Original Article

Is metabolic syndrome associated with high tumor grade and stage of bladder cancer: a systematic review and meta-analysis

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Background: The aim of our study was to elaborate the association between metabolic syndrome (MS) and the tumor stage and grade of bladder cancer (BC).

Methods: A systematic review and pooled analysis on PubMed, the Cochrane Library, Embase, Web of Science, CNKI, WANFANG and VIP from databases inception to July 24, 2020 was conducted by two independent authors. Relative risk (RR) was used as pooled effect estimates. The data analysis was accomplished by STATA 14.2.

Results: Three English and four Chinese articles were included in the final analysis. A pooled analysis of six studies showed that patients in MS group were at a 1.94-fold risk of high-stage BC when compared to their counterparts (RR: 1.94; 95% CI: 1.59–2.37), and the difference was statistically significant. For the components of MS, except for hypertension, patients with obesity (RR: 1.61; 95% CI: 1.33–1.95), hyperglycemia (RR: 2.20; 95% CI: 1.49–3.26) and low high-density lipoprotein cholesterol (HDL) (RR: 1.98; 95% CI: 1.51–2.58) had significantly higher risks of high-stage BC than the control groups. A pooled analysis of six studies indicated that MS can contribute substantially to the vulnerability of high-grade BC with significant difference (RR: 1.50; 95% CI: 1.37–1.65). Furthermore, patients with obesity (RR: 1.41; 95% CI: 1.18–1.69), hyperglycemia (RR: 1.42; 95% CI: 1.30–1.56), hypertension (RR: 1.13; 95% CI: 1.03–1.24), low HDL (RR: 1.29; 95% CI: 1.14–1.46) and high triglyceride (TG) (RR: 1.28; 95% CI: 1.11–1.46) were at a higher risk of high-grade BC than their counterparts.

Conclusions: This meta-analysis revealed that MS and its components might be associated with high BC stage and grade.

Keywords: Metabolic syndrome (MS); bladder cancer (BC); stage; grade; meta-analysis

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Introduction

Bladder cancer (BC) is one of the most common fatal urological tumors in the world, with an estimated 573,000 new cases and 213,000 death yearly (1). Regardless of gender, the incidence of BC in China has increased year by year in both urban and rural areas (2), which not only negatively affected the patients' quality of life but also increased the economic burden on families and the national health care system (3). Thus, enough attention should be paid to the management of BC.

BC is multifactorial in origin, including internal genetic factors and external environmental factors, and the mechanism responsible for this condition is unclear. Cigarette smoking and occupational exposure are two relatively clear risk factors of BC, and the carcinogenesis of these pathogenic factors is likely to be associated with the presence of aromatic amines, such as 2-naphthylamine, 4-aminobiphenyl and 4-chloro-ortho-toluidine (4). The other controversial factors include urinary tract infection (5,6) and metabolic syndrome (MS) (7). MS is multifactorial condition, characterized by overweight or obesity, hypertension, hyperglycemia, and dyslipidemia. In recent years, MS has become an emphatic public health problem due to its close association with a further increase of risk of cardiovascular diseases and type 2 diabetes, and its prevalence is increasing (8-11). It is notable that MS has been demonstrated as a possible predisposing factor for the development and progression of various malignant tumors, including renal cell cancer, live cancer, oesophageal cancer, pancreatic cancer, prostate cancer and bladder cancer (7,12,13). However, there are limited data so far reporting the correlations either between MS and the tumor stage and grade of BC. In such situations, we performed a systematic review and meta-analysis to explore these potential relationships. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-3350).

