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Original Research

Effects of the COVID-19 Pandemic on Prostate Cancer Screening and Diagnosis

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Abstract

Background: COVID-19 pandemic clearly demonstrates that not only is it causing unprecedented morbidity and death worldwide, its almost unstoppable spread is affecting the diagnosis and treatment of many other acute and chronic diseases. These changes created by the COVID-19 pandemic have had a direct negative impact on cancer screening and new cancer diagnosis. **Methods**: We aimed to compare prostate specific antigen (PSA) requested, TRUS guided biopsy (TRUS-Bx) and new prostate cancer (PCa) diagnoses from 1 January 2019 to the end of 31 December 2021 both on an annual basis and as a monthly change, and evaluate the percentage change. Patients' age, prostate volume, PSA values, pathology results of biopsies were analyzed as basic demographic information. **Results**: From January 2019 through December 2021, there were 18618 PSA testing and 141 TRUS-Bx results from men in the hospital database. When we look at the distribution of PSA test requests by years, we see that 8473 in 2019, 4763 with a decrease of 44% in 2020 and a 12% increase in 2021 compared to 2020, but still 36.5% less in 2019. When we look at the number of TRUS-Bx, we see that we performed a total of 141 TRUS-Bx between January 2019 and December 2021. While we performed 65 TRUS-Bx in 2019 before the pandemic, this figure decreased to 40 with a 38.5% decrease in 2020, while we observed that the similar situation continued with 36 cases in 2021. **Conclusions**: As a result, our findings show that a significant number of PCa screening opportunities and cancer diagnoses are missed. Delays in cancer diagnosis will cause adverse clinical outcomes in the coming years. Considering that PCa does not pause due to the COVID-19 pandemic, it may cause patients to progress to more advanced disease stage at the time of diagnosis, require more aggressive treatment and even succumb to cancer due to the delays that occur. Further work is required to analyze the assessment of the clinical prognostic impact of cancer diagnosis delays.

Keywords: COVID-19; cancer diagnosis; prostate cancer

1. Introduction

In the past two decades, zoonotic coronaviruses have caused large-scale disease outbreaks. Severe Acute Respiratory Syndrome (SARS) emerged in 2003 and Middle East Respiratory Syndrome (MERS) emerged in 2012, causing a pandemic that has killed thousands of people worldwide [1]. The observation of several cases of pneumonia of unknown etiology in China at the end of 2019 aroused intense interest not only in China but also internationally. With the rapid increase in the number of cases, the Chinese province of Wuhan became the center of an epidemic of pneumonia of unknown origin in December 2019. Chinese scientists isolated an unprecedented coronavirus from patients with this pneumonia in Wuhan on January 7, 2020 [2]. The causative virus was originally named as "novel coronavirus 2019" (2019-nCoV) by the World Health Organization (WHO), but was later renamed as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the international Coronavirus Study Group. Finally on January 12, 2020 WHO determined the final decision in naming as COVID-19 [3]. The rapid spread of the COVID-19 disease and rising deaths necessitated declaring a global pandemic.

The first COVID-19 case in Turkey was announced on March 11 2020, by the Ministry of Health and on the same day WHO declared a pandemic all over the world [4]. On March 21, 2020 almost 10 days after the first case, the lockdown was declared with the increase in the number of new cases per day in Turkey. Unlike many other European countries, a nationwide lockdown was not implemented in Turkey and only covered certain age groups ($\leq$20 and $\geq$65 years). During the COVID-19 pandemic, no restrictions were applied in any laboratory tests including PSA.

COVID-19 initially started with symptoms of dry persistent cough, fever and shortness of breath, and in severe cases, pneumonia developed and caused acute respiratory distress syndrome that may require respiratory support [5]. Despite social distancing and isolation measures, the number of cases are still increasing. The rapid increase in patient numbers and the COVID-19 pandemic, which requires inpatient treatment, have caused a great strain for global health systems. At the beginning of the pandemic, stay-at-home orders began to be implemented because of with the increasing number of in cases across the country. To reduce the risk of an overload of the healthcare system, there were restrictions and access to primary and secondary healthcare were limited, potentially causing diagnostic delays, underdiagnosis and inadequate treatment of non-COVID-19 related diseases. After the declaration of the pandemic, some

non-urgent clinical appointments were postponed, elective surgeries were canceled, intensive care capacities were increased, and social life was restricted with a national quarantine. The ongoing COVID-19 pandemic clearly demonstrates that not only it is causing unprecedented morbidity and death worldwide, its almost unstoppable spread is affecting the diagnosis and treatment of many other acute and chronic diseases. These changes which were created by the COVID-19 pandemic have had a direct negative impact on cancer screening and new cancer diagnosis. It has been reported in various series that sudden decreases at different rates (25–75%) were observed in both the number of cancer screenings and the number of new cancer cases all over the world after the COVID-19 pandemic [6–14].

