REVIEW

Effects of Androgen Deprivation Therapy on COVID-19 in Patients with Prostate Cancer: A Systematic Review and Meta-Analysis

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Purpose: Transmembrane serine protease 2 (TMPRSS2) facilitates SARS-CoV-2 cellular entry. Androgens regulate this protein and may increase the risk of COVID-19. Therefore, androgen deprivation therapy (ADT) may protect patients with prostate cancer from SARS-CoV-2 infection or decrease the severity of the disease. Therefore, we conducted a meta-analysis to study the effect of androgen deprivation therapy (ADT) on COVID-19 in patients with prostate cancer.

Methods: We systematically searched PubMed, Embase, Scopus, and Cochrane databases. All records underwent a two-step screening process to identify the eligible studies. The registered PROSPERO number of this study was CRD42021228398. We evaluated the effect of ADT on the risk of infection, hospitalization, ICU admission, and mortality.

Results: Six studies met inclusion criteria and were evaluated in this study. We performed meta-analysis on four eligible studies. The overall incidence of COVID-19 was 2.65% among patients with prostate cancer receiving ADT. COVID-19 mortality rate was about 22.7% in ADT (+) patients. ADT did not decrease the risk of any of the major outcomes; infection risk (OR= 0.63, 95% CI= 0.27- 1.48, P = 0.29), hospitalization rate (OR= 0.51, 95% CI= 0.10- 2.53, P = 0.41), ICU admission (OR= 1.11, 95% CI= 0.43- 2.90, P = 0.82), and mortality risk (OR= 1.21, 95% CI= 0.34- 4.32, P = 0.77).

Conclusion: We did not observe a protective effect on the risk of infection, hospitalization, ICU admission, and mortality in patients receiving ADT; therefore, it should not be considered as a prophylactic or treatment for COVID-19. On the other hand, ADT did not increase the mortality and morbidity of COVID-19 and should be considered a safe treatment for patients with prostate cancer during the pandemic. Further studies are necessary to confirm our findings.

Keywords: Androgens; COVID-19; Prostatic neoplasms; SARS-CoV-2

INTRODUCTION

As of January 27th, Coronavirus disease 2019 (COVID-19) has imposed a tremendous human toll of 99,638,507 deaths and 2,141,468 cases since its inaugural.[1,2] This devastating burden resulted in an explosion of ideas and hypotheses to cure or prevent the disease.[3] Androgen deprivation therapy (ADT) turned out to be one of these hypothetical solutions.[4-7]

Transmembrane serine protease 2 (TMPRSS2) facilitates severe acute respiratory syndrome- coronavirus-2 (SARS-CoV-2) cellular entry and serves as the principal protease in this process.[8-12] TMPRSS2 initiates viral fusion and host cell-receptor binding by cleaving the SARS-CoV-2 spike (S) protein and angiotensin-converting enzyme- 2 (ACE-2).[11-15] Many patients with prostate cancer also suffer from TMPRSS2 fusion as a common genetic abnormality in this disease.[6] Higher testosterone levels upregulate TMPRSS2 and can theoretically increase the risk of viral transmission.[4,5] Earlier studies raised the idea that the increased risk of infection and mortality in men might correlate with this molecular phenomenon.[16-19] Therefore, ADT raised hopes as a novel approach to fight COVID-19.[4-6]

ADT is a standard treatment for many patients with high-risk and advanced prostate cancer.[20-24] This approach constitutes various treatments with similar ideas, ranging from bilateral orchiectomy, to novel medications such as LHRH (luteinizing hormone-releasing hormone) antagonists and CYP17 inhibitors.[6,25-27] To examine the aforementioned hypothesis, several articles assessed the outcomes of COVID-19 in patients with prostate cancer who received ADT compared with those who did not. In this meta-analysis, we aim to examine the effect of ADT prescribed for prostate cancer patients on their risk of COVID-19 infection and the subsequent outcomes.

