

The clinical impact of androgen deprivation therapy on SARS-CoV-2 infection rates and disease severity

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ABSTRACT

Objective: The protective effect of androgen deprivation therapy (ADT) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel hypothesis. ADT may protect patients with prostate cancer through the inhibition of androgen receptor-dependent transmembrane serine protease type 2. We analyzed the role of ADT on SARS-CoV-2 infection risk and disease severity.

Material and methods: Between August 2020 and June 2021, patients with prostate cancer were included in our study. Patients were divided into two groups as men receiving ADT or not. Patients' characteristics such as prostate cancer grade and stage, comorbidities, SARS-CoV-2 infection status, and infection severity were assessed. SARS-CoV-2-infected close relatives and patients' compliance with the precautions against SARS-CoV-2 were also analyzed.

Results: A total of 365 patients, 138 (37.8%) with ADT and 227 (62.2%) without ADT, were included in our analysis. Patients with ADT were older (71.8 vs 66.9 years, $P = .001$) and had a higher rate of chronic obstructive pulmonary disease (11.6% vs 5.7%, $P = .044$). Patients receiving ADT were more often locally advanced and metastatic (80.4% vs 32.6%, $P = .001$). SARS-CoV-2 infection rates were statistically similar between patients who received and did not receive ADT (9.4% vs 13.2%, $P = .275$, respectively). There was no significant difference between two groups in terms of hospitalization rates (2.9% vs 0.9%, $P = .205$). In multivariate analysis, the presence of SARS-CoV-2-infected close relatives and precautions score were only independent predictors for both risk of SARS-CoV-2 infection and infection severity.

Conclusion: We could not find any effect of ADT on risk and severity of SARS-CoV-2 infection. SARS-CoV-2 infection and hospitalization rates were similar between patients with and without ADT.

Keywords: Androgen deprivation therapy; prostate cancer; SARS-CoV-2; TMPRSS-2.

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Introduction

Novel coronavirus infection known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) imposes a great burden on the health system all over the world and deeply affects daily life. Due to the fragile immune system and necessity of regular hospital visits, patients with cancer are considered in high-risk category and may be more susceptible to SARS-CoV-2 infection.¹ Recent studies have also shown that patients with cancer have an increased risk of severe infection.^{2,3}

Although the prevalence of SARS-CoV-2 is similar between men and women, it has been shown that men face more severe infections, and mortality rates are higher in men than in women.⁴ When the pathophysiology of gender difference in SARS-CoV-2 infection is investigated, androgen receptor-related transmembrane serine protease type 2 (TMPRSS-2) is often blamed. The main step of viral host-cell entry starts with binding to angiotensin converting enzyme-2 (ACE-2). Subsequently, viral and cellular membranes are joined by TMPRSS-2. TMPRSS-2 is highly expressed

in prostate cancer tissue, and its transcription is regulated by the androgen receptor (AR).⁵ It has been shown in in-vitro and in vivo studies that TMPRSS-2 is also expressed in the lung.⁶ The demonstration of TMPRSS-2 in the lung tissue has led to the hypothesis that men receiving androgen deprivation therapy (ADT) may be protected against SARS-CoV-2 infection.

In this study, we aimed to compare the risk and the severity of SARS-CoV-2 infection in prostate cancer patients with and without ADT.

Material and Methods

Patients and Method

Between August 2020 and June 2021, 365 patients who were followed-up for prostate cancer in the uro-oncology outpatient clinic and agreed to participate in the study were included. Patients were divided into two groups as those who received ADT due to prostate cancer and those who did not. The two groups were compared according to their characteristics such as age, body mass index (BMI), smoking status, comorbidities, prostate cancer Gleason grade, TNM stage, and SARS-CoV-2 infection status, and severity of infection. Mild infection, hospitalization, admission to intensive care unit, and death were evaluated in the severity of infection. Factors affecting the infection rate and the severity of infection were also evaluated.

