

## Evaluation of Risk Factors and Outcomes of Bladder Cancer in Smokers' Vs Non-Smokers.

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### ABSTRACT

**Background:** Bladder cancer is a widespread urological cancer that is closely associated with smoking. Exposure to tobacco adds carcinogenic burden, leading to tumour formation and development. Nonetheless, the variations in risk factors and clinical outcomes among smokers and non-smokers are not well examined, particularly in developing nations.

**Objectives:** To make comparisons of risk factors and clinical outcomes of bladder cancer between smokers and non-smokers and determine whether smoking is correlated with the severity of the disease, its progression, and prognosis.

**Methodology:** The Prospective study on 100 bladder cancer patients was recorded in this Prospective study in a tertiary care hospital, categorised as smokers (n=50) and non-smokers (n=50). Demographic information, risk factors, tumour, staging and treatment outcomes were noted. The analysis of data was done with the help of SPSS v. 25. Continuous variables were presented in the form of mean + standard deviation, and categorical variables in the form of frequencies. Independent t-test and chi-square test were used with  $p < 0.05$  as significant.

**Results:** The mean age was  $58.4 \pm 10.2$  years, higher in smokers ( $60.2 \pm 9.8$ ) than non-smokers ( $56.6 \pm 10.4$ ;  $p=0.08$ ). Male predominance was greater in smokers (88% vs 64%;  $p=0.01$ ). High-grade tumors (62% vs 38%;  $p=0.02$ ), muscle-invasive disease (54% vs 30%;  $p=0.01$ ), and recurrence (40% vs 22%;  $p=0.03$ ) were significantly more common in smokers. Smokers also showed poorer treatment response and higher progression rates.

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**Conclusion:** Aggressive bladder cancer and poorer outcomes are highly related to smoking. Early screening and smoking cessation interventions are necessary to minimize the disease burden and enhance the prognosis.

**Keywords:** Bladder Cancer, Smoking, Risk Factors, Outcomes

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**Introduction**

Bladder cancer is a type of cancer of the urinary tract, and it is one of the most prevalent types of cancer worldwide, and is a serious health burden in many countries around the world. It is one of the ten most commonly diagnosed cancers globally, with a disproportionate occurrence in men. Older adults are the most susceptible to the disease, and the disease incidence is high after 50 years of age. Histologically, most bladder cancers are urothelial (transitional cell) carcinomas that exhibit a mixed clinical behaviour of non-invasive tumors to muscle-invasive disease of high grade [1,2]. The most significant modifiable risk factor of bladder cancer is smoking, which is known to cause about 50-60 per cent of cases among men and 20-30 per cent among women. Aromatic amines and polycyclic aromatic hydrocarbons are some of the carcinogens present in tobacco smoke and are excreted in urine, and have a direct harmful effect on the urothelial lining of the bladder. This chronic exposure results in genetic alterations, dysplasia of the cells and ultimate malignant conversion. The risk of bladder cancer is dependent on the duration and intensity of smoking, and even former smokers are still at high risk in comparison with non-smokers [3,4]. Besides smoking, other risk factors have also been established that include occupational exposure to industrial chemicals like dyes, rubber, leather and petroleum products. Carcinogenesis is also caused by chronic bladder irritation, urinary tract infections and environmental toxins like arsenic in drinking water. Individual susceptibility may be further adjusted by genetic predisposition and lifestyle factors [5,6]. Clinically, bladder cancer is characterized by hematuria as the most frequent symptom and is commonly associated with irritative symptoms of the urinary tract, which include frequency, urgency, and dysuria. Tumour stage and grade during diagnosis are key factors that determine the prognosis of bladder cancer. NMIBC has a relatively good prognosis and a high recurrence rate, whereas muscle-invasive bladder cancer (MIBC) has a worse prognosis because it has a greater progression and metastasis rate [7,8]. A range of studies have shown that smokers are more likely to present with aggressive disease, such as high tumour grade, advanced stage, and high rates of recurrence. Poor response to treatment and poor survival outcomes have also been linked to smoking. Nevertheless, there is a paucity of data on the comparisons of the risk profile and outcome of smokers and non-smokers in third-world countries, where environmental exposures and access to healthcare may vary considerably [9,10]. It is important to comprehend how smoking affects the character and prognosis of bladder cancer to enhance disease management and prevention methods. Recognizing high-risk groups will help to detect them earlier, provide individualized care, and apply effective preventive measures to public health. The proposed study

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will compare and contrast the risk factors and clinical outcomes of bladder cancer in smokers and non-smokers, and thus, add to the evidence-based clinical practice and development of policies.

**Study Objectives**

To compare risk factors and clinical outcome of bladder cancer between smokers and non-smokers, and to understand the relationship between smoking and severity, recurrence and prognosis of the disease.

**Materials and Methods**

**Study Design & Setting**

This is a Prospective study conducted at department of Renal Transplant Unit Institute of Kidney Diseases Hayatabad Peshawar, Pakistan from June 2020 to Dec 2020 six months in which the patients who were diagnosed with bladder cancer and treated in the urology department were included.

**Participants**

One hundred patients with bladder cancer were identified and split into two groups: smokers (n=50) and non-smokers (n=50). The patients were chosen using non-probability consecutive sampling. Cases included both newly diagnosed and follow-ups. A structured proforma was used to enter demographic information, smoking history, and clinical data.

**Sample Size Calculation**

The sample size of 100 patients was estimated with a confidence level of 95, a power of 80 and an anticipated difference in outcomes between smokers and non-smokers in the past based on previous studies. To make a sufficient comparison between the two groups, an equal allocation (1:1 ratio) was applied.

**Inclusion Criteria**

- Bladder cancer patients  $\geq 18$  years old.
- Both genders included
- Histopathologically confirmed cases
- Smokers and non-smokers who would like to participate.

**Exclusion Criteria**

- Other malignancy patients.
- History of previous bladder resection that is not cancer-related.
- Incomplete medical records
- Patients who do not wish to give consent.

**Diagnostic and Management Strategy.**

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Cystoscopy, imaging and histopathological examination were performed to confirm the diagnosis. TNM staging of the tumour was done. The patients were treated normally with transurethral resection, chemotherapy or surgery based on the severity of the disease and clinical guidelines.

#### Statistical Analysis

Data analysis was done in SPSS version 22. Continuous variables were presented in terms of mean and standard deviation, whereas categorical variables were presented in terms of frequencies and percentages. Chi-square test, and an independent t-test were used. A p-value below 0.05 was taken to be significant.

#### Ethical Approval statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of the respective institution. Written informed consent was obtained from all participants prior to data collection. Confidentiality and anonymity of participant information were strictly maintained throughout the study.

#### Results

A total of 100 patients were included, equally divided between smokers and non-smokers. The overall mean age was  $58.4 \pm 10.2$  years. Smokers had a higher mean age ( $60.2 \pm 9.8$  years) compared to non-smokers ( $56.6 \pm 10.4$  years), although the difference was not statistically significant ( $p=0.08$ ). Male predominance was significantly higher among smokers (88%) compared to non-smokers (64%) ( $p=0.01$ ). High-grade tumors were more frequently observed in smokers (62%) compared to non-smokers (38%) ( $p=0.02$ ). Similarly, muscle-invasive bladder cancer was significantly more common in smokers (54%) than non-smokers (30%) ( $p=0.01$ ). Recurrence rates were also higher in smokers (40%) compared to non-smokers (22%) ( $p=0.03$ ). Additionally, smokers demonstrated poorer response to treatment and increased disease progression. Occupational exposure to carcinogens and environmental toxins was more commonly reported among smokers, though this difference was not statistically significant ( $p=0.09$ ). Overall, smoking showed a strong association with more aggressive tumor characteristics and unfavorable clinical outcomes.

#### Intervention Outcome

The outcome of the patients who were standardly treated varied with smoking status. The non-smokers showed a positive response to treatment and reduced recurrence rates, whereas the smokers showed poor prognosis and progression. This is because smoking cessation was identified to relate to better outcomes, as it is an important modifiable factor in the management of bladder cancer.

**Table 1: Demographic Characteristics of Study Participants**

Variable	Smokers (n=50)	Non-Smokers (n=50)	p-value
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Mean Age (years)	60.2 ± 9.8	56.6 ± 10.4	0.08
Gender (Male)	44 (88%)	32 (64%)	0.01*
Gender (Female)	6 (12%)	18 (36%)	—

Table 1 shows demographic characteristics of patients. Smokers were slightly older and had a significantly higher proportion of males compared to non-smokers ( $p < 0.05$ ).

**Table 2: Tumor Characteristics in Smokers vs non-smokers**

Variable	Smokers (n=50)	Non-Smokers (n=50)	p-value
High-grade Tumor	31 (62%)	19 (38%)	0.02*
Low-grade Tumor	19 (38%)	31 (62%)	—
Muscle-invasive Disease	27 (54%)	15 (30%)	0.01*
Non-muscle invasive Disease	23 (46%)	35 (70%)	—

Table 2 demonstrates tumor characteristics. Smokers had significantly higher rates of high-grade tumors and muscle-invasive disease compared to non-smokers ( $p < 0.05$ ), indicating more aggressive disease.

**Table 3: Risk Factors Distribution Among Study Groups**

Risk Factor	Smokers (n=50)	Non-Smokers (n=50)	p-value
Occupational Exposure	18 (36%)	10 (20%)	0.09
Environmental Toxin Exposure	15 (30%)	9 (18%)	0.12
Chronic Irritation/UTI	12 (24%)	14 (28%)	0.65

Table 3 presents distribution of risk factors. Occupational and environmental exposures were more common in smokers but did not reach statistical significance ( $p > 0.05$ ).

**Table 4: Clinical Outcomes and Prognosis**

Outcome Variable	Smokers (n=50)	Non-Smokers (n=50)	p-value
Recurrence	20 (40%)	11 (22%)	0.03*
Disease Progression	18 (36%)	9 (18%)	0.04*
Good Treatment Response	22 (44%)	34 (68%)	0.02*
Poor Outcome	28 (56%)	16 (32%)	0.01*

Table 4 shows clinical outcomes. Smokers had significantly higher recurrence, progression, and poorer treatment response compared to non-smokers ( $p < 0.05$ ), indicating worse prognosis.

## Discussion

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The current research reveals that smoking is substantially related to unfavourable clinicopathological characteristics of bladder cancer, such as higher grade of tumour, invasion of muscular infiltration and worse clinical results. The results are not new but in line with modern literature, which supports smoking as the strongest modifiable risk factor that contributes to the development of bladder cancer as well as its progression [11]. The recent analyses of the world have revealed a heavy load of smoking-associated bladder cancer, and the absolute numbers of deaths and disability are increasing, even though the age-standardised rates are decreasing. This tendency is the increase in population and long-term smoking, especially in the male population, which is consistent with our research since a much greater percentage of males were smokers ( $p=0.01$ ). The same gender differences have been reported consistently in recent epidemiological studies with a focus on the importance of smoking patterns in distributing diseases [12,13]. A higher rate of high-grade tumours and muscle-invasive disease was observed among smokers in our study. This has been reinforced by the recent evidence that tobacco carcinogens cause genetic mutations resulting in aggressive tumour biology. Moreover, research in the past five years has shown that smokers tend to have higher chances of being diagnosed with an advanced stage of the disease than non-smokers [14]. Our findings were also confirmed by a meta-analysis found that smoking is a significant risk factor in the development of non-muscle invasive to muscle-invasive bladder cancer [15]. There were higher recurrence and progression rates among smokers in our cohort. The observation is in line with some of the recent clinical reports that have found smoking to be linked with recurrence and poor response to treatment, especially in patients receiving chemotherapy or intravesical therapy. Mechanistically, the persistence of tumours in the presence of carcinogens may be facilitated by the impairment of immune response in the continued exposure to the carcinogens, which is the reason why the outcome of smokers is poorer [16]. Our analysis also found that there existed a trend of increased occupational and environmental exposures in smokers, although this was not statistically significant. This observation can be reinforced by some recent literature that indicates a synergistic interaction between smoking and occupational carcinogens, including aromatic amines, which increase the risk of bladder cancer even further [17]. This type of combined exposure is specifically applicable in developing countries, where the level of industrial safety regulations can be lower [18]. The average age gap between smokers and non-smokers in our study was not significant; nevertheless, the smokers were more likely to turn up at a slightly older age. This can be likened to recent findings that cumulative exposure to tobacco with time plays a role in delayed yet more aggressive manifestation of diseases [19]. The dose-response relationship between smoking duration and cancer risk has already been well established, and it stresses the significance of long-term exposure. Notably, our results on worse treatment outcomes in smokers are also backed by recent reports that indicate that smoking adversely affects treatment outcomes and survival rates. The recent developments in the treatment of bladder cancer, such as immunotherapy and combination regimens, have shown better results, but smoking status is one of the primary factors influencing the outcome, and patients who smoke respond poorly [20]. On the whole, the research is in agreement with and supports the results of recent global and regional

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research undertaken in the last five years. Not only does smoking raise the risk of bladder cancer, but it also has a significant impact on tumour aggressiveness, recurrence, and survival. The findings underscore the importance of specific interventions, such as smoking cessation programs, early detection of high-risk groups, and an individual approach.

**Limitations**

There are several limitations of this study, such as a small sample size and a single-centre design, which restricts the generalizability of its results. Causal inference is not possible due to the cross-sectional nature. The exposure to smoking was self-reported, which created bias in recall. Lack of long-term follow-up restricted survival analysis. The possible confounders (diet, genetic factors) were not fully measured.

**Conclusion**

Aggressive bladder cancer, increased recurrence, and worse treatment outcomes are closely linked with smoking. Smokers had more advanced disease compared to non-smokers. The importance of smoking cessation and early diagnosis is important in enhancing the prognosis. Tobacco control interventions can also play a big role in decreasing the burden of bladder cancer and increasing the survival rates of patients.

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**Authors Contributions**

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