

# Journal Pre-proof

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Original Study

### **The Impact of the Covid-19 Pandemic on Genitourinary Cancers Stage and Grade**

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## **Abstract**

**Introduction:** Our study aims to evaluate the impact of the COVID-19 pandemic on the number of uro-oncological surgeries (cystectomy, nephrectomy, prostatectomy, orchiectomy, and transurethral resection of bladder tumor (TURBT)) and pathological staging and grading.

**Materials and Methods:** The present study is a retrospective study on patients with genitourinary cancers treated from 2018 to 2021 in a referral tertiary center. The data were obtained from the hospital records with lengths of 22 and 23 months, labeled hereafter as non-COVID and COVID pandemic, respectively (2018/3/21-2020/1/20 and 2020/1/21-2021/12/21). The total number of registered patients, gender, age, stage, and grade were compared in the targeted periods. Moreover, all the pathologic slides were reviewed by an expert uropathologist before enrolling in the study. The continuous and discrete variables are reported as mean (standard deviation (SD)) and number (percent) and the Chi-squared test for the comparison of the discrete variables' distribution.

**Results:** In this study total number of 2077 patients were enrolled. The number of procedures performed decreased during the Covid pandemic. The tumors' distribution stage and grade and patients' baseline characteristics were not significantly different in non-COVID and COVID pandemic periods for Radical Nephrectomy, Radical Cystectomy, Radical Prostatectomy, and orchiectomy. For TURBT only, the tumor stage was significantly different ( $p$ -value $<0.001$ ) from the higher stages in the COVID pandemic period.

**Conclusion:** Among urinary tract cancers, staging of bladder cancer and TURBT are mainly impacted by the COVID-19 pandemic with higher stages compared to the non-COVID period.

We evaluate the impact of the COVID-19 pandemic on the number of uro-oncological surgeries based on pathological staging and grading. Total number of 2077 patients were enrolled. Among urinary tract cancers, staging of bladder cancer and TURBT are mainly impacted by the COVID-19 pandemic with higher stages compared to the non-COVID period.

**Keywords:** COVID-19 pandemic, Nephrectomy, Cystectomy, Prostatectomy, Orchiectomy, TURBT

## **Introduction**

Since COVID-19's discovery in Wuhan, China, in December 2019, more than 468 million people have been infected, and more than 6 million have died worldwide (1). The Covid-19 outbreak has been a significant setback for healthcare systems, particularly for vulnerable populations such as cancer patients. The influx of large numbers of COVID-19 patients requiring intensive monitoring and mechanical ventilation has caused healthcare systems to become overburdened. Therefore, oncology patients' outcomes are likely to be harmed by standard delayed treatment (2-4). Previous research has linked the COVID-19 pandemic to lower diagnosis rates for malignancies, including breast, colorectal, lung, pancreatic, gastric, and esophageal cancers (5, 6).

Timely diagnosis of cancer is essential to optimize the clinical outcomes of patients and has been considered to improve in recent decades (7, 8). Like many other oncologists, urologists are fighting the pandemic on two fronts: the pandemic itself and cancers. It confronts Urologists because therapeutic delays may lead to adverse oncological outcomes and patients with higher cancer stages. Urologic cancers such as the bladder and prostate are among the most prevalent cancers worldwide, and delays in recognizing them can be life-threatening. Patients in their late 60s and early 70s have a higher risk of urologic cancers; these groups are

more prone to COVID-19 and have several comorbidities. Approximately 80% of COVID-19 deaths in China occurred in adults over 60 (9-13). Several recommendations and guidelines have been published to improve the triage and treatment of uro-oncological patients in times of limited resources. These guidelines are beneficial in dealing with the current pandemic situation. Still, due to differences in healthcare systems, demographic features, genetics, stage, grade, and fear of pandemic in any country, we encourage optimization of these guidelines by each country's characteristics (14-16).