The presence of SARS-CoV-2-infected close relatives and patients' compliance with the preventive measures against SARS-CoV-2 were evaluated. A simple questionnaire was created. Precautions were questioned under three main headings and scored between 0 and 100. These were as follows: (1) keeping the physical distancing was questioned in terms of "Avoiding closed and crowded workplace" and "Always outdoor gatherings," (2) wearing mask properly in terms of "Mask covers both nose and mouth all time" and "Mask only in closed places," and (3) hygiene precautions in terms of "Regularly cleaning hands," "Avoid touching eyes, nose, mouth," and "Disinfecting surfaces regularly."

Main Points

- The protective effect of androgen deprivation therapy (ADT) against SARS-CoV-2 through the inhibition of TMPRSS-2 is a matter of interest to clinicians.
- Association between the SARS-CoV-2 infection risk and ADT is controversial.
- Other factors causing SARS-CoV-2 infection should not be overlooked.

İstanbul Medeniyet University local ethics committee approved this study (2021/440). An informed consent was obtained from all individual participants included in this study.

Statistical Analysis

Statistics were performed using SPSS v22.0 (IBM SPSS Corp.; Armonk, NY, USA). Independent samples t-test was used for comparing the means. Normal distribution between groups was assessed using Kolmogorov-Smirnov test. Comparison of means between the two groups was performed by independent samples t-test. To compare the median values, the Mann-Whitney U test was used. The Chi-square test or Fisher's exact test was used for categorical variables. Comparing categorical variables more than two Bonferroni adjustment was performed. Logistic regression was performed for multivariate analysis, and *P*-value <.05 was considered as statistically significant.

Results

Among 365 prostate cancer patients, 138 (37.8%) patients were receiving ADT. Patients with ADT were older than other group (71.8 vs 66.9 years, *P* = .001). BMI of patients with ADT was lower than the patients without ADT (26.9 vs 27.8 kg m⁻², *P* = .029). The rates of diabetes, hypertension, and coronary artery disease were similar in both groups. Chronic obstructive pulmonary disease (COPD) prevalence was higher in patients receiving ADT (11.6% vs 5.7%, *P* = .044). Patients who received ADT were more frequently in the locally advanced or metastatic stage (80.4% vs 32.6%, *P* = .001) and had higher ISUP grades than those who did not receive ADT (median 4 vs 2, *P* = .001). Infection rate in the group of patients receiving ADT was lower than the patients without ADT; however, it was not statistically significant (9.4% vs 13.2%, *P* = .275). No mortality or intensive care unit admission was detected due to SARS-CoV-2 infection in both groups. Hospitalization rates were also similar between the two groups (2.9% vs 0.9%, *P* = .205) (Table 1).

The effects of ADT on the risk and severity of SARS-CoV-2 were re-evaluated by excluding patients with COPD, since more comorbidity in patients receiving ADT may mask the effects of SARS-CoV-2, and no difference was found between the two groups (12.6% vs 9.0%, *P* = .316; 0.5% vs 2.5%, *P* = .105, respectively). To analyze the effect of ADT on SARS-CoV-2 infection risk and infection severity according to prostate cancer stages, we divided patients according to stages, and we found no relationship (Supplementary Table 1).

In univariate analysis, age, ISUP grade in prostate biopsy, the presence of SARS-CoV-2-infected close relatives, and precautions score were the factors affecting SARS-CoV-2 infection

Table 1. Clinical Characteristics of Patients According to Androgen Deprivation Therapy

	ADT		<i>P</i>
	No (n = 227)	Yes (n = 138)	
Age (years), mean ± SD	66.9 ± 7.71	71.8 ± 9.17	.001 [¶]
BMI (kg m⁻²), mean ± SD	27.8 ± 3.77	26.9 ± 3.69	.029 [¶]
Smoking status	145 (63.9%)	90 (65.2%)	.795 [†]
Diabetes mellitus	60 (26.4%)	38 (27.5%)	.817 [†]
Hypertension	107 (47.1%)	70 (50.7%)	.506 [†]
Coronary artery disease	39 (17.2%)	31 (22.5%)	.214 [†]
COPD	13 (5.7%)	16 (11.6%)	.044 [†]
Prostate cancer stage			
• Localized	153 (67.4%) ^a	27 (19.6%) ^b	
• Locally advanced	67 (29.5%) ^a	55 (39.9%) ^b	.001 [†]
• Metastatic	7 (3.1%) ^a	56 (40.6%) ^b	
ISUP grade median (min – max)	2 (1-5)	4 (1-5)	.001 [‡]
SARS-CoV-2			
• Noninfected	197 (86.8%)	125 (90.6%)	.275 [†]
• Infected	30 (13.2%)	13 (9.4%)	
SARS-CoV-2 severity			
• Non-hospitalized	225 (99.1%)	134 (97.1%)	.205 [§]
• Hospitalized	2 (0.9%)	4 (2.9%)	

COPD: chronic obstructive pulmonary disease.

