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# Effect of COVID-19 mRNA vaccination on prostate specific antigen levels in prostate cancer patients

**Ali Borekoglu[1], Barıs Saylam[1], Nebil Akdogan[2], Tunahan Ates[3], Ali Inal[4], Fatih Gokalp[5]**

[1]Mersin City Training and Research Hospital, Department of Urology, Mersin, Türkiye
[2]Cukurova University Faculty of Medicine, Department of Urology, Adana, Türkiye
[3]Defne State Hospital, Department of Urology, Hatay, Türkiye
[4]Mersin City Training and Research Hospital, Department of Medical Oncology, Mersin, Türkiye
[5]Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Urology, Hatay, Türkiye

## Abstract

**Objective**: The effect of COVID-19 mRNA vaccines on prostate specific antigen (PSA) levels in prostate cancer patients remains unclear. In this study, we aimed to evaluate the effects of COVID-19 mRNA vaccination on PSA levels in patients with prostate cancer.

**Method**: Retrospective data were collected from patients diagnosed with prostate cancer (ICD-10 code C61). Inclusion criteria encompassed patients with pre-vaccination PSA levels of ≤2 ng/mL, no metastases, no active urinary tract infection and no history of urinary catheterization.

**Results**: Of the 333 patients initially screened, 176 were excluded due to missing data. Sixty-eight patients with PSA level > 2 ng/mL and 10 patients who developed urinary tract infection during follow-up were also excluded. The study included 89 patients (mean age: 70.77±5.88 years). Fifteen of these patients were between the ages of 55-65 years and the remaining 64 patients were between the ages of 65-83 years. There was no significant difference in PSA measurements between the first, second, and third doses of COVID-19 mRNA vaccine.

**Conclusion**: Invaluable information about the effect of COVID-19 mRNA vaccination on PSA levels in prostate cancer patients was provided. The findings suggest that COVID-19 mRNA vaccination has no significant effect on PSA levels in prostate cancer patients admitted to our urology and oncology clinics. However, further studies with larger sample size and longer follow-up period are needed to confirm these findings and better understand the relationship between COVID-19 vaccination and PSA levels in prostate cancer patients.

**Keywords**: COVID-19, mRNA vaccines, severe acute respiratory syndrome coronavirus 2, prostate cancer, prostate specific antigen, pandemic

## INTRODUCTION

Coronavirus disease (COVID-19) unexpectedly entered our lives in December 2019 and has affected millions. In the early stages of the pandemic, SARS-CoV-2 was thought to target only the respiratory system. However, recent studies have shown that the virus can target all tissues expressing angiotensin-converting enzyme 2 (ACE-2), which is responsible for attachment to host cells. Furthermore, studies have shown that SARS-CoV-2 invades and spreads into host cells using the transmembrane protease serine 2 (TMPRSS2) in addition to the ACE-2 protein (1). After binding to the ACE-2 receptor, SARS-CoV-2 is separated from the spike protein by the TMPRSS2 enzyme, and binds to the cell membrane to enter the cell (2). The TMPRSS2 gene is highly expressed in human prostate epithelial cells (3). In addition to the expression of angiotensin-converting enzym-2 (ACE2) receptors and TMPRSS2 enzyme in the human prostate, the regulation of TMPRSS2 by androgens makes prostate tissue a potential target for SARS-CoV-2 infection (2,4). Similarly, COVID-19 has been detected in many body fluids including urine, and it has also been detected in prostate tissue (5,6). In addition, infection with COVID-19 has been associated with a slight increase in prostate specific antigen (PSA) levels in patients with benign prostatic hyperplasia (7).

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**Corresponding Author:** Dr. Tunahan Ateş, Defne State Hospital, Department of Urology, Hatay, Türkiye
**Email:** drtunahanates0101@gmail.com
**ORCID iD:** 0000-0001-9087-290X

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Vaccination is a type of immunotherapy that induces a local inflammatory response in the body. The spike protein has been the target of many vaccines because of the virus's constant ability to infect host cells through interaction with the ACE2 receptor (8). A literature search revealed that no clinical trials have examined the effects of COVID-19 vaccines on PSA levels, and the available studies are limited to case reports (9).

The spike protein has gained attention as a potential target for virus entry into cells and for the development of vaccine-induced immunity. It has been suggested that SARS-CoV-2 infection could affect the prostate and disrupt its structure (7). Therefore, the present study aims to investigate the effects of COVID-19 vaccines produced with the spike protein of SARS-CoV-2 on PSA levels in patients with prostate cancer.

## METHOD

After approval by the local ethics committee (ethics committee decision dated 20/04/2022, number 2022/293), the data of patients who were diagnosed with prostate cancer with code C61 (International Statistical Classification of Diseases and Related Health Problems (ICD-10)) and followed up by Health Sciences University, Mersin City Training and Research Hospital (between August 2019 and January 2021) were retrospectively collected. Patients with a pre-vaccination laboratory PSA level (Kit: Immunoassay Program, Ref: 02676506, Siemens ADVIA Centaur XPT) of 2 ng/mL or less and patients with clinically and radiologically proven absence of metastases were included in the study. In addition, patients who had not been diagnosed with COVID-19, had no active infection such as urinary tract infection (UTI), and had no urinary catheter placed were included in the study.

