic.[16] A *P*-value of <0.10 for the Q statistic was considered statistically significant. The value of I^2 was used to evaluate the degree of heterogeneity (weak heterogeneity: $I^2<25\%$; moderate heterogeneity: $I^2=25$–50%; large heterogeneity: $I^2>50\%$). Publication bias was assessed using Begg's funnel plot[17] and Egger's test.[18] All statistical analyses were performed with STATA 11.0 (StataCorp, College Station, Texas USA), using two-sided *P*-values. $P<0.05$ was considered statistically significant.

Results

Literature search and study characteristics

Figure 1 shows the flow diagram of the literature search process. Eight studies[10–12,19–23] were eventually included in this meta-analysis evaluating the association between c-Met status and the clinicopathological features of bladder cancer. These studies were performed retrospectively in the following regions: China (n=5), Japan (n=1), South Korea (n=1) and Germany (n=1). All the included studies were published between 2002 and 2016, and a total of 1,336 cases were included. Except for one study that used real-time PCR (RT-PCR), information on c-Met expression was obtained using immunohistochemistry (IHC). The study quality scores, which were assessed by the NOS, ranged from 5 to 7 (with a mean score of 6). Table 1 shows the primary characteristics of each study included in this meta-analysis.

c-Met expression and OS of bladder cancer

Three studies were eligible to be included in the OS analysis of high c-Met expression versus low expression. The HRs for each study and for the combination of all the studies are shown in Figure 2. We detected a significantly increased risk of poor OS associated with high expression of c-Met (HR=2.42, 95% CI 1.36–4.32). There was no obvious heterogeneity among the studies (P=0.289 for heterogeneity; I^2=19.3%).

c-Met expression and nuclear grade of bladder cancer

Five articles reported data on the correlation between c-Met expression and the nuclear grade of bladder cancer. The pooled data from all these studies indicated that c-Met expression was not related to nuclear grade with a pooled OR of 0.82 (95% CI 0.29–2.31) (Figure 3). Obvious heterogeneity was observed across studies (I^2=83.4%, P<0.001).

c-Met expression and tumor stage of bladder cancer

The relationship between c-Met expression and primary tumor stage of bladder cancer was analyzed in six published studies. The pooled OR (95% CI) for all these studies was 1.42 (0.41–4.89) (Figure 4), and there was significant heterogeneity among studies (I^2=89.4%, P<0.001).

Publication bias

There was no evidence of publication bias according to Begg's funnel plot (Figure 5, P=0.806 for grade, P=0.707 for stage) or Egger's test (P=0.586 for grade, P=0.167 for stage).

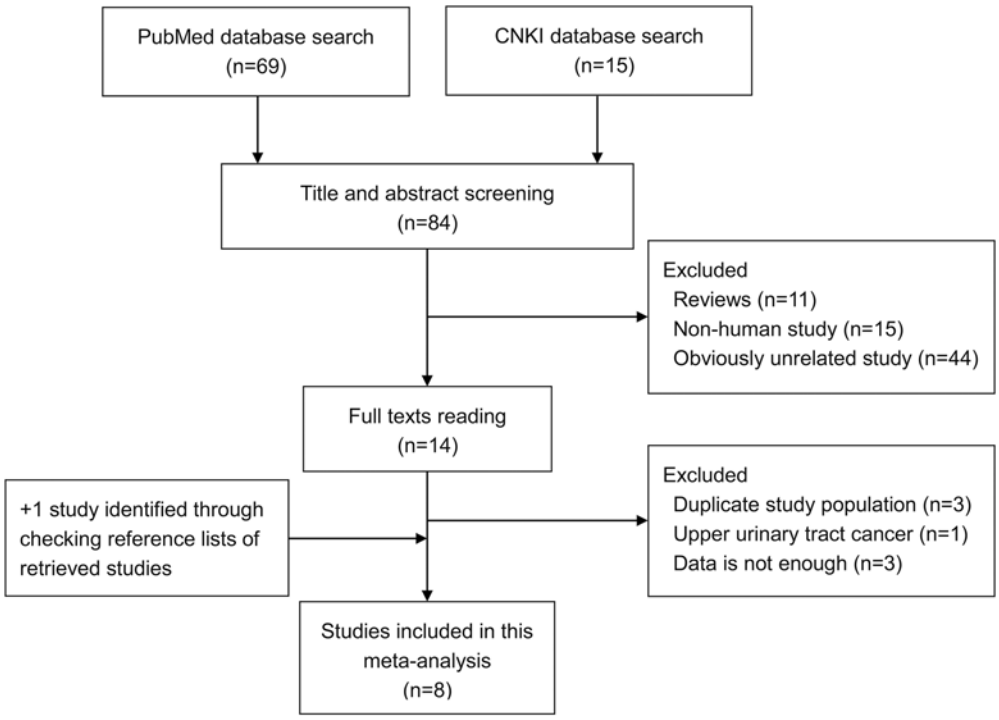

Figure 1 Flow diagram of search process. **Abbreviation:** CNKI, China National Knowledge Infrastructure.

