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Impact of Metabolic Syndrome on grade and stage of Urothelial Carcinoma of Bladder in Indian population.

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ABSTRACT
PURPOSE
To elucidate the relationship between metabolic syndrome with respect to grade and stage on histopathologic findings in bladder cancer in our population
MATERIALS AND METHODS
We retrospectively analyzed data of patients, their tumour characteristics, metabolic syndrome and its components, (Diabetes, hypertension, BMI and triglyceride levels) and included total of 176 patients who were first time detected cases of carcinoma bladder and were operated in Department of Urology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar from September 2018- August 2021. Noninvasive papillary urothelial neoplasms of low malignant potential (PUNLMP), Ta and T1 tumors were classified as lower stage and T2, T3, and T4 tumors as higher stage bladder cancers. Tumor grading was done according to the World Health Organization grading system(2016).Stasticial Analyses was done using chi-square tests and logistic regression analysis.
RESULTS
Of the 176 patients, 145 (82.5%) were males and 31 (17.7%) were females. Majority (76%) were >50yrs of age. 45 (25.6%) had diabetes mellitus, 58 (32.9%) had hypertension, and 69 (39.2 %) had a body mass index ≥25 kg/m^2. Metabolic syndrome was significantly associated with histologic grade (p<0.05) and stage (p=0.04) of bladder cancer. Components such as diabetes (p=0.005, OR=1.92) and BMI (p=0.05. OR= 2.1) were individually associated with stage whereashypertension (p=0.2 OR=1.12) and hypertriglyceridemia (p=0.1 OR=1.24) were not. Grade followed similar pattern of association. Adjusted for age in binary logistic regression analysis, the presence of Metabolic syndrome predicts the risk of higher T stage (OR=3.05, p=0.003) and grade (OR =3.05, p=0.04) of bladder cancer.
CONCLUSION
The study revealed that metabolic syndrome and its components (diabetes and high BMI)was found to have statistically significant higher T stage and grade of bladder cancer. Hypertension and hypertriglyceridemia didn't have significant association.
KEYWORDS: *diabetes mellitus, hypertension, obesity, stage, bladder cancer, grade, metabolic syndrome*

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I. INTRODUCTION

Carcinoma bladder occurs with an overall incidence of 2.25% (10,000 annually), 3.67% among males and 0.83% for females[1]. It is the sixth leading cause of new cancer cases and ninth leading cause of cancer-related mortality worldwide[2].Metabolic syndrome (MS) is characterized by overweight, hypertension, elevated blood glucose, and dyslipidemia. The prevalence of MS among adult population in India is 30% (95%CI: 28%-33%)[3]. Gender distribution of MS showed that the females had higher prevalence (35%; 95%CI: 31%-38%) when compared to males 26% (95%CI: 22%-29%)[3].The main reason why MS is attracting scientific interest is that the factors defining the syndrome are associated with increased morbidity and mortality in general especially fromcardiovascular diseases. In India, MS has become an emerging public health problem due to improved economic conditions and relatively sedentary lifestyle. Metabolic syndrome has been demonstrated as a possible risk factor for the development and progression of various malignant urological tumors, such as renal cell cancer, prostate cancer and bladder cancer and various non-urologicmalignanciesincluding liver cancerand pancreatic cancer[4,5]. Evidence from various clinical studies, suggest that the MS may increase the risk, recurrence, and mortality of bladder carcinoma. Few studies were carried out to find out association between metabolic syndrome and stage/grade of tumour. In this context we tried to find out any significant relationship between MS and grade/stage of bladder cancer in our population subset.

II. MATERIALS AND METHODS.

We retrospectively analyzed data of 176 patients who were first time detected cases of carcinoma bladder and were operated in Department of Urology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar from September 2018- August 2021. Consent was required for surgical procedure as mandatory for the procedure. Patient related factors (Age, height and weight), histopathological analysis (stage and grade,) and comorbid conditions (the presence of hypertension, diabetes mellitus, triglyceride level and body mass index) were evaluated. Noninvasive papillary urothelial neoplasms of low malignant potential (PUNLMP), Ta and T1 tumors were classified as lower stage and T2, T3, and T4 tumors as higher stage bladder cancers. Tumor grade was done according to the World Health Organization grading system(2016). All patients had primary bladder urothelial carcinoma. Patients with metastatic bladder urothelial carcinoma, carcinoma in situ, adenocarcinoma, or squamous cell carcinoma at diagnosis were excluded from this study. The most commonly used definition for metabolic syndrome in various studies has been the NCEP-ATP-III criteria[6] which requires any three of the following five to be fulfilled: (1) WC ≥102 cms for males or ≥88 cms for females (for Indian populations, this criteria has been revised to ≥90 cms for males or ≥80 cms for females (2) Triglycerides ≥150 mg/dL (3) HDL-C < 40 mg/dL in males or <50 mg/dL in females (4) systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥85 mmHg or both and (5) Fasting plasma glucose ≥100 mg/dL. In addition, existing drug treatment for dyslipidemia/dysglycemia/raised blood pressure would also be qualifying criteria.

Statistical analysis was performed using statistical software (SPSS, version 28.0; 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.

III. RESULTS

Among the 176 patients 145 (82.3 %) were males and 31 (17.7%) were females with mean age of 65.5±4.8 years MS was found in 64 (19.8%) patients. Hypertriglyceridemia, Hypertension, Diabetes mellitus (DM), and BMI ≥25 kg/m2 were present in 25%, 32.9%, 25.6%, and 39.2% of patients, respectively as shown in table 1. The pathological characteristics between patients with or without MS is demonstrated in Table 2. 52 (29.5%) patients were diagnosed with MS. Lower (Ta, T1) and higher (T2, T3, T4) tumor pathologic stages were found in 73.1% and 26.9% of patients with MS, respectively, and histopathologic low grade and high grade were found in 32.6%% and 67.3% of patients, respectively. According to our data, statistically significant differences were observed in tumor pathologic stage (P=0.003) and tumor histologic grade (P=0.004) between patients with and without MS. Also, some MS parameters such as diabetes and high BMI were also found to be associated with higher grade and stage of b

No of patients		176
Sex	Male	145 (82.3 %)
	Female	31 (17.7%)
Age	<45	15 (8.5%)
	45-54	28 (15.9%)
	55-64	52 (29.5 %)
	≥65	81(46.0%)
BMI	<25	107 (60.8%)
	≥25	69 (39.2%)
Smoker	Yes	97 (55.1%)
	No	79 (44.8%)
Hypertension	Yes	58 (32.9%)
	No	118 (67.1%)
DM	Yes	45 (25.6 %)
	No	131 (74.4 %)
Stage	Ta	90 (51.1%)
	Tis	1 (0.5 %)
	T1	53 (30.1%)
	T2	16 (9%)
	T3	12 (6.8%)
	T4	4 (2.2%)
Triglycerides	Normal	120 (68.1%)
	Elevated	56(31.9%)
MS	Present	52 (29.5%)
	Absent	124 (70.5%)

Table 1; patient characteristics and components of metabolic syndrome.
BMI= Body mass index, DM= Diabetes mellitus, MS=metabolic syndrome

Variable	MS	No- MS	p-value
No. of patients	52	124	
Age (mean±SD)	64.02±2.1	60±1.6	<.001
Sex			0.7
MALE	41	95	
FEMALE	11	29	
T- STAGE (%)			0.003
HIGH	14 (26.9 %)	17 (13.7 %)	
LOW	38 (73.0%)	107 (86.2%)	
GRADE			0.04
HIGH	35 (67.3%)	43 (34.6 %)	
LOW	17 (32.6 %)	81 (65.3 %)	

Table 2; Grade and stage of bladder carcinoma with respect to presence or absence of metabolic syndrome.