In Türkiye, the use of mRNA vaccines against COVID-19 is recommended by the World Health Organization as the first dose and a booster dose after six months. Patients who had been vaccinated according to this protocol were included in the study. Patients with PSA levels of 2 ng/mL or more during the relevant period were excluded from the study due to the possibility of metastatic disease causing a PSA increase. In addition, patients who underwent radical prostatectomy, diagnosed clinically and/or by laboratory testing UTI, and had a history of urethral trauma or catheterization were excluded from the study because they were associated with a potentially elevated PSA level. Prevaccination and postvaccination PSA were recorded and documented on a standard sheet.

### Statistical analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Since the data did not follow a normal distribution, non-parametric tests were applied. Quantitative data were presented as mean and standard deviation and qualitative data were presented as frequency and percentage. Comparisons between groups were conducted using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. Analyzes were performed with the Statistical Package for Social Sciences program (SPSS Inc, Chicago, IL) version 20.0. Statistical significance was set at $p<0.05$.

## RESULTS

The data of 333 patients were retrospectively screened. Of those, 176 patients whose data could not be accessed fully were excluded from the study. Additionally, 68 patients with a PSA level over 2 ng/mL and 10 patients who developed urinary tract infections during follow-up were excluded. A total of 89 patients were enrolled in this study (Figure 1). The

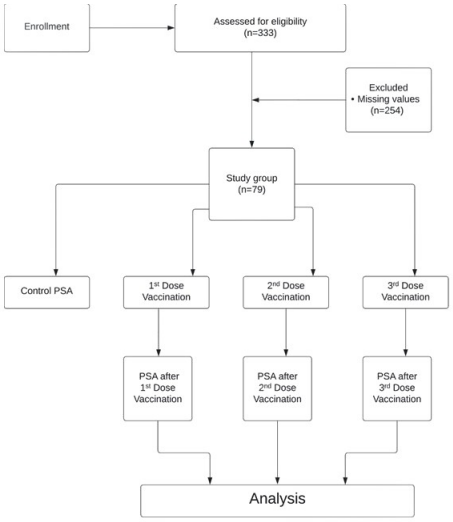


**Figure 1.** Flow chart of patient selection

mean age was 70.77±5.88 years. A total of 15 patients were between the ages of 55-65 and the remaining 64 were between 65-83 years. In this study, no significant difference was found in PSA measurements between mRNA first, second and third doses of COVID-19 vaccinations ($p>0.05$; Table 1).

## DISCUSSION

In this study, it was found that mRNA-based vaccines employed for COVID-19 and the administered number of doses did not have an effect on PSA levels. The importance of early diagnosis of oncological diseases is crucial, and it allows for a higher chance of cure with lower progression to metastatic disease, limited use of aggressive treatments, and improvement in quality of life, as well as a reduction in disease-specific mortality, among other advantages. Screening programs have also great importance for early diagnosis.

**Table 1. Prostate specific antigen values of the patients**

| | Control | 1st Measurement | 2nd Measurement | 3rd Measurement |
|---|---|---|---|---|
| Mean±Standart deviation | 0.189±0.365 | 0.853±3.324 | 0.399±1.748 | 0.116±0.190 |
| | | Difference 1 | Difference 2 | Difference 3 |
| Difference (%) | | 296.698±1386.88 | 68.092±210.088 | 188.395±483.701 |

Wilcoxon rank sum test was used. Intragroup comparisons of Means; 1st Measurement–Control: p=0.537; 2nd Measurement–Control: p=0.460; 3rd Measurement–Control: p=0.619; 2nd Measurement–1st Measurement: p=0.293; 3rd Measurement–1st Measurement: p=0.307; 3rd Measurement–2nd Measurement: p=0.373. Intragroup comparisons of Differences of means in percentage; Difference 1: 1st Measurement–Control; Difference 2: 2nd Measurement – 1st Measurement; Difference 3: 3rd Measurement – 2nd Measurement; Difference 2 – Difference 1: p=0.934; Difference 3–Difference 2: p=0.735.