[¶]Independent samples t-test.

[†]Chi-square test.

[‡]Mann-Whitney U test.

[§]Fisher's Exact test.

^{a-b}Bonferroni adjustment.

risk in prostate cancer patients. Chronic obstructive pulmonary disease, close relative with SARS-CoV-2 infection, and precautions score were the factors affecting severe SARS-CoV-2 infection in univariate analysis. In multivariate analysis, the presence of SARS-CoV-2-infected close relatives and precautions score were the only independent predictors for both risk of SARS-CoV-2 infection and infection severity (Tables 2 and 3).

Discussion

In our study, we investigated the effect of ADT on the risk and severity of SARS-CoV-2. We did not detect any protective effect of ADT against the risk and severity of SARS-CoV-2 infection. In this study, we included in detail the comorbidities of patients who received and did not receive ADT, and factors such as prostate cancer disease stage and grade. We also included factors such as physical contact and precautions, which are known to have the greatest impact on infection risk. The impact of ADT on SARS-CoV-2 is a fairly novel topic, which needs validation.

SARS-CoV-2 viral entry into host cells is essentially dependent on TMPRSS-2 and ACE-2. After SARS-CoV-2 enters the cell, the B domain of the viral S protein binds to ACE-2 of the host cell. TMPRSS-2 enables the S protein to cleavage to S1/S2 and viral interaction with host cells.⁷ Previous studies showed that the expression of ACE-2 and TMPRSS-2 in the lung is AR dependent. While AR stimulates the expression of TMPRSS-2, it inhibits the expression of ACE-2.⁸ It was also showed that men have higher TMPRSS-2 expression levels in lung than women.⁹

ADT decreases the TMPRSS-2 expression in prostate cancer.¹⁰ As a result of androgen deprivation, there is also a decrease in estradiol levels. Estradiol is known to have a strengthening effect on the immune system and increases the expression of TMPRSS-2.¹¹ Deprivation of estradiol levels also leads to a decrease in TMPRSS-2. The inhibition of AR-dependent TMPRSS-2, which is also expressed in the lung, by ADT may have a potential protective role against SARS-CoV-2. In the study of Montopoli et al,¹² it was shown that the risk of SARS-

Table 2. Factors Affecting SARS-CoV-2 Infection

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Age	0.95	0.914-0.987	.009*			
Smoking	0.74	0.445-1.238	.253			
BMI	1.03	0.944-1.114	.548			
Any comorbidity	0.75	0.365-1.552	.441			
DM	0.81	0.381-1.704	.572			
HT	1.02	0.537-1.920	.962			
CAD	0.80	0.340-1.880	.608			
COPD	1.63	0.589-4.535	.346			
Multiple comorbidities	0.75	0.365-1.552	.441			
ISUP grade	0.79	0.619-0.999	.049*			
Metastatic	0.86	0.553-1.326	.487			
ADT	0.68	0.343-1.359	.278			
Relatives with SARS-CoV-2	30.37	13.419-68.744	.001**	23.24	9.680-55.784	.001**
Precautions score	0.92	0.900-0.947	.001**	0.93	0.898-0.959	.001**

ADT: androgen deprivation therapy; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HT: hypertension.

