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Systematic Meta Analysis

Androgen Deprivation Therapy and SARS-CoV-2 Infection in Patients with Prostate Cancer: A Systematic Review and Meta-Analysis

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Abstract

Objectives: The main treatment for metastatic prostate cancer is androgen deprivation therapy. The relationship between ADT and SARSCoV-2 virus was intensively investigated since the COVID 19 pandemic began. To perform a meta-analysis to evaluate the effect of androgen deprivation therapy (ADT) on COVID-19 in patients with prostate cancer.

Methods: On January 11th, a comprehensive literature search was conducted following PRISMA guidelines in the PubMed, Scopus, Embase, and Web of Science databases, and an update was conducted on January 24 for this search.

Results: Eight papers were included for systematic review. Five studies were suitable for meta-analysis. The incidence of SARS-CoV-2 infection among patients who were receiving ADT was 3.0%. ADT was not associated with a lower incidence of SARS-CoV-2 infection (95% CI: 0.56-1.58, RR = 0.94, p=.91; I^2 = 60%, p=.03). Mortality was around 28% and there was no significant relationship between ADT use and mortality (95% CI: 0.61-1.69, RR = 1.01, p=.96).

Conclusion: It is difficult to say that there is a relationship between use of ADT and the risk of death due to COVID-19 infection. But there is also no evidence to suggest that ADT causes the risk of death from COVID-19.

Keywords: Androgen deprivation therapy, prostate cancer, SARS-CoV-2

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The COVID-19 outbreak caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which started with a case detected in China on 12 December 2019, was defined as a pandemic by the World Health Organization (WHO) on 11 March 2020.[1] As of 21 July, WHO reported 14,348,858 confirmed cases of COVID-19 and 603,691 deaths worldwide.[2] One of the most important problems caused by pandemics is the difficulty in the management of chronic diseases, the frequency of which is increasing with the prolongation of life expectancy in today's world. Today, cancer constitutes a very important subset of chronic diseases. It is obvious that the fight against this disease, which is currently very difficult to manage, requires the participation of many branches and is quite deadly, has become even more difficult during the COVID-19 pandemic. But cancer and cancer-related deaths are just as important as the COVID-19 outbreak.[3] This reveals the need to continue follow-up and treatment of patients even during the pandemic. Studies conducted after the onset of the pandemic showed that advanced age and

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the presence of comorbidities cause more severe COVID 19 clinical tableau and increased mortality.[4] Cancer patients constitute the highest risk patient group during the pandemic due to both underlying disease, most cancers occur at advanced age, and many chronic diseases increase with age. One of the most important of these cancers is prostate cancer. Prostate cancer is the second most common cancer in men.[5] The main method in the treatment of metastatic prostate cancer (mPCa) is testosterone suppressive therapies, also called androgen deprivation therapy (ADT). Testosterone suppression can be achieved by surgical castration (orchiectomy) or medical castration (with luteinizing hormone-releasing hormone analogues or antagonists). The relationship between androgens, anti-androgen therapies, ADT and SARSCoV-2 virus was intensively investigated since the COVID 19 pandemic began. Since the beginning of the pandemic, a rich literature has emerged, from studies showing that the spike proteins of the virus inhibit the growth of prostate cancer cells, to studies showing that anti-androgen drugs can be used for the treatment of COVID-19.[6,7] The TMPRSS2 protein was shown to have proteolytic activity for entry of SARS-CoV2 into airway epithelium. [8] The TMPRSS2 gene and protein, which are already known to have a role in the pathogenesis of prostate carcinoma, were the focus of research in this patient group after the pandemic.[9] The TMPRSS2 protein, whose expression is increased in the presence of high androgens, was expected to decrease in prostate carcinoma patients receiving ADT, and thus, ADT would theoretically be protective against COVID-19.[10] Unfortunately, clinical practice did not match this theory. The relationship between androgen-suppressing therapies and COVID 19 has not been clarified yet. New studies are emerging on this subject every day. For this reason, there is a need to conduct a meta-analysis of studies examining this issue.

Methods

Literature Search

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines were followed during the design, analysis, and reporting of this systematic review and meta-analysis.[11] On January 11th, a comprehensive literature search was conducted of the PubMed, Scopus, Embase, and Web of Science databases, and an update was conducted on January 24 for this search. Four factors were considered for the search query lines when choosing the keywords: "ADT", "androgen deprivation therapy", "SARS-CoV-2", and "COVID-19". The keywords were combined using Medical Subject Headings (MeSH), text terms, and the Boolean operators AND/OR were used to integrate the keywords. The search strategy was developed in the PubMed database and applied to other databases (Web of Science, Scopus and Embase).