We aimed to check whether the COVID-19 pandemic can change the number of uro-oncological surgeries (radical cystectomy, radical nephrectomy, radical prostatectomy, radical orchiectomy, and transurethral resection of bladder tumor (TURBT)) and the tumor staging and grading during non-pandemic and pandemic period in Iran's referral tertiary center.

## **Material and Methods**

### **Study design and sampling**

A retrospective study on patients confirmed by post-operative or biopsy pathology reports with urology cancer treated from 2018 to 2021, at Sina Hospital affiliated to Tehran University of Medical Sciences, and MohebMehr Hospital affiliated to Iran University of Medical Sciences designed to compare patients' gender and age and tumors stage and grade over two time periods: 1. non-covid pandemic (2018/3/21-2020/1/20), 2. covid pandemic (2020/1/21-2021/12/21), with lengths of 22 and 23 months, labeled hereafter as non-COVID and COVID pandemic, respectively. The Scientific and Ethics Committee approved this study at the Tehran University of Medical Science (*IR.TUMS.SINAHOSPITAL.REC.1400.037*).

Tumors were classified according to the prognostic AJCC tumor, lymph node, metastasis (TNM)-based staging system (17), ISUP 2016 grading for bladder and prostate (18), and Fuhrman Nuclear Grade for renal carcinoma based on cellular appearance (19).

In the Fuhrman Nuclear grading system, chromophobe renal cell carcinoma (ChRCC) is not classified, so we excluded 6 cases of ChRCC in non-COVID and 6 cases of ChRCC in the COVID pandemic from the study. In addition, we excluded urothelial carcinoma of the renal pelvis (14 cases of TCC in non-COVID and 8 cases of TCC during the COVID pandemic).

The known cancer cases with recurrence malignancy or post-chemotherapy biopsy were excluded from the study, and all the pathological slides were reviewed by an expert uropathologist before enrolling in the study.

### Statistical analysis

The continuous and discrete variables are reported as mean (standard deviation (SD)) and number (percent), respectively. The Chi-squared test compared the discrete variables' distribution between the time intervals.

### Results

In this study total number of 2077 patients were enrolled. The tumors' distribution and patients' age and sex characteristics are reported in Table 1.

