RESEARCH ARTICLE

Epidemiology and clinicopathological characteristics of tumoral and non-tumoral bladder lesions in Bistrița-Năsăud county, Romania: A retrospective analysis (2018-2023) and the impact of the COVID-19 pandemic

Petre Carabașa[1], Georgian Nicolae Radu[2]*, Ioan Alin Nechifor-Boilă[3], Adela Nechifor-Boilă[4]

1. Department of Pathology, Bistrița-Năsăud County Emergency Clinical Hospital, Romania
2. Department of Pathology, Mureș County Clinical Hospital, Targu Mures, Romania
3. Department of Anatomy and Embryology, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania
4. Department of Histology, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania

Objective: The primary aim of this study was to analyze the temporal trend and the histopathological and demographic characteristics of tumoral and non-tumoral bladder lesions diagnosed at the Pathology Department of the Bistrița-Năsăud County Emergency Clinical Hospital, Romania between 2018 and 2023. A secondary objective was to assess the impact of the COVID-19 pandemic on tumor diagnosis.

Methods: We conducted a retrospective observational study including 279 cases diagnosed via bladder biopsy, transurethral resection of bladder tumor, and cystectomy. Variables such as age, sex, environment, intervention type, histopathological diagnosis, and TNM staging were collected. Statistical analysis was performed using Epi Info and Microsoft Excel, with a significance threshold set at $p<0.05$.

Results: Invasive urothelial tumors were the most common (n=144 cases, 51.61%), followed by non-invasive urothelial tumors (n=95, 34.05%), non-tumoral lesions (n=31, 11.11%), and non-urothelial tumors (n=9, 3.22%). Most cases occurred in men (n=226, 81%), particularly in the 61–70 and 71–80 age groups. Non-muscle invasive bladder cancers (pTa, T1) were triple as frequent as muscle-invasive bladder cancers. Comparing the pre-pandemic/pandemic (2018–2020) and post-pandemic (2021–2023) periods, we observed a 88% increase in total diagnosed cases ($p<0.0001$) along with a significant rise in both non-muscle invasive bladder cancers (+70%, $p=0.002$) and muscle invasive bladder cancers (+106%, $p=0.017$), the latter showing a more pronounced increase.

Conclusions: Our study provides a comprehensive overview on the impact that COVID-19 pandemic has had on the diagnosis of bladder lesions within Bistrița County area. The post-pandemic group exhibited a marked rise in both tumoral and non-tumoral lesions, as well as in the number of MIBCs, highlighting the effect of pandemic related restriction on patients care. Nevertheless, our results need further confirmation through future larger scale studies.

Keywords: bladder cancer, urothelial carcinoma, TUR-BT, COVID-19, Romania

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Introduction

Bladder cancer (BC) represents a significant global health burden, being one of the most common malignancies of the urinary tract [1,2]. Its prevalence, diagnostic patterns, and the impact of external factors such as global health crises can vary significantly across different geographical regions and healthcare systems [3,4]. BC is tenth most commonly diagnosed cancer, with an estimated 573,000 new cases and 213,000 deaths reported worldwide in 2020 [5]. The majority of bladder tumors are urothelial carcinomas (UC), often presenting with hematuria and requiring cystoscopic evaluation and histopathological confirmation for diagnosis. Early detection and accurate staging are crucial in determining the prognosis and guiding therapeutic strategies [6,7].

Histopathological assessment remains the gold standard in BC diagnosis, providing essential information on tumor grade, depth of invasion, and associated features such as carcinoma in situ. Additionally, immunohistochemical (IHC) analysis is often employed for differential diagnosis and subclassification, especially when dealing with a challenging diagnosis of UC variant [8,9].

The onset of the Coronavirus Disease 2019 (COVID-19) pandemic in early 2020 placed an unprecedented strain on global healthcare systems. In an effort to prioritize COVID-19 care, many healthcare institutions temporarily suspended elective procedures, postponed consultations, and routine diagnostic services, including endoscopic and pathological evaluations [10-12]. Urological oncology, although recognized as high priority, experienced considerable delays, particularly for non-muscle-invasive bladder cancer (NMIBC), which is generally managed with close surveillance and timely intervention [13,14].