Inclusion/Exclusion Criteria

Original clinical studies about the impact of ADT on COVID-19 from the beginning of the pandemic to January 24th were included in this study. Original research that was published in the English language were researched, and no other types of paper were examined. Exclusion criteria: i) reviews, guidelines, opinions, or other non-original data publications; ii) case studies; iii) projects and clinical trials that were incomplete; and iv) no clinical evidence from animal and laboratory studies

PICOs:

1. Population: "Patients with prostate cancer"
2. Intervention: "Receiving ADT"
3. Comparison: "Not receiving ADT"
4. Outcomes: i) "COVID-19 infection risk"; ii) "COVID-19 severity risk", including: a) "ICU admission", and b) "Mortality risk".

Data Extraction and Acquisition

Two independent reviewers examined the article titles and abstracts, and any differences amongst co-authors regarding which papers were eligible and which were not were handled using Delphi consensus criteria.[12] Paper abstracts and full-texts were read, and the data was extracted into a pre-defined spreadsheet created using Microsoft Excel®. COVID-19 infection incidence, intensive care unit (ICU) admission, and death (mortality) were separated into three groups and their risks were evaluated. Location, population, and mean age (if given) were also extracted into the same excel file, in addition to the three key outcomes indicated above.

To overcome data limitations - in case of missing data or doubt- the corresponding author(s) of the articles were contacted via email to obtain more details.

Statistical Analysis

Forest plots were utilized to compute and graphically illustrate the risk ratio (RR) with 95% confidence interval (CI) of COVID-19 infection, incidence and mortality rates in the treatment and control groups, and to summarize them. All research that reported COVID-19 infection and/or mortality and ICU admission rates as an outcome were evaluated in primary and secondary meta-analyses. Cochrane's Q test and I^2 statistics were used to assess study heterogeneity.[12] A $p \leq 0.05$ in Cochrane's Q tests and a ratio of less than 50% in I^2 statistics revealed significant heterogeneity.[13] If the findings were heterogeneous, the analysis was carried out using random-effect models. Non-heterogeneous findings were calculated using fixed-effects models. For each significant

outcome in our research, Egger's test and a funnel plot were utilized to examine the possibility of publication bias. The risk of bias in the included studies was calculated using the Newcastle-Ottawa Scale (NOS)[14] risk assessment method (Table 1). For each study, this instrument assigns a maximum score of nine in three categories: selection, comparability, and exposure. The statistical significance level was determined at $p<0.05$. The Cochrane Collaboration Review Manager (RevMan v.5.4; Cochrane Collaboration, Oxford, UK) and ProMeta3® software were used to conduct all of the analyses.

Results

A total of 289 articles were found, with 73 in the Web of Science, 57 in the PubMed, 62 in the Embase, and 97 in the Scopus databases. After a preliminary review and the elimination of duplicates, 143 papers were chosen for further evaluation. Figure 1 shows a flow diagram demonstrating the selection process. Eight papers were included for systematic review after applying the inclusion and exclusion criteria. Because of the lack of SARS-Cov-2 infection incidence, Godeborg et al. and Schmidt et al. were omitted from the meta-analysis.[15,24] Six studies were suitable for meta-analysis because they included both ADT (+) and ADT (-) groups.[16-21] In the other two studies, only data about ADT (+) patients were available.[22,23] Therefore, these studies were excluded from the comparative meta-analysis.

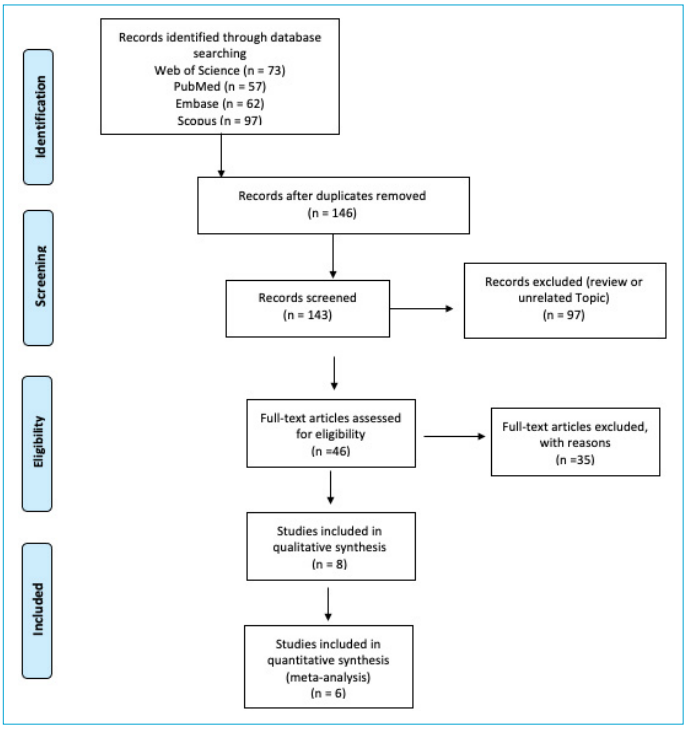


Figure 1. PRISMA flow diagram used in study selection process.

Table 2 shows the parameters of the eight included studies. Comorbidities were found in three trials.[16,17,19] Although one research found that the prevalence of different comor-

Table 1. Characteristics of all studies in quantitative synthesis according to Newcastle-Ottawa Scale

First author	Country	Type of study	Newcastle-Ottawa scale (NOS) risk of bias assessment			
			Selection	Comparability	Outcome	Total
Klein et al.	USA	Pros. Cohort	****	**	***	9
Koskinen et al.	Finland	Res. Cohort	****	**	**	8
Montopoli et al.	Italy	Res. Cohort	**	**	**	6
Patel et al.	USA	Res. Cohort	****	**	**	8
Caffo et al. (a)	Italy	Res. Cohort	***	**	**	7
Caffo et al. (b)	Italy	Res. Cohort	***	**	***	8
Kwon et al.	USA	Res. Cohort	****	**	**	8
Jiménez-Alcaide et al.	Spain	Res. Cohort	****	**	**	8

Table 2. Characteristics of COVID-19-infected prostate cancer patients included in the research

Study/Year	Design	Total patients	ADT	No ADT	Outcomes
Klein et al., 2021	Pros. Cohort	1779	304	1475	Infection risk Severity of disease
Koskinen et al., 2020	Res. Cohort	352	134	218	Infection risk Severity of disease
Montopoli et al., 2020	Res. Cohort	42434	5273	37161	Infection risk Severity of disease
Patel et al., 2020	Res. Cohort	465	148	317	Severity of disease
Caffo et al. (a), 2020	Res. Cohort	1949	36	None	Infection risk Severity of disease
Caffo et al. (b), 2020	Res. Cohort	1433	34	None	Infection risk Severity of disease
Kwon et al., 2020	Res. Cohort	5211	799	4412	Infection risk Severity of disease
Jiménez-Alcaide et al., 2021	Res. Cohort	1349	156	1193	Infection risk Severity of disease

bidities was equal in the ADT (+) and (-) groups,[17] two other studies found that ADT (+) patients had increased comorbidity frequencies.[16,19] Patients receiving ADT had greater incidences of metastatic disease (64% vs. 0%, p=.001) and underlying pulmonary illnesses (27% vs. 6%, p=.02) in the Patel et al. study.[19] In Klein et al., patients receiving ADT were more likely to have smoking history (68.1% vs. 59.3% p=.005), immunosuppressive disease (34.2% vs. 27.5% p=.02), and steroid use (43.8% vs. 23.3% p=.001), and less likely to have a history of asthma (9.2% vs. 14.2% p=.02).[16]

According to a pooled analysis, the incidence of SARS-CoV-2 infection among patients who were receiving ADT was 3.0%.[16,18-23] The results of the analysis is presented in Figure 2. As seen in Figure 3, ADT was not associated with a lower incidence of SARS-CoV-2 infection (95% CI: 0.56-1.58, RR = 0.94, p=.91; I^2 = 60%, p=.03). It was determined that 19% of ADT (+) patients infected with COVID-19 were hospitalized in the intensive care unit (Fig. 4).[16-18,21,23] Seven studies were evaluated to determine the mortality rate and the relationship between ADT use and risk of death.[16,18-23] The mortality rate was calculated and is presented in Figure 5. The heterogeneity was low (I^2 = 15%, p=0.32), so a fixed effect model was used. Mortality was around 28% and there was no significant relationship between ADT use and mortality (95% CI: 0.61-1.69, RR = 1.01, p=.96) (Fig. 6).

The funnel plot was performed to test publication bias for the two major outcomes. None of the variables had significant publication bias: COVID-19 infection risk (funnel plot as Supplementary Fig. 1) and mortality (funnel plot as Supplementary Fig. 2).

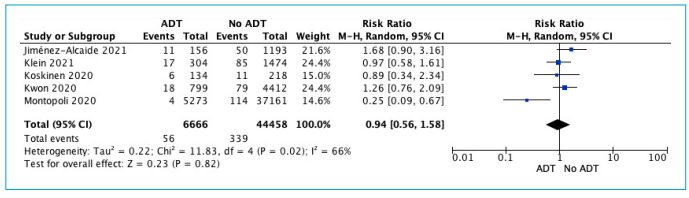


Figure 2. Forest plot for relative risk (RR) of COVID-19 infection risk among prostate cancer patients who received ADT compared to those who did not receive ADT.

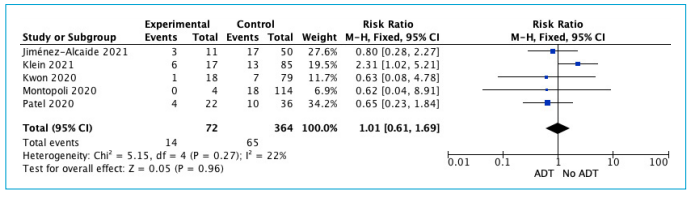


Figure 3. Forest plot for relative risk (RR) of COVID-19 mortality risk among prostate cancer patients who received ADT compared to those who did not receive ADT.

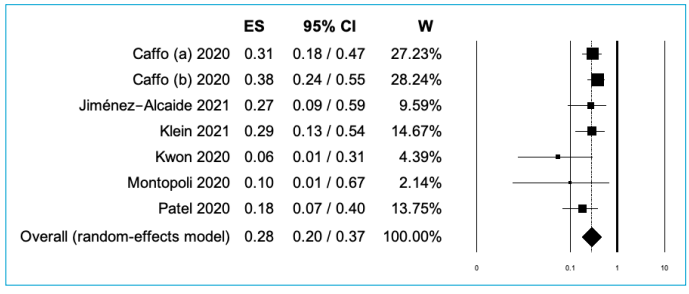


Figure 4. Pooled analysis of mortality rate in SARS-CoV-2 infected patients receiving ADT.

Discussion

This meta-analysis found no association between ADT use and risk of COVID-19-related death. This also shows that the relationship between TMPRSS and androgens, which has a strong theoretical foundation, is not reflected in clinical practice. However, it is a fact in clinical practice that patients diagnosed with prostate carcinoma have advanced age and many comorbidities. Comorbidities of patients were reported in only three of the studies included in this meta-analysis. In only one of these three studies, comorbidity rates were similar between groups that received and did not receive ADT, whereas in the other two studies, the comorbidity rate in the group that received ADT was higher than the group that did not receive ADT. In the study by Patel et al., underlying lung disease was higher in patients receiving ADT than in the group not receiving ADT. In the study by Klein et al., smoking and the presence of immunosuppressive disease were higher in the ADT group than in the non-ADT group.[16,17,19] All of these play a role

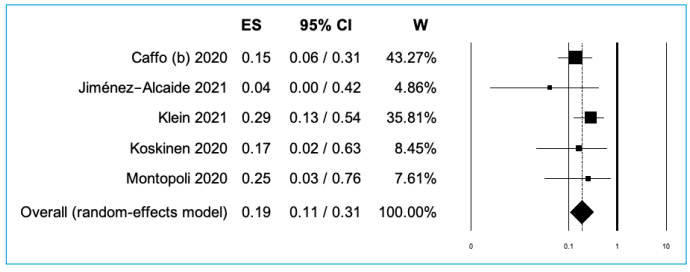


Figure 5. Pooled analysis of ICU-admission rate in SARS-CoV-2 infected patients receiving ADT.

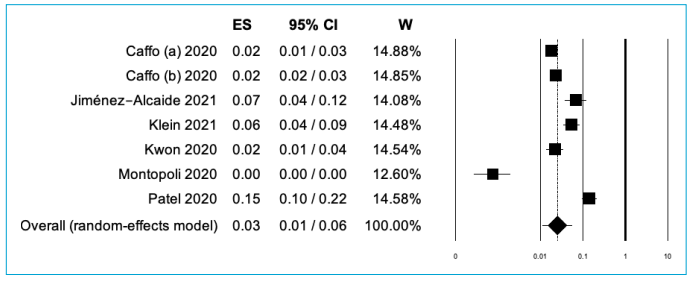
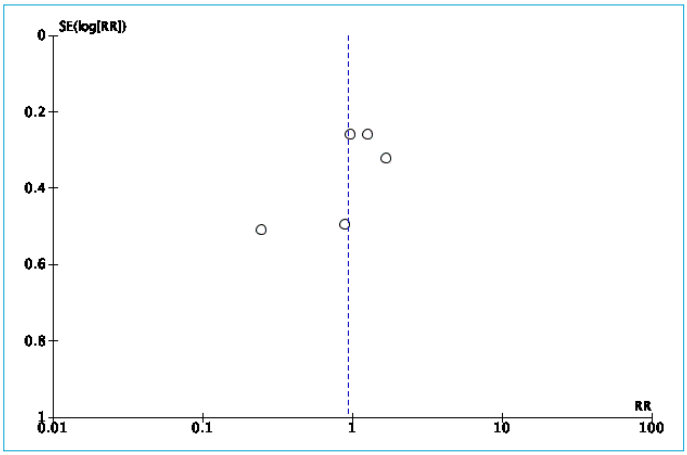
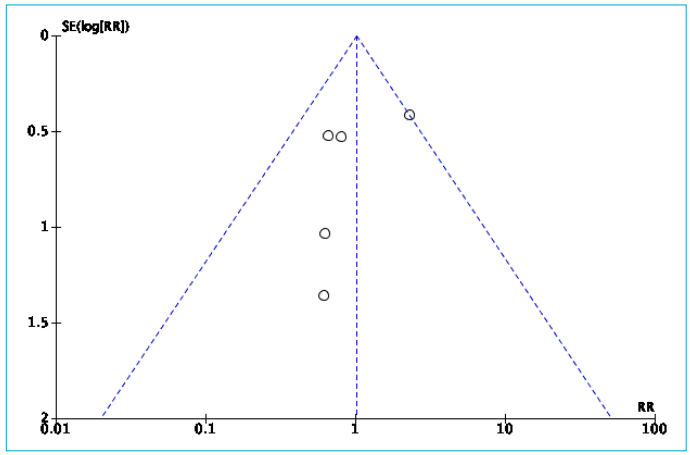


Figure 6. Pooled analysis of incidence in SARS-CoV-2 infected patients receiving ADT.



Supplementary Figure 1. Funnel plot of COVID-19 infection risk among prostate cancer patients who received ADT compared to those who did not receive ADT.



Supplementary Figure 2. Funnel plot of COVID-19 mortality risk among prostate cancer patients who received ADT compared to those who did not receive ADT.

as confounding factors when determining the relationship between ADT and COVID-19. In this meta-analysis, the frequency of COVID-19 infection was 3% in patients receiving ADT. The rate of hospitalization in the intensive care unit was 19%. When these figures are evaluated in the light of the literature, the use of ADT does not reduce mortality.[4] However, considering factors such as the chaos in the provision of health services all around the world at the beginning of the pandemic, the frequency of COVID-19 in patients with prostate carcinoma may not have been detected correctly as patients did not attend hospital without very significant complaints and the inability to diagnose because some patients had mild symptomatic or asymptomatic COVID-19 infection.[25] Therefore, mortality rates can be misleading. It should be kept in mind that only one of the clinical trials included in this meta-analysis was prospective and the others were retrospective. In addition, ADT is not used alone in the treatment of prostate carcinoma. There are also many treatment options such as chemotherapy (docetaxel or cabazitaxel), new generation hormonal agents (abiraterone, enzalutamide), radionuclide treatments and definitive radiotherapy, which are commonly used with ADT.[26,27] However, these treatments were not mentioned in the studies included in the meta-analysis. In addition, these studies, mostly retrospective and conducted with different patient groups (stage, disease burden, etc.) in different clinics, are unlikely to reveal the relationship between ADT and the risk of death due to COVID-19. The presence of many confounding factors also reduces the power of this meta-analysis.

Conclusion

Currently, it is difficult to say that there is a relationship between the use of ADT and the risk of death due to COVID-19 infection. But there is also no evidence to suggest that ADT causes a jump in the risk of death from COVID-19 at least. To date, the pandemic has caused the loss of many people. But it should be kept in mind that prostate cancer is at least as deadly as COVID-19. For this reason, efforts should be made to ensure that patients reach standard treatments without ignoring pandemic conditions.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.S.S., M.E.A., H.E.; Design – H.S.S., M.E.A., H.E.; Supervision – M.E.A., H.E.; Materials – H.S.S., M.E.A., H.E.; Data collection &/or processing – H.S.S., M.E.A., H.E.; Analysis and/or interpretation – M.E.A.; Literature search – H.S.S., M.E.A., H.E.; Writing – H.S.S., M.E.A., H.E.; Critical review – H.S.S., M.E.A., H.E.

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