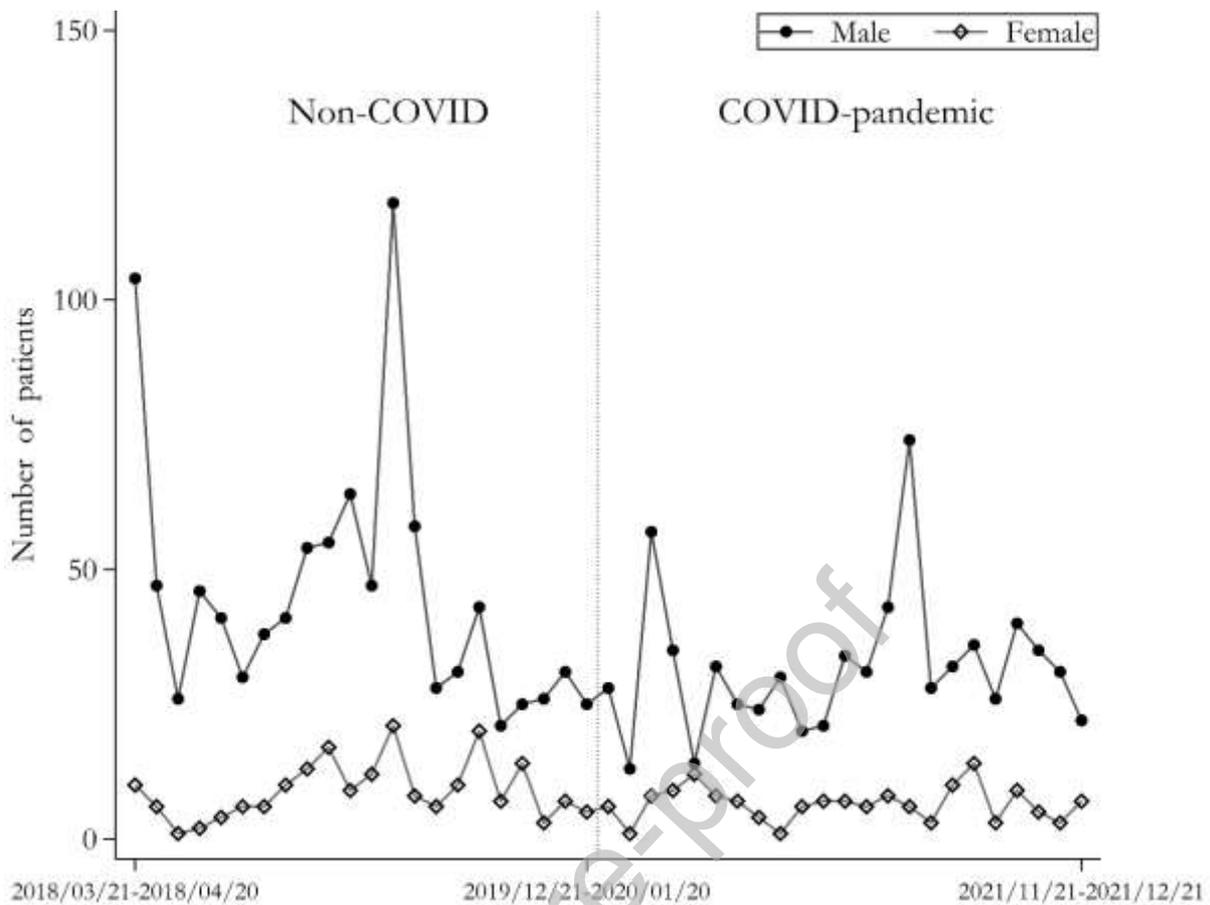
**Table 1.** Tumors' distribution was compared for the two target time intervals.

<b>Tumor</b>		<b>non-COVID</b>	<b>COVID pandemic</b>	<b>p-value</b>
	Number total/monthly	43 / 2.0	18 / 0.8	
<b>Cystectomy</b>	Age, mean (SD)	62.3 (9.1)	63.6 (6.1)	0.585
	Sex (male), num. (%)	40 (93.0 %)	17 (94.4 %)	0.838

	Number total/monthly	199 / 9.0	145 / 6.6	
<b>Nephrectomy</b>	Age, mean (SD)	58.9 (12.9)	59.7 (11.8)	0.540
	Sex (male), num. (%)	124 (62.3 %)	91 (62.8 %)	0.933
<b>Prostatectomy</b>	Number total/monthly	284 / 12.9	188 / 8.5	
	Age, mean (SD)	64.4 (6.6)	64.2 (6.6)	0.712
<b>Orchiectomy</b>	Number total/monthly	18 / 0.8	12 / 0.5	
	Age, mean (SD)	40.3 (14.8)	38.3 (14.8)	0.716
	Number total/monthly	652 / 29.6	518 / 23.5	
<b>TURBT</b>	Age, mean (SD)	67.2 (11.4)	65.9 (12.4)	0.061
	Sex (male), num. (%)	533 (81.8 %)	423 (81.7 %)	0.969