* Correspondence to: Georgian Nicolae Radu
E-mail: george.radu098@gmail.com

Furthermore, pathology laboratories faced significant logistical challenges, including staff shortages, supply chain disruptions, and the need to implement strict biosafety protocols. These factors contributed to diagnostic delays and potentially influenced tumor staging at the time of diagnosis [15].

From a pathological perspective, the delay or omission of biopsy and resection procedures may have led to an increase in late-stage diagnoses and more aggressive disease presentations [16,17]. Understanding how the pandemic has influenced the histopathological characteristics of BC is vital for anticipating future challenges in the field of uro-oncology and ensuring setup conditions for similar disruptions in the future [18-20].

The current study aims to assess the impact of the first year of COVID-19 pandemic on the diagnosis of BC within the Pathology Department of a county-level hospital in Romania (Bistrița-Năsăud County Emergency Clinical Hospital). Additionally, the study offers a comprehensive overview of the epidemiological trends, demographic features (age, sex) and histopathologic characteristics (tumor stage, histologic subtype) of patients diagnosed with BC within our institution.

Methods

Study Design

We conducted a 6-year retrospective study (observational study) including all patients who underwent urologic procedures for bladder lesions (tumoral and non-tumoral) and who were registered in the Pathology Department of Bistrița County Emergency Clinical Hospital, Romania between January 2018 - December 2023, a time period centered by the COVID-19 pandemic.

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Committee of Bistrița-Năsăud County Emergency Clinical Hospital (Letter of Approval no. 3818/4 27.03.2024).

Data collection

All patients who underwent surgical procedures (bladder biopsy, transurethral resection of bladder tumor (TUR-BT), cystectomy) between January 2018 and December 2023, were included in the study. Demographic characteristics (age, sex) and pathological data (tumor histological subtype, grade, pT category) were collected from patient records and pathological reports. All cases were reviewed by two experienced pathologists, following inclusion and exclusion criteria:

Inclusion Criteria: (1) all patients with a histopathological confirmed diagnosis of bladder tumor or non-tumoral lessions on bladder biopsy, TUR-BT, or cystectomy specimens, (2) registered in the database of the Pathology Department of Bistrița-Năsăud County Emergency Clinical Hospital (3) between 2018 and 2023.

Exclusion Criteria: (1) cases with an uncertain histopathological diagnosis (e.g., bladder tumor suspicion that failed confirmation following IHC studies); (2) bladder tumor cases confirmed with tumor recurrence(s) were included only once in the statistical analysis.

The histopathological diagnosis of various bladder lesions was established based on their morphological features in accordance to the 2016 and 2022 WHO Classification of Urinary and Male Genital Tumors diagnostic criteria [21], [22]. The staging of each BC variant was performed according to the 8th edition of the TNM Classification of Malignant Tumours [23]. Different types of bladder lesions were divided into 4 distinct categories:

1. Non-invasive Urothelial Tumors (encompassing urothelial papilloma, inverted urothelial papilloma, papillary urothelial neoplasm of low malignant potential, non-invasive low-grade papillary UC, non-invasive high grade papillary UC, UC in situ, dysplasia);
2. Invasive Urothelial Tumors (infiltrative UC with various types of differentiation, eg. squamous, nested, microcystic, micropapillary, etc.);
3. Non-Urothelial Tumors;
4. Non Tumoral Lesions.

For a more standardized assessment of tumor invasiveness, NMIBCs were defined as tumors confined to the mucosa or submucosa (pTa, pT1), while muscle-invasive bladder cancers (MIBCs) were defined as tumors infiltrating the detrusor muscle or beyond (pT2, pT3, pT4).

To assess the impact of the first year of COVID-19 pandemic on the annual rate of urinary bladder pathology in our department, data were analyzed in comparison: Cohort A – pre-pandemic/pandemic (3 years, January 2018–December 2020) *versus* Cohort B – post-pandemic (3 years, January 2021–December 2023).