Table 1 Main characteristics of all studies included in this meta-analysis

Author	Year	Region	No. of cases	Age	Method	Cut off	Protein location	Analyzed outcomes	NOS
Zhou et al.[23]	2016	China	60	53.13	IHC	Positive cells >20%	Membrane/ cytoplasm	Stage/grade	5
Xu et al.[12]	2016	China	58	67	IHC	Positive cells >7%	Membrane/ cytoplasm	OS	7
Kim et al.[20]	2015	South Korea	165	65	RT-PCR	NA	NA	OS	6
Kluth et al.[10]	2014	Germany	686	NA	IHC	Positive cells >30%	Membrane	Stage/grade	7
Long et al.[21]	2012	China	47	30–82	IHC	Positive cells >5%	NA	Stage/grade	5
Miyata et al.[22]	2009	Japan	133	NA	IHC	NA	Membrane/ cytoplasm	Stage	6
Jiang et al.[19]	2006	China	45	57	IHC	Positive cells >6%	Membrane/ cytoplasm	Stage/grade	5
Cheng et al.[11]	2002	Taiwan	142	63	IHC	Positive cells >5%	Membrane	Stage/grade/OS	7

Abbreviations: No., number; IHC, immunohistochemistry; RT-PCR, real-time PCR; NOS, Newcastle-Ottawa Scale; OS, overall survival; NA, not available.

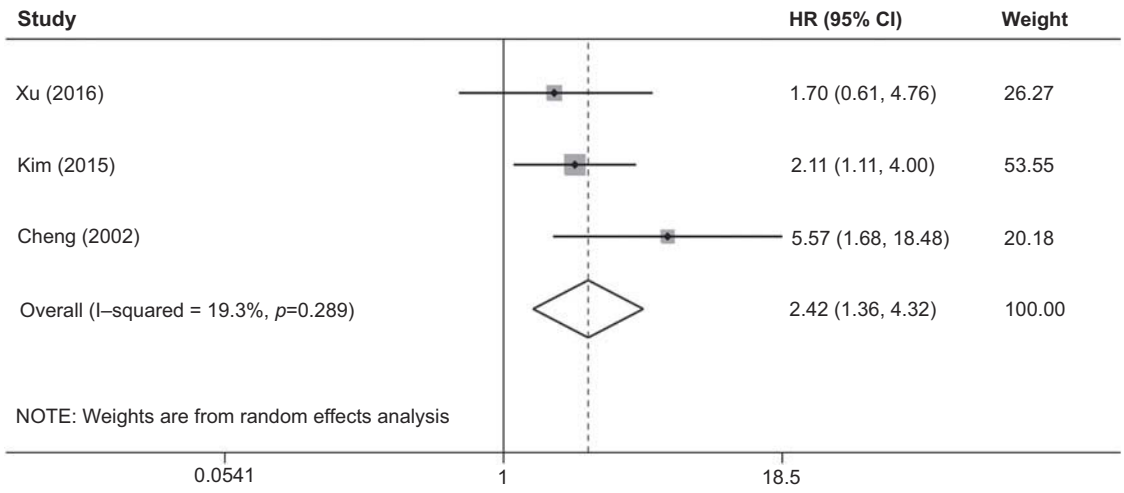

Figure 2 Forest plots of the hazard ratio for overall survival. **Abbreviation:** HR, hazard ratio.

Discussion

This meta-analysis summarizes the results of eight studies that evaluated the relationship between c-Met status and the clinicopathological features of bladder cancer. To the best of our knowledge, this is the first meta-analysis on this topic. The results indicate that high c-Met expression is positively associated with a poor OS in bladder cancer patients.