Prostate cancer (PCa) is the second most common cancer in men (14.1%) after lung cancer (14.3%) and ranks fifth in cancer-related deaths (lung 21.5%, liver 10.5%, colorectal 9%, stomach 9.1% prostate 6.8%) [15]. Stamey's work on prostate specific antigen (PSA) was a landmark, and PSA has become the most important biomarker for PCa [16]. PSA has been shown to be a superior predictor of PCa diagnosis to both digital rectal examination and transrectal ultrasound (TRUS) [17]. In the last three decades, widespread use of PSA screening has resulted in an increased incidence of PCa.

In this study, we compared the PSA requested, TRUS guided biopsy (TRUS-Bx) and new PCa diagnoses between the pre-pandemic and the pandemic period in order to determine the effect of the COVID-19 pandemic on PCa screening and new PCa diagnosis. We wanted to investigate how the ongoing COVID-19 pandemic affects routine practices in the secondary care hospital in Izmir Turkey.

2. Material and Method

2.1 Study Design

We have retrospectively identified PSA test requests for outpatients in the last three years (1 January 2019–31 December 2021) through the laboratory information system of the Laboratory Medicine Service of the hospital database. PSA was assayed in Roche Cobas 6000 by electro chemiluminescence method and the results were reported as ng/mL (Roche Diagnostics, Rotkreuz, Switzerland). The records of patients who underwent TRUS-Bx between the same dates in our hospital were investigated retrospectively.

In our hospital PCa screening on a yearly base starts at the age of 45 years by palpation. As a cutoff, age-specific PSA reference ranges according to Oesterling *et al.* [18] were used. Biopsy indications were set as high PSA level and/or suspicious prostate examination findings. In the pandemic period, TRUS-Bx was continued by giving priority to high-risk patients under local anesthesia. Standard 12 core TRUS-Bx, which were taken according to the routine protocol until the declaration of the pandemic, were taken within the framework of the measures applied to both the patient and the team, which were newly determined by the hospital infection control committee after the declaration of the pandemic. A negative result of reverse transcriptase-polymerase chain reaction (RT-PCR) for coronavirus was obtained from each patient before the biopsy procedure.

Prostate biopsy results were graded according to the Gleason score according to the 2005 and 2014 consensus of the International Society of Urological Pathology. In this study, Gleason scores in prostate biopsy were reported in two grouping: Gleason score $\leq$7 and Gleason score $\geq$8. TRUS prostate biopsy and accordingly PCa rates between 2019, when there was no pandemic, and between 2020, when the pandemic started in Turkey, and 2021, were compared to investigate the potential impact of the COVID-19 pandemic on the diagnosis of PCa. Patients' age, prostate volume, PSA values, pathology results of biopsies were analyzed as basic demographic information. We aimed to compare PSA requested, TRUS-Bx and new PCa diagnoses from January 2019 to the end of December 2021 both on an annual basis and as a monthly change, and evaluate the percentage change.

2.2 Statistical Analysis

The data were collected from medical records and uploaded to Excel 2019 database (Microsoft Corp., Redmond, WA, USA). An independent samples *t*-test was performed to compare average monthly PSA requests in the pre-pandemic and pandemic periods. Patient's age, PSA levels, prostate volumes, pathology results, and Gleason scores were also compared during these periods. Assumptions for normality, outliers, and homogeneity of variances were checked before analysis. Categorical variables (pathology groups and Gleason scores) were analyzed with Chi-square tests. All analyzed were performed with SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and significance level accepted $p < 0.05$.

Ethical approval was obtained from Ethical Research Committee of the Izmir Demokrasi University (Committee Board Approval No.: 2022/03-74). Informed consent was received from the participants before the TRUS-Bx.