Methods

Study selection

Electronic literature search of seven domestic and foreign databases and manual search of bibliographies of key retrieved articles and relevant reviews were conducted systematically without language restrictions in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines (14) from inception to July 24, 2020. The English databases included PubMed, the Cochrane Library, Embase and Web of Science, and the Chinese databases involved CNKI, WANFANG and VIP. The searched terms or keywords related to this article included "Metabolic Syndrome" and "Urinary Bladder Neoplasms", and the detailed strategy used in PubMed was as follows: ((((((((((((((((((((Urinary Bladder Neoplasms[Title/Abstract]) OR (Neoplasm, Urinary Bladder[Title/Abstract])) OR (Urinary Bladder Neoplasm[Title/Abstract])) OR (Neoplasms, Bladder[Title/Abstract])) OR (Bladder Neoplasms[Title/Abstract])) OR (Bladder Neoplasm[Title/Abstract])) OR (Neoplasm, Bladder[Title/Abstract])) OR (Bladder Tumors[Title/Abstract])) OR (Bladder Tumor[Title/Abstract])) OR (Tumor, Bladder[Title/Abstract])) OR (Tumors, Bladder[Title/Abstract])) OR (Urinary Bladder Cancer[Title/Abstract]))) OR (Cancer, Urinary Bladder[Title/Abstract])) OR (Malignant Tumor of Urinary Bladder[Title/Abstract])) OR (Cancer of the Bladder[Title/Abstract])) OR (Bladder Cancer[Title/Abstract])) OR (Bladder Cancers[Title/Abstract])) OR (Cancer, Bladder[Title/Abstract])) OR (Cancer of Bladder[Title/Abstract])) AND ((((((((((((((((((((Metabolic Syndrome[Title/Abstract]) OR (Metabolic Syndromes[Title/Abstract])) OR (Syndrome, Metabolic[Title/Abstract])) OR (Syndromes, Metabolic[Title/Abstract])) OR (Metabolic Syndrome X[Title/Abstract])) OR (Insulin Resistance Syndrome X[Title/Abstract])) OR (Syndrome X, Metabolic[Title/Abstract])) OR (Syndrome X, Insulin Resistance[Title/Abstract])) OR (Metabolic X Syndrome[Title/Abstract])) OR (Syndrome, Metabolic X[Title/Abstract])) OR (X Syndrome, Metabolic[Title/Abstract])) OR (Dysmetabolic Syndrome X[Title/Abstract])) OR (Syndrome X, Dysmetabolic[Title/Abstract])) OR (Reaven Syndrome X[Title/Abstract])) OR (Syndrome X, Reaven[Title/Abstract])) OR (Metabolic Cardiovascular Syndrome[Title/Abstract])) OR (Cardiovascular Syndrome, Metabolic[Title/Abstract])) OR (Cardiovascular Syndromes, Metabolic[Title/Abstract])) OR (Syndrome, Metabolic Cardiovascular[Title/Abstract])). The specific strategy is showed in Supplementary material. All observational studies reporting the following outcomes of interest were pooled and analyzed. Two authors independently checked and reviewed the titles and abstracts of identified studies. Then, the articles meeting the inclusion criteria were searched for further evaluation, and data were extracted independently by two reviewers. Disagreements were settled by discussion or a third party. We extracted the following data in accordance

with a predetermined table: (I) the first author and year of publication; (II) study design; (III) the characteristics of the recruited patients, and (IV) percentages of upstage and upgrade.

Selection criteria

We used the following PICOS method to determine the eligibility of included studies: Patients (P): patients diagnosed with primary BC; Intervention (I): MS patients who satisfied at least three of the following four criteria: (I) overweight or obesity (BMI ≥25 kg/m^2); (II) blood pressure (BP) >135/85 mmHg or undergoing treatment for hypertension; (III) fasting plasma glucose ≥6.1 mmol/L or 2-hour plasma glucose ≥7.8 mmol/L or undergoing treatment for hyperglycemia; (IV) dyslipidemia: triglyceride (TG) ≥1.70 mmol/L or high-density lipoprotein cholesterol (HDL) <0.9 mmol/L in males and >1.0 mmol/L in females, or undergoing treatment for high TG or low HDL; Comparison (C): studies comparing MS group to non-MS group; Outcomes (O): BC stage and grade; Ta and T1 tumors were defined as lower stage BC. T2, T3 and T4 tumors were defined as higher stage BC; The pathological grade was determined based on the 2004 World Health Organization grading system. Study design (S): observation studies published in full text. For articles which might include the same population, we only enrolled the largest one unless different outcomes of interest were reported.

Quality assessment

We used the Newcastle-Ottawa Quality Assessment Scale to assess the quality of the observational studies (15). This tool evaluates the case-control studies from three domains: selection, comparability, and exposure. Each study can be given a maximum of one star for each numbered item within the selection and exposure categories, and a maximum of two stars can be given for comparability. The rated studies with seven or more stars were considered as high quality. Additionally, two authors independently evaluated the level of evidence of included articles according to the Oxford Centre for Evidence-Based Medicine criteria (16). This scale rated studies from strongest (level 1) to weakest (level 5) strength of evidence on the basis of study design and data quality.