MATERIALS AND METHODS

Design

This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews (PRISMA) 2020 guidelines. We systematically searched PubMed, Scopus, Embase, and Cochrane libraries on December 26th. The retrieved records followed a two-step screening process. First, the articles were screened based on

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Table1. Characteristics and NOS risk of bias assessment scale of the studies

ID	First author	Country	Type of study	Newcastle-Ottawa scale (NOS) risk of bias assessment			
				Selection	Comparability	Exposure	Total score (out of 9)
1	Klein, E. A. (29)	USA	Prospective cohort	****	**	***	9
2	Koskinen, M. (30)	Finland	Retrospective cohort	****	**	**	8
3	Montopoli, M. (31)	Italy	Retrospective cohort	****	-	**	6
4	Patel, V. G. (32)	USA	Retrospective cohort	****	**	**	8
5	Caffo, O. (33)	Italy	Retrospective cohort	***	-	**	5
6	Caffo, O. (34)	Italy	Retrospective cohort	***	-	***	6

the overall coherence of their title and abstract to our inclusion criteria. The qualified articles were assessed by their full-texts, and the eligible articles were included for the qualitative and quantitative synthesis. This meta-analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews) with the ID CRD42021228398.

PICO

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

Search strategy

We searched the keywords for ADT and COVID-19 using the search strategy [C].

[Androgen deprivation therapy] (Title/Abstract) OR [Androgen deprivation therapies] (Title/Abstract) OR [Androgen targeted therapy] (Title/Abstract) OR [Androgen targeted therapies] (Title/Abstract) OR [Androgen deprivation] (Title/Abstract) OR [Androgen] (Title/Abstract)

[COVID-19] (Title/Abstract) OR [SARS-CoV-2] (Title/Abstract) OR [SARS-CoV2] (Title/Abstract) OR [Novel Coronavirus] (Title/Abstract) OR [2019-nCoV] (Title/Abstract)

[A] AND [B]

Inclusion/Exclusion criteria

Original clinical articles, from the start of the pandemic until December 26th, demonstrating the effect of ADT on the COVID-19 were included. No language restriction was considered in this study. Exclusion criteria were the following:

1) Review, guidelines, editorials, or other articles not possessing original data
2) Case reports
3) Incomplete projects and clinical trials
4) Animal and laboratory studies without clinical data

Data acquisition and analysis

We completely read the full-texts and extracted the data into an excel sheet. We classified the major extracted outcomes into four categories and estimated their risks;

