Influence of androgen deprivation therapy on the severity of COVID-19 in prostate cancer patients

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Abstract
Background: The TMPRSS2 protein has been involved in severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2). The production is regulated by the androgen receptor (AR). It is speculated that androgen deprivation therapy (ADT) may protect patients affected by prostate cancer (PC) from SARS-CoV-2 infection.

Methods: This is a retrospective study of patients treated for COVID-19 in our institution who had a previous diagnosis of PC. We analyzed the influence of exposure of ADT on the presence of severe course of COVID-19.

Results: A total of 2280 patients were treated in our center for COVID-19 with a worse course of disease in males (higher rates of hospitalization, intense care unit [ICU] admission, and death). Out of 1349 subjects registered in our PC database, 156 were on ADT and 1193 were not. Out of those, 61 (4.52%) PC patients suffered from COVID-19, 11 (18.0%) belonged to the ADT group, and 50 (82.0%) to the non-ADT group. Regarding the influence of ADT on the course of the disease, statistically significant differences were found neither in the death rate (27.3% vs. 34%; \( p = 0.481 \)), nor in the presence of severe COVID-19: need for intubation or ICU admission (0% vs. 6.3%; \( p = 0.561 \)) and need for corticoid treatment, interferon beta, or tocilizumab (60% vs. 34.7%; \( p = 0.128 \)). Multivariate analysis adjusted for clinically relevant comorbidities did not find that ADT was a protective factor for worse clinical evolution (risk ratio [RR] 1.08; 95% confidence interval [CI], 0.64–1.83; \( p = 0.77 \)) or death (RR, 0.67; 95% CI, 0.26–1.74; \( p = 0.41 \)).

Conclusions: Our study confirms that COVID-19 is more severe in men. However, the use of ADT in patients with PC was not shown to prevent the risk of severe COVID-19.

Keywords
androgen deprivation therapy, COVID-19, prostatic neoplasms, SARS-CoV-2
1 | INTRODUCTION

In late 2019, a new human coronavirus (SARS-CoV-2) causing severe acute respiratory syndrome (SARS) was isolated for the first time in Wuhan, China. SARS-CoV-2 causes a broad spectrum of diseases that are included under the term COVID-19 (coronavirus disease 2019) ranging from moderate respiratory infection to severe pneumonia, multiorgan failure, and even death. As of February 2021, SARS-CoV-2 has spread to 192 countries with more than 107 million people infected and causing more than 2.3 million deaths worldwide.

The different pathophysiological mechanisms involved in cell entry causing COVID-19 are currently being studied. The transmembrane serine protease 2 (TMPRSS2) has been found to be involved as a critical host cell factor for the spread of several clinically relevant viruses including SARS-CoV-2.

TMPRSS2 protein production is regulated by the androgen receptor (AR), which is an important molecular driver of both localized and metastatic prostate cancer (PC).

The presence of severe COVID-19 pneumonia was also analyzed. Although most of the patients with this pathology meet a series of common characteristics (alteration of the pulmonary radiological pattern or treatment with certain drugs such as antibiotics, heparin and supplemental oxygen requirements), a set of criteria was selected to assess the severity of pneumonia:

(i) Need for intubation or intense unit care (ICU) admission.
(ii) Type of treatment received, considering the need for corticotherapy, interferon beta, and tocilizumab as indicators of greater severity.
(iii) Radiological pattern: Given the great variability of radiological patterns, was decided to group them into three classes: (a) extensive, multilobar, and/or bilateral involvement (estimated as the most severe disease presentation), (b) unilobar involvement, and (c) no radiological signs of pneumonia.

Finally, the differences in mortality rates in both groups were analyzed.

2 | MATERIALS AND METHODS

We conducted a review of all the patients who visited our center between March 15 and May 15, 2020 with SARS-CoV-2 infection. Of all the patients attended during the study period, we selected those who were also previously diagnosed with PC. For this purpose, data from two institutional databases of patients treated with COVID-19, and of those under treatment or follow-up for PC were cross-referenced.

