

Late-Stage Burden and Histopathology of Bladder Cancer in Pakistan: A Retrospective Cohort Study

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Abstract

Bladder cancer remains a significant urological malignancy in Pakistan, with rising incidence and mortality largely attributed to diagnostic delays and limited access to specialized care. Despite this growing burden, large-scale epidemiological data documenting the histological characteristics and stage-based distribution of bladder cancer in the Pakistani population are scarce. This retrospective cohort study analyzed 438 patients diagnosed with histologically confirmed bladder cancer between January 2015 and December 2024. Data on patient demographics, tumor histology, and staging (based on AJCC 8th edition) were retrieved from electronic medical records and analyzed using SPSS version 25.0, with statistical significance set at $p < 0.05$. The majority of patients were male (81.7%), with a mean age of 64.2 years. Urothelial carcinoma was the most prevalent histological subtype (85.6%), followed by squamous cell carcinoma (8.2%) and adenocarcinoma (3.6%). At diagnosis, 37.4%

of patients had non-muscle-invasive bladder cancer (Stage 0–I), whereas 62.6%

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presented with muscle-invasive or advanced-stage disease (Stage II–IV). Late-stage presentation was significantly more common among patients from rural areas ($p=0.014$), and female patients were more likely to present with advanced disease compared to males ($p=0.028$). The findings underscore a high burden of late-stage bladder cancer in Pakistan and highlight critical disparities related to gender and geographic access. These results emphasize the urgent need for early detection strategies, enhanced public awareness, and equitable access to diagnostic and treatment services in underserved populations. Targeted interventions based on these findings may contribute significantly to reducing bladder cancer morbidity and mortality in South Asia.

Introduction

Bladder cancer is one of the most common malignancies of the urinary tract and ranks among the top ten cancers globally in terms of incidence and mortality (Zi *et al.*, 2024). As per GLOBOCAN 2020 estimates, approximately **573,000 new cases** and **213,000 deaths** were reported worldwide, with the majority of cases occurring in men, where it ranks as the sixth most prevalent cancer (Bray *et al.*, 2024). Despite advancements in diagnosis and treatment, significant disparities exist in disease presentation, histological variants, and clinical outcomes between high-income and low- to middle-income countries (LMICs) (Fedoriw *et al.*, 2025). In particular, **South Asian countries like Pakistan** are witnessing an increasing burden of bladder cancer, yet remain underrepresented in global cancer databases and epidemiological literature. The true epidemiological burden of bladder cancer in Pakistan is not fully known due to the **absence of a centralized cancer registry, limited screening infrastructure, and underreporting from rural and peripheral regions**. Available hospital-based data suggest a **rising incidence**, especially among males aged 60 years and above. Several region-specific risk factors have been implicated in the etiology of bladder cancer in Pakistan (Raza, 2018). Chief among these are:

Tobacco consumption (both smoked and smokeless forms like gutka and naswar) (Saginala *et al.*, 2020),

Occupational exposure to carcinogenic substances in dye, rubber, textile, and leather industries (Kogevinas, 2020),

Chronic urinary tract infections and prolonged catheterization (Mert *et al.*, 2023),

Poor sanitation and use of **arsenic-contaminated drinking water** in rural areas (Fernández *et al.*, 2012).

These factors, compounded by **late health-seeking behavior**, result in a high proportion of patients being diagnosed at an **advanced clinical stage**, where curative treatment options are limited and outcomes are poor.

Histological Variability and Stage at Diagnosis

Histologically, **urothelial carcinoma** (formerly termed transitional cell carcinoma) is the most common type of bladder cancer, accounting for over 90% of cases in Western populations (Alifrangis *et al.*, 2019). However, in South Asian settings like Pakistan, **non-urothelial variants**, including **squamous cell carcinoma** and **adenocarcinoma**, are encountered with greater frequency (Rafique & Javed, 2006).

These subtypes are often associated with chronic irritation, infection, and other inflammatory conditions of the bladder and tend to exhibit **more aggressive behavior, poor response to conventional therapies, and higher recurrence rates**.