Statistical analysis

The dichotomous variables were presented as proportions and corresponding 95% confidence intervals (CIs). Relative risk (RR) was estimated of for dichotomous variables. The Cochran Q test (17) and I^2 test (18) were used to assess heterogeneity among studies, and I^2>50% was seemed to be significant. The random effects model was used when heterogeneity was yielded (P<0.1), otherwise the fixed effects model was used. Sensitivity analysis was conducted to determine the source of heterogeneity. A subgroup analysis of Chinese studies was conducted due to ethnicity of included studies. Statistical significance was regarded as P<0.05. The data analysis was accomplished by STATA 14.2.

Results

Literature search results

We searched PubMed, Embase, the Cochrane Library, Web of Science and three other Chinese databases for subject headings and text words related to "Metabolic Syndrome" and "Urinary Bladder Neoplasms" in articles published from inception to July 24, 2020 without language restrictions. Besides, we also conducted a manual search of references of retained articles and previous reviews to pledge a comprehensive retrieve. After excluding duplicates and screening titles and abstracts, seven studies were potentially eligible. Eventually, three English (19-21) and four Chinese (22-25) articles were enrolled in the analysis. The flow chart of study selection was showed in *Figure 1*. A total of seven articles (19-25) evaluated the association of MS and its components with tumor stage and grade of bladder cancer. Of the seven included studies, five are from China (19,22-25), one from Japan (21), and one from Turkey (20). *Table 1* presents the basic characteristic of the included studies.

MS and BC stage

A pooled analysis of six studies (19,21-25) with a total of 1,311 participants showed that patients in MS group were at a 1.94-fold risk of high-stage BC when compared to their counterparts (RR: 1.94; 95% CI: 1.59–2.37) (*Figure 2*), and the difference was statistically significant. For the components of MS, except for hypertension, patients with obesity, hyperglycemia and Low HDL had significantly higher risks of high-stage BC than the control groups, and the corresponding RRs and 95% CIs were 1.61 (1.33, 1.95), 2.20 (1.49, 3.26) and 1.98 (1.51, 2.58), respectively (*Figure 2*).