The biological function of c-Met in bladder cancer cells has been widely studied in previous publications, including several papers published by our team. The overexpression of c-Met may promote migration and invasion by regulating Akt/GSK-3β/Snail signaling[12,24,25] in bladder cancer cells. In addition, phosphor-c-Met also plays important roles for malignant aggressiveness and prognosis in cancer patients. The phosphorylation of c-MET contributes to the activation of a variety of intracellular signaling pathways that eventually promote cell proliferation, motility, invasiveness, epithelial-mesenchymal transition (EMT) and drug resistance.[26,27] High expression of phospho-c-MET was significantly associated with poor prognosis in invasive bladder cancer.[28] Urine c-Met status was reported as a promising diagnostic marker for urothelial carcinoma of the bladder.[29] The expression of c-Met was shown to be post-translationally regulated by many non-coding RNAs, including miR-409,[30]

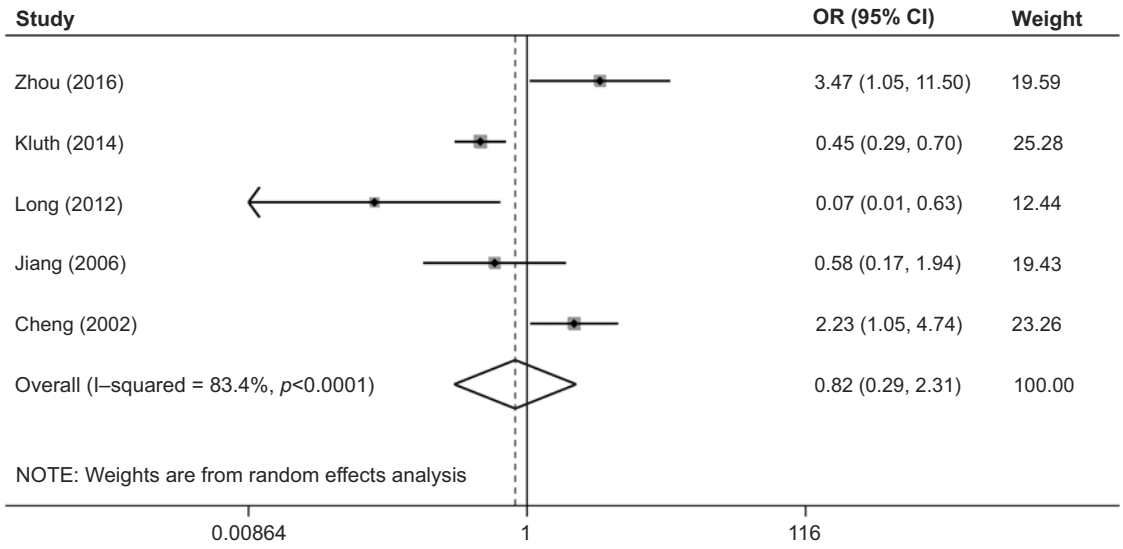

Figure 3 Forest plots of the odds ratio for nuclear grade. **Abbreviation:** OR, odds ratio.

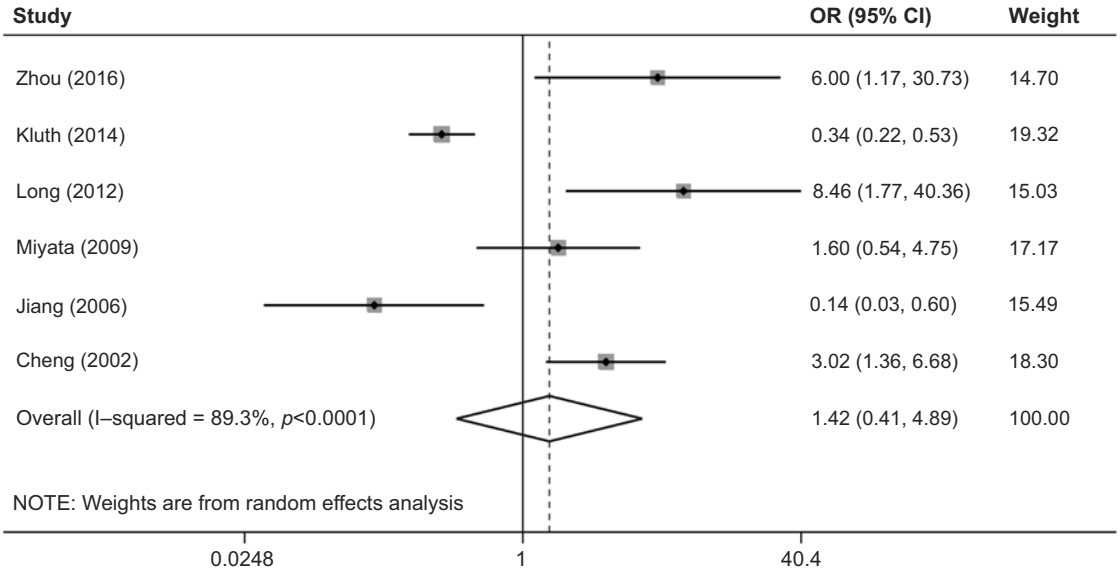

Figure 4 Forest plots of the odds ratio for tumor stage. **Abbreviation:** OR, odds ratio.

miR-433,[12] miR-323,[24] miR-101[31] and miR-381[25] in bladder cancer. Overall, the oncogene c-Met plays a crucial role in the progression and metastasis of human bladder cancer.