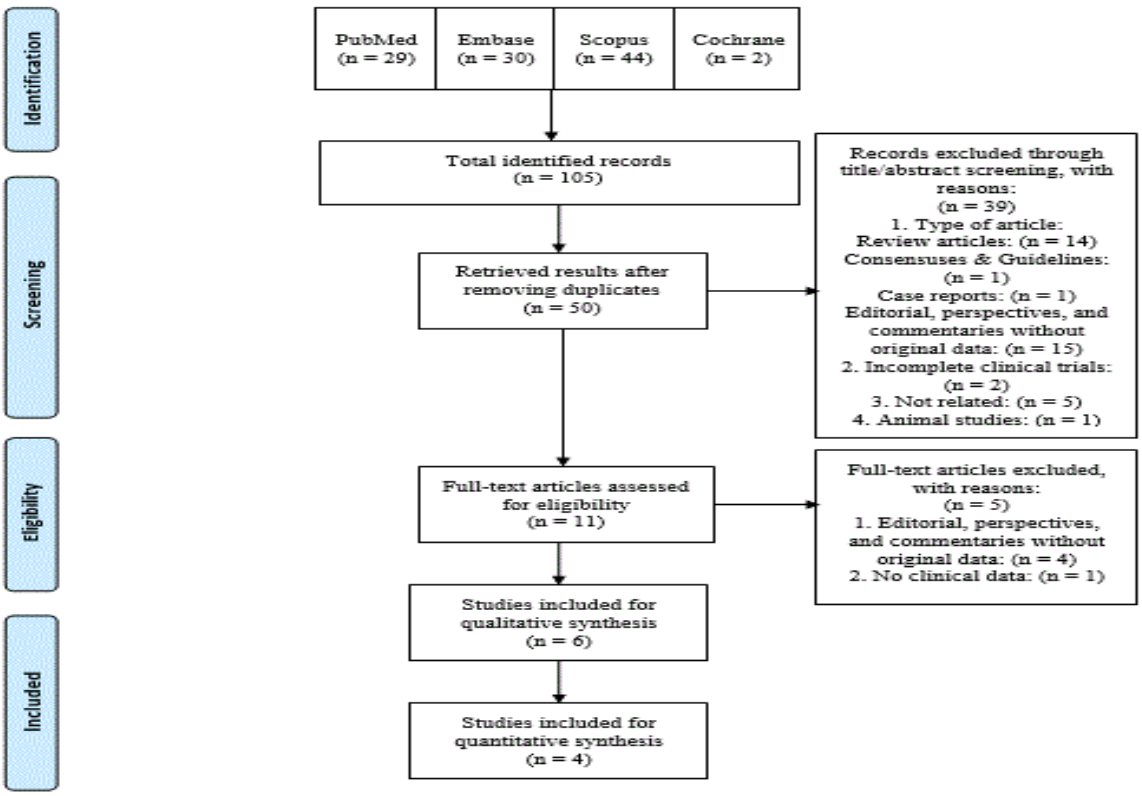

Figure 1. Prisma flow diagram of the study selection process

Table 2. Characteristics of prostate cancer patients with SARS-CoV-2 infection in the included studies

ID	First author	Total no. (b)	Age (mean ± SD)	Dosage and duration of ADT	Comorbidities	Total no. of infected patients	Assessed variables
1	Klein, E. A. (29)	Total: 1779 ADT (+): 304 ADT (-): 1475	Total: 74.1 ± 10.3 ADT (+): 75.7 ± 10.9 ADT (-): 73.8 ± 10.2 (P < .009)	N/A	1. Smoking history: ADT (+): 68.1% ADT (-): 59.3% (P < .005) 2. Immune-suppressive disease: ADT (+): 34.2% ADT (-): 27.5% (P = .02) 3. Steroid use: ADT (+): 43.8% ADT (-): 23.3% (P < .001) 4. Asthma: ADT (+): 9.2% ADT (-): 14.2% (P = .02) 5. No significant difference in HTN, CAD, HF, and diabetes mellitus.	Total: 102 ADT (+): 17 ADT (-): 85	COVID-19 infection Hospitalization ICU admission Death
2	Koskinen, M. (30)	Total: 352 ADT (+): 134 ADT (-): 218	Total: 77.2 ± 9.0 ADT (+): 78.4 ± 8.1 ADT (-): 76.5 ± 9.4	N/A	No significant differences in: HTN, CAD, COPD, diabetes mellitus, arrhythmia, smoking history	Total: 17 ADT (+): 6 ADT (-): 11	COVID-19 infection ICU admission
3	Montopoli, M. (31)	Total: 42434 ADT (+): 5273 ADT (-): 37161	N/A	N/A	N/A	Total: 118 ADT (+): 4 ADT (-): 114	COVID-19 infection Disease severity Hospitalization ICU admission Death
4	Patel, V. G. (32)	N/A	N/A	1. GnRH analog/agonis within 3 months and/or 2. documented testosterone concentrations ≤ 50 ng/dL within 6 months of COVID-19 diagnosis	1. Metastatic disease: ADT (+): 64% ADT (-): 0% (P < .001) 2. Underlying pulmonary disease: ADT (+): 27% ADT (-): 6% (P = .02) 3. No significant difference in other comorbidities (not mentioned specifically)	Total: 58 ADT (+): 22 ADT (-): 36	Hospitalization O_2 supplementation Intubation Death
5	Caffo, O. (33)	1949	Median age: 74.5	N/A	N/A	36	COVID-19 infection Hospitalization Death
6	Caffo, O. (34)	1433	75.4 ± 9.6	Median duration: 50 months (IQR: 19-66)	N/A	34	COVID-19 infection Hospitalization ICU admission O_2 supplementation Intubation Death

a Abbreviations: SD: Standard deviation, ADT: Androgen deprivation therapy, ICU: Intensive care unit, HTN: Hypertension, CAD: Coronary artery disease, HF: Heart failure, N/A: data "Not available", COPD: Chronic obstructive pulmonary disease, GnRH: Gonadotropin releasing hormone, IQR: Interquartile range,
b Total number applies to the prostate cancer patients reported in each study. For the last two studies, all of the patients received ADT.

COVID-19 infection, hospitalization, ICU (Intensive care unit) admission, and mortality. Besides the above-mentioned four major outcomes, we also extracted country, population, mean age, and comorbidities into the same excel sheet.