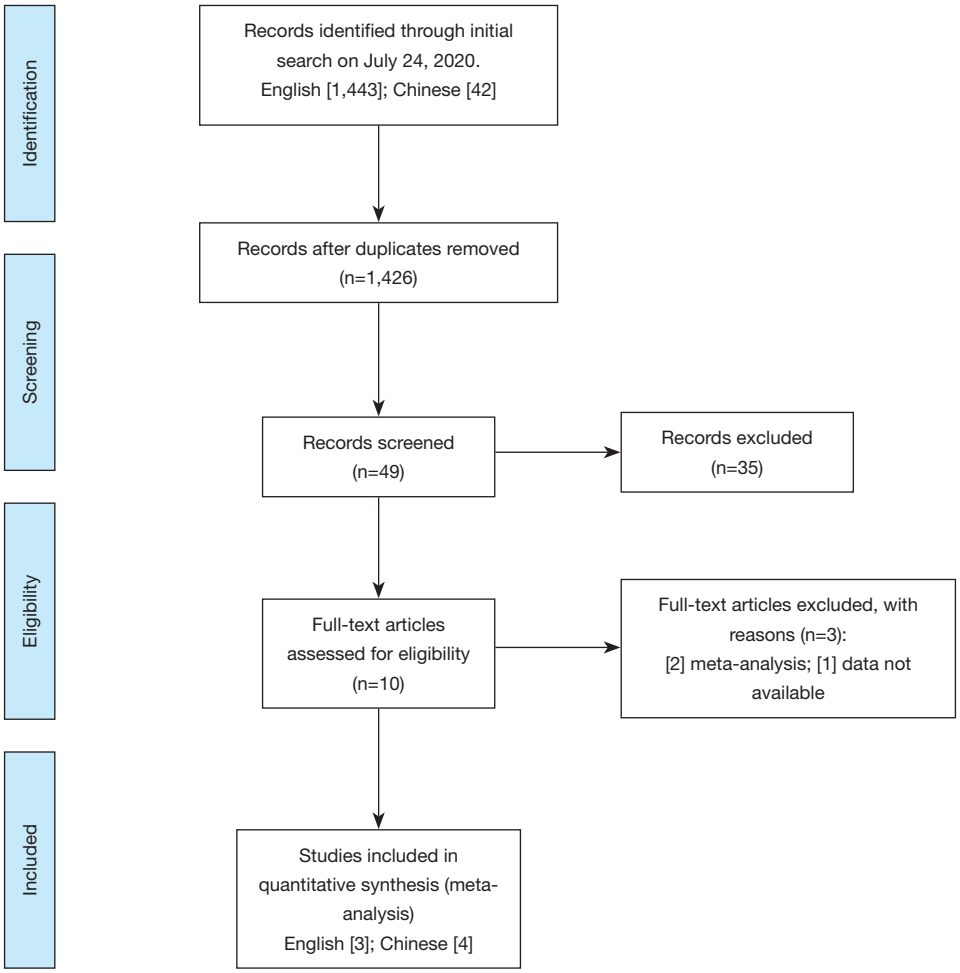


Figure 1 The flow chart of the study selection.

Besides, only two articles (21,25) reported the results of high TG, and the pooled analysis indicated that patients with high TG were prone to high-stage BC with borderline statistical significance (RR: 1.74; 95% CI: 1.00–3.01; P=0.05) (*Figure 2*).

MS and BC grade

A total of six studies (19,21-25) reported the effect of MS on BC, and the pooled analysis indicated that MS can contribute substantially to the vulnerability of high-grade BC with significant difference (RR: 1.50; 95% CI: 1.37–1.65) (*Figure 3*). Furthermore, patients with obesity, hyperglycemia, hypertension, low HDL and high TG were at a higher risk of high-grade BC than their counterparts, and the corresponding RRs and 95% CIs were 1.41 (1.18, 1.69), 1.42 (1.30, 1.56), 1.13 (1.03, 1.24), 1.29 (1.14, 1.46) and 1.28 (1.11, 1.46), respectively (*Figure 3*).

Subgroup analysis of Chinese studies

There were no significant changes in subgroup analysis of Chinese studies (22-25) except for the association between hypertension and BC grade (Supplementary material). We observed no significant difference between hypertension and BC grade (RR: 1.12, 95% CI: 0.99–1.27).

Discussion

Currently, we observed that patients with MS presented a higher incidence of high-stage BC than those without MS. The similar effects were also observed in single MS

Table 1 The baseline characteristics of included studies

Authors	Year	Region	Study design	Sample size	Duration	MS criteria	Percentages of upstage (EG *vs.* CG)	Percentages of upgrade (EG *vs.* CG)	NOS	LoE
Nagase *et al.*	2018	Japan	Case-control study	169	2005.1–2011.3	MS was diagnosed in patients who satisfied at least 3 of the following 5 criteria: (I) BMI >25 kg/m^2; (II) TG >150 mg/dL or undergoing treatment for hypertriglyceridemia; (III) HDL level <40 mg/dL or undergoing treatment for a low HDL-C level; (IV) BP >130/85 mmHg or undergoing treatment for hypertension; (V) FBG level >100 mg/dL or undergoing treatment for hyperglycemia	MS: 33% *vs.* 27% Obesity: 39% *vs.* 24% Hyperglycemia: 30% *vs.* 26% Hypertension:29% *vs.* 27% Low high-density lipoprotein: 45% *vs.* 23% Triglyceride: 33% *vs.* 27%	MS: 71% *vs.* 47% Obesity: 58% *vs.* 47% Hyperglycemia: 52% *vs.* 48% Hypertension: 51% *vs.* 49% Low high-density lipoprotein: 57% *vs.* 48% Triglyceride: 64% *vs.* 46%	9	3b
Sha *et al.*	2016	China	Case-control study	323	2012.1–2014.1	Patients were diagnosed with MS when they had three or more of the following indications: (I) BMI ≥25.0 kg/m^2; (II) FBG ≥6.1 mmol/L or 2-hour plasma glucose ≥7.8 mmol/L, (III) systolic BP≥140 mmHg or diastolic BP ≥90 mmHg, (IV) TG ≥1.70 mmol/L or HDL level <0.9 mmol/L in males and >1.0 mmol/L in females. Participants met the criteria for high BP or high fasting glucose concentration if they underwent hypertension or hyperglycemia treatment	MS: 30% *vs.* 14% Obesity: 21% *vs.* 11% Hyperglycemia: 30% *vs.* 6% Hypertension: 19% *vs.* 16%	MS: 73% *vs.* 49% Obesity: 61% *vs.* 40% Hyperglycemia: 63% *vs.* 45% Hypertension: 57% *vs.* 50%	8	3b
Ozbek *et al.*	2014	Turkey	Case-control study	509	2005.10–2011.3	MS was diagnosed in those who satisfied at least 3 of the following 5 criteria: waist circumference >88 cm in women and >102 cm in men; TG >150 mg/dL or undergoing treatment for hypertriglyceridemia; HDL level <40 mg/dL in men and <50 mg/dL in women or undergoing treatment for low HDL-C level; BP >130/85 mmHg or undergoing treatment for hypertension and FBG level >100 mg/dL or undergoing treatment for hyperglycemia	Not reported	Hyperglycemia: 34% *vs.* 18% Hypertension: 26% *vs.* 22% Low high-density lipoprotein: 26% *vs.* 22% Triglyceride: 28% *vs.* 20%	8	3b
Liu *et al.*	2017	China	Case-control study	260	2011.4–2016.4	Patients were diagnosed with MS when they had three or more of the following indications: (I) TG ≥1.70 mmol/L; (II) HDL level <1.04 mmol/L; (III) BP ≥140/90 mmHg or undergoing treatment for hypertension; (IV) FBG >6.1 mmol/L or 2-hour plasma glucose >7.8 mmol/L or undergoing treatment for hypertriglyceridemia; (V) overweight or obesity: BMI >25 kg/m^2	MS: 41% *vs.* 24% Obesity: 34% *vs.* 21% Hyperglycemia: 37% *vs.* 22% Hypertension: 29% *vs.* 25%	MS: 74% *vs.* 49% Obesity: 64% *vs.* 46% Hyperglycemia: 64% *vs.* 48% Hypertension: 56% *vs.* 51%	7	3b

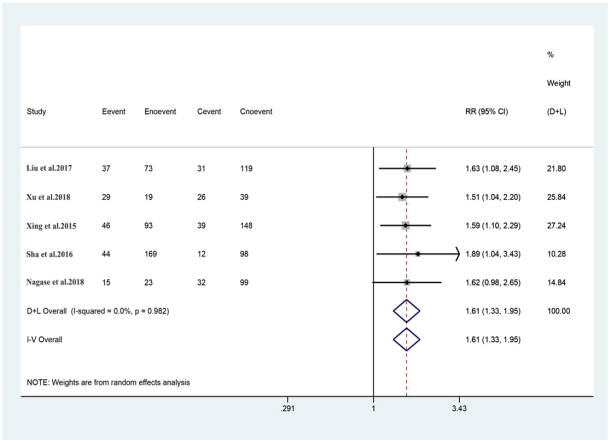
Table 1 *(continued)*

Table 1 (*continued*)