Polymerase chain reaction (PCR) was carried out on all those patients presenting symptoms suggestive of the disease at the emergency department. In those patients who presented with clinical/radiological disease consistent with COVID-19 and with negative PCR, the test was repeated by extracting a bronchial lavage sample, as this was considered to be more cost-effective. In case of continuing negative results, with high clinical suspicion, patients were considered and treated in the same way as patients who had microbiological confirmation.

For the analysis, we divided the patients with a previous diagnosis of PC and SARS-CoV-2 infection into two groups: one including those under active treatment with ADT or treated during the year before the diagnosis of SARS-CoV-2 infection, and another group of subjects with PC not treated with ADT.

First of all, demographic characteristics of both groups of patients were analyzed including age and comorbidity measured according to the Charlson Index, as well as data related to PC: prostate-specific antigen (PSA), tumor-node-metastases (TNM) stage, Gleason grading system, and the primary treatment regime received at diagnosis (radical prostatectomy, radiotherapy, ADT, or watchful waiting with or without subsequent need for ADT during follow-up).

Variables considered relevant for SARS-CoV-2 pneumonia were examined: pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma and other relevant comorbidities not included in the Charlson Index (hypertension, tobacco smoking, obesity, and obstructive sleep apnea syndrome [OSAS]).

Statistical analysis

The cumulative incidence of SARS-CoV-2 infection in PC patients was estimated and 95% confidence interval (95% CI) was calculated by considering Poisson distribution.

The distribution of qualitative data was presented by mean and SD or median and interquartile range and in the case of qualitative data was presented by absolute and relative frequencies.

To analyze if the hormonal treatment influenced the evolution of the disease (prognosis and mortality) in COVID-19 patients, a univariate analysis was first performed to determine the homogeneity of the two groups. We calculated the \( \chi^2 \) test or Fisher’s exact test for qualitative variables and the Student t test or the nonparametric Mann–Whitney U test for quantitative variables, according to data distribution.

As a treatment effect, the unadjusted relative risk was estimated and also adjusted for the heterogeneous variables between the two groups and clinically relevant variables (age, Charlson Comorbidity Index, hypertension, and obesity), using modified Poisson regression models (with robust standard errors).
All tests were considered bilateral and values of \( p < 0.05 \) were considered to be statistically significant.

The statistical analysis was performed using the SPSS (SPSS Inc. Released 2009; PASW Statistics for Windows, Version 17.0.; SPSS Inc.) and Stata (StataCorp. 2015; Stata Statistical Software: Release 14; StataCorp LP) data analysis packages.

### 3 RESULTS

During the study period, a total of 2280 patients were treated in our center for SARS-CoV-2 infection, of which 1227 (53.8%) were male and 1053 (46.2%) were female. The mean age of the series was 64.2 years (SD, 18.38). The mortality rate was 13% (297 deaths). The severity of the disease was worse in men, with a higher rate of hospitalization (74.9% vs. 67.4%; \( p < 0.001 \)), ICU admissions (8.0% vs. 4.5%, \( p = 0.001 \)), as well as a higher rate of death (15.7% vs. 9.9%, \( p < 0.001 \)) with statistically significant differences.

From a total of 2383 patients included in the institutional base of PC, those who had died or were lost to follow-up before January 2020 were excluded. This left a total of 1349 subjects, of whom 156 were receiving active treatment with ADT at that time or in the year before the start of the study and 1193 were not on hormone treatment in that period. We analyzed the number of these patients who had been registered in the COVID-19 database, obtaining a total of 61 patients with PC who had suffered SARS-CoV-2 infection. Thus, the cumulative incidence of COVID-19 in patients with PC was 4.5% (95% CI, 3.46–5.81).