Higgins I2 test was utilized to examine heterogeneity among the studies. I2 levels of above 40% represented heterogeneity among data of the subgroups and warranted a random effects analysis.[28] We used fixed effect analysis to evaluate the groups that were classified as low in the heterogeneity test.

We used Egger's test and funnel plot to assess the potential publication bias for each major outcome in this study.

Meta-analyses were conducted using the latest version of the Cochrane review manager released in September 2020 (Revman 5.4.1). Publication bias and pooled analyses were performed using Stata version 16. The visualizations for each part were illustrated using their corresponding software. We used Odds ratio (OR) to assess the outcomes and P= 0.05 as the threshold of significance.

Risk of bias assessment

Newcastle-Ottawa Scale (NOS) risk assessment tool was applied to calculate the risk of bias of the included studies. This tool provides a maximum score of nine for each study in three categories of selection, comparability, and exposure.

RESULTS

We identified 50 non-duplicate records by searching PubMed, Embase, Scopus, and Cochrane databases. Following the title/abstract and full-text screening, six related original articles were included for conducting this systematic review. Four studies were eligible for meta-analysis as they comprised both ADT (+) and ADT (-) groups (**Figure 1**).(29-32) The remaining two studies comprised only ADT (+) patients, and did not have ADT (-) controls. Therefore, they were exclud-

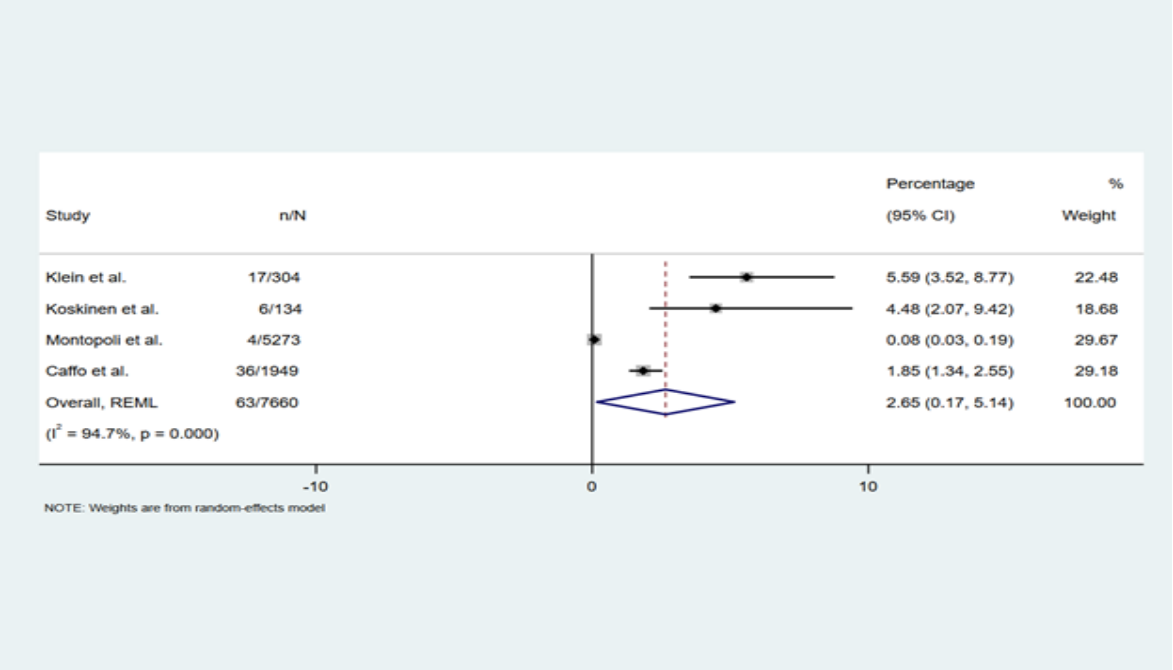

Figure 2. Pooled analysis of COVID-19 rate in patients receiving ADT

ed from meta-analysis between ADT (+) and ADT (-) groups.[33,34] In addition, these studies were performed on a similar population. Therefore, if both studies reported a variable in ADT (+) patients, we only considered the larger study.[33]

Table 1 describes the risk of bias for the included studies. Five studies (three of those included in the comparative analysis) belonged to Italy and the USA, both highly stormed by the COVID-19 pandemic. Most studies scored well according to the NOS (Mean ± SD = 7 ± 1.1).