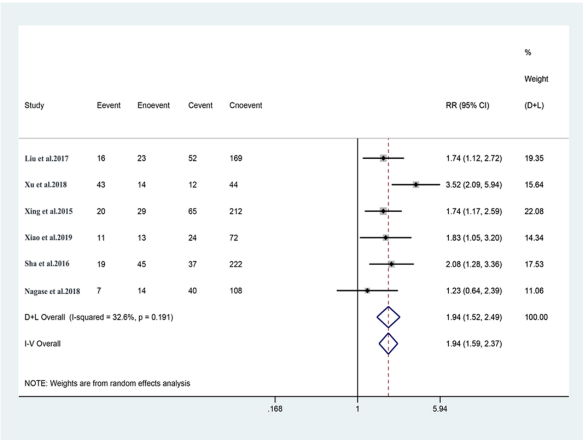
Authors	Year	Region	Study design	Sample size	Duration	MS criteria	Percentages of upstage (EG *vs.* CG)	Percentages of upgrade (EG *vs.* CG)	NOS	LoE
Xiao *et al.*	2019	China	Case-control study	120	2014–2017	Patients were diagnosed with MS when they had three or more of the following indications: (I) TG ≥150 mg/d (1.7 mmol/L); (II) HDL level: male <40 mg/dL (1.03 mmol/L), female <50 mg/dL (1.29 mmol/L); (III) BP ≥140/90 mmHg or undergoing treatment for hypertension; (IV) FBG >6.1 mmol/L or 2-hour plasma glucose >7.8 mmol/L or undergoing treatment for hypertriglyceridemia; (V) overweight or obesity: BMI >25 kg/m^2	MS: 46% *vs.* 25% Hyperglycemia: 41% *vs.* 19% Hypertension: 31% *vs.* 22% Low high-density lipoprotein: 36% *vs.* 17%	MS: 71% *vs.* 45% Hyperglycemia: 79% *vs.* 43% Hypertension: 57% *vs.* 51% Low high-density lipoprotein: 66% *vs.* 44%	7	3b
Xing *et al.*	2015	China	Case-control study	326	2010.10–2013.10	Patients were diagnosed with MS when they had three or more of the following indications: (I) TG ≥1.7 mmol/L; (II) HDL level: male <0.9 mmol/L), female <1.0 mmol/L); (III) BP ≥140/90 mmHg or undergoing treatment for hypertension; (IV) FBG >6.1 mmol/L or 2-hour plasma glucose >7.8 mmol/L or undergoing treatment for hypertriglyceridemia; (V) overweight or obesity: BMI ≥25 kg/m^2	MS: 41% *vs.* 23%; Obesity: 33% *vs.* 21%; Hyperglycemia: 38% *vs.* 21% Hypertension: 29% *vs.* 24%	MS: 73% *vs.* 49%; Obesity: 71% *vs.* 39%; Hyperglycemia: 64% *vs.* 48% Hypertension: 56% *vs.* 51%	8	3b
Xu *et al.*	2018	China	Case-control study	113	2010.11–2017.7	Patients were diagnosed with MS when they had three or more of the following indications: (I) TG ≥1.7 mmol/L; (II) HDL level: male <0.9 mmol/L), female <1.0 mmol/L); (III) BP ≥140/90 mmHg or undergoing treatment for hypertension; (IV) FBG >6.1 mmol/L or 2-hour plasma glucose >7.8 mmol/L or undergoing treatment for hypertriglyceridemia; (V) overweight or obesity: BMI ≥25 kg/m^2	MS: 75% *vs.* 21% Obesity: 60% *vs.* 40%; Hyperglycemia: 68% *vs.* 18% Hypertension: 51% *vs.* 43% Low high-density lipoprotein: 69% *vs.* 35% Triglyceride: 71% *vs.* 32%	MS: 95% *vs.* 66% Obesity: 88% *vs.* 75% Hyperglycemia: 91% *vs.* 64% Hypertension: 84% *vs.* 70% Low high-density lipoprotein: 93% *vs.* 72% Triglyceride: 90% *vs.* 74%	8	3b

NOS, Newcastle-Ottawa Scale; LoE, level of evidence; MS, metabolic syndrome; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein cholesterol; BP, blood pressure; FBG, fasting blood glucose; BC, bladder cancer; EG, experimental group; CG, control group.

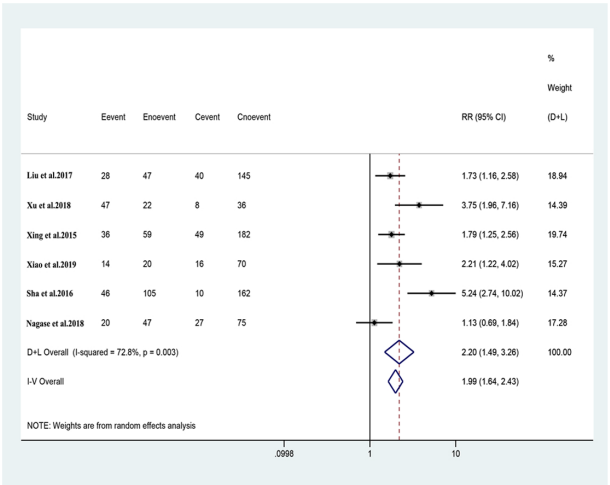
Obesity



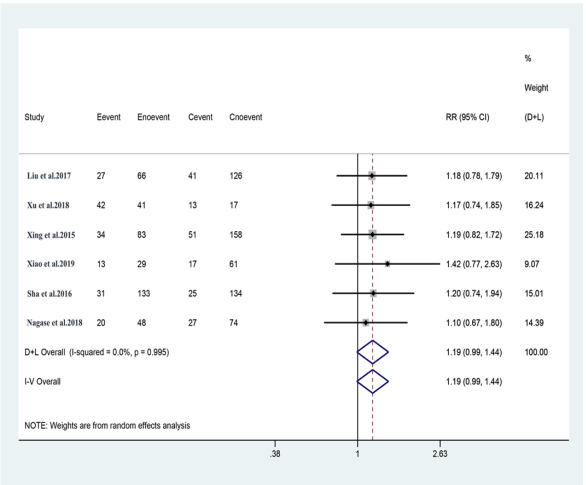
Metabolic syndrome



Hyperglycemia



Hypertension



Low high-density lipoprotein

Triglyceride

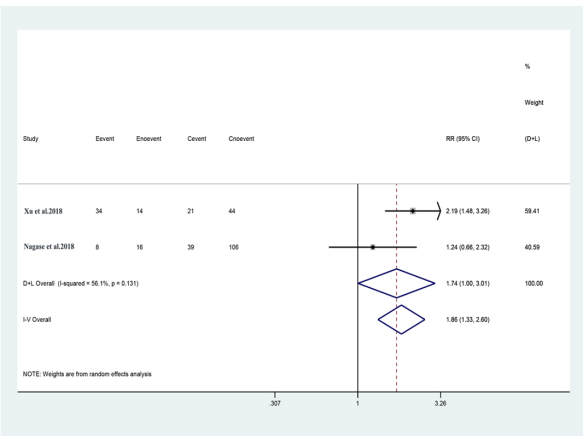


Figure 2 The meta-analysis results of metabolic syndrome and tumor stage of bladder cancer.