The **clinical stage at diagnosis** is a key determinant of treatment decisions and survival outcomes (Lopez-Beltran *et al.*, 2024). Patients diagnosed at an early stage—typically non-muscle-invasive bladder cancer (NMIBC)—can often be managed

conservatively with transurethral resection and intravesical therapy (Woldu *et al.*, 2017). In contrast, those presenting with muscle-invasive bladder cancer (MIBC) or metastatic disease require radical interventions, including cystectomy, systemic chemotherapy, or radiotherapy (Witjes *et al.*, 2021). Unfortunately, **most patients in Pakistan present at stage II or higher**, reflecting **delayed diagnosis, low awareness of warning signs like hematuria**, and **limited diagnostic facilities** in rural regions (Badar *et al.*, 2009). Female patients often experience additional diagnostic delays due to the misattribution of hematuria to gynecological conditions or menopausal symptoms (Zhou *et al.*, 2019).

Rationale for the Study

There is a glaring absence of **comprehensive, multi-year data** on the **histopathological spectrum** and **stage distribution** of bladder cancer in Pakistan. Without this evidence, public health planning remains reactive, and early detection initiatives are difficult to implement effectively. Most existing studies are limited in scope, single-centered, and fail to capture the broader picture of how bladder cancer presents across different sociodemographic groups.

This retrospective cohort study was designed to address this gap by analyzing bladder cancer cases over ten years at a **high-volume tertiary urology referral center** in Pakistan. The study aims to:

Determine the **histological subtypes** of bladder cancer encountered in clinical practice,

Assess the **stage at diagnosis** using internationally accepted TNM staging,

Explore **associations between demographic variables (age, gender, and place of residence)** and the likelihood of late-stage presentation.

By presenting this real-world data, the study intends to **highlight critical disparities, support the development of early detection strategies**, and **inform policy-level decisions** that can improve outcomes for bladder cancer patients in Pakistan and similar LMIC settings.

Materials and Methods

Study Design and Setting

This study employed a **retrospective cohort design** to analyze the histological and stage-based distribution of bladder cancer cases. Data were collected from patient medical records maintained at a **tertiary care urology referral center** in Pakistan. The center receives referrals from multiple districts and serves as a major diagnostic and surgical hub for urological malignancies in both urban and rural populations.

Study Period and Population

The review covered 10 years, from **January 2015 to December 2024**. All patients who were diagnosed with **primary bladder cancer** during this time and had complete medical and histopathological records were eligible for inclusion. A total of **438 patients** met the inclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria:

Age ≥ 18 years at the time of diagnosis

Histopathologically confirmed diagnosis of bladder cancer

Available data on clinical staging and histological subtype

Patients managed or followed at the center during the study period

Exclusion criteria:

Incomplete medical or pathology records

Metastatic bladder involvement from other primary cancers

Cases treated only on an outpatient basis without staging workup or histopathological confirmation

Data Collection Procedure

Patient records were retrieved from the hospital's medical archives and electronic database. A structured data abstraction form was used to extract the following information:

Demographics: age, gender, and place of residence (urban/rural)

Clinical presentation: presenting symptoms (e.g., hematuria, dysuria)

Histopathology reports: histological subtype (urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, others)

Tumor grading: as per WHO/ISUP 2016 classification

Tumor staging: based on the **American Joint Committee on Cancer (AJCC) TNM classification**, 8th edition

Follow-up information: where available, recurrence and mortality status were also noted

Two independent researchers performed data abstraction. Any discrepancies were resolved through mutual discussion and consultation with a senior urologist.

Histopathological Classification

Histological classification was based on standardized reporting by board-certified pathologists. The primary categories included:

Urothelial carcinoma (including papillary and non-papillary variants)

Squamous cell carcinoma

Adenocarcinoma

Other rare subtypes (including small cell carcinoma and undifferentiated tumors)

Tumors were further stratified by **grade (low vs high)** and **depth of invasion**, which formed the basis for stage assignment.