Baseline characteristics

Mean patient age was comparable between ADT (+) and ADT (–) groups in one study(30) whereas another study reported higher mean age among ADT (+) patients (mean age: 75.7 vs. 73.8, $P < .009$) (**Table 2**).(29) Three studies reported comorbidities.[29,30,32] Although one study reported similar frequency of various comorbidities in ADT (+) and (-) groups,[30] two other studies

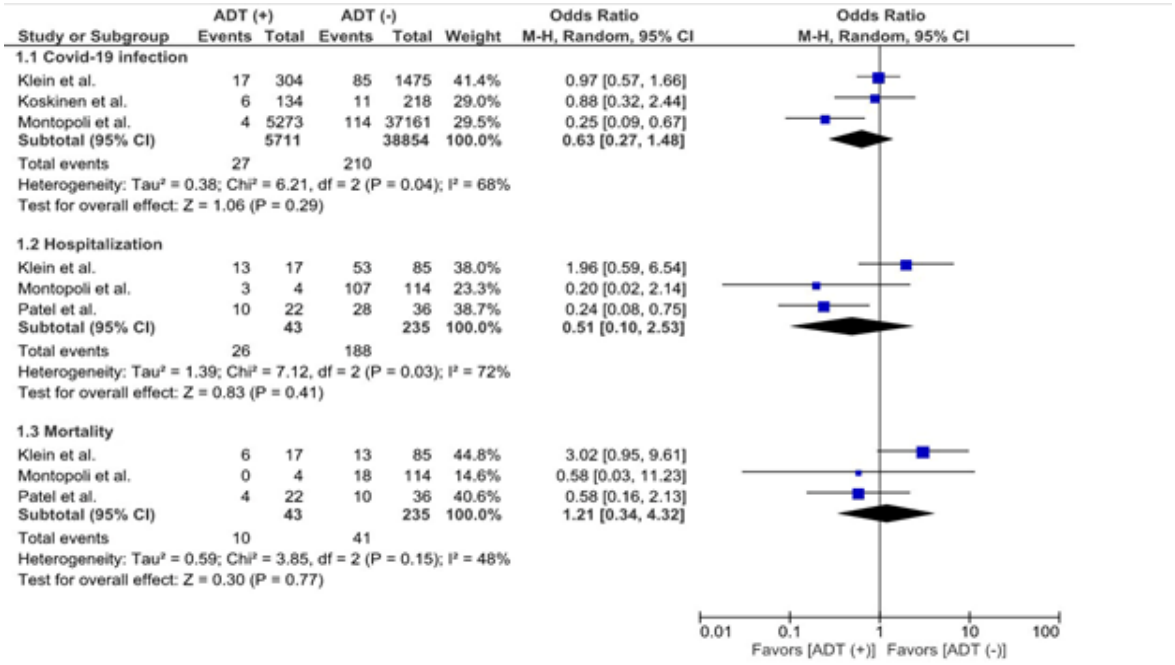

Figure 3. Meta-analysis of the subgroups with high heterogeneity

reported higher comorbidity rates among ADT (+) patients.[29,32] In Patel et al. study, patients using ADT endured higher rates of metastatic (64% vs. 0%, $P < .001$) and underlying pulmonary diseases (27% vs. 6%, $P = .02$).[32] Patients receiving ADT in Klein et al.'s study were more likely to have smoking history (68.1% vs. 59.3% $P < .005$), immune-suppressive 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%, $P = .02$).[29]

COVID-19 infection risk

Pooled analysis showed that SARS-CoV-2 infection rate among patients receiving ADT was 2.65% (**Figure 2**).[29-31,33] ADT was not associated with a decreased COVID-19 infection risk (95% CI: 0.27-1.48, OR = 0.63, $P = .29$) (**Figure 3**).

Components of disease severity

Hospitalization risk:

Hospital admission was recorded in 62.1% of the infected patients in the ADT (+) group (**Figure 4**).[29-33] ADT use did not affect the risk of hospