Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Urology

Relationship between Metabolic Syndrome on Grade and Stage of Urothelial Carcinoma of Bladder

Biswanath Kundu[1], Furkan Ahmed[1], Mohammad Haris Uddin[1], Muhammad Zia Uddin[2], AKM Akramul Bari[3], Md. Rafiqul Islam[4]

[1]Assistant Professor, Department of Urology, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh
[2]Registrar (Urology), National Institute of Kidney Diseases & Urology, Dhaka, Bangladesh
[3]Assistant Professor (Transplant Surgery), National Institute of Kidney Diseases & Urology, Dhaka, Bangladesh
[4]Assistant Professor (Surgery), OSD, DGHS, Attach- Jashore Medical College, Jashore, Bangladesh

DOI: 10.36347/sjams.2022.v10i12.041 | **Received:** 23.10.2022 | **Accepted:** 06.12.2022 | **Published:** 10.12.2022

***Corresponding author:** Dr. Biswanath Kundu
Assistant Professor, Department of Urology, Sir Salimullah Medical College, Mitford, Dhaka, Bangladesh

Abstract **Original Research Article**

Introduction: Bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012. Carcinoma bladder occurs with an overall incidence of 2.25% (10,000 annually), 3.67% among males and 0.83% for females. Metabolic syndrome (MS) is characterized by overweight, hypertension, elevated blood glucose, and dyslipidaemia. Cigarette smoking and occupational exposure are the main risk factors for upper tract urothelial carcinoma and urinary bladder cancer. ***Objective:*** To elucidate the relationship between metabolic syndrome on grade and stage of urothelial carcinoma of bladder**.** ***Methods:*** We retrospectively analyzed study was carried out at Dept. of Urology, Sir Salimullah Medical College Hospital, Dhaka, Bangladesh from January to December 2021. One hundred (100) patients who were first time detected cases of carcinoma bladder and were operated. 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, and triglyceride level and body mass index) were evaluated. Non-invasive 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. Stasticial Analyses was done using chi-square tests and logistic regression analysis. ***Results:*** Total 100 patients 82 (82%) were males and 18(18%) were females with mean age of 65.5±4.8 years. MS was found in 32 (32%) patients. Hypertriglyceridemia, Hypertension, Diabetes mellitus (DM) and BMI ≥25 kg/m2 were present in 25%, 32%, 25%, and 40% of patients respectively. The pathological characteristic between patients with or without MS is demonstrated. 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 where as hypertension ($p=0.2$ 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:*** In concluded, the 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, Bladder Cancer, Grade, Metabolic Syndrome.

INTRODUCTION

Bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012 [1]. Carcinoma bladder occurs with an overall incidence of 2.25% (10,000 annually), 3.67% among males and 0.83% for females [2]. It is the sixth leading cause of new cancer cases and ninth leading cause of cancer related mortality worldwide [3]. Metabolic syndrome (MS) is characterized by overweight, hypertension, elevated blood glucose, and dyslipidaemia. Cigarette smoking and occupational exposure are the main risk factors for upper tract urothelial carcinoma and urinary bladder cancer. Both genetic and environmental factors are considered to play important roles in the carcinogenesis of bladder cancer [4]. Although these well-established risk factors are directly associated with an increased risk of bladder

cancer, the mechanism underlying the development of bladder cancer remains unclear. 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 tumor. In this context we tried to find out any significant relationship between MS and grade/stage of bladder cancer in our population subset [6]. 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 from cardiovascular diseases. 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-urologic malignancies including liver cancer and pancreatic cancer [7, 8]. Evidence from various clinical studies, suggest that the MS may increase the risk, recurrence, and mortality of bladder carcinoma.

MATERIALS AND METHODS

We retrospectively analyzed study was carried out at Dept. of Urology, Sir Salimullah Medical College Hospital, Dhaka, Bangladesh from January to December 2021. One hundred (100) patients who were first time detected cases of carcinoma bladder and were operated. 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, and triglyceride level and body mass index) were evaluated. Non- invasive 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. 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. Tumor grading was done according to the World Health Organization grading system (2016). The most commonly used definition for metabolic syndrome in various studies has been the NCEP-ATP-III criteria [8] which requires any three of the following five to be fulfilled: (1) WC ≥102 cms for males or ≥88 cms for females (criteria has been revised to ≥90 cms for males or ≥80 cms for females (2) Triglycerides ≥150 mg/dL (3) HDLC <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 dyslipidaemia /dysglycemia /raised blood pressure would also be qualifying criteria. Statistical analysis was performed using statistical software (SPSS, version 20.0; 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.

RESULTS

Total 100 patients 82 (82%) were males and 18 (18%) were females with mean age of 65.5±4.8 years. MS was found in 32 (32%) patients. Hypertriglyceridemia, Hypertension, Diabetes mellitus (DM) and BMI ≥25 kg/m2 were present in 25%, 32%, 25%, and 40% of patients respectively (Table-1). The pathological characteristic between patients with or without MS is demonstrated in Table-2. Lower (Ta, T1) and higher (T2, T3, T4) tumor pathologic stages were found in 68.8% and 31.2% of patients with MS, respectively, and histopathologic low grade and high grade were found in 31.2% and 68.8% 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 ladder cancer depicted. Components such as diabetes (p=0.005, OR=1.92) and BMI (p=0.05. OR= 2.1) were individually associated with stage where as hypertension (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 (Table-3, 4).

Table-1: Patient characteristics and components of metabolic syndrome (N=100)

No of patients	N	%
Sex		
Male	82	82%
Female	18	18%
Age		
<45	09	9%
45-54	16	16%
55-64	30	30%
≥65	45	45%
BMI		
<25	60	60%

≥25	40	40%
Smoker		
Yes	55	55%
No	45	45%
Hypertension		
Yes	32	32%
No	68	68%
DM		
Yes	25	25%
No	75	75%
Stage		
Ta	51	51%
Tis	01	1%
T1	30	30%
T2	09	9%
T3	06	6%
T4	03	3%
Triglycerides		
Normal	68	68%
Elevated	32	32%
MS		
Present	32	32%
Absent	68	68%

Table-2: Grade and stage of bladder carcinoma with respect to presence or absence of metabolic syndrome (N=100)

Variable	MS	No-MS	P=value
No. of patients	32	68	
Age (mean± SD)	64.02±2.1	60±1.6	<.001
Sex			0.7
MALE	21	43	
FEMALE	11	25	
T- STAGE (%)			0.003
HIGH	10(31.2%)	17(25%)	
LOW	22(68.8%)	51(75%)	
GRADE			0.04
HIGH	22(68.8%)	26(38.2%)	
LOW	10(31.2%)	42(61.8%)	

Table-3: Impact of components of metabolic syndrome of bladder carcinoma (N=100)

Variable	Low stage	High stage	OR	P-value
Diabetes				
Yes	17	08	1.92	0.005
No	69	06		
Hypertension				
Yes	26	07	1.12	0.2
No	55	12		
BMI				
>25	44	10	2.12	0.05
<25	40	06		
Triglycerides				
Elevated	25	07	1.24	0.1
Normal	57	11		

Table-4: Impact of components of grade and stage of bladder carcinoma (N=100)

Variable	Low grade	High grade	Or	P=value
Diabetes				
Yes	10	16	1.71	0.03
No	40	34		
Hypertension				
Yes	14	20	1.01	0.35
No	35	31		
BMI				
>25	22	32	1.87	0.01
<25	27	19		
Triglycerides				
Elevated	14	18	1.37	0.65
Normal	35	33		

DISCUSSION

The association between the components of MS and the aggressiveness of urothelial carcinoma of the bladder. Our study demonstrated that primary urothelial bladder carcinoma with MS could become a risk factor for the malignant potential of urothelial carcinoma of the bladder. MS could decrease insulin sensitivity and induce a permanent state of excess insulin secretion [9]. Moreover, our reports have demonstrated that a low HDL level could be a risk factor for the upstaging of urothelial carcinoma of the bladder. Bladder cancer is common and costly malignancy due to frequent monitoring, with possibilities of grade and stage progression, which brings considerable burden to patients [10]. In this study, retrospectively reviewed 100 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 [11]. 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. There is insulin resistance and elevated serum level of insulin-like growth factor (IGF) -1), [12] and this IGF-1 might contribute to proliferation and restrain apoptosis, and eventually lead to cancer development and progression. 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 [14]. 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 [15]. Adipose tissue secretes leptin and it has been found that leptin could also enhance angiogenesis [16]. Lower mitochondrial function with rise of circulating reactive oxygen species (ROS) can also cause damage to DNA [17]. Hyperglycemia can cause dysfunction of the important cell signalling system regulated by the protein kinase C family, thus inducing tumor growth and metastasis [14]. Although the reports about the association between low HDL levels and arteriosclerosis are common, reports about the association between low HDL levels and malignant disease are rare. This is the first report to demonstrate an association between the components of MS and the aggressiveness of urothelial carcinoma of the bladder. 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. 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 [18, 19]. 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. However, physicians should take care, as this condition may be associated with a worsening of urothelial carcinoma of the bladder. On the other hand, physicians should also keep in mind that a low HDL level can worsen a patient's metabolic disorder; without proper treatment, this has the potential to lead to MS and a worsening of urothelial carcinoma of the bladder.

CONCLUSION

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. In concluded, the 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.

Conflict of Interest: None.
Sources of Fund: Nil.

REFERENCES

1. Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: a cancer journal for clinicians*, *65*(2), 87-108.
2. Wyszynski, A., Tanyos, S. A., Rees, J. R., Marsit, C. J., Kelsey, K. T., Schned, A. R., ... & Andrew, A. S. (2014). Body mass and smoking are modifiable risk factors for recurrent bladder cancer. *Cancer*, *120*(3), 408-414.
3. Behera, P., & Patro, B. K. (2018). Population Based Cancer Registry of India–the challenges and opportunities. *Asian Pacific Journal of Cancer Prevention: APJCP*, *19*(10), 2885-2889. doi:10.22034/APJCP.2018.19.10.2885
4. Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA: a cancer journal for clinicians*, *61*(2), 69-90. doi: 10.3322/caac.20107. Epub 2011 Feb 4. Erratum in: CA Cancer *J Clin*, 2011 Mar-Apr; 61(2), 134.
5. Krishnamoorthy, Y., Rajaa, S., Murali, S., Rehman, T., Sahoo, J., & Kar, S. S. (2020). Prevalence of metabolic syndrome among adult population in India: A systematic review and meta-analysis. *PLoS One*, *15*(10), e0240971. doi:10.1371/journal.pone.0240971
6. Stocks, T., Bjørge, T., Ulmer, H., Manjer, J., Häggström, C., Nagel, G., ... & Stattin, P. (2015). Metabolic risk score and cancer risk: pooled analysis of seven cohorts. *International journal of epidemiology*, *44*(4), 1353-1363. doi: 10.1093/ije/dyv001.
7. Gacci, M., Russo, G. I., De Nunzio, C., Sebastianelli, A., Salvi, M., Vignozzi, L., ... & Serni, S. (2017). Meta-analysis of metabolic syndrome and prostate cancer. *Prostate cancer and prostatic diseases*, *20*(2), 146-155. doi: 10.1038/pcan.2017.1. Epub 2017 Feb 21. PMID: 28220805.
8. Huang, P. L. (2009). A comprehensive definition for metabolic syndrome. *Disease models & mechanisms*, *2*(5-6), 231-237. doi:10.1242/dmm.001180
9. Serel, T. A., Turan, T., Soyupek, S., Aybek, Z., & Perk, H. (2003). Urine and serum free IGF-1 levels in patients with bladder cancer: a brief report. *Urological research*, *31*(5), 297-299.
10. Leal, J., Luengo-Fernandez, R., Sullivan, R., & Witjes, J. A. (2016). Economic burden of bladder cancer across the European Union. *European urology*, *69*(3), 438-447. doi:10.1016/j.eururo.2015.10.024
11. Ford, E. S., Giles, W. H., & Dietz, W. H. (2002). Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *Jama*, *287*(3), 356-359. doi:10.1001/jama.287.3.356
12. Hursting, S. D., & Hursting, M. J. (2012). Growth signals, inflammation, and vascular perturbations: mechanistic links between obesity, metabolic syndrome, and cancer. *Arteriosclerosis, thrombosis, and vascular biology*, *32*(8), 1766-1770.
13. Quail, D. F., & Dannenberg, A. J. (2019). The obese adipose tissue microenvironment in cancer development and progression. *Nature Reviews Endocrinology*, *15*(3), 139-154. Doi: 10.1038/s41574-018-0126-x .
14. Sha, N., Xu, H., Chen, T., Tian, D. W., Xie, W. Q., Xie, L. G., ... & Wu, C. L. (2016). The evaluation of the association between the metabolic syndrome and tumor grade and stage of bladder cancer in a Chinese population. *OncoTargets and therapy*, *9*, 1175-1179. doi:10.2147/OTT.S102424.
15. Kolb, R., Sutterwala, F. S., & Zhang, W. (2016). Obesity and cancer: inflammation bridges the two. *Current opinion in pharmacology*, *29*, 77-89. Doi: 10.1016/j.coph.2016.07.005
16. Cirillo, D., Rachiglio, A. M., La Montagna, R., Giordano, A., & Normanno, N. (2008). Leptin signaling in breast cancer: an overview. *Journal of cellular biochemistry*, *105*(4), 956-964. Doi: 10.1002/jcb.21911.
17. Hang, D., Nan, H., Kværner, A. S., De Vivo, I., Chan, A. T., Hu, Z., ... & Song, M. (2018). Longitudinal associations of lifetime adiposity with leukocyte telomere length and mitochondrial DNA copy number. *European journal of epidemiology*, *33*(5), 485-495. Doi: 10.1007/s10654-018-0382-z.
18. Heckman-Stoddard, B. M., DeCensi, A., Sahasrabuddhe, V. V., & Ford, L. G. (2017). Repurposing metformin for the prevention of cancer and cancer recurrence. *Diabetologia*, *60*(9), 1639-1647. doi: 10.1007/s00125-017-4372-6.
19. Esposito, K., Chiodini, P., Colao, A., Lenzi, A., & Giugliano, D. (2012). Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes care*, *35*(11), 2402-2411.