Clinical Staging

Staging was conducted using the **TNM system (AJCC 8th Edition)**. Patients were grouped into:

Non-muscle-invasive bladder cancer (NMIBC): Ta, Tis, T1

Muscle-invasive bladder cancer (MIBC): T2 or higher

Locally advanced or metastatic: T3–T4 and/or positive lymph node or distant metastasis (N1–3, M1)

Imaging, including CT urography, ultrasound, and cystoscopy reports, was reviewed alongside operative and pathology notes to determine stage at diagnosis.

Ethical Considerations

This study was conducted under the ethical standards of the institutional research committee and the **Declaration of Helsinki (2013 revision)**. As a retrospective chart review, formal informed consent was waived. Patient confidentiality and anonymity were maintained throughout the data extraction and reporting process.

Data Analysis

Data were entered and analyzed using **IBM SPSS Statistics for Windows, Version 25.0**. Descriptive statistics were used to summarize demographic and clinical variables. Frequencies and percentages were calculated for categorical variables (histological types, stages, gender distribution). Chi-square tests were used to assess associations between stage at diagnosis and demographic characteristics (e.g., gender, rural vs. urban residence). A p-value of **<0.05** was considered statistically significant.

Table 1 Operational Definitions

Term	Operational Definition
Bladder Cancer	A malignant tumor originating from the epithelial lining of the urinary bladder, confirmed histopathologically.
Urothelial Carcinoma	The most common histological type of bladder cancer, arising from the transitional epithelium of the bladder.
Squamous Cell Carcinoma	A histological subtype of bladder cancer characterized by squamous differentiation, commonly associated with chronic irritation or infection.
Adenocarcinoma	A rare histological type of bladder cancer arising from glandular epithelium, often associated with urachal remnants or chronic inflammation.
Non-Muscle-Invasive Bladder Cancer (NMIBC)	Tumors confined to the urothelium or lamina propria (Stages Ta, Tis, T1), without invasion of the muscularis propria.
Muscle-Invasive Bladder Cancer (MIBC)	Tumors that invade the detrusor muscle or beyond (Stage T2 or higher).
Late-Stage Disease	Defined in this study as clinical Stage II or higher at the time of diagnosis.
Rural Residence	Patients originating from non-urbanized areas outside major metropolitan cities, as per documented address in hospital records.
Urban Residence	Patients residing within municipal city limits of major metropolitan centers.
Histological Grading	Classification of tumors as low-grade or high-grade based on WHO/ISUP 2016 guidelines.
TNM Staging	Tumor staging based on the AJCC TNM classification system, 8th edition.

Results

Demographic Characteristics

A total of **438 patients** with histologically confirmed bladder cancer were included in the analysis. The **mean age at diagnosis** was **64.2 ± 9.8 years** (range: 38–87 years).

A significant **male predominance** was observed, with **358 male patients (81.7%)** and **80 female patients (18.3%)**, resulting in a male-to-female ratio of approximately 4.5:1 as shown in figure 1.