3. Results

From January 2019 through December 2021, there were 18618 PSA tests and 141 TRUS-Bx results from men in the hospital database. When we look at the distribution of PSA test requests by years, we see that 8473 in 2019, 4763 with a decrease of 44% in 2020 and a 12% increase in 2021 compared to 2020, but still 36.5% less in 2019. After the first case was officially announced in our country in March 2020, the biggest decrease was found in April 2020 with 54 PSA tests requests. Considering that the PSA tests requests in April 2019 were 729 before the pandemic, it was seen that the decrease was 92.5%. Although the increases started in May, it was observed that they were quite far from the previous year's levels. It was observed that it continued at a

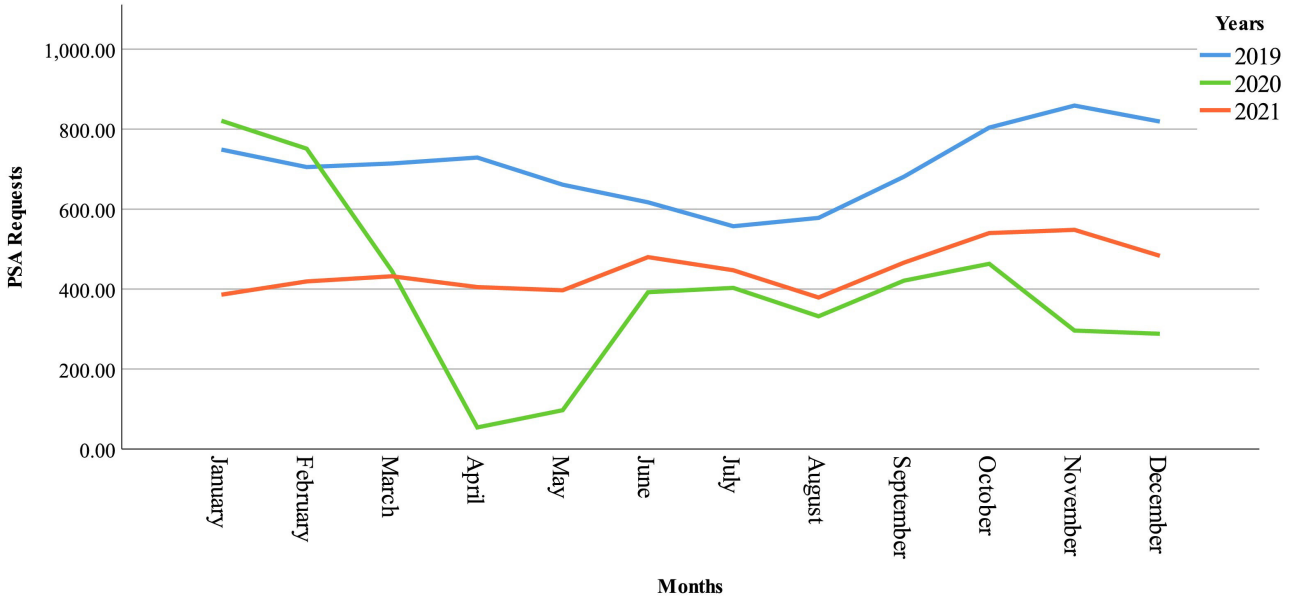

Fig. 1. Prostate specific antigen (PSA) requests s in the pre-pandemic and pandemic periods.

Table 1. Characteristics of the study population who underwent TRUS guided prostate biopsy (n = 141).

Variables	n		Mean	SD	Min	Max	*t*/*p* value
Age	94	Pre-pandemic period	66.71	8.19	46	88	–0.05/0.95
	47	Pandemic period	66.78	6.36	51	83	
PSA, ng/mL	94	Pre-pandemic period	15.14	23.77	2.3	100	0.13/0.89
	47	Pandemic period	14.61	21.61	1.3	100	
Prostate Volume cm^3	94	Pre-pandemic period	63.52	35.54	4	215	–0.21/0.83
	47	Pandemic period	64.85	33.5	18	155	

PSA, prostate specific antigen; SD, standard deviation.

lower level throughout the year compared to the previous year. Although there is an increase of 12% in 2021 compared to the previous year, it is observed that it still cannot reach the figures of 2019 before the pandemic and is below 36.5% in total. The monthly PSA requests in 2019, 2020 and 2021 are shown in Fig. 1.

