Association between Metabolic Syndrome and tumor histologic grade and pathologic stage of bladder cancer

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Abstract

Background: As we all know,The Metabolic syndrome (MetS) is an emerging condition worldwide, has become an important public health problem. MetS is consistently associated with an increased risk of several cancers.This study aimed to evaluate the association between the MetS and tumor grade and stage of bladder cancer.

Methods: We retrospectively analyzed data of 280 patients who were diagnosed bladder cancer from the Department of Urology, Shandong Provincial Hospital between May 2013 and January 2019. Clinical staging was determined accriding to the 2002 TNM classification. Tis,Ta and T1 tumors were accepted as lower stage and T2,T3 and T4 as higher stage. The histologic grade was determined according to the 2004 World Health Organization grading system. We evaluated the predictive risk factors for the bladder cancer and MetS, including age,sex,BMI,the presence of hypertension, diabetes mellitus, High-Density Lipoprotein (HDL) and triglyceride. Analyses were completed using chi-square tests and logistic regression analysis.

Results: Among the 280 patients in our study,225 were male and 55 were female. MetS was found in 84 patients. 148 patients had hpertension, 114 patients had diabetes mellitus and 129 had a body mass index ≥25 kg/m2. MetS was significantly associated with histologic stage (P=0.021) of bladder cancer.In the binary logistic regression analysis, the presence of MetS predicts the risk of higher T stage(odds ratio=0.204,P=0.001).

Introduction

Bladder cancer is one of the most common malignancy of the urinary system,ranks among the 10 highest incident cancers worldwide. It's a leading cause of cancer-related deaths [1]. The data which provided by the International Agency for Research on Cancer in 2012 suggested that 55,486 cases and 26,820 deaths were estimated for the population in the People's Republic of China, accounts for a large proportion of bladder cancer in East Asia (85,451 cases and 37,491 deaths). Several risk factors are directly associated with an increased risk of bladder cancer, such as smocking and occupational exposure [2]. Besides, some studies have reported that obesity is involed in the increased risk of incident bladder cancer [3-5]. Extensive epidemiological evidence suggests that obesity is associated with an increased risk of cancer, while physical activity can reduce the risk of cancer [6], but bladder cancer is not always associated with body size or physical activity [7]. However, little data are available with regard to Body Mass Index (BMI) and the tumor grade and stage of bladder cancer.In epidemiological studies examining obesity and bladder cancer [8-22], no statistically significant association was found in most populations [3,9-11,13,15-18,20-22]. Although three prospective studies [8,12,14] and a large case-control study

085

[19] had found a positive association between obesity and the risk of bladder cancer, only one [14] of these studies examined the association in detail.

As we all know, Metabolic Syndrome (MetS) is a complicated disorder described as a cluster of abnormal metabolic factors related to excess calorie intake and sedentary lifestyles. To our knowledge, MetS is characterized by overweight, blood glucose, hypertension, and dyslipidemia, which has become a global health problem with growing prevalence. With the improvement of living standard, the incidence and prevalence of obesity continues to rise. The Body Mass Index (BMI) is an important international measure of obesity and health. Association beetween BMI and outcomes after surgery has been reported; however ,there is a limited large-sample research to evaluate the relationship between the BMI and grade and stage of malignancy of bladder cancer in a Chinese population. In our study, we investigated the relationship between the grade and stage of malignancy of bladdeer cancer and BMI and Mets in a Chinese population.

Materials and methods

After obtaining approval from the Shandong Provincial Hospital, we retrospectively analyzed the data of 280 patients who were diagnosed bladder cancer from May 2013 to January 2019. Clinical and pathological data were retrospectively obtained from patient electronic medical records, including age, sex, height, weight, Body Mass Index (BMI), blood pressure, diabetes mellitus, high-density lipoprotein (HDL), triglyceride, tumor grade, and stage. Pathologic staging was determined according to the 2002 TNM classification. Tis, Ta and T1 tumors were defined as lower stage and T2, T3 and T4 tumors were defined as higher stage. The histologic grade was determined according to the 2004 World Health Organization grading system.

Statistical analysis was carried out on a personal computer using statistical software (SPSS, version 17.0; SPSS Inc., Chicago, IL, USA). Analyses were completed using chi-square tests and logistic regression analysis. All tests were two-sided with $P<0.05$ considered to be significant.

MetS was diagnosed when complying with three or more of the following abnormalities:1) BMI≥25.0 kg/m2 , 2) fasting plasma glucose≥6.1 mmol/L or 2-hour plasma Glucose≥7.8mmol/L, 3) systolic blood pressure≥140mmHg or diastolic blood pressure≥90 mmHg, 4) triglyceride (TG)≥1.70 mmol/L or High-Density Lipoprotein Cholesterol (HDL-C)<0.9 mmol/L in males and<1.0 mmol/L in females. BMI was calculated as weight in kilograms divided by the square of height in meters.