### TABLE 1 Demographic and SARS-CoV-2 pneumonia-related variables in patients with PC on ADT group and non-ADT group

| Variable                        | ADT (N = 156) | Non-ADT (N = 1193) | \( p \) |
|---------------------------------|---------------|--------------------|-------|
| Global PC series                |               |                    |       |
| Incidence of SARS-CoV-2 infection | 11 (7.1)      | 50 (4.2)           | 0.106 |
| PC patients with SARS-CoV2      |               |                    |       |
| Age\(^{a}\)                     | 75 (6.2)      | 78.2 (7.9)         | 0.093 |
| Charlson Index\(^{a}\)          | 6 (4.0)       | 4.7 (2.7)          | 0.480 |
| COPD/asthma                     | 0 (0.0)       | 13 (26.0)          | 0.100 |
| Hypertension                    | 6 (54.5)      | 41 (82.0)          | 0.106 |
| Current smoker                  | 3 (27.2)      | 11 (22.0)          | 0.598 |
| Obesity                         | 1 (9.1)       | 9 (18.0)           | 0.673 |
| OSAS                            | 1 (9.1)       | 7 (14.0)           | 1.000 |
| Atrial fibrillation             | 0 (0.0)       | 9 (18.0)           | 0.191 |

### TABLE 2 Prostate cancer characteristics in ADT group and non-ADT group

| Variable                        | ADT (N = 11) | Non-ADT (N = 50) | \( p \) |
|---------------------------------|--------------|-----------------|------|
| PSA\(^{a}\)                     | 14.4 (4.9–82)| 8.8 (7–12)      | 0.225|
| Grade group (ISUP)              |              |                 | 0.001|
| 1                               | 1 (9.1)      | 26 (52.0)       |      |
| 2–3                             | 1 (9.1)      | 14 (28.0)       |      |
| 4–5                             | 9 (81.8)     | 10 (20.0)       |      |
| Clinical stage                  |              |                 | 0.210|
| T1                              | 6 (54.5)     | 39 (78.0)       |      |
| T2                              | 2 (18.2)     | 6 (12.0)        |      |
| T3                              | 3 (27.3)     | 5 (10.0)        |      |
| N1                              | 3 (27.3)     | 0 (0.0)         | 0.005|
| M1                              | 3 (27.3)     | 0 (0.0)         | 0.005|
| Treatment at diagnosis          |              |                 | 0.344|
| Radical prostatectomy           | 3 (27.3)     | 22 (44.0)       |      |
| Radiotherapy                    | 4 (36.4)     | 20 (40.0)       |      |
| ADT/watchful waiting\(^{b}\)    | 4 (36.4)     | 8 (16.0)        |      |

### TABLE 3 Poor prognosis variables for SARS-CoV-2 pneumonia

| Variable                        | ADT (N = 11) | Non-ADT (N = 50) | \( p \) |
|---------------------------------|--------------|-----------------|------|
| Radiological pattern            |              |                 |      |
| Extensive, multilobar, bilateral| 7 (63.6)     | 21 (43.8)       | 0.411|
| Poor prognosis treatment        | 6 (60.0)     | 17 (34.7)       | 0.166|
| ICU admission/intubation        | 0 (0.0)      | 3 (6.3)         | 0.561|
| Death rate                      | 3 (27.3)     | 17 (34.0)       | 0.481|

Note: Each patient may fit more than one variable.

Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen.

\(^{a}\)Variable expressed in median (interquartile range).

\(^{b}\)ADT at diagnosis versus watchful waiting with or without subsequent need for ADT during follow-up.

\(^{c}\)These patients were included in watchful waiting at diagnosis and they have never received ADT.
without finding statistically significant differences in any of the variables. Charlson Comorbidity Index score, COPD, and asthma were slightly higher in the group treated with ADT (Table 1).

Statistically significant differences were found in the pathological characteristics of the tumor between groups. As expected, higher risk disease with a higher rate of metastasis was described in the ADT group (Table 2).