SD: standard deviation

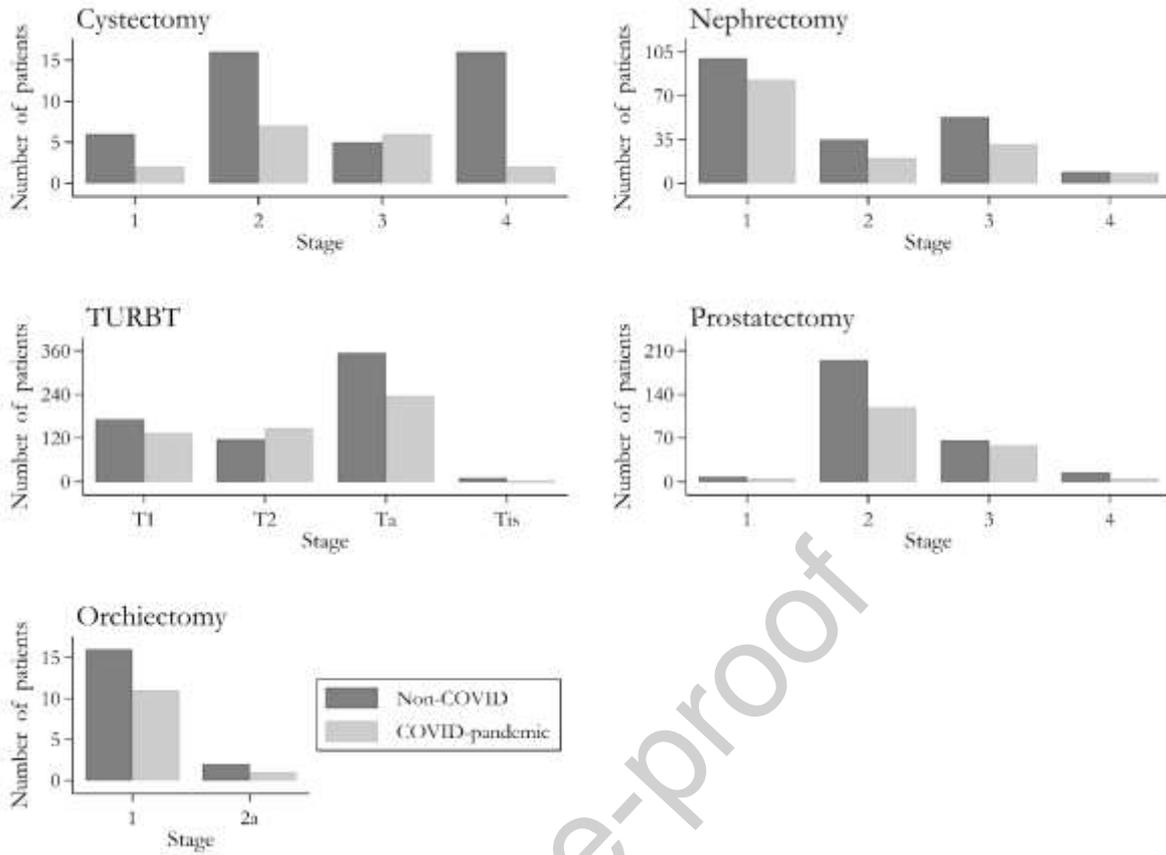
The total number of kidney cancers was 219 non-COVID and 159 COVID pandemics and finally, 199 non-COVID nephrectomy cases and 145 COVID pandemic cases of nephrectomy remain for additional analysis. The number of tumor related surgical procedures decreased during the Covid pandemic. The age and sex distributions showed no significant difference. The monthly frequencies of all tumors are also presented in Figure 1. While an almost seasonal pattern is apparent in the case of men, with the peaks in the spring, the women are almost uniformly distributed.



**Figure 1.** The monthly frequencies of tumors

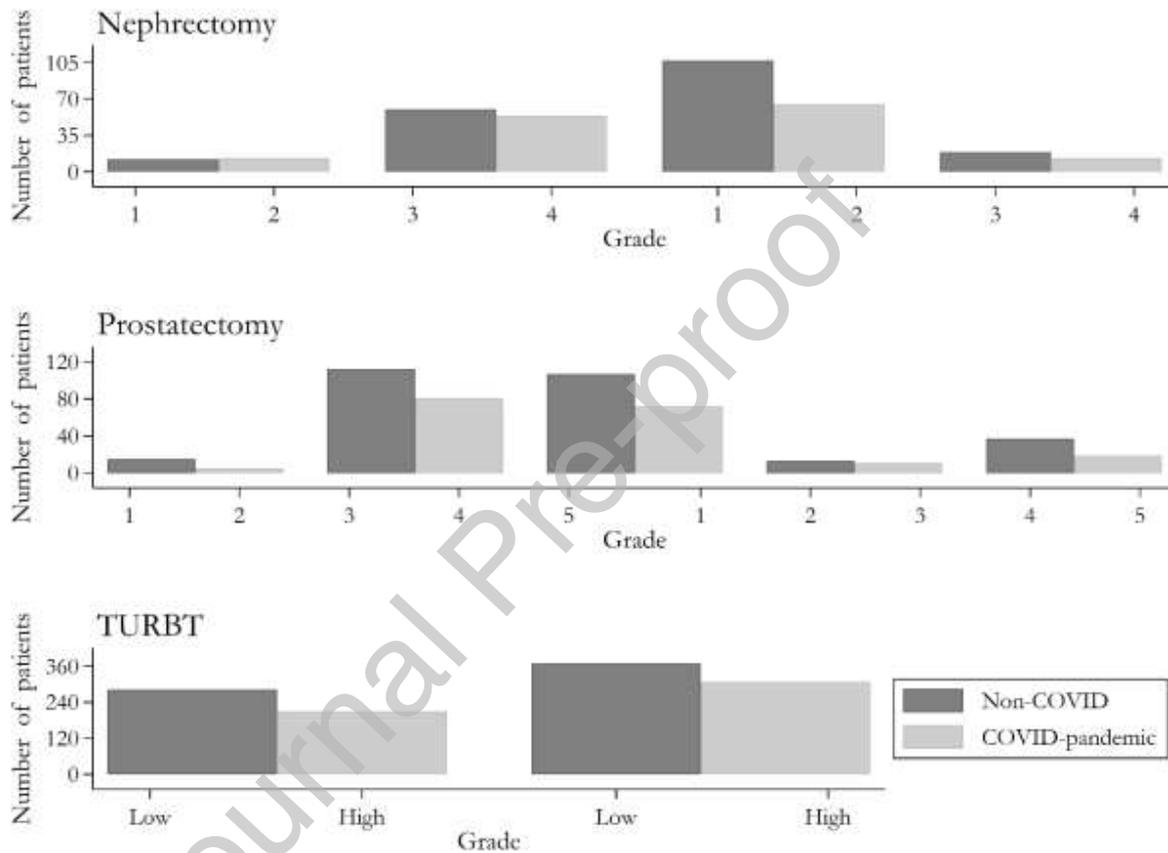
Figure 2 presents the tumors' staging in the two target periods as percentages of each period.

The only significant difference between non-COVID and COVID pandemic periods was observed for TURBT ( $p$ -value $<0.001$ ), obtained through the Chi-squared test.



**Figure 2.** The distribution of tumors' staging, compared for the non-COVID and COVID pandemic periods (numbers over the bars are percentages)

Similarly, in Figure 3, tumor grading is reported as percentages comparing the periods. The cystectomy tumors were all high grades, and no grading was documented for the orchiectomy tumors. There was no significant difference between the two periods for nephrectomy, prostatectomy, and TURBT tumors.



**Figure 3.** The distribution of tumors' grading, compared for the non-COVID and COVID pandemic periods (numbers over the bars are percentages)

Additionally, enough observations were collected to compare men's and women's stages and grades of nephrectomy and TURBT tumors. Table 2 presents these findings.

**Table 2** Nephrectomy and TURBT tumors' staging and grading, compared between men and women

Tumor		non-COVID		p-value	COVID-pandemic		p-value
		Women	Men		Women	Men	
<b>Nephrectomy</b>	<b>Stage</b>						
	1	39 (52.0 %)	61 (50.0 %)	0.373	33 (61.1 %)	50 (56.8 %)	0.972
	2	9 (12.0 %)	26 (21.3 %)		7 (12.9 %)	13 (14.8 %)	
	3	23 (30.7 %)	30 (24.6 %)		11 (20.4 %)	20 (22.7 %)	
	4	4 (5.3 %)	5 (4.1 %)		3 (5.6 %)	5 (5.7 %)	
	<b>Grade</b>						
	1	3 (4.0 %)	9 (7.3 %)	0.442	7 (13.0 %)	6 (6.6 %)	0.086
	2	27 (36.0 %)	33 (26.8 %)		20 (37.0 %)	34 (37.4 %)	
	3	37 (49.3 %)	70 (56.9 %)		19 (35.2 %)	46 (50.5 %)	
	4	8 (10.7 %)	11 (8.9 %)		8 (14.8 %)	5 (5.5 %)	
<b>TURBT</b>	<b>Stage</b>						
	T1	22 (18.5 %)	150 (28.1 %)	0.061	17 (17.9 %)	117 (27.7 %)	0.004
	T2	18 (15.1 %)	98 (18.4 %)		21 (22.1 %)	126 (29.8 %)	

		%)	%)		%)	
	Ta	77 (64.7 %)	277 (52.0 %)		56 (58.9 %)	180 (42.5 %)
	Tis	2 (1.7 %)	8 (1.5 %)		1 (1.1 %)	0 (0 %)
	Grade					
	Low	66 (55.5 %)	216 (40.5 %)	0.003	51 (53.7 %)	159 (37.6 %)
	High	53 (44.5 %)	317 (59.5 %)		44 (46.3 %)	264 (62.4 %)
						0.004

Values inside the table are numbers (percent). P-values were obtained from the Chi-squared test.

While no sex difference was observed in the nephrectomy's staging and grading, before and during the pandemic, men and women were significantly different in TURBT. Finally, the Gleason scores for prostatectomy are reported in Table 3, comparing the periods. No significant differences were observed in the Gleason scores corresponding to the two target time intervals.

**Table 3.** The Gleason scores for prostatectomy reported as number (%), compared to the time intervals

Score	non-COVID	COVID pandemic	p-value
3+3	15 (5.3 %)	5 (2.7 %)	0.835
3+4	116 (40.8 %)	80 (42.6 %)	
3+5	3 (1.1 %)	2 (1.1 %)	
4+3	105 (37.0 %)	73 (38.7 %)	
4+4	10 (3.5 %)	9 (4.8 %)	
4+5	26 (9.2 %)	16 (8.5 %)	
5+4	8 (2.8 %)	3 (1.6 %)	
5+5	1 (0.4 %)	0 (0.0 %)	

P-value from the Chi-squared test

## Discussion

We investigate whether the COVID-19 pandemic has affected the stage and grade of genitourinary malignancies at diagnosis in Iran. Several reports are on the impact of the COVID-19 pandemic on the numbers of patients for almost all cancer types (20, 21). Worries about contracting COVID-19 and fear of higher incidence risk in healthcare systems have prevented patients from referring to their doctors (22). Our findings showed that during the COVID-19 pandemic, the number of nephrectomies, prostatectomies, and the total number of urology procedures decreased but not significantly. Same as the report by Van Deukeren D. and colleagues that showed an initial decrease of 17% in prostate cancer in the first COVID-19 wave

but restored the number by the end of 2020 (23). Contrary to some data on reducing all urologic activities (24).