In this meta-analysis, we found that c-Met expression was not associated with nuclear grade or tumor stage. In fact, the role of c-Met in the progression of bladder cancer is still unclear. Although most published studies indicated that c-Met status was positively related to the malignant biological behavior of bladder cancer cells,[11,20] some studies reported that c-Met overexpression may primarily occur in early-stage tumors and play a more important role in the progression of early-stage bladder cancer.[10] Because the sample size of our meta-analysis is limited, further prognostic study is warranted to confirm the exact role of c-Met in bladder cancer.

This study had some important strengths. Emerging studies have indicated that c-Met overexpression is significantly associated with worse clinicopathological features in various human cancers, including renal cell cancer,[32] breast cancer,[33] colorectal cancer[34] and others. However, the exact effects of c-Met expression on the pathologic and prognostic features in bladder cancer

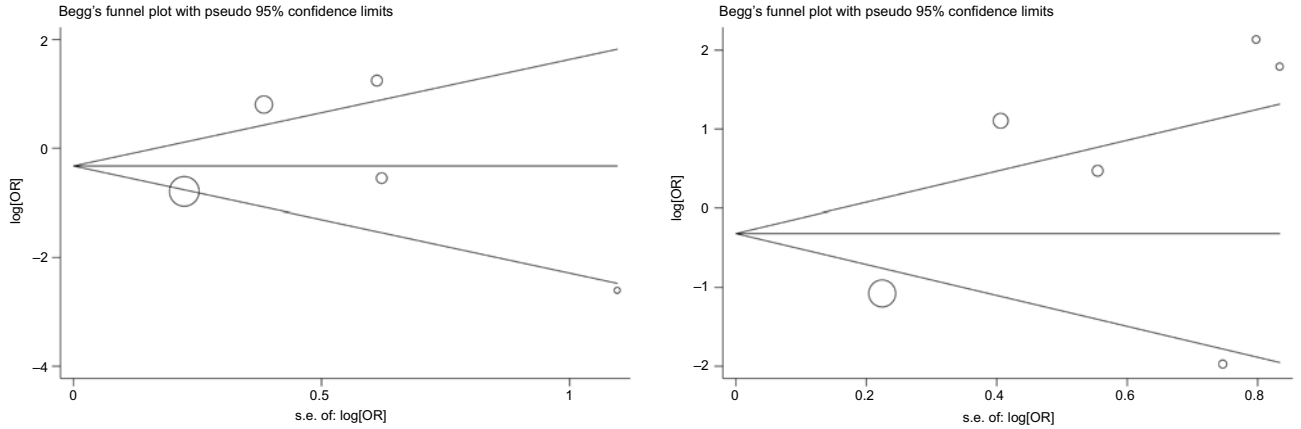

Figure 5 Funnel plots for publication bias.

patients are still unclear. Several previous studies have been performed to evaluate the relationship between c-Met status and the clinicopathological features of bladder cancer, but the results were inconsistent and conflicting. As individual studies had limited statistical power, this systematic review and meta-analysis of eight studies included enormous bladder cancer cases, which improved the power to detect a potential association and allowed for more reliable estimates.

However, several important limitations should be considered when interpreting the results of this meta-analysis. First, although neither Begg's test nor Egger's test revealed any evidence of publication bias, some inevitable publication bias may exist as only articles published in English or Chinese were searched and included in this meta-analysis. Second, limited studies were eligible for the OS analysis, which may affect the reliability of the pooled risk estimate. Third, different methods were used to evaluate the expression of c-Met and there was a wide range of values for the cut-off points across the included studies, which may lead to heterogeneity and distort the summary analysis.

Conclusion

This study shows that the overexpression of c-Met in primary cancer tissues is associated with a worse OS in human bladder cancer. However, larger studies using standardized methods and criteria are warranted to verify the prognostic roles of c-Met status in bladder cancer patients.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Search strategy for meta-analysis evaluating clinico-pathological impacts of c-Met overexpression in bladder cancer

#1 urinary bladder neoplasms [MeSH]

#2 malign* [tiab] OR neoplasm* [tiab] OR carcinoma* [tiab] OR cancer* [tiab] OR tumor* [tiab] OR tumour* [tiab]

#3 bladder [tiab] OR urinary [tiab] OR urothelial [tiab]

#4 #1 OR (#2 AND #3)

#5 Proto-Oncogene Proteins c-met [MeSH]

#6 c-Met [tiab] OR hepatocyte growth factor receptor [tiab] OR HGFR [tiab] OR HGF Receptor [tiab] OR scatter factor [tiab]

#7 #5 OR #6

#8 #4 AND #7

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