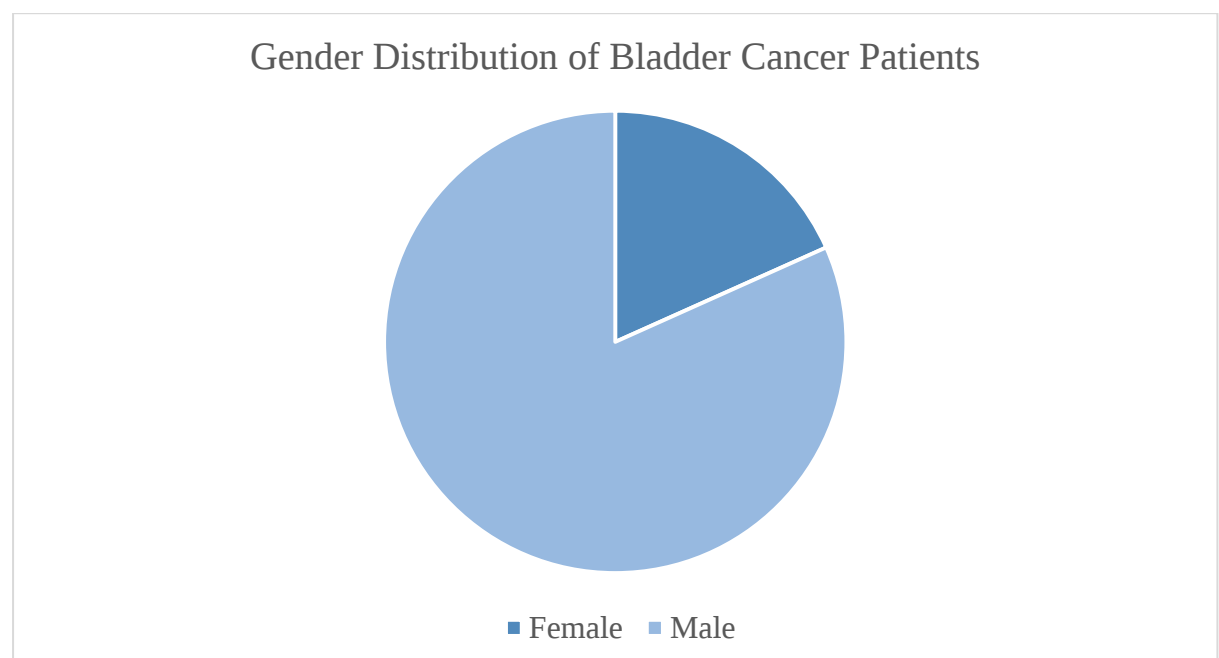


Figure 1: Gender Distribution of Bladder Cancer Patients

Regarding geographic distribution, **67.3% (n=295)** of patients were from **rural areas**, while **32.7% (n=143)** resided in **urban regions** as shown in figure 2

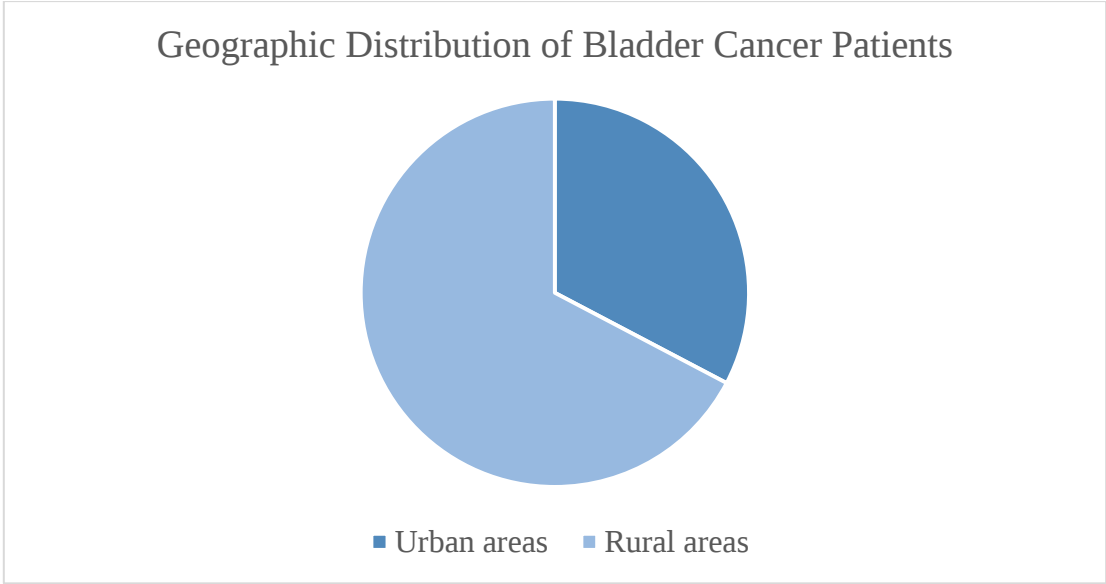


Figure 2: Geographic Distribution of Bladder Cancer Patients

Histological Subtypes

The most frequently observed histological subtype was **urothelial carcinoma**, accounting for **85.6% (n=375)** of all cases. **Squamous cell carcinoma** was diagnosed in **8.2% (n=36)** of patients, followed by **adenocarcinoma** in **3.6% (n=16)**. A minority of cases (**2.6%, n=11**) represented rare histological variants, including small cell carcinoma and undifferentiated carcinoma as presented in figure 3.

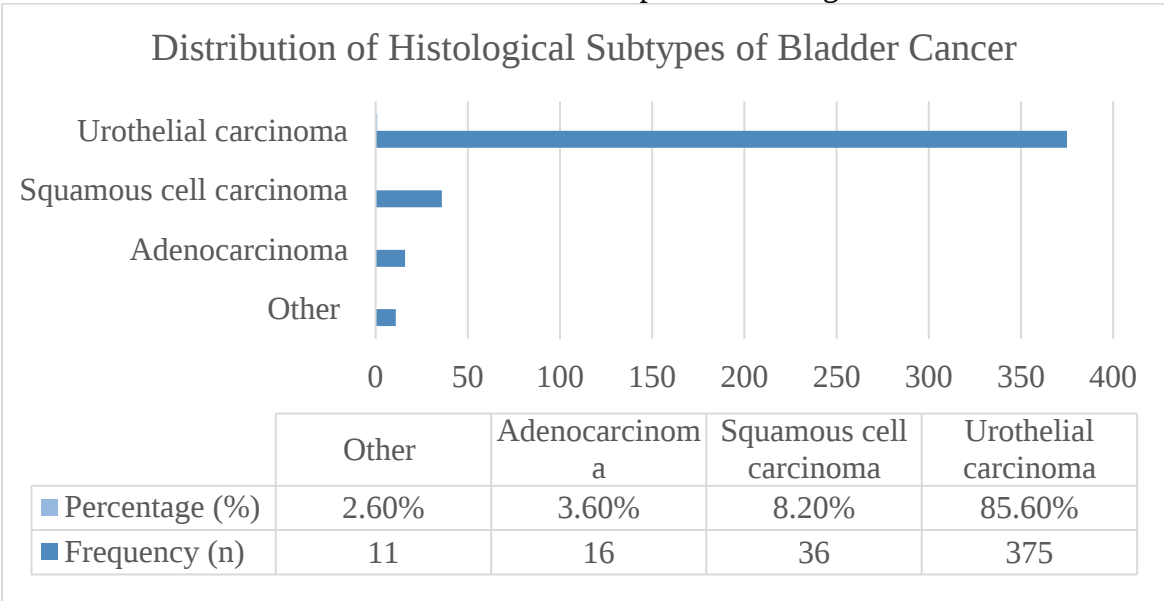


Figure 3: Distribution of Histological Subtypes of Bladder Cancer

Tumor Stage at Diagnosis

Clinical staging data revealed that **164 patients (37.4%)** presented with **non-muscle-invasive disease (Stage 0–I)**, whereas the majority (**274 patients, 62.6%**) were diagnosed with **muscle-invasive or advanced-stage disease (Stage II–IV)**.

Table 2: Stage-Based Distribution of Bladder Cancer at Initial Diagnosis

Stage	Frequency (n)	Percentage (%)
Stage 0a/0is (Ta, Tis)	82	18.7%
Stage I (T1)	82	18.7%
Stage II (T2)	109	24.9%
Stage III (T3)	104	23.7%
Stage IV (T4 or M1)	61	13.9%

Gender and Stage Association

A significant association was found between **gender** and **stage at presentation**. Among **female patients, 58 (72.5%)** presented with muscle-invasive or advanced-stage disease, compared to **216 (60.4%)** of male patients (**p = 0.028**). This suggests a diagnostic delay in women, possibly due to sociocultural factors or misattribution of hematuria.