The mean testosterone level in the group of patients treated with hormone therapy was 0.14 ng/ml. In the ADT group, four patients treated with radiotherapy at diagnosis received ADT as part of a neo/adjuvant treatment. In one patient, ADT was given during follow-up due to progression. Of the four patients treated with ADT at diagnosis, three were metastatic at baseline and two of them received abiraterone associated with ADT. Of these two patients, one of them eventually received chemotherapy treatment due to disease progression despite treatment with abiraterone.

The results about the influence of hormone therapy on the course of the disease are presented in Table 3. No differences were found between groups either in the death rate or in the comparison of poor prognostic COVID-19 factors between groups.

Treatment with ADT was not found to be a protective factor for poor outcomes such as need for ICU, use of specific treatment (risk ratio [RR], 1.11; 95% CI, 0.67–1.85; \( p = 0.68 \)), or death rate (RR, 0.80; 95% CI, 0.28–2.27; \( p = 0.68 \)). Likewise, no statistically significant differences were found when multivariate analysis was performed, adjusted for clinically relevant comorbidities (age, Charlson Comorbidity Index, hypertension, and obesity) (Tables 4 and 5).

TABLE 4 | Univariate analysis of criteria for poor prognosis of SARS-CoV-2 infection according to risk groups

| ADT/non-ADT | Unadjusted (RR) | \( p \) value | 95% CI |
|-------------|-----------------|---------------|--------|
| Death rate  | 0.80            | 0.68          | 0.28–2.27 |
| Death rate/ICU admission/poor prognosis treatment | 1.11 | 0.68 | 0.67–1.85 |

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; ICU, intensive care unit; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

4 | DISCUSSION

TMPRSS2 transcription is regulated by the AR,\(^{11}\) being overexpressed in the prostate gland.\(^{12}\) In vitro studies have already shown that TMPRSS2 inhibition may be beneficial in preventing SARS-CoV-2 infection.\(^{13}\) However, preclinical/clinical trials have not been developed yet to corroborate this hypothesis in vivo.

TMPRSS2 expression is regulated by ARs not exclusively in prostatic tissues, but also in other organs including lung,\(^{15}\) which is why it is speculated that men suffer from SARS-CoV-2 disease with greater severity than women. This suggests that future lines of treatment for male patients with severity criteria of COVID-19, may be based on ADT.\(^{16}\)

In addition, androgens could even exacerbate SARS-CoV-2 infection by different pathways. On the one hand, androgens acts by modulating the immune response, activating the inflammatory cascade, and lowering the antibodies that act as a response mechanism to viral infection.\(^{17}\) On the other hand, androgens, such as other steroid hormones, may increase TMPRSS2 transcription at the nuclear level.\(^{18}\)

For these reasons, exposed above linking the androgen pathway to the regulation of TMPRSS2 expression, it has been hypothesized that androgen blockade by ADT treatment could ameliorate SARS-CoV-2 infection.

Regarding the relationship between the androgenic environment and SARS-CoV-2 infection, as well as its severity, we found that, in our series, there was a higher incidence of SARS-CoV-2 infection in men (55.82%) than in women (44.18%). In addition, men had a higher rate of hospitalization (79.4% vs. 73.8%; \( p = 0.015 \)), of ICU admissions (9.2% vs. 5.3%; \( p = 0.007 \)), and a higher death rate (21.3% vs. 12.9%; \( p < 0.001 \)).\(^{15}\) Our data are in line with recent reports that find this association between male gender and the severity of SARS-CoV-2 infection.\(^{20}\)

At present, there are few published studies evaluating the influence of in vivo ADT in SARS-CoV-2 infection, and the results are controversial. To our knowledge, ours is one of the largest studies to report the severity of COVID-19 in patients under ADT. Regarding the influence of ADT on the course of the disease, statistically significant differences were found neither in the death rate (27.3% vs. 34%; \( p = 0.481 \)), nor in the presence of severe COVID-19: need for intubation or ICU admission (0% vs. 6.3%; \( p = 0.561 \)) and need for corticoid treatment, interferon beta, or tocilizumab (60% vs. 34.7%, \( p = 0.128 \)).