Variable	Low stage	High stage	OR	P-value	Low grade	High grade	0R	p-value
Diabetes								
Yes	30	15	1.92	0.005	17	28	1.71	0.03
No	121	10			70	61		
Hypertension								
Yes	46	12	1.12	0.2	24	34	1.01	0.35
No	96	22			61	57		
BMI								
≥25	77	18	2.12	0.05	38	57	1.87	0.01
<25	72	9			48	33		
Triglycerides								
Elevated	44	12	1.24	0.1	24	32	1.37	0.65
Normal	102	18			62	58		

Table 3; Impact of components of metabolic syndrome on grade and stage of bladder carcinoma.
BMI= Body Mass Index, OR = odds ratio.
ladder cancer depicted in Table 3.

IV. DISCUSSION

Bladder cancer is common and costly malignancy due to frequent monitoring, with possibilities of grade and stage progression, which brings considerable burden to patients[7]. In this study, retrospectively reviewed 176 patients comparing patients with metabolic syndrome and those without metabolic syndrome to assess their association with stage and grade of tumour.We reported an increased risk of high risk and high grade of urothelial cancer related to MS (defined by NCEP-III and IDF criteria). The individual components of MS, including diabetes and BMI were associated significantly with higher grade and stage whereas hypertension and elevated triglycerides were not associated with increased risks of higher grade and stage.Similar to bladder cancer, MS is prone to affect older adults disproportionately with the highest prevalence in those aged 60 years and older[8].

Obesity and hyperglycemia represent two substantial components of MS, and these two metabolic conditions are highly correlated with each other. The mechanisms of their carcinogenesis are known to be similar and synergistic. The potential relationships between obesity and BC include the following reasons: (I) There is insulin resistance and elevated serum level of insulin-like growth factor (IGF) -1)[9]and this IGF-1 might contribute to proliferation and restrain apoptosis, and eventually lead to cancer development and progression. (II) Obesity status is associated with insulin resistance, higher blood free fatty acids, and chronic micro-inflammatory status, which is mediated and affected by several pro-inflammatory cytokines, such as C-reactive protein (CRP) and tumor necrosis factor-α[13]. These molecules promote tumor development and suppress immune response. Excess fat is related to systemic inflammatory response, which might play a key part in cancer[10].(III) Patients with MS tend to have high levels of cholesterol, which stimulates the proliferation of epithelial cells and have higher levels of vascular endothelial growth factor (VEGF) in plasma. Both of these two stimulate proliferation of epithelial cells[11].(IV) Adipose tissue secretes leptin and it has been found that leptin could also enhance angiogenesis[12]. Lower mitochondrial function with rise of circulating reactive oxygen species (ROS) can also cause damage to DNA[14]. (V) Hyperglycemia can cause dysfunction of the important cell signaling system regulated by the protein kinase C family, thus inducing tumor growth and metastasis [10].

So far, little is known about potential pathways between elevated triglyceride level, hypertension, and malignant tumors. Several studies indicated that hypertension itself is an important risk factor for malignant tumors **.** Our study found that hypertension and high triglycerides were not associated significantly with upstaging and upgrading of bladder cancer.Impact of hypertension on grade and stage is still a controversial issue.Our findings may have some clinical implications for reduction approaches to control the epidemic of MS and its components may contribute to a reduction in the bladder cancer burden and its aggressiveness. Drugs such as statins and metformin used to treat components of metabolic syndrome, have been proved to improve the cancers specific survival significantly. Recently several studies have also proved the cancer protective effect of these drugs[15]. As clinical doctors we should not pay attention to cure only but also prevention of the disease especially malignant tumours having association with metabolic syndrome.

Limitations of our study include retrospective nature, limited sample size and possibility of selection biasthat discouraged us from making definite conclusions.

CONFLICT OF INTEREST: None

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ETHICS STATEMENT;Ethical review and approval was not required for this study in accordance with the local legislation and ethical requirements**.**

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