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Relationship Between Androgen Deprivation Therapy for Prostate Cancer and Risk of SARS-CoV-2 Infection: A Systematic Review and Meta-Analysis

Do Kyung Kim [1], **Jae Joon Park** [1], **Won Jae Yang** [1], **Seung Whan Doo** [1], and **Jae Heon Kim** [1,2]

[1]Department of Urology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea
[2]Urological Biomedicine Research Institute, Soonchunhyang University Seoul Hospital, Seoul, Korea

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Address for Correspondence:
Jae Heon Kim, MD, PhD
Department of Urology, College of Medicine, Soonchunhyang University Seoul Hospital, Soonchunhyang University Medical College, 59, Daesagwan-ro, Yongsan-gu, Seoul 140-743, Republic of Korea.
Email: piacekjh@hanmail.net

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ORCID iDs
Do Kyung Kim
https://orcid.org/0000-0002-3696-8756
Jae Joon Park
https://orcid.org/0000-0002-7199-0764
Won Jae Yang
https://orcid.org/0000-0002-7356-4312
Seung Whan Doo
https://orcid.org/0000-0002-5924-6908
Jae Heon Kim
https://orcid.org/0000-0002-4490-3610

ABSTRACT

Background: Several cohort studies have explored the relationship between androgen deprivation therapy (ADT) and the severity of coronavirus disease 2019 (COVID-19). This study aimed to characterize the relationship between ADT and the severity of COVID-19 in patients with prostate cancer.
Methods: A systematic search was conducted using PubMed, Embase, and Cochrane Library databases from the inception of each database until February 31, 2020. Patients with prostate cancer who were treated with ADT were assigned to treatment group while those patients who were not treated with ADT were assigned to the control group. Outcomes were severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) positivity, hospitalization, intensive care unit (ICU) admission, and death. The risk of bias was evaluated using ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool.
Results: Three studies with qualitative synthesis were included. Finally, two studies with quantitative synthesis having a total of 44,213 patients were included for the present systematic review. There was no significant difference in SARS-CoV-2 positive rate (odds ratio [OR], 0.52; 95% confidence intervals [Cis], 0.13–2.09; $P = 0.362$), hospitalization (OR, 0.52; 95% CIs, 0.07–3.69; $P = 0.514$), ICU admission (OR, 0.93; 95% CIs, 0.39–2.23, $P = 0.881$), or death (OR, 0.88; 95% CIs, 0.06–12.06; $P = 0.934$) between ADT and non-ADT groups.
Conclusion: Qualitative and quantitative analyses of previous studies revealed no significant effect of ADT on COVID-19. However, more studies with higher quality that explore biochemical and immunological factors involved are needed to confirm this finding in the future.

Keywords: Prostate Cancer; Androgen Deprivation Therapy; COVID-19; SARS Virus

INTRODUCTION

Since the outbreak of coronavirus disease 2019 (COVID-19) in December 2019, several studies undertaken in different regions and countries around the world have revealed sex-based differences of this disease. Whilst males and females appear to be equally vulnerable

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Ethical approval
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Author Contributions
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to contracting the disease, there are differences in the severity of the infection, with males suffering more severely.[1] Multiple potential factors have been proposed to account for such sex-based difference including biological factors, such as hormones, immunity, enzymes, genetic diversity and lifestyle factors.[2,3] Some studies have focused on androgen and suggested that androgen in males might have influenced immunity and made males more vulnerable to severe infection or that hormones might have potentially increased the virulence of COVID-19.[4,5]

Thus far, only three cohort studies have explored the relationship between androgen deprivation therapy (ADT) and the severity of COVID-19,[4-6] showing inconsistent results. Compared to patients not receiving ADT, those who have received ADT are four times less likely to experience severe COVID-19 infection. The risk of severe infection is five times less in patients who are receiving ADT for prostate cancer than in patients who have other cancers.[4,5]

The evidence provided by these studies suggests that the severity of COVID-19 is intensified by elevated concentrations of androgen. Moreover, ADT could be an alternative treatment for severe COVID-19 in addition to currently introduced vaccines and remedies. More research studies are needed to determine whether there is a relationship between androgen level and the severity of COVID-19. If such relationship is confirmed, responsible biochemical and molecular mechanisms involved in such relationship need to be elucidated.

This study performed a systematic review of published cohort studies. The aim of this study was to characterize the relationship between ADT and the severity of COVID-19 in patients with prostate cancer. It considers the quality of cohort studies' methodologies in relation to the existing body of knowledge about biochemistry and immunology.

MATERIALS AND METHODS

This systematic review is registered in PROSPERO, CRD 42021235232.

Search strategy

In the present study, PubMed, Embase, and Cochrane Library databases were systematically searched for English language studies published from the inception of each database until February 31, 2020. All studies that examined the effect of ADT on the risk of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in patients with prostate cancer were identified. Search terms consisted of MeSH terms of "prostate cancer," "coronavirus infections," "SARS-CoV-2," and "androgen deprivation therapy." Natural headings in the abstract or title included "prostate cancer," "androgen-deprivation," "androgen deprivation therapy," and "SARS-CoV-2." Searches were limited to human and English studies. All study designs were searched. All conference and meeting abstracts and non-English articles were excluded regardless of relevance.

Trial inclusion and exclusion criteria

The PICOS (participants, interventions, comparators, outcomes, and study design) approach was used to assess the eligibility of identified studies in accordance with the PRISMA guidelines.[7] Human research studies on patients with prostate cancer and the effect of ADT on SARS-CoV-2 infection with outcomes of the present study were included. Exclusion criteria were: non-human study, no control group, and non-English study. Final included articles were determined through assessment and discussion among all authors.

Data extraction

Two independent authors extracted the data of included studies using a predesigned form. Any conflicts between them were resolved via discussion and consensus. Final included studies were agreed by all authors. Extracted data included the first author, publication year, country, study design, treatment and control groups, number and mean age of patients, definition of ADT, inclusion and exclusion criteria, follow-up period, and outcomes.

Types of interventions and outcomes

Patients with prostate cancer who were treated with ADT were assigned to the treatment group while those patients who were not treated with ADT were assigned to the control group. Patients in both groups had undergone a SARS-CoV-2 test. The primary outcome was SARS-CoV-2 positivity. Secondary outcomes were hospitalization, intensive care unit (ICU) admission, and death.

Study quality assessments and quality of evidence

The risk of bias in each included study was evaluated using ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool. Bias domains included in the ROBINS-I tool: 1) confounding, 2) selection of participants for the study, 3) classification of interventions, 4) deviations from intended interventions, 5) missing data, 6) measurement of outcome, and 7) selection of reported result.[8] Based on judgements for each bias domain, the overall risk of bias was classified into four levels: 'Low,' 'Moderate,' 'Serious,' and 'Critical.'

The certainty of evidence reported in the present study was assessed using Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE).[9] The GRADE system assesses the methodology, precision, consistency of results, directness, and risk of publication bias constitute. Based on these five criteria, the certainty of evidence was assessed at four levels: high, moderate, low, and very low.

Statistical analysis

We performed meta-analysis for dichotomous outcomes to compare the efficacy of ADT with respect to outcomes using the random effects model. Outcomes were evaluated as risk ratios (RRs) in stratified 2 × 2 contingency tables. Results are reported as RRs and 95% confidence intervals (CIs) of included studies.

Statistical heterogeneity among included studies was identified by Cochran Q statistic and I^2 statistic. A P value < 0.05 of the Cochran Q statistic or an I^2 statistic > 50% suggested significant heterogeneity.[10] We used funnel plot to evaluate publication bias. Symmetry reversal funnel diagrams meant no publication bias.

Meta-analysis was performed using Review Manager v.5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2008). All P values were two-sided and P < 0.05 was considered statistically significant.

RESULTS

Systematic review process

Fig. 1 shows the process of systematic review in the present study. Literature searches found a total of 18 studies, with 13 remaining after removing duplicates. After reviewing titles and

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abstracts, 10 were removed as they were Editorials, letters, review articles, or case reports. The remaining three full-text articles were assessed for eligibility for final inclusion. Through this process, all three studies were included in qualitative synthesis.[4-6] However, one study had no control group. It was excluded. Finally, the present study included two studies for quantitative synthesis,[5,6] with a total of 44,213 patients. Detailed information of each included study is shown in **Table 1**.

Outcome

SARS-CoV-2 positivity

For the two included studies, there was no significant difference in SARS-CoV-2 positive rate between ADT and non-ADT groups (OR, 0.52; 95% CI, 0.13–2.09; $P = 0.362$, **Fig. 2A**). Heterogeneity among included studies was observed ($P = 0.01$; $I^2 = 84\%$).

Hospitalization

The two included studies showed no significant difference in hospitalization rate between ADT and non-ADT groups (OR, 0.52; 95% CI, 0.07–3.69; $P = 0.514$, **Fig. 2B**). Heterogeneity among included studies was observed ($P = 0.01$; $I^2 = 85\%$).

ICU admission

Two included studies showed no significant difference in ICU admission rate between ADT and non-ADT groups (OR, 0.93; 95% CI, 0.39–2.23; $P = 0.881$, **Fig. 2C**). Heterogeneity among included studies was not observed ($P = 0.56$; $I^2 = 0\%$).

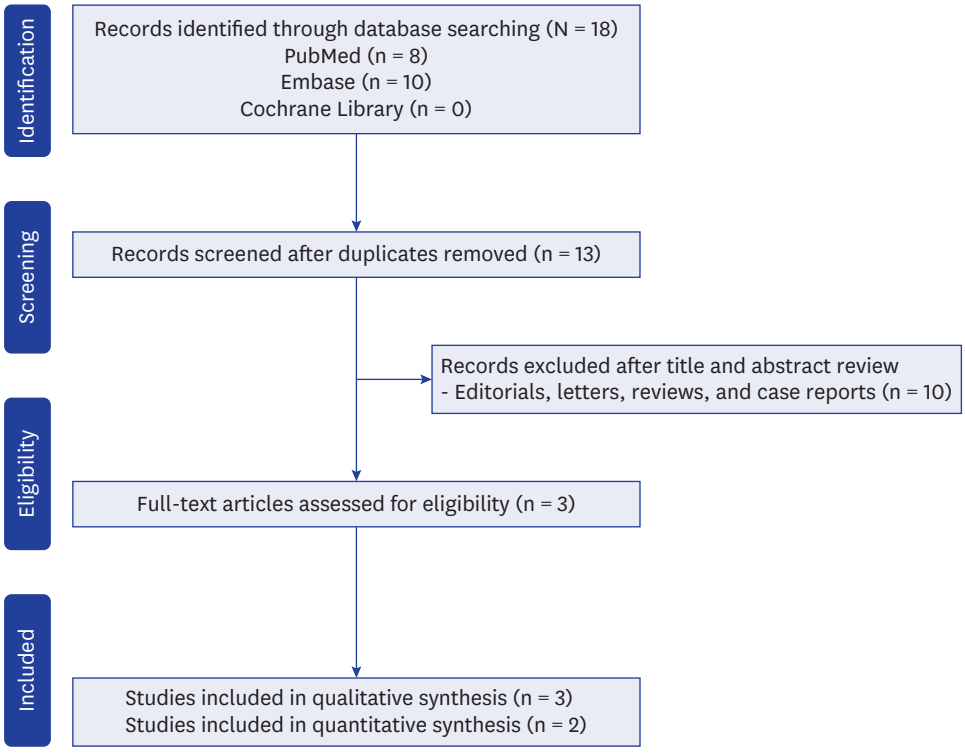

Fig. 1. Preferred reporting items for systematic reviews and meta-analysis.

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Table 1. Characteristics of eligible studies

Study	Design	Group characteristics (total number)		Definition of ADT	Outcomes OR (95% CI)		Conflict of interest
Klein et al.[6] 2021	Prospective study	Treatment group	Patients with PCa who underwent ADT (304)	NA	SARS-CoV-2 positivity	OR (95% CI): 0.9 (0.54–1.61)	None
		Control group	Patients with PCa who were not on ADT (1475)		Hospitalization	OR (95% CI): 2.0 (0.57–7.32)	
					Admission of ICU	OR (95% CI): 1.3 (0.38–4.09)	
					Death	OR (95% CI): 2.9 (0.86–9.81)	
Montopoli et al.[5] 2020	Retrospective study	Treatment group	Patients with PCa who underwent ADT (5273)	NA	SARS-CoV-2 positivity	OR (95% CI): 4.05 (1.55–10.59)	European Research Council Consolidator Grant
					Hospitalization	OR (95% CI): 5.39 (1.32–21.96)	; Swiss Cancer League
		Control group	Patients with PCa who were not on ADT (37161)		Admission of ICU	OR (95% CI): 4.40 (0.76–25.50)	; Swiss National Science Foundation (SNSF)
					Death	OR (95% CI): 5.25 (0.31–87.14)	; Prostate Cancer Foundation ; and Italian Association for Cancer Research Investigator Grant
Caffo et al.[4] 2020	Retrospective study	Treatment group	Patients with mCRPC who underwent ADT (1433)	NA	SARS-CoV-2 positivity	Number of case: 34	None
					Hospitalization	Number of case: 22	
		Control group	NA		Admission of ICU	Number of case: 5	
					Death	Number of case: 13	

ADT = androgen deprivation therapy, OR = odds ratio, CI = confidence interval, PCa = prostate cancer, NA = not available, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, ICU = intensive care unit, mCRPC = metastatic castration-resistant prostate cancer.

Death

Two studies showed no significant difference in death rate between ADT and non-ADT groups (OR, 0.88; 95% CI, 0.06–12.06; $P = 0.934$, **Fig. 2D**). Heterogeneity among included studies was observed ($P = 0.07$; $I^2 = 70\%$).

Quality assessment, qualitative risk of bias, and certainty of evidence

The risk of bias graph and assessment results using the ROBINS-I tool are presented in **Figs. 3** and **4**. The study of Klein et al.[6] had a relatively lower risk of bias than other studies. Results of assessment of the certainty of evidence using the GRADE approach are presented in **Table 2**. The certainty was low for SARS-CoV-2 positivity, hospitalization, and ICU admission. The certainty was very low for death. Funnel plots for publication bias demonstrated a certain degree of symmetry (**Fig. 5**).

DISCUSSION

To the best of our knowledge, this is the first systematic review about the relationship between ADT for prostate cancer and risk of SARS-CoV-2 infection. We found that there was no significant difference in SARS-CoV-2 positive rate, hospitalization, ICU admission, or death between ADT and non-ADT groups of patients with prostate cancer. Due to limited number of relevant cohort studies available, more evidence will be required to confirm the relationship between COVID-19 and ADT. However, we proposed fundamental methodological elements as shown in methodological qualities.

The importance of methodological quality includes the point that current studies could not reflect various aspects such as biochemical and immunological background. Covariate data such as comorbidities, such as asthma, coronary artery disease, diabetes, heart failure, hypertension and immune suppressive disease, use of steroids, and smoking status should be incorporated into cohort studies. To determine severity, outcome measures of admission to hospital, admission to ICU, and death were used. Montopoli et al.[5] failed to report COVID-19

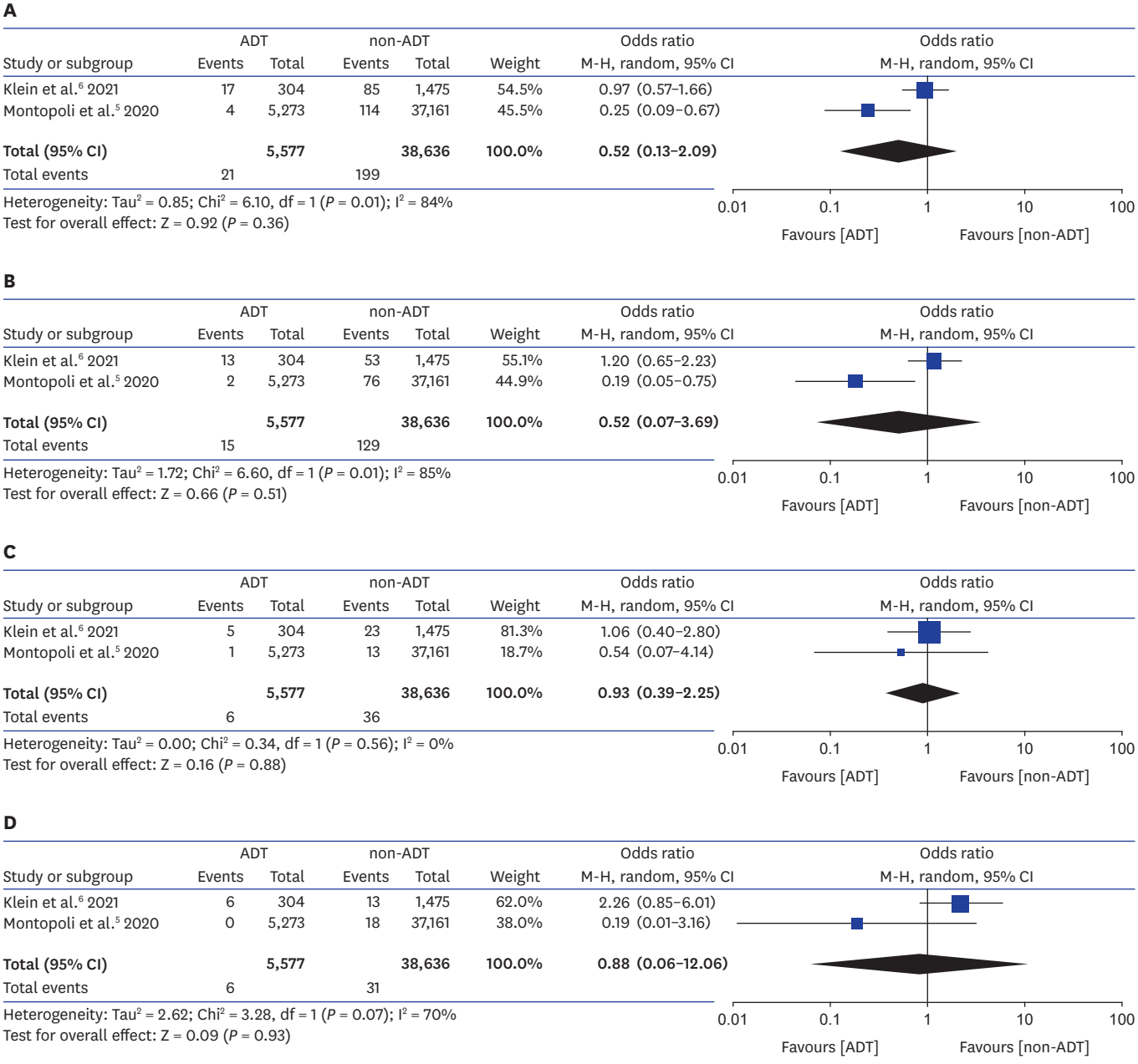

Fig. 2. Forest plots of (**A**) SARS-CoV-2 positivity, (**B**) hospitalization, (**C**) ICU admission, (**D**) death.
ADT = androgen deprivation therapy, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, ICU = intensive care unit.

mortality rate. However, Caffo et al.[4] found that the mortality rate in those under 70 years was 25%, which was higher than that (< 13%) expected for the whole population of infected Italian men with the same age. These findings suggest that ADT is unlikely to be a suitable intervention for patients with acute respiratory distress syndrome as it potentially could initiate or aggravate a cytokine storm.

No cohort studies included for the present study used matched controls. One failed to include key covariates. To determine the risk of bias in results, we used the ROBINS-I tool, which showed that the study of Klein et al.[6] had a relatively lower risk of bias than other

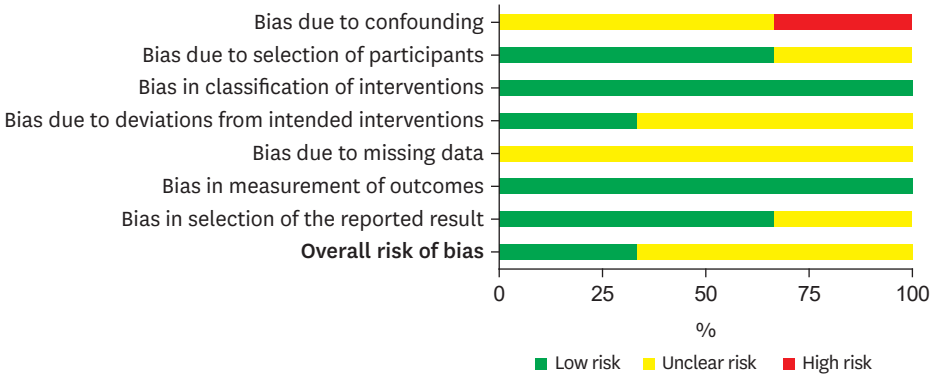

Fig. 3. Risk of bias graph.

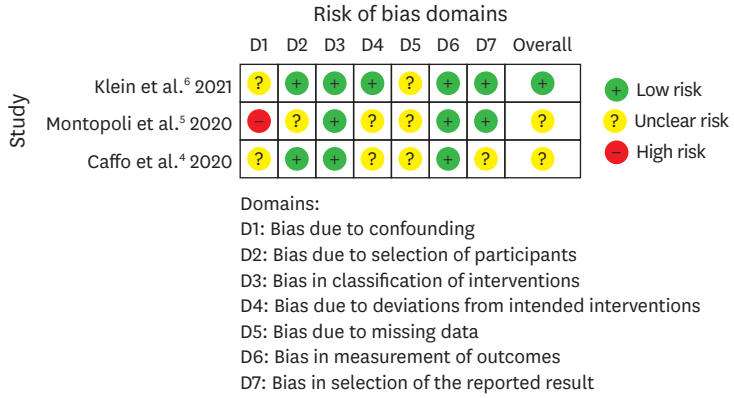

Fig. 4. Risk of bias assessment. Green plus: low risk of bias; Yellow question: unclear risk of bias; Red minus: high risk of bias.

Table 2. Grading of Recommendations, Assessments, Developments, and Evaluation (GRADE) quality assessment for direct evidence of each comparison

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADT	non-ADT	Relative (95% CI)	Absolute (95% CI)		
SARS-CoV-2 positivity												
2	Observational studies	Serious[a]	Serious[b]	Not serious	Serious[c]	Strong association	21/5,577 (0.4%)	199/38,636 (0.5%)	OR 0.52 (0.13–2.09)	2 fewer per 1,000 (from 4 fewer to 6 more)	●●○○ LOW	CRITICAL
Hospitalization												
2	Observational studies	Serious[a]	Serious[b]	Not serious	Serious[c]	Strong association	15/5,577 (0.3%)	129/38,636 (0.3%)	OR 0.52 (0.07–3.69)	2 fewer per 1,000 (from 3 fewer to 9 more)	●●○○ LOW	CRITICAL
ICU care												
2	Observational studies	Serious[a]	Not serious	Not serious	Serious[c]	None	6/5,577 (0.1%)	36/38,636 (0.1%)	OR 0.93 (0.39–2.25)	0 fewer per 1,000 (from 1 fewer to 1 more)	●●○○ LOW	CRITICAL
Death												
2	Observational studies	Serious[a]	Serious[b]	Not serious	Serious[c]	None	6/5,577 (0.1%)	31/38,636 (0.1%)	OR 0.88 (0.06–12.06)	0 fewer per 1,000 (from 1 fewer to 9 more)	●○○○ VERY LOW	CRITICAL

ADT = androgen deprivation therapy, CI = confidence interval, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, OR = odds ratio, ICU = intensive care unit.
[a]There were some moderate and serious domains; [b]Significant heterogeneity was observed; [c]Upper and lower limits of 95% CI included both meaningful benefit and harm.

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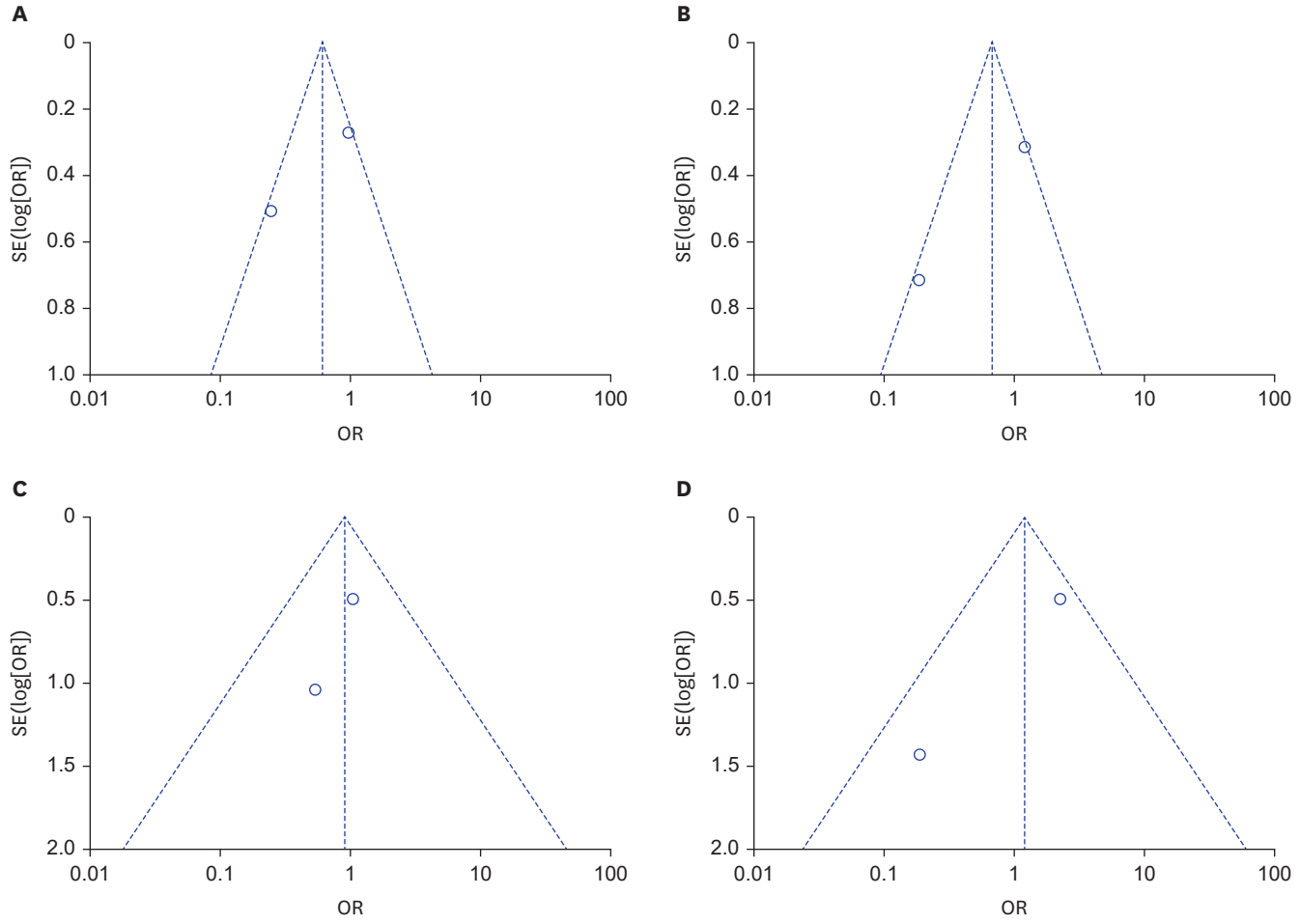

Fig. 5. Funnel plots for publication bias: (**A**) severe acute respiratory syndrome-coronavirus-2 positivity, (**B**) hospitalization, (**C**) ICU admission, and (**D**) death.
SE = standard error, OR = odds ratio.

studies.[4,5] ROBINS-I tool has been designed to compare health effects of two or more interventions in non-randomized studies.

Among various aspects that future COVID-19 severity research should focus on is the relationship and functional effect that androgen has on TMPRSS2, an androgen-regulated gene. Upregulated TMPRSS2 can facilitate tumor progression in prostate cancer.[11,12] Moreover, the expression of TMPRSS2 in tissues other than prostate (such as lung tissue) appears to be regulated by the same androgen receptor.[11] Based on the activity and expression of TMPRSS2 downregulated by ADT, there is an implied positive correlation between expression levels of TMPRSS2 and androgen.[12] Despite this, results of some studies have suggested that the role of TMPRSS2 in the severity of COVID-19 infection is probably minimal. The evidence supporting a role of overexpressed TMPRSS2 protein in SARS-CoV-2 lung pathology so far has only been from *in vitro* studies. There has been no patient data to support such hypothesis. In addition, expression levels of AR and TMPRSS2 proteins in lung tissues do not seem to be high, although high levels of TMPRSS2 mRNA isolated from human lung tissues have been reported.[13]

https://doi.org/10.3346/jkms.2022.37.e237

Secondly, research into the role of androgen in COVID-19 should also examine the relationship between oestrogen and COVID-19. It is well recognized that oestrogens exerts protective effects as demonstrated in pregnant women whose oestrogen levels, particularly E3 levels, are elevated.[14] Murine SARS studies have verified the immunomodulatory capacity of oestrogen.[15] This evidence, along with other immunomodulatory effects of oestrogen reported, lends weight to the hypothesis that oestrogen confers some protection against severe COVID-19 infection. Consequently, oestrogen therapy should be regarded as a potentially significant intervention. Thus, clinicians should fully consider its use for treating COVID-19. Indeed, there are ongoing studies evaluating a short-term use of oestrogen in COVID-19 patients to limit disease progression and patient deterioration.[16,17]

Thirdly, it is important to explore the relationship between immunological factors and COVID-19 outcome in male patients who also have prostate cancer. In the presence of single-strand RNA viruses, like SAR-CoV-2, innate immune cells such as B cells, circulating monocytes, dendritic cells, and macrophages overexpress toll-like receptor 7 (TLR7).[18,19] In a study of SARS-CoV infected male and female mice, it was found that levels of proinflammatory cytokine (IL-6) and chemokines (CCL2 and CXCL-1) during the early phase of infection were comparable in both sexes with similar efficacy. However, by the third day, expression levels of these inflammatory cytokines and chemokines in male mice were significantly greater than those in females.[20] This finding indicates that, when challenged with SARS-CoV-2, male mice would be more susceptible to the infection with an elevated recruitment of inflammatory cells. This phenomenon can account for the protracted inflammation instigated by SARS-CoV-2 infection, which is more commonly experienced by males than females. It may also contribute to the severity of COVID-19 in men.

Fourthly, by studying the protective effect of soluble ACE2 in prostate cancer patients, a deeper understanding may emerge about the relationship between androgen and severe COVID-19. Plasma concentration of renin is increased in response to the androgen hormone. Androgen can stimulate the transcription of angiotensinogen mRNA and the translation of angiotensinogen protein. Functionally active angiotensin is a vasoconstrictor. It has implications in severe COVID-19 as it is associated with complications. Therefore, androgen may nullify protective effects conferred by high levels of soluble ACE2. The corollary of the androgen-angiotensin relationship is that males are more vulnerable to severe infection.[20]

Finally, more studies are needed to explore interactions between new-generation androgen signalling inhibitors and testosterone. According to Caffo et al.,[4] patients with mCRPC frequently receive taxane treatments and new-generation androgen-targeting therapies in addition to ADT. It is noteworthy that none of those studies reported here has addressed the effect of total testosterone (TT) on immune responses in males or the extent of that effect on infectious respiratory diseases. The activity of respiratory muscles, general strength, and exercise capacity can be adversely affected when testosterone levels are low.[21] On the other hand, a number of respiratory outcomes are improved when circulating levels of testosterone are normal, indicating a protective effect.[22] From observed effects of androgens, their roles in immune responses and, their changing levels throughout life,[23] it is possible that hypogonadism could confer some protection against the onset of COVID-19 infection. However, it could also increase the risk of severe infection in patients with comorbidities who have high basal levels of pro-inflammatory cytokines. This scenario is borne out by evidence collected by Rastrelli et al.[24] These researchers noted that baseline TT levels were lower in 31 male SARS-CoV-2 pneumonia patients who were followed-up in the respiratory ICU. These

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researchers concluded that low TT levels were predictive of poor prognosis and mortality in men with COVID-19.

COVID-19 can affect almost all organ systems of the body. This complex disease caused by infection with SARS-CoV-2 can stimulate secretion of pro-inflammatory cytokines, which in turn stimulates chronic systemic inflammation and persistent activation of the innate immune system. Autopsies of COVID-19 patients have commonly revealed heightened immune response that leads to organ failure. The risk of severe infection is greater in individuals with pre-existing comorbidities. This study reviewed previous studies qualitatively and quantitatively and found that there was no significant effect of ADT on COVID-19. However, more higher quality studies that explore biochemical and immunological factors involved are needed to confirm this finding in the future.

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