In the same line of our results, Klein et al.\(^{21}\) published a multicenter study in which they concluded that in patients with PC (\( n = 102 \)) who had been treated with ADT (\( n = 17 \)) were not protected against SARS-CoV-2 infection (odds ratio [OR], 0.93; 95% CI, 0.54–1.61; \( p = 0.8 \)). Caffo et al., reached the same conclusion in another small study on patients with metastatic (hormone-sensitive or castration-resistant) PC (mPC), under treatment with ADT and COVID-19 infection, in which the death rate in patients <70 years was higher in patients with mPC than in the general series of patients without PC. They conclude that there does not seem to be a protective role for ADT against SARS-CoV-2 infection, at least in patients with mPC.\(^{22}\)

On the contrary, Montopoli et al.\(^{20}\) have performed a multicenter study with the largest number of SARS-CoV-2-positive patients tested. In this study, evaluating the relationship of COVID-19 with the diagnosis of PC, they conclude that patients treated with ADT are four times less likely to be infected with SARS-CoV-2 than those who did not receive ADT (OR, 4.05; 95% CI, 1.55–10.59; \( p = 0.0043 \)), which would support the theories previously mentioned.
Likewise, Patel et al.,\(^{23}\) in another study with a small number of patients (N=58), found that after adjusting for risk factors such as age, cardiac, or pulmonary disease, patients treated with ADT had lower rates of hospitalization and supplemental oxygen requirements than patients without ADT, interestingly finding no statistically significant differences in the need for intubation and mortality.

Analyzing the inconsistency of the results shown by different studies, we found that Montopoli et al. only had 4 of 5273 patients treated with ADT (0.07%) who were SARS-CoV-2-positive and those patients had a significantly lower risk of SARS-CoV-2 infection than patients who did not receive ADT. However, in our study where known risk factors for developing respiratory infection were analyzed, no differences between ADT and non-ADT groups were found. In addition, we performed a multivariate analysis adjusted for clinically relevant risk factors in which ADT was not found to be a protective factor for poor outcomes such as the need for ICU, use of specific treatment, or death rate.

These differences found between the series can also be attributed to the worse baseline health status of patients undergoing ADT according to their clinical scenario.

Montopoli et al. evaluated a cohort of patients identified by means of a regional cancer registry without specifying which patients had received ADT for metastatic disease or for biochemical recurrence. In our cohort, many of our patients receiving ADT had metastatic disease which may explain their worse evolution, as found by Caffo et al.

As in the other studies published to date, one of the most important limitations of our study is the small sample size. In addition, it should be taken into account that some patients in our PC series may have been treated for SARS-CoV-2 infection in other centers and also those patients with mild disease who have not been admitted for which we have no record. The retrospective design of our study makes it necessary to proceed with caution when drawing conclusions.

In summary, despite the association found in vitro between the enhanced response of SARS-CoV-2 infection and the inhibition of TMPRSS2 by hormone blockade, clinical experience published to date shows contradictory results. Our results, do not support that hypothesis.

Despite the limitations of our study, we speculate that perhaps other factors such as smoking, previous comorbidities, performance status, and their PC stage may play a more determinant role in SARS-CoV-2 infection than the hormonal influence. Therefore, this association should be taken with caution and verified or rejected by large prospective studies with longer follow-up.

In this regard, there are two ongoing trials, evaluating the role of 5-alpha-reductase inhibitors, dutasteride\(^{25}\) and proxalutamide,\(^{25}\) in the severity of COVID-19, both with pending results.

### CONCLUSIONS

Our study confirms that COVID-19 is more severe in men. However, the use of ADT in patients with PC was not shown to prevent the risk of severe COVID-19. Our findings do not support the positive results of this association published by other series, and it will be necessary to develop clinical trials to assess if ADT could be added in the therapeutic arsenal against SARS-CoV-2 infection.

### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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