Results

As showned in the Table 1, among the 280 patients who were analyzed in our study, 225 were male and 55 were female, with an average of 69.44±9.158 years. There were 71(25.4%) patients who were defined as higher stage and 209(74.6%)

patients were defined as lower stage. MetS was found in 84(30.0%) patients. 148 patients had hpertension, 114 patients had diabetes mellitus and 129 had a body mass index ≥25 kg/m2. Besides, 154(55.0%) patients were defined as higher grade and 126(45.0%) patients were difined as lower grade. Figure 1 displayed the MetS stratified MetS condition distribution. It is obvious that hypertension and obesity are the most frequent MetS components in both groups.

The clinicopathological demographics of characteristics between patients with or without MetS are demonstrated in Table 2. According to our analysis, MetS was significantly associated with pathologic stage ($P=0.021$) of bladder cancer. Besides, there also had an significant association between MetS and BMI(P<0.001. To some extent, MetS were related to obesity.

The association between MetS (and the components of MetS) and the pathologic stage and histologic grade are depicted at Table 3. In the binary logistic regression analysis, the presence of MetS predicts the risk of higher T stage (odds ratio=0.204,P=0.001). Besides, BMI also has an siginificantly association with pathologic stage(odds ratio=0.785,P<0.001 and histologic grade odds ratio=0.881,P=0.006.

Table 1: Patients and tumor characteristics (n = 280).

Clinical characteristics		N (%)
No of patients		280
Sex	Male	225(80.4)
	Female	55(19.6)
Age (mean ± SD) (years)		69.44±9.158
T stage	Higher stage (T2,T3,andT4)	71(25.4)
	Lower stage (Tis,Ta,andT1)	209(74.6)
Histologic grade	High grade	154(55.0)
	Low grade	126(45.0)
HBP		148(52.3)
DM		114(40.7)
BMI(kg/m²)	≥25	129(46.1)
	25	151(53.9)
MetS	Yes	84(30.0)
	NO	196(70.0)
Hypertruglyceridemia		63(22.5)
Low HDL		38(13.6)

SD: Standard Deviation; HBP: High Blood Pressure(hypertension); DM: Diabetes Mellitus; BMI: Body Mass Index; MetS: Metabolic Syndrome; HDL: High-Density Lipoprotein Cholesterol
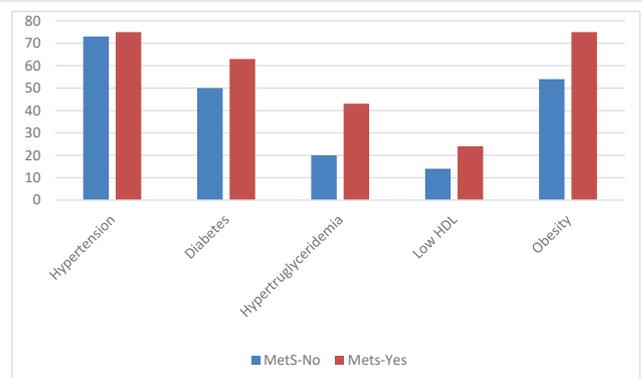

Figure 1: Frequencies of individual metabolic syndrome (MetS) traits stratified by MetS status.

Discussion

In recent years, a number of epidemiological studies have shown that the patients with MetS in a Chinese population were found to have statistically significant with the occurrence and development of urinary tract diseases, and a large number of research confirmed that MetS was significantly associated with the pathogenesis and prognosis of prostate cancer. However, there are few information was available on the association between MetS, as well as the components of MetS, and bladder cancer.

Why is Mets associated with the pathogenesis and prognosis of the bladder cancer? Mets can reduce insulin sensitivity and lead to permanent insulin excess [23]. In addition, our report suggests that high BMI levels may be a risk factor for upper stage of bladder urothelial carcinoma.

The link mechanism between MetS and cancer risk is not fully understood. However, some MetS components have been extensively studied as risk factors for cancer. Increasing evidence shows the negative impact of obesity on genitourinary malignancies [24]. Some epidemiological studies have shown a positive correlation between obesity and increased bladder cancer risk, although other studies have not found any significant associations [7,14].

In our preseant study, we retrospectively analyzed 280 patients undergoing transurethral resection or radical cystectomy surgery of a bladder tumor to assess the relationship between the MetS and the sgressiveness of urothelial carcinoma of the bladder. Besides, we also investigated the association between the components of the MetS(DM, BMI , hypertension, hypertruglyceridemia, low HDL) and bladder cancer histologic grade and stage. We found an significantly association of obesity and bladder cancer including the tumor histologic grade and pathologic stage in a Chinese population.