Statistical Analysis

Statistical analysis was conducted using Epi Info version 7.2.0.1. Descriptive statistical analyses were performed, and all data were expressed as nominal or quantitative variables. Continuous variables are presented as the median and interquartile range (IQR), while qualitative data are expressed using frequencies and percentages. The normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Differences between continuous variables were analyzed using Mann–Whitney test. To compare the change in distribution of different bladder lesions between the two cohorts, the Z test was applied. The significance level was set at $\alpha = 0.05$. All tests were two-sided, with a p-value of <0.05 considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Committee of Bistrița-Năsăud County Emergency Clinical Hospital (Letter of Approval no. 3818/4 27.03.2024).

Results

Patients characteristics

During the six-year study period, a total of 279 cases of bladder lesions/neoplasms were registered in our department. Of these, 97 cases (34.8%) were registered in the first 3-years (Cohort A – pre-pandemic/pandemic: 2018–2020), while 182 cases (65.2%) in the latter three years (Cohort B – post-pandemic: 2021–2023).

Table 1 illustrates the demographic (age, sex) and histopathological characteristics (tumor histology) of the study cases, in comparison between the two study periods (pre-pandemic/pandemic – Cohort A versus post-pandemic – Cohort B).

When stratified by gender, a male predominance was observed in both periods. However, the number of bladder lesion cases increased in both men (+55 cases; p = 0.004) and women (+35 cases; p = 0.327) after the first year of COVID-19 pandemic, leading to a shift in population composition towards a reduction in male-to-female ratio in Cohort B compared to Cohort A (Cohort A - pre-pandemic/pandemic: M/F=9:1; Cohort B- post-pandemic: M/F=3:1).

The median age at the time of diagnosis was comparable between the two groups. Patients in Cohort A-pre-pandemic/pandemic had a median age of 70 years-old (IQR: 65–77), while those in Cohort B- post-pandemic had a median age of 66 years-old (IQR: 60–74). The number of new diagnoses of bladder lesions was highest among patients aged >60 years-old, with peak frequencies observed in the age groups 61–70 (n=99; 35.48%) and 71–80 (n = 92; 32.97%) years-old respectively. In contrast, the frequency of bladder lesions was significantly lower among patients aged 50 years-old or less (n=21 cases, 7.51%) (Tabel 1).

Pathological data

For most of the cases included in the study, the histopathological diagnosis of bladder lesion/neoplasm was established on TUR-BT (n=258, 92.47%); only 8 (3%) and 9 (4%) cases, respectively, were diagnosed on bladder biopsy samples and surgical resection specimens (cystectomies).

Among the 279 cases analyzed, invasive urothelial tumors were the most frequent (n=144, 51.61%), followed by non-invasive urothelial tumors (n=95, 34.05%), non-tumoral lesions (n=31, 11.11%), and non-urothelial tumors (n=9, 3.22%).

With regard to the histologic subtypes, the most prevalent bladder tumor was infiltrative UC (n=131, 46.94%), followed by low-grade non-invasive UC (n=59, 21.15%). Non-neoplastic lesions, primarily cystitis, represented the third most common category (n=32, 11.11%). Among the 131 cases of infiltrative UC, 97 (74.04%) were of the pure type, while 34 (25.95%) exhibited divergent differentiation, including squamous (n=11, 32.35%), glandular (n=4, 11.76%), trophoblastic (n=4, 11.76%), micropapillary (n=5, 14.70%), plasmacytoid (n=6, 17.64%), and sarcomatoid (n=4, 11.76%) variants.

Pathological TNM (pTNM) staging data was available for 225 cases. The majority of bladder tumors were classified as NMIBCs (n=162, 72%), while 49 (21.77%) cases were MIBCs, with pT2 being the most common stage (n=38, 77.55%). In 14 (6.22%) cases, staging could not be determined (pTx).

Temporal trend and impact of COVID-19 pandemic

The number of cases of bladder lesions/neoplasms per year and their time trend frequency over the six-year study period is illustrated in Figure 1. A significant decline (-38%; n=15) in the number of new bladder lesion cases was recorded in 2020 (which corresponded to the first year of COVID-19 pandemic), compared to the previous year (2019), followed by an upward trend in the subsequent years.

Figure 2 highlights the temporal trend of each diagnostic category (non-invasive urothelial tumors, invasive urothelial tumors, non-urothelial tumors, non-tumoral

Table 1. Clinico-demographic and histological characterstics of the study cases, in comparison between pre-pandemic/pandemic (Cohort A) versus post-pandemic period (Cohort B).