As shown in Fig. 1, the PSA requests, that have decreased with the pandemic period since April 2020 have not reached the level of 2019 and the first three months of 2020 in the next 21 months. The result of the performed was used *t*-test to compare the average monthly PSA requests in the pre-pandemic and pandemic periods and the results shows that the average monthly PSA requests were higher in the pre-pandemic period (Mean = 699.33, SD = 134.30) than in the pandemic period (Mean = 387.04, SD = 150.81) and the difference between the two periods was statistically significant t(34) = 6.40, $p < 0.001$.

The total number of TRUS-Bx made between January 2019 and December 2021 was 141. While we performed 65 TRUS-Bx were performed in 2019 before the pandemic, this figure decreased to 40 with a 38.5% decrease in 2020, while we observed that the similar situation continued with 36 cases in 2021.

From January 2019 to December 2021, 141 prostate biopsies were performed. 66.7% of these biopsies were performed during the pre-pandemic period and 33.3% were performed during the pandemic period. The mean age of patients with biopsy results was 66,74 (SD = 7.60) years. Of 141 prostate biopsy results, 62.4% (n = 88) were benign and 37.6% (n = 53) were malign. To compare the age, PSA levels and prostate volume of patients in the pre-pandemic and the pandemic periods independent samples *t*-test were conducted. The results were given in Table 1.

As shown in Table 1 age, PSA level and prostate volume of patients in the pre-pandemic and the pandemic period were not significantly different.

A chi-square test was performed to evaluate the pathology group (malign and benign) and Gleason scores (Gleason score $\leq$7 and Gleason score $\geq$8) in the pre-pandemic and pandemic periods (Table 2).

There was no significant relationship between pathology group and pandemic periods, $X^2 = 0.24$, $p = 0.62$, also Gleason scores and pandemic period, $X^2 = 0.96$, $p = 0.76$.

Table 2. Prostate biopsy results in the pre-pandemic and the pandemic periods.

	Malign		Benign		Chi-square/*p* value
	n	%	n	%	
Pre-pandemic period	34	36.2	60	63.8	0.24/0.62
Pandemic period	19	40.4	28	59.6	
	Prostate cancer Gleason ≤7		Prostate cancer Gleason ≥8		Chi-square/*p* value
	n	%	n	%	
Pre-pandemic period	13	38.2	21	61.8	0.96/0.76
Pandemic period	7	36.8	12	63.2	

4. Discussion

Although screening for cancer can vary between different types of malignant disease, there is clear, unquestionable evidence that timely diagnosis can improve cancer-related survival and patient quality of life [19]. As a result of our retrospective research, there was a dramatic decrease in PSA test requests with the onset of the COVID-19 pandemic. When the results of the secondary care hospitals we worked with were evaluated on an annual basis, it was found that PSA test requests decreased by 44% in 2020 compared to 2019. Although there was a 12% increase in the PSA figures in 2021 compared to 2020, it was determined that there was still a 36.5% decrease compared to 2019 before the pandemic. These findings in this study suggests that a significant number of men fall behind in routine PSA screening and follow-up.

Decreases in TRUS-Bx numbers as well as decreases in PSA test requests after the pandemic were seen. While 65 TRUS-Bx were performed in 2019, 40 biopsies were performed in 2020 and 36 biopsies were performed in 2021, with a decrease of 38.5% and 44.5%, respectively. It was observed that there was a decrease in parallel with the decrease in the number of biopsies in patients diagnosed with PCa after TRUS-Bx. PCa was detected in 24 of 65 (36.9%) patients in 2019, 16 of 40 (40%) patients in 2020, and 13 of 36 (36.1%) patients in 2021. Thus, it was revealed that there was a decrease in the number of patients newly diagnosed with PCa. The effects of the decrease in the number of new PCa diagnoses cases related to COVID-19 seem to be only in the lockdown period and then the number of new PCA diagnoses return to normal again in some countries [20,21]. When we look at the data of our hospital, we see that we still do not return to the old levels in both PSA requests and TRUS-Bx.

Xiao *et al*. [22] showed in their study that viral RNA was still present in the stool in more than 20% of patients with COVID-19 disease and negative RRT-PCR results. The team performing TRUS prostate biopsy in our hospital were aware of the risk of contamination during the procedure and necessary precautions were taken [23]. AUA guidelines recommend perineal prostate biopsy after pandemic onset [24]. We continued to take biopsies transrectally under local anesthesia and we did not encounter any COVID-19 related problems.