The biological mechanism of carcinogenesis associated with obesity is unclear, but many possibilities have been proposed.High levels of adipose tissue are related to high levels of cholesterol, which is the precursor of the androgen testosterone, which stimulates the proliferation of epithelial cells.High fat levels are also associated with high plasma levels of vascular endothelial growth factor (VEGF), both of which stimulate the proliferation of epithelial cells.Adipose tissue also secretes leptin, which is related to promoting angiogenesis, so it may also promote tumor development [25].

Table 2: Comparison of characteristics between patients with or without MetS.

Variable	MetS	Non-MetS	*P*-value
No of patients	84	196	
Age(mean±SD)	70.73±8.836	68.90±9.186	0.086
Sex			0.622
Male	63	182	
Female	16	39	
BMI (mean±SD)	27.31±2.218	23.68±2.836	P<0.001
T stage, n (%)			0.021
Higher stage	27(34.2)	73(33.0)	
Lower stage	52(65.8)	148(67.0)	
Histologic grade	n (%)		0.402
High grade	40(50.6)	133(60.2)	
Low grade	39(49.4)	88(39.8)	

SD: Standard Deviation; MetS: Metabolic Syndrome

Table 3: Distribution of cases of bladder cancer, odds ratio (OR) and corresponding 95 % confidence interval (CI), according to indicators of metabolic syndrome (MetS).

Variable	Stage		OR (95% CI)$_a$	P-value	Grade		OR (95% CI)$_a$	P-value
	Lower	Higher			Low	High		
MetS			0.204(0.084-0.500)	0.001			0.995(0.483-2.048)	0.988
Yes	55	29			41	43		
No	154	42			85	111		
BMI(kg/m²)			0.785(0.698-0.882)	P<0.001			0.881(0.804-0.964)	0.006
<25	101	28			71	58		
<25	108	43			55	96		
DM			0.971(0.829-1.137)	0.715			1.037(0.917-1.174)	0.56
Yes	80	34			52	62		
No	129	37			74	92		
HBP			1.008(0.992-1.025)	0.304			1.006(0.992-1.019)	0.424
Yes	106	42			64	84		
No	103	29			62	70		
Hypertruglyceridemia			0.722(0.450-1.157)	0.176			0.950(0.656-1.377)	0.788
Yes	46	17			30	33		
No	163	54			96	121		
Low HDL			0.500(0.173-1.443)	0.2			0.575(0.243-1.363)	0.209
Yes	22	16			12	26		
Yes	187	55			114	128		

MetS: Metabolic Syndrome; BMI: Body Mass Index; DM: Diabetes Mellitus; HBP: High Blood Pressure(hypertension); HDL: High-Density Lipopr otein Cholesterol

Obesity is closely related to many major chronic diseases, including coronary heart disease and tumors, and has become a global public health problem. Studies have shown that overweight/obesity is an important cause of diabetes, and weight status in early adulthood and weight changes in middle age can increase the risk of chronic diseases such as diabetes and coronary heart disease. Increased body size and physical inactivity are associated with an increased risk of several cancers, but there are few studies suggested the relationship between Body Mass Index (BMI) and bladder cancer. So, in addition to the analysis of the relationship between MetS and bladder cancer, we researched the association between the BMI≥25.0 which as an individual factor and bladder cancer. As was shown in the Tables 2,3, we can found that BMI was sigficantly associated with bladder cancer including the tumor histologic grade and pathologic stage in a Chinese population. The positive correlation between BMI and bladder cancer was independent of other known bladder cancer risk factors, including age, race, and smoking, implying that avoiding obesity may play an important role in bladder cancer prevention.

Obesity exerts an influence on the condition of the metabolic which it can cause downstream metabolic changes, such as inflammation, higher insulin levels, insulin–like growth factor production, and changes in sex hormones, all of these factors are related to cancer [26,27]. However, obesity and MetS are complex problems in the elderly. With the growth of age, the body will have some changes, such as the decrease of height, the decrease of muscle, the increase of fat in insulin resistance area, etc., but BMI is often not so accurate.(such as visceral, subcutaneous, intramuscular, and intrahepatic fat) [28]. With age, sarcopenia or sarcopenia is particularly important as it results in insulin resistance and MetS.

On the contrary, older adults are subject to the"Obesity Paradox" in which certain outcomes,such as survival,compared with normal weight or morbidly obese patients, obese patients have better curative effects.Research on other malignancies has shown that there is an Obesity Paradox, despite limited data specific to older people [29–30].

Conclusion

Our research implying that the MetS and obseity had associstion with the bladder caner, not only the tumor pathologic stage but also the histologic grade. In other words, when the patients are considered MetSs, they were found to have statistically significant higher T stage and histologic grade of bladder cancer.

Author contributions

STZ and YG designed this study; SJ performed the statistical analysis and drafted the manuscript; and QFX, KD, ZHX, and YG, collected the data and helped design the manuscript. All authors read and approved the final manuscript.

Acknowledgments

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