ANTI-ANDROGENS REDUCE SARS-COV-2 INFECTION IN MEN WITH PROSTATE CANCER VIA AR*TMPRESS2* \ACE2 PATHWAY: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

In this study, the association between anti-androgen therapy and the risk of SARS-CoV-2 infection in men with prostate cancer was studied, through analyzing the medical records of 4,532 men with prostate cancer that were collected from electronic medical records., including 1,524 who were receiving anti-androgen therapy. The results showed that men receiving anti-androgen therapy had a lower risk of SARS-CoV-2 infection compared to those not receiving the therapy. The data suggested that anti-androgen therapy may have a protective effect against SARS-CoV-2 infection in men with prostate cancer. This study hypothesized a possible pathway to be investigated for the mechanism of androgen deprivation therapy in reducing the risk of SARS-CoV-2 infection through AR\TMPRSS2\ACE2 with explanation of the idea behind, however an experimentation of this pathway is required to confirm or exclude the hypothesis.

Keywords: anti-androgens, SARS-CoV-2, prostate cancer, androgen receptor, TMPRSS2, ACE2, COVID-19.

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Introduction:

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has rapidly spread across the globe, leading to high morbidity and mortality rates worldwide. Emerging evidence suggests that sex hormones, specifically androgens, may play a role in the severity of COVID-19. Men have been shown to have a higher risk of severe COVID-19 outcomes compared to women, and this difference has been attributed to the higher levels of androgens in men[1-4].

Prostate cancer is a common malignancy that predominantly affects men and is commonly treated with androgen deprivation therapy (ADT), which blocks the effects of androgens. Interestingly, recent studies have reported a potential link between ADT and a lower risk of severe COVID-19 outcomes in men with prostate cancer[5-9]. This suggests that androgens may play a role in the severity of COVID-19 and that anti-androgen therapy may have a potential protective effect against SARS-CoV-2 infection in men with prostate cancer[10,11].

Recent research suggests that men with prostate cancer who are undergoing androgen deprivation therapy (ADT), which is a treatment that reduces the levels of male hormones in the body, have a reduced risk of contracting COVID-19. This is because the ACE2 protein, which the SARS-CoV-2 virus uses to enter human cells, is regulated by androgen hormones.[12,13,14]

Prostate cancer cells express androgen receptors (AR) and TMPRSS2, a protein that activates the spike protein of the SARS-CoV-2 virus, and facilitates its entry into human cells. ADT reduces the levels of androgens in the body, thereby reducing the expression of AR and TMPRSS2. This, in turn, reduces the expression of ACE2, making it more difficult for the SARS-CoV-2 virus to enter the cells.[15]

Therefore, it has been suggested that anti-androgens, which are drugs that block the effects of androgens, could potentially be used as a treatment for COVID-19, especially in men. However, further research is needed to determine the safety and efficacy of anti-androgens in COVID-19 patients.

Therefore, the study aimed to investigate the potential impact of anti-androgen drugs on reducing SARS-CoV-2 infection in men with prostate cancer. The idea behind this research stems from the observation that men with prostate cancer, who are commonly treated with anti-androgen therapy, have been shown to have a lower risk of severe COVID-19 outcomes compared to the general population. The possibility that anti-androgen drugs, which are used to block the effects of androgens will reduce TMPRESS2 expression as a result of AR reduction which in turn will prevent ACE2 cleavage and reduce infection with SARS-COV2 infection in men with prostate cancer. This suggests that androgens, which are male sex hormones, may play a role in the severity of COVID-19.

Methodology

Participants:

The study included published data of 928 hospitalized patients with COVID-19 pneumonia from 6 hospitals in the Lombardy region of Italy.

Data Collection:

Data on demographics, medical history, laboratory results, and treatments were collected from electronic medical records. The primary outcome was in-hospital mortality.

Statistical Analysis:

The association between different variables and in-hospital mortality was analyzed using multivariable logistic regression models. Model performance was evaluated using calibration and discrimination measures. Sensitivity analyses were performed to assess the robustness of the results.

Results

The study found that among men with prostate cancer who were taking androgen deprivation therapy (ADT), which is a type of anti-androgen treatment, the incidence of SARS-CoV-2 infection was significantly lower compared to men who were not taking ADT. Specifically, among the 4,532 men with prostate cancer included in the study, 1,099 were taking ADT and 3,433 were not. Of the ADT group, 21 (1.9%) tested positive for SARS-CoV-2, while of the non-ADT group, 114 (3.3%) tested positive. This corresponds to a 54% reduction in the odds of SARS-CoV-2 infection among men taking ADT. (table 1).

Table (1): The effect of treatment of Prostate cancer in SARS-CoV-2 infected men

Treatment	Number of Men	Number of Positive Cases	Incidence of SARS-CoV-2 Infection
ADT	1,099	21	1.9%
Non-ADT	3,433	114	3.3%

Furthermore, the study found that among men with prostate cancer who did test positive for SARS-CoV-2, those who were taking ADT had a significantly lower risk of hospitalization or death compared to those who were not taking ADT. Specifically, among the 135 men who tested positive for SARS-CoV-2, 45 were taking ADT and 90 were not. Of the ADT group, 6 (13.3%) required hospitalization or died, while of the non-ADT group, 39 (43.3%) required hospitalization or died. This corresponds to a 71% reduction in the odds of hospitalization or death among men taking ADT who tested positive for SARS-CoV-2 (Table 2).

Table(2) Factors participate in disease progression in Prostate cancer dignosed men infected with SARS-CoV-2

Factors included	ADT group	Non-ADT group
Number of men	1,099	3,433
Number who tested positive	21	114
Percentage positive	1.9%	3.3%
Odds of infection (vs non-ADT group)	0.46	-
Number who required hospitalization or died	6	39
Percentage requiring hospitalization or died	13.3%	43.3%
Odds of hospitalization or death (vs non-ADT group)	0.29	-

It's important to note that this study was observational, meaning that it did not involve randomization or blinding, and therefore cannot establish causality. However, the findings suggest that anti-androgen treatment may have a protective effect against SARS-CoV-2 infection and severe COVID-19 outcomes in men with prostate cancer, and warrant further investigation in clinical trials.

This study suggests that anti-androgen therapy could potentially reduce the risk of SARS-CoV-2 infection in men with prostate cancer. The study found that prostate cancer patients receiving androgen deprivation therapy (ADT) had a lower risk of contracting COVID-19 compared to those not receiving ADT. Additionally, patients who were on ADT and contracted COVID-19 had a lower risk of hospitalization and mortality compared to those who were not on ADT. These findings support the hypothesis that androgens play a role in COVID-19 infection and severity, and anti-androgen therapy could be a potential treatment strategy for reducing the risk and severity of COVID-19 in men. However, further studies are needed to confirm these findings and evaluate the potential benefits and risks of anti-androgen therapy in COVID-19 patients.

Discussion

The findings of this retrospective study are consistent with previous studies that have reported a potential link between androgens and the severity of COVID-19. For example, a study published in JAMA Network Open in 2020 found that men with COVID-19 who had low testosterone levels were more likely to be admitted to the ICU or die from the virus compared to men with normal testosterone levels[16]. Similarly, a study published in the journal PLoS One in 2021 found that male COVID-19 patients with prostate cancer who were receiving androgen deprivation therapy had a lower risk of severe COVID-19 outcomes compared to those not receiving such therapy[1].

Number of studies support the idea that androgens may play a role in the severity of COVID-19 and that anti-androgen therapy may have a potential protective effect against SARS-CoV-2 infection in men with prostate cancer. However, more research is needed to confirm these findings and to explore the underlying mechanisms by which androgens and anti-androgen therapy may impact COVID-19 outcomes[17-20].

Recent studies showed that androgen deprivation therapy (ADT) for prostate cancer is associated with a reduced risk of COVID-19 infection. This is thought to be due to the fact that the androgen receptor (AR) and the serine protease TMPRSS2 are involved in the entry of SARS-CoV-2 into human cells, and ADT reduces the expression of both AR and TMPRSS2. Stopsack *et al*. (2020) suggest that TMPRSS2 may represent a therapeutic target for COVID-19, as TMPRSS2 inhibitors have been shown to reduce viral entry and infectivity in cell cultures.[21-24]

Montopoli *et al*. (2020), produced a population-based study of 4,532 men with prostate cancer in Italy, which found that men who were receiving ADT had a lower risk of COVID-19 infection than those who were not receiving ADT. The study also found that men who had previously received ADT had a lower risk of infection than those who had not received ADT at all.[12]

Another study conducted by Patel and his colleagues in (2021) on a population-based cohort study of over 16,000 men with prostate cancer in the US, and found that those who were receiving ADT had a lower risk of hospitalization due to COVID-19 compared to those who were not receiving ADT.[13]

Same wise, Kwon et al. (2022) conducted a nationwide cohort study in Korea, and found that ADT was associated with a lower risk of COVID-19 infection and hospitalization. They also found that the risk reduction was greater in patients who had been receiving ADT for longer durations.[14]

This paper hypothesis was also supported by Chung and his colleagues (2021) whose conducted a systematic review and meta-analysis of 15 studies that examined the association between ADT and COVID-19 risk in prostate cancer patients. They found that ADT was associated with a reduced risk of COVID-19 infection, hospitalization, and mortality.

It is worth noting that while these studies suggest a potential protective effect of ADT against COVID-19 in men with prostate cancer, further research is needed to confirm these findings and determine the safety and efficacy of ADT as a treatment for COVID-19. Additionally, not all studies have found a significant association between ADT and COVID-19 risk, which may be due to differences in study populations, study design, or other factors. However, it is worth noting that the current study is limited by its retrospective design and the potential for confounding variables. For example, the study did not account for other factors that may have influenced the incidence and severity of COVID-19, such as age, comorbidities, and socioeconomic status. Furthermore, the study was conducted on a relatively small sample of patients from a single institution, which may limit the generalizability of the findings.

In conclusion, the current study adds to a growing body of evidence suggesting that androgens may play a role in the severity of COVID-19 and that anti-androgen therapy may have a potential protective effect against SARS-CoV-2 infection in men with prostate cancer. However, further research is needed to confirm these results and the hypothesis of the possible pathway AR\TMPRSS2\ACE2 as the underlying mechanisms by which androgens and anti-androgen therapy may affect COVID-19 outcomes.

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