Due to the high number of patients infected with COVID-19 at the start of the pandemic, healthcare systems were quickly overloaded and non-urgent care and primary care in hospitals were delayed or suspended [25]. Patients with any symptoms hesitated to seek medical attention for fear of contracting COVID-19 [26]. A study conducted in the United States revealed that patients often view hospitals as contagious reservoirs and are therefore reluctant to go to the hospital [27]. In a study by Barten *et al*. [28] in the Netherlands, it was shown that the use of emergency rooms in three hospitals decreased after the quarantine, and that fear reduced the desire to use health services. The widespread public avoidance of hospitals during the pandemic for fear of contracting the disease is likely to result in missed opportunities to provide timely and appropriate treatments and a huge burden of underdiagnosis.

Reduction in PSA screening will result in a reduction in PCa detection, with an inevitable increase in PCa-specific mortality. Hugosson *et al*. [29] showed that PCa mortality in patients followed by measuring PSA levels was reduced by almost half over 14 years compared to the control group without PSA screening in a randomized, population-based screening study. Gulati *et al.* [30] concluded that continuing to screen men younger than 70 years could prevent half of PCa-related deaths. In the same study, they stated that discontinuing PSA screening for all men could lead to many preventable cancer deaths. Significant reductions in the number of PSA screening and related prostate biopsies emerged after the US Preventive Services Task Force Recommendation against PSA screening. Two and a half years later, Banerji *et al*. [31] determined in their study that high-risk PCa diseases increased and moderate-risk PCa patients, who were curable cases, decreased. Similarly, Bhindi *et al*. [32] reported in their study that there was an increase in the number of Gleason 8–10 PCa after the discontinuation of PSA screening. PCa is a heterogeneous neoplasm that includes clinically insignificant or slowly progressing diseases, as well as high-risk, clinically important and life-threatening cancers. Because there is no known way to prevent PCa or cure metastatic disease, the only hope of reducing death from PCa is early detection and appropriate and effective patient management.

These data suggest that, in parallel with the decrease in the number of PSA tests and the decrease in biopsies, the majority of cancer cases in our hospital are either undiagnosed or diagnosed with some delay, and this may have short and long-term consequences. While the delays in the diagnosis and treatment of non-COVID-19 diseases at the beginning of the COVID-19 pandemic could be explained by the use of medical resources for the treatment of COVID-19, the negative thoughts of the patients about the hospitals contributed to the delay in diagnosis and treatment in the following months. We think that the course of the pandemic with a higher mortality in middle age and older people than younger adults during the pandemic and more stay-at-home suggestions to this age group during the pandemic may have frightened the patients in this age group more. It is of great importance to provide support by informing patients about diseases that delay can have serious consequences. After vaccination, patients should be informed about effective prevention methods to get rid of the odor of contagious disease and should be encouraged to come to hospital controls. Since there is evidence that early diagnosis is associated with more favorable outcomes for PCa and many other malignancies, necessary information should be given about not abandoning or delaying basic cancer screenings, along with restrictive measures implemented to contain the spread of COVID-19 in the community.

The COVID-19 pandemic is not over yet and it is not possible to say that it will be the last. Understanding this gap in cancer screening and patients diagnosed with cancer and planning accordingly will be meaningful in terms of being prepared for similar situations that may occur in the future. Finally, more research is needed to better understand the factors that contribute to the decline in the number of patients newly diagnosed with cancer, and to understand the consequences of this delay.

5. Conclusions

As a result, our findings show that a significant number of PCa screening opportunities and cancer diagnoses are missed. We evaluate in the light of other studies that the reduction of PSA screening obtained from our study and may lead to delayed diagnosis of PCa and potentially preventable cancer deaths. Delays in cancer diagnosis will cause adverse clinical outcomes in the coming years. Considering that PCa does not pause due to the COVID-19 pandemic, it may cause patients to progress to more advanced disease stage at the time of diagnosis, require more aggressive treatment and even succumb to cancer due to the delays that occur. Further work is required to analyze the assessment of the clinical prognostic impact of cancer diagnosis delays.

Author Contributions

ES designed the study. ES collected data. ES analysed the quantitative data. ES wrote the manuscript and checked editorial changes in the manuscript. ES approved the final manuscript.

Ethics Approval and Consent to Participate

Ethical approval was obtained from Ethical Research Committee of the Izmir Demokrasi University (Committee Board Approval No.: 2022/03-74). Informed consent was received from the participants before the TRUS biopsy.

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Conflict of Interest

The author declares no conflict of interest.

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