The PSA is the screening test commonly used worldwide, which was first used in 1981 for monitoring patients with prostate cancer (10). However, the PSA levels do not increase only in malignant diseases, various benign conditions may cause raised levels leading to questions about the specificity of PSA. Therefore, serum PSA level entered clinical practice as a tumor marker to confirm diagnosis and monitor treatment effectiveness, rather than a screening tool in 1987 (11). Although there are rules regarding the limitation of PSA in community screening due to health policies implemented in many countries today, PSA is still used in treating and following patients diagnosed with prostate cancer (12). First reported in December 2019, COVID-19 devastated populations, social structures, and economic growth worldwide, by evolving into a pandemic. Subsequent studies on the disease were accelerated, and it was determined that the agent responsible for this impact was an RNA virus, known as SARS-CoV-2, containing a spike protein that enters the cell using the ACE-2 protein and transmembrane protease serine 2 (TMPRSS2) (13). During the early stages of the pandemic, it was thought that the virus only affected the lungs, in contrast, studies have shown that SARS-CoV-2 can infect all cells expressing ACE-2 protein and TMPRSS2 (1). The prostate gland, similar to the lungs, heart, kidneys, and liver, is an organ with a significant expression of ACE2 receptors. Furthermore, the TMPRSS2 gene is prominently expressed in prostate epithelial cells, making the prostate gland an evident target for SARS-CoV-2. Indeed, recent studies have demonstrated an increase in PSA levels during the active period of COVID-19, and the presence of the COVID-19 genome in prostate tissue supports the idea of prostatic involvement of SARS-CoV-2 (6, 7).

There is evidence to suggest that the overall effect of prostatic involvement of SARS-CoV-2 is likely due to an inflammatory process caused by cytokine release, systemic procoagulant and disseminated intravascular coagulation (DIC), structural damage, local vascular permeability increase, and tissue damage. This is likely due to the mechanism behind the PSA elevation during the acute phase of the infection.

Vaccine applications can sometimes lead to a local inflammatory response in the injection site and its surroundings, and occasionally a systemic response such as hypermetabolic lymph nodes distant from the injection site (9). These responses may sometimes cause dilemmas in the follow-up and management of oncological patients. In particular, in the case of prostate cancer, PSA elevation may be related to disease recurrence, hence it may require additional treatment. In this respect, it is essential to distinguish the cause of the elevation of PSA levels. The knowledge of vaccination might be an evident factor to contribute to the management of patients with prostate cancer. It is estimated that the present study will shed light on the management of these patients. In a recent study, it was shown that exposing human prostate cancer cell lines (LNCaP) to the isolated spike protein of SARS-CoV-2 in vitro resulted in a decrease in cell survival. Authors suggested that the SARS-CoV-2 spike protein has a significant negative effect on the proliferation of LNCaP cells, and in vitro experiments have shown that the spike protein reduces cell proliferation and induces apoptosis through a two-pronged approach, leading to a decreased survival of prostate cancer cells. Researchers also suggested that COVID-19 vaccination could potentially provide additional benefits in the management of prostate cancer (14). Nucleic acid vaccines, such as mRNA vaccines, mimic natural infection by inducing endogenous antigen production and generating strong T and B cell responses, although they are not completely infectious (15). The mRNA vaccine used for COVID-19 also contains the mRNA sequence of the spike protein. After the vaccine reaches the body, millions of copies of the sSpike protein are produced within cells through this mRNA sequence. This stimulates the body to create antibodies against the cells producing the protein (8, 16).

The findings of this study suggest that mRNA vaccines do not significantly impact PSA levels in prostate cancer patients, providing reassurance for clinicians regarding their safety and use in this population. These results are particularly important for alleviating concerns about potential vaccine-related fluctuations in PSA, which could otherwise lead to unnecessary clinical interventions or misinterpretations of disease progression. However, despite the overall stability

of PSA levels observed in our study, individualized PSA monitoring remains essential. Certain patient subgroups, such as those with advanced disease, those undergoing androgen deprivation therapy, or individuals with unique immunological responses, may exhibit variations that were not captured in our study. Additionally, potential transient fluctuations in PSA following vaccination, even if not clinically significant on a broader scale, warrant further investigation to ensure optimal patient management. Given these considerations, further research is needed to explore potential subgroup differences and to provide more comprehensive clinical guidance. Such investigations will contribute to more personalized prostate cancer monitoring strategies and ensure that vaccination remains a safe and effective preventive measure in this patient population.

### Limitations of the study

The absence of PSA elevation or reduction observed in the present study after administering mRNA vaccines produced using spike protein may be attributed to the fact that the vaccine was developed in an in vitro environment, and the results may be influenced by the complex inflammatory response that can sometimes have a widespread effect on the body.

As can be seen, our study was performed retrospectively. This situation brings along some limitations. Although no significant overall changes in PSA levels were observed, individual variations were not specifically analyzed. This represents a limitation, as some patients may exhibit different biological responses to mRNA vaccination. Future studies should focus on assessing PSA level fluctuations at an individual level to better understand potential variations and their clinical implications. Since our study was single-center, the number of patients was not relatively high. Studies with a larger number of patients are needed. Future studies should focus on multicenter studies with larger cohorts to validate these results and provide more comprehensive insights into the potential effects of mRNA vaccines on PSA levels in prostate cancer patients.

## CONCLUSION

It can be suggested that mRNA vaccines showed no interaction with PSA levels which might cause confusion in the management of patients with prostate cancer. The present study is the first research in the literature to evaluate the effect of mRNA-based vaccines on PSA levels. Further studies with larger sample sizes and development in mRNA technologies might trigger new treatment modalities in which the spike protein can be used to treat prostate cancer cells.

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