Residence and Stage Association

Late-stage presentation was also significantly higher among **rural patients**, with **201 (68.1%)** diagnosed at Stage II or higher, compared to **73 (51.0%)** of urban patients (**p = 0.014**). This reflects disparities in healthcare access, awareness, and referral pathways between rural and urban populations.

Discussion

This study provides a comprehensive analysis of the histological and clinical stage distribution of bladder cancer patients over a ten-year period in a tertiary care setting in Pakistan. The findings highlight several critical trends that have significant implications for clinical management, early detection, and public health planning. Consistent with global trends, **urothelial carcinoma** was found to be the predominant histological subtype, accounting for 85.6% of all cases. However, the proportion of **non-urothelial variants**—particularly squamous cell carcinoma (8.2%) and adenocarcinoma (3.6%)—was notably higher than reported in Western populations. These findings are likely reflective of region-specific risk exposures, including **chronic urinary tract infections, prolonged catheter use, and industrial toxin exposure**, particularly in underregulated occupational settings.

The most concerning finding was the **high burden of late-stage disease**. Nearly two-thirds of patients (62.6%) presented with **muscle-invasive or advanced-stage bladder cancer**, which significantly limits treatment options and negatively impacts long-term survival. This late-stage predominance is likely due to **low health literacy, delayed symptom recognition, and limited access to diagnostic facilities**, especially in rural regions.

The study also found a **statistically significant association between rural residence and late-stage diagnosis**. Rural patients were more likely to present at Stage II or higher (**p = 0.014**), likely due to the lack of urology services, poor referral systems, and financial barriers to care. Moreover, **female patients had significantly higher rates of advanced-stage presentation** compared to males (**p = 0.028**). This supports existing literature on gender disparities in cancer diagnosis, suggesting that hematuria in women is often misattributed to benign gynecological causes, leading to diagnostic delays.

These findings call for **urgent interventions**, including public awareness campaigns about early symptoms of bladder cancer, particularly **painless hematuria**, and improved access to diagnostic services like cystoscopy in peripheral health centers. Establishing a **national cancer registry** is also essential to track regional trends, guide policy, and allocate resources effectively.

In summary, this study adds valuable evidence to the limited bladder cancer literature in Pakistan, emphasizing the need for **early detection strategies, equity in diagnostic access, and gender-sensitive healthcare delivery models**. Future prospective studies and multi-institutional collaborations will be critical in validating these findings and guiding national bladder cancer control strategies.

Conclusion

This ten-year retrospective cohort study highlights a concerning pattern in the **histopathological and stage-based profile of bladder cancer patients** in Pakistan. The data reveal a **dominance of urothelial carcinoma**, consistent with global trends, but also a **noteworthy proportion of squamous cell carcinoma and adenocarcinoma**, likely linked to region-specific risk factors such as chronic infections and occupational exposures.

A particularly striking finding is the **high burden of late-stage diagnosis**, with **over 60% of patients presenting at Stage II or higher**, significantly reducing the scope for organ-preserving treatment and negatively affecting survival outcomes. **Gender- and geography-based disparities** were also evident: female and rural patients were disproportionately affected by late-stage presentation, suggesting deep-rooted **structural, cultural, and health system barriers** to early detection and treatment. These findings underscore the **urgent need for public health interventions**, including:

Early symptom recognition campaigns, particularly targeting awareness of painless hematuria;

Strengthening primary and secondary care referral systems, especially in rural and underserved areas;

Integrating urological services at the district hospital level;

And establishing a **national bladder cancer registry** for ongoing surveillance and policy formulation.

Overall, this study provides essential baseline evidence for clinicians, health policymakers, and cancer control planners in Pakistan and across South Asia.

Addressing the late-stage burden of bladder cancer will require **multidisciplinary collaboration**, targeted resource allocation, and context-sensitive strategies to improve early diagnosis, ensure timely care, and ultimately, enhance patient outcomes.

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