*: P < .05, **: P < .01

Table 3. Factors Affecting Severe SARS-CoV-2 Infection

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.05	0.952-1.148	.354			
Smoking	0.50	0.125-2.000	.329			
BMI	1.13	0.93-1.357	.217			
Any comorbidity	1.13	0.204-6.271	.887			
DM	0.54	0.062-4.682	.576			
HT	2.15	0.389-11.888	.380			
CAD	2.14	0.384-11.923	.385			
COPD	6.15	1.077-35.102	.041*			
Multiple comorbidities	1.13	0.204-6.271	.887			
ISUP grade	0.84	0.464-1.528	.572			
Metastatic	1.71	0.619-4.708	.301			
ADT	3.36	0.607-18.582	.165			
Relatives with SARS-CoV-2	8.09	2.301-28.426	.001**	7.21	2.052-25.322	.02*
Precautions score	0.94	0.907-0.976	.001**	0.95	0.919-0.990	.013*

ADT: androgen deprivation therapy; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HT: hypertension.

*: P < .05, **: P < .01

CoV-2 infection was 4.05 times higher in prostate cancer patients who did not receive ADT (OR: 4.05, $P = .0043$). Klein et al¹³ could not show this protective effect of ADT on SARS-CoV-2; both groups had similar infection rates (5.6% vs 5.8%, OR: 0.93, $P = .8$). They defined only the accompanying comorbidities as risk factors. Koskinen et al¹⁴ also did not find any relationship between ADT and SARS-CoV-2 infection. In the systematic review of Karimi et al,¹⁵ they could not find any effect of ADT on SARS-CoV-2 infection risk and its severity. An ongoing clinical trial by Bennink et al¹⁶ investigates the use of ADT and high-dose estrogen in the treatment of severe SARS-CoV-2 in the light of these studies. In our study, we could not detect any relationship between the frequency of SARS-CoV-2 infection between patients who received and did not receive ADT (9.4% vs 13.2%, $P = .275$). Considering the effect on the severity of infection, we found that ADT was not associated with hospitalization (2.9% vs 0.9%, $P = .205$). We determined only the presence of SARS-CoV-2-infected close relatives and precautions score as risk factors for hospitalization. Montopoli et al¹² stated that patients who received ADT had milder symptoms compared to those who did not (OR: 3.93, $P = .0014$). Patel et al¹⁷ also showed the protective role of ADT against severe infection. None of the recent studies analyzed the role of physical distancing or precautions against SARS-CoV-2. However, the effect of these factors cannot be ignored in a respiratory disease that is transmitted very quickly through droplets and affects the whole world in a short time. Although it is not easy to evaluate the social distance and the precautions taken, we think that it should be questioned. In our detailed inquiries, we saw that the presence of SARS-CoV-2-infected close relatives and precautions score were the independent predictors that affect the risk and severity of infection.

Patients receiving ADT may have more comorbidities, which may affect disease severity. In our study, COPD was more common in patients receiving ADT. Therefore, after adjustment, the effect of ADT was re-evaluated, and no relationship was found. Klein et al¹³ determined that only the comorbidities increased the rate of hospitalization. Another adjustment we made was according to prostate cancer stages. In our study, the protective role of ADT could not be demonstrated in locally advanced or metastatic patient groups (Supplementary Table 1). Caffo et al¹⁸ analyzed the effect of ADT on SARS-CoV-2 infection in metastatic prostate cancer, and they did not find any relationship.

This is the first study to include transmission-related factors among studies investigating the effect of ADT on SARS-CoV-2. The limited number of SARS-CoV-2 patients, its inability to

generalize due to high case rates in our country, the inability to determine the rates of hospital admission and PCR testing of cancer patients compared to other groups, and the inability to question the vaccination status of patients can be counted among its limitations.

To conclude, there was no effect of ADT on the risk of SARS-CoV-2 infection and hospitalization rates. The most important risk factors in SARS-CoV-2 risk and severity were found to be transmission-related factors.

Ethics Committee Approval: Ethical committee approval was received from the İstanbul Medeniyet University (2021/440).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Supplementary Table 1. Effect of ADT on SARS-CoV-2 Infection Risk and Infection Severity According to Prostate Cancer Stages

	ADT		<i>P</i>
	No	Yes	
<i>Infection risk</i>			
Localized prostate cancer	20 (13.1%)	3 (11.1%)	.778
Locally advanced or metastatic prostate cancer	10 (13.5%)	10 (9.0%)	.334
<i>Infection severity (hospitalization)</i>			
Localized prostate cancer	2 (1.3%)	1 (3.7%)	.370
Locally advanced or metastatic prostate cancer	0 (0%)	3 (2.7%)	.154