Characteristics	Total (n=279)	Cohort A (n=97)	Cohort B (n=182)	p
Sex				
Male	226 (81%)	88 (90.72%)	138 (75.82%)	**0.004**
Female	53 (19%)	9 (9.27%)	44 (24.17%)	0.327
M:F ratio		9:1	3:1	
Age				
Median		70 (65-77)	66 (60-74)	**0.009**
21-30	2 (0.71%)	1 (1.03%)	1 (0.54%)	-
31-40	4 (1.43%)	0 (0%)	4 (2.19%)	-
41-50	15 (5.37%)	1 (1.03%)	14 (7.69)	-
51-60	40 (14.33%)	12 (12.37%)	28 (15.38%)	0.804
61-70	99 (35.48%)	36 (37.11%)	63 (34.61%)	0.802
71-80	92 (32.97%)	37 (38.14%)	55 (30.21%)	0.423
81-90	24 (8.60%)	7 (7.21%)	17 (9.34%)	0.866
Histology				
Non-invasive Urothelial Tumors	95 (34.05%)	29 (29.89%)	66 (36.26%)	0.547
Invasive Urothelial Tumors	144 (51.61%)	59 (60.82%)	85 (46.70%)	0.095
Non-Urothelial Tumors	9 (3.22%)	1 (1.03%)	8 (4.39%)	-
Non Tumoral Lesions	31 (11.11%)	8 (8.24%)	23 (12.63%)	0.737

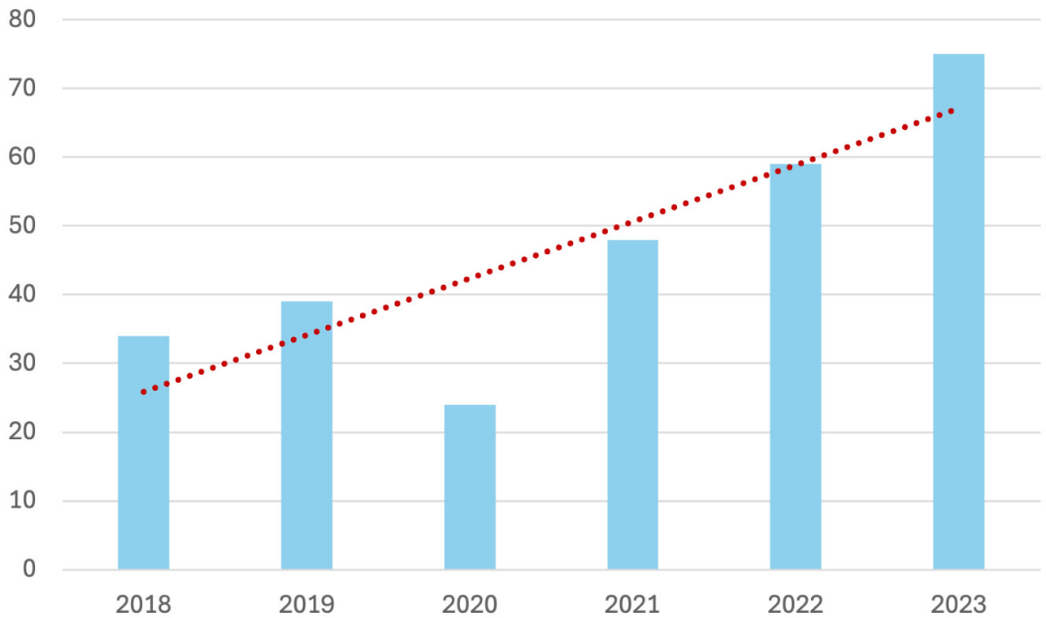

Fig. 1. Number of cases of bladder lesions per year and their time trend frequency over the study period (2018-2023)

lesions) over the entire study period. In 2018, invasive urothelial tumors were the most frequently diagnosed tumors (n=22; 64.70%), surpassing non-invasive urothelial tumors (n=10; 29.41%). Both invasive and non-invasive urothelial tumors revealed a descending trend between 2019 and 2020. In 2022, the number of invasive urothelial tumors slightly declined compared to 2021, but a 41% (n=10) increase was observed in 2023. Non-urothelial tumors demonstrated an increasing trend between 2021 and 2023. The highest frequency of non-neoplastic lesions was reported in 2022 (n=12; 26.66%).

To assess the pandemic's impact, the total number of cases were divided in two cohorts: Cohort A-pre-pandemic/pandemic: 2018-2020 (n=97 cases, 34.76%), and Cohort B- post-pandemic: 2021-2023 (n=182 cases, 65.23%). A significant 87.62% increase in the total number of bladder lesions/neoplasms was observed in Cohort B- post-pandemic compared to Cohort A- pre-pandemic/pandemic p<0.0001) (Figure 3).

Regarding different histological diagnostic categories, a significant increase was observed in all four categories in Cohort B- post-pandemic, compared to Cohort A- pre-pandemic/pandemic: Non-invasive Urothelial Tumors (+127.58%); Invasive Urothelial Tumors (+44.06%); Non-Urothelial Tumors (+700%); Non Tumoral Lesions (+187.5%). However, none were statistically significant.

Tabel 2 illustrates the distribution of NMIBCs and MIBCs in comparison between the two study periods, pre-pandemic/pandemic (Cohort A) versus post-pandemic period (Cohort B). NMIBCs were more frequent

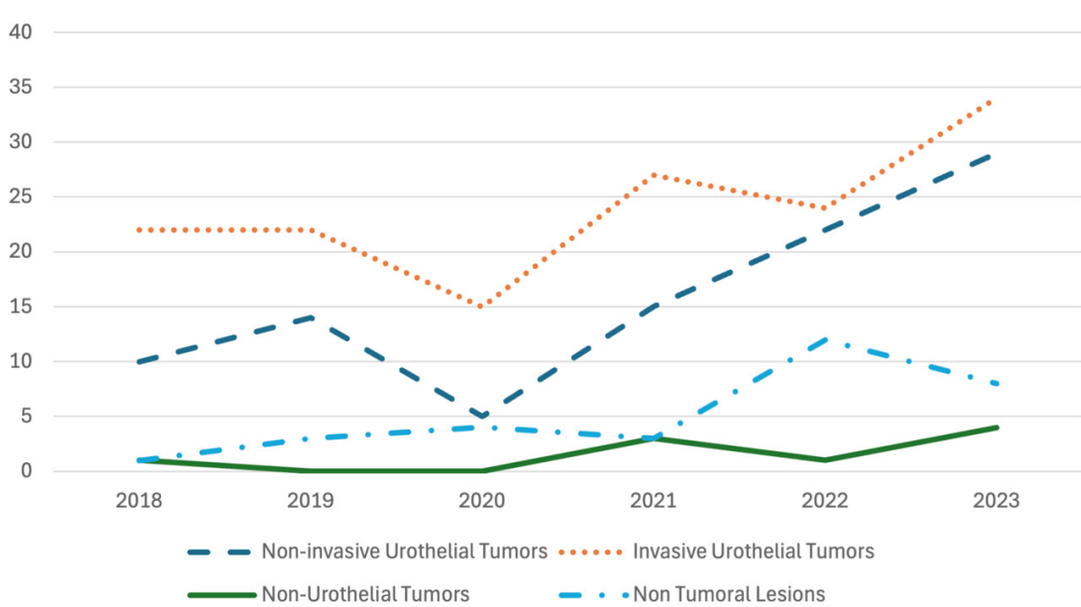

Fig. 2. Time trend evolution of the four study groups categories (non-invasive urothelial tumors, invasive urothelial tumors, non-urothelial tumors and non-tumoral lesions) over the study period (between 2018-2023).

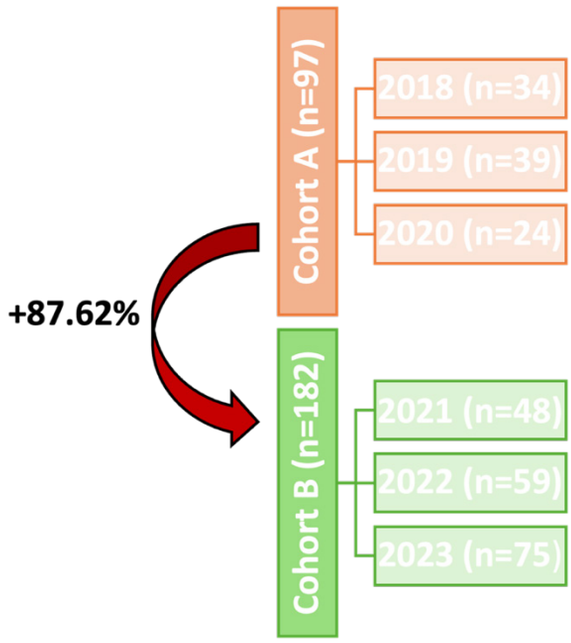

Fig. 3. Our cohort consisted of 279 cases, which were divided into two groups: cohort A, pre-COVID-19 (n=97) and cohort B, post-COVID-19 (n=182). A significant 87.62% increase in the number of cases was observed in the second study period, compared to previous period.

than MIBCs in both cohorts (Cohort A- pre-pandemic/pandemic - NMIBCs: n=60, 37.07%; MIBCs: n=16, 32.65%; Cohort B- post-pandemic – NMIBCs: n=102, 62.96%; MIBCs: n=33, 67.34%). After the first year of the COVID-19 pandemic, the number of both NMIBCs and MIBCs increased, with a significantly more pronounced increase in muscle-invasive cases (NMIBCs: +70%, p=0.002; MIBCs: +106%, p=0.017).

Discussions

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov2) virus and COVID-19 pandemic has had a major negative impact on healthcare systems all over the globe. Since the onset of COVID-19 pandemic in March 2020, more than 7 million deaths were reported [24]. During this period, Romania faced multiple challenges, including limited access to healthcare services and delays in the screening, diagnosis, and treatment of oncologic patients [25]. This study aimed to provide a comprehensive analysis of the diagnosis volume and clinicopathological characteristics of tumoral and non-tumoral lesions of the bladder diagnosed in a regional hospital in Romania over a six-year period (2018-2023), a time period centered by the COVID-19 pandemic.

Consistent with global trends, invasive urothelial tumors represented the largest proportion of diagnoses, with pure infiltrative UC being the most common subtype. The presence of specific differentiation patterns (e.g., squamous, glandular, plasmacytoid) was less frequent, aligning with current literature. The demographic profile, showing a male predominance and peak incidence in the 6th and 7th decades of life, is also typical for BC.

A notable finding was related to the annual trend in the case volume of bladder lesions and neoplasms in our institution, highlighting a marked decrease in the number of newly diagnosed cases in 2020 (-38.46%), coinciding with the onset of the COVID-19 pandemic. This trend is consistent with findings from other studies that have analyzed the impact of the pandemic on different types of cancer. The phenomenon mainly reflects the limited access of patients to medical services during the same period [26]. A study published in 2021 by Leow et al. analyzed the impact of delays caused by the pandemic and demonstrated a decrease in the frequency of diagnostic and therapeutic procedures in the first half of 2020, compared to the previous year. Another important result of the study was the observation of a "stage migration", where patients diagnosed during the pandemic often presented with more advanced and aggressive stages of the disease [27].

The delay in pursuing medical care has likely affected how often diagnoses were made and may have also influenced the stage at which tumors were detected.

The analysis of pTNM staging showed that NMIBCs (pTa, T1) were three times more common than MIBCs (pT2, pT3, pT4). This distribution is crucial for guiding management strategies, as NMIBC usually has a better prognosis, but a higher recurrence rate. Consistent with our findings, a recent meta-analysis examining global BC incidence and mortality reported an increase in the proportion of cases diagnosed at advanced stages, a phenomenon observed particularly in low- and middle-income countries. [28]. This trend highlights a continuing challenge in early detection and appropriate management of the disease.

Assessing the impact of the COVID-19 pandemic on the number of new diagnoses of bladder lesions/neoplasms and their pathological characteristics was a key objective of our study. Pre-pandemic period (2018-2020) was analyzed in comparison with post-pandemic period (2021-2023). Our results have demonstrated a significant increase in the total number of new bladder lesion cases in the post-pandemic period, compared to the previous period (+87.62%). More important, a statistically significant increase in MIBCs in

Table 2. Distribution of non-invasive and muscle-invasive bladder tumors in comparison between the two study periods, pre-pandemic (Cohort A) versus post-pandemic period (Cohort B).

	Total	Cohort A	Cohort B	Increase	p
Non-muscle invasive tumors (pTa, pT1)	162 (100%)	60 (37.07%)	102 (62.96%)	+70%	**0.002**
Muscle invasive tumors (pT2, pT3, pT4)	49 (100%)	16 (32.65%)	33 (67.34%)	+106%	**0.017**

the post-pandemic group was observed compared to the previous period. This finding strongly indicates that delays in presentation to the Urology Department during the COVID-19 pandemic may have resulted not only in postponed diagnoses but also in more advanced disease stages potentially affecting patient outcomes. This underscores the broader implications of healthcare disruptions on cancer diagnosis and management of COVID-19 pandemic.

Our analysis aligns with recent observations from a European multicenter study that assessed the impact of the COVID-19 pandemic on the diagnosis and management of BC. M. Ferro et al. revealed significant changes in the profile of newly diagnosed patients during this period [29]. More specifically, a decrease in the number of cases of NMIBC diagnosed was noted, in parallel with an increase in the proportion of MIBC. However, our findings indicated an increase in both NMIBCs and MIBCs, with a more substantial rise among MIBCs. This change is most likely attributed to the postponement of medical consultations and specialized investigations due to the restrictions imposed by the pandemic, the fear of patients to present themselves to the hospital and the redistribution of medical resources and it has been observed in other studies [30] [31]. Similarly, C. E. Alexander et al. and A. L. Schmidt et al reported an increase in the proportion of patients diagnosed at advanced stages, with muscle invasion (T2-T4) and the presence of metastases (N+ or M+) [32], [33]. Consistent with the present findings, these observations underscore the adverse consequences of diagnostic delays, which may contribute to disease progression and, consequently, poorer patient outcomes.

Several limitations of our study should be acknowledged. First, this is a single-center study with a moderate sample size, which may limit the generalizability of our findings. Nevertheless, although the hospital is not a tertiary institution, it is a county-level healthcare facility serving the entire population of the area, approximately 320,000 inhabitants. Therefore, our findings are likely to be representative of similar county-level hospitals. Additionally, the retrospective design of the study is particularly prone to selection bias and confounding variables.

Conclusion

Our study provides new insights into the temporal trends and histopathological characteristics of urothelial lesions/neoplasms registered in the Department of Pathology, Bistrița County, Romania over the last six years (2018-2023). Invasive urothelial carcinoma was the predominant histological tumor type and non-muscle invasive tumors (pTa, T1) were three times more frequent compared to muscle-invasive tumors (pT2, pT3, and pT4).

COVID-19 pandemic has had a significant impact in our study group, reflected by a significant increase in the total number of cases (herein including both tumoral and non-tumoral lesions), as well as a significant increase in the number of MIBCs in the post-pandemic group compared to pre-pandemic/pandemic group. These results most likely indicate that reduced patients' addressability to the Urology Department during the pandemic has led to the detection of more advanced stage tumors in the post-pandemic period that followed. Nevertheless, our results need further confirmation through future larger scale studies.

Abbreviations

BC – Bladder Cancer
COVID-19 - Coronavirus Disease 2019
IHC - Immunohistochemistry
IQR - Interquartile Range
MIBC – Muscule-Invasive Bladder Cancer
NMIBC - Non-Muscle-Invasive Bladder Cancer
SARS-Cov2 - Severe Acute Respiratory Syndrome Coronavirus 2
TNM - Tumor, Node, and Metastasis staging system
TUR-BT - Transurethral Resection of Bladder Tumor
UC – Urothelial Carcinoma

Authors' contribution

PC (Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft)
GNR (Formal Analysis, Writing – original draft, Methodology, Software)
IANB (Data curation, Methodology, Visualization, Formal Analysis)
ANB (Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision, Validation, Visualization)

Conflict of interest

None to declare.

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