Other studies in the urologic oncology field have already described a decrease in elective oncological surgical activity; however, this finding has been associated with an increase in the average waiting time for surgery (25-28). This decrease is related to the healthcare system's overburdening, pandemic fears, public reluctance, social isolation, and quarantine not change in guidelines and recommendations for urology standard of care during the COVID-19 pandemic (29). New cancer diagnoses dropped during the COVID-19 pandemic because patients with symptoms (e.g., hematuria or stomach ache) may avoid seeking medical attention due to concern about contracting COVID-19 (30, 31). Semi-structured interviews in the United States found that patients may be reluctant to receive primary care from a physician because they consider hospitals where contagious diseases can spread (32). Moreover, healthcare systems were quickly overburdened, and non-urgent care services in hospitals and primary care settings were delayed or discontinued (33). A recent survey by Dotzauer et al. showed that 93% of urologists from 44 countries appealed that COVID-19 had decreased their patient number; less TURBT (27%), radical cystectomy (21-24%), nephroureterectomy (21%) and radical nephrectomy (18%) (34).

Except for TURBT, which had a significant decline in the Ta, Tis stages and an increase in T2 during the COVID pandemic, no considerable tumor stage change was observed in our study. Ferro M. et al. explained that the COVID-19 pandemic represented an unprecedented challenge to their health system. They did not display noteworthy differences in TURBT quality, but a delay in treatment schedule and disease management was observed (35).

It was shown that 2-5 months of delay in follow-up cystoscopy as suggested in the COVID-19 pandemic raises the risk of recurrence (36). A study by Tulchiner G. and colleagues indicated

that the COVID-19 pandemic gap can increase rates of advanced and aggressive tumors in patients with primary bladder cancer, and additional awareness is required to avoid adverse consequences (37). A recent meta-analysis by Kang DH et al. highlighted the EAU guidelines Rapid Reaction Group in which patients with T2N0M0 muscle-invasive bladder cancer (MIBC) should strongly consider omitting neoadjuvant chemotherapy (NAC) until the end of the COVID-19 pandemic (38). However, NAC in T3-4aN0M0 MIBC should be considered (38). According to a review published in the Journal of Urology, this delay should be less than ten weeks, and neoadjuvant chemotherapy should be considered (39).

A systematic review also stated that except for MIBC, high-grade and upper tract urothelial carcinoma, large renal masses, and testicular and penile cancer, most urologic oncologic surgeries could be safely postponed without affecting long-term cancer-specific or overall survival (40). despite the report of no decrease in uro-oncological surgical procedures in an Italian tertiary referral center, an increase was reported in lymph node metastasis, and non-organ confined disease in MIBC T2-T4 (41).

We have many patients in the TURBT groups in our study, which allows us to go deep into the data to investigate if gender differences influence the stage and grade of tumors. The TURBT surgery process in Men has shown higher stage and grade than women during the pandemic. No other study compares gender differences in pathological staging and grading of TURBT tumors before and during the COVID-19 pandemic. This disparity could be attributed to male patients' lack of attention or fear of a pandemic in seeking medical treatment. We propose that future research might employ questionnaires to assess the gap between clinical presentation and seeking medical care and the Fear of COVID-19 Scale (FCV-19S) to determine this gender difference in bladder cancer patients (42).

Several novel biomarkers and treatment strategies are considered in genitourinary cancers, dependent on timely tumor diagnosis (7, 43-46). A significant reduction in radical prostatectomy during the COVID-19 pandemic was reported in our study. However, during the COVID-19 pandemic, the stage, grade, and Gleason prostate cancer scores have no significant difference in non-COVID and COVID pandemics. Findings from a contemporary prostate cancer cohort by Diamand R., et al. indicate no evidence that a delay in radical prostatectomy is associated with a decrease in oncologic outcomes (47). Similarly, in a systematic review published on intermediate-risk and high-risk prostate cancer, time to surgery can be delayed up to 3 months without adverse effects on their health, and delays of more than 6 to 9 months have been linked to worse pathological results. There have been no reports of worse cancer-specific survival or overall survival due to delaying therapy for intermediate and high-risk prostate cancer (48). Also, in a recent article, Ginsburg et al. state that in radical prostatectomy, early oncological outcomes such as upgrading on radical prostatectomy, lymph node involvement, and secondary treatments after surgery were not related to delays up to 12 months (49). According to the findings, our study did not precisely determine how long each participant had a prostatectomy delay; it can be estimated that this time was probably less than 12 months. In comparison to our study, only one cross-sectional study in Sweden found no decline in the number of radical prostatectomies during the peak of the first phase of the COVID-19 pandemic (50). Based on most studies' results, we can highlight prostate cancer's slow progression and the necessity for an effective telemedicine system to assist in diagnosing, triaging, and treating patients and minimize the risk of COVID-19 exposure.

Based on the findings, and given that the COVID-19 pandemic is still active in Iran and many countries, strategies should be done to improve cancer detection with limited healthcare

resources. Patients should be better educated about symptoms that necessitate immediate medical attention as a first step. Second, patients should have access to more teleconsultations with their primary care physicians and be referred to specialists as soon as further investigation is required. Third, COVID-19 patients should be assigned to specific hospitals, while other clients should access various facilities. Patients' worry about contracting the sickness will be decreased by attending the hospital in this manner. Certain limitations apply to this investigation. The number of patients in the cystectomy and orchiectomy categories is minimal. We conduct multicenter research, but we do not have a separate report from each center.

### **Conclusion**

The numbers and rates of uro-oncological surgical procedure decreased during the Covid19 period. This phenomenon affected only pathologic tumor stage at trans-urethral resection of the bladder, where a clinically meaningful and statistically significant higher rates of T2/muscle-invasive bladder cancer were diagnosed during the Covid 19 outbreak than during the previous time-period.

### **Clinical practic epoint**

Our study aims to evaluate the impact of the COVID-19 pandemic on the number of uro-oncological surgeries (cystectomy, nephrectomy, prostatectomy, orchiectomy, and transurethral resection of bladder tumor (TURBT)) and pathological staging and grading. The total number of registered patients, gender, age, stage, and grade were compared in the targeted periods. Moreover, all the pathologic slides were reviewed by an expert uropathologist before enrolling in the study. The continuous and discrete variables are reported as mean (standard deviation (SD)) and number (percent) and the Chi-squared test for the comparison of the discrete variables' distribution. Total number of 2077 patients were enrolled. All tumors tend to decrease in the

COVID pandemic period. The tumors' distribution stage and grade and patients' baseline characteristics were not significantly different in non-COVID and COVID pandemic periods for Radical Nephrectomy, Radical Cystectomy, Radical Prostatectomy, and orchiectomy. For TURBT only, the tumor stage was significantly different ( $p$ -value $<0.001$ ) from the higher stages in the COVID pandemic period. Among urinary tract cancers, staging of bladder cancer and TURBT are mainly impacted by the COVID-19 pandemic with higher stages compared to the non-COVID period.

### **Credit Author statement**

Seyed Mohammad Kazem Aghamir: Conceptualization, Methodology, Software  
Alireza Khajavi.: Data curation, Writing - original draft. Fatemeh Kafi, Alireza Pouramini, Reza Mohammadi Farsani: Visualization, Investigation. Yasamin Alizadeh, Maryam Akbarzadeh: Supervision.: Leonardo Oliveira Reis, Fatemeh Khatami: Software, Validation.: Diana Taheri, Fatemeh Jahanshahi: Writing - reviewing & editing

### **Availability of data and material**

All information, data, and photos are all provided through the manuscript, and additional will be provided if requested.

### **Ethical considerations**

All patients signed the written informed consent, and the study was approved by the Tehran University of Medical Sciences ethical committee (*IR.TUMS.SINAHOSPITAL.REC.1400.037*).

### **Authors' contributions**

SMKA and DT are principal investigators, FK and AP wrote the manuscript, FJ, RMF, and YA collected data, AKH and FKH analyzed the data, and LOR and MA edited the manuscript.

### **Declaration of Competing Interest**

All authors claim that there is not any potential competing or conflict of interest

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