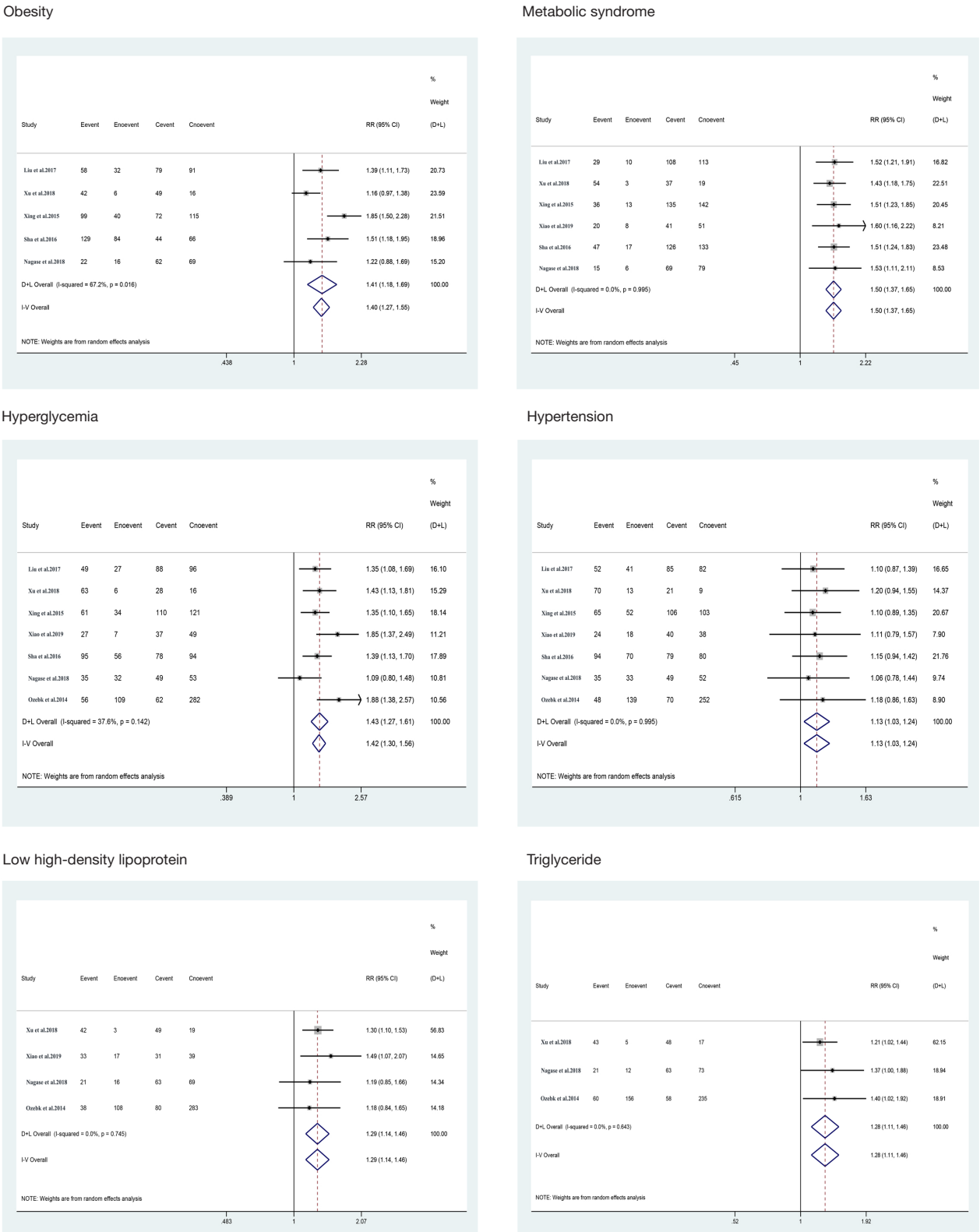


Figure 3 The meta-analysis results of metabolic syndrome and tumor grade of bladder cancer.

parameters except for hypertension. In addition, MS and its components can contribute substantially to the vulnerability of high-grade BC with significant difference.

It is well-known that BC is a common and costly malignant tumor due to lifelong routine monitoring and treatment after diagnosis, and more importantly, some recurrence cases may develop into higher stage and grade, which brings about abundant burden to patients and medial resources (3). Similar to BC, MS is prone to affect older adults disproportionately with the highest prevalence in those aged 60 years and older (8). The previous meta-analyses focused on the association between BC susceptibility and the overall MS and its certain specific components, mainly involving in diabetes and excessive body weight (7,26-28). However, the impact of MS, as well as the components of MS, on the pathological features of BC remains controversial, and recently there have been publications exploring these correlations. A meta-analysis has been done under these circumstances.

As is well known, obesity and hyperglycemia represent two substantial components of MS, and these two metabolic conditions are highly correlated with each other. Thus, we assumed that the mechanisms of their carcinogenesis are similar and synergistic. The potential relationships between obesity and BC include the following three aspect: (I) insulin resistance and elevated serum level of insulin-like growth factor (IGF) -1 (29). IGF-1 might contribute to proliferation and restrain apoptosis, and eventually lead to cancer development and progression. (II) excess energy in the hosts can increase the risks of carcinogenesis (19); (III) Excess fat is also related to systemic inflammatory response, which might play a key part in cancer (19). As for the link between hyperglycemia and BC, in addition to decreased insulin sensitivity and increased level of IGF-1, the possible reason is that hyperglycemia can cause dysfunction of the important cell signaling system regulated by the protein kinase C family, thus inducing tumor growth and metastasis (19).

So far, little is known about potential pathways between low HDL levels, hypertension, and malignant tumors. Both low HDL levels and hypertension play an important role in arteriosclerosis. Several studies indicated that hypertension itself is an important risk factor for malignant tumors (30,31). Our study found that low HDL level was associated with upstaging and upgrading of BC, and hypertension was related to high tumor grade. The potential mechanism of these findings necessitates to be further studied. At the same time, physicians should remember that low HDL levels and hypertension might worsen a patient's metabolic disorder and upstage and upgrade the BC, and appropriate treatments should be provided to such patients (21).

A limitation of this analysis is that due to the study design, the studies included in this meta-analysis have inherent limitations. Retrospective study can contribute to selection bias, such as Berkson bias and Neyman bias, so we use RR to control bias and improve the reliability of analysis results and conclusions. Secondly, the broad heterogeneity of populations, designs and definitions of outcomes should be considered. For example, there were no accurate definitions of MS. Finally, the limited number of studies and sample size discouraged us from making definite conclusions.

Based on these data, MS should be studied within screening protocols to detect more aggressive tumors early; furthermore, MS could be included in current clinical nomograms to improve clinical staging and to personalize the treatment.

Conclusions

This meta-analysis revealed that MS and its components might be associated with high BC stage and grade. Further larger cohort studies are needed to confirm our findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-3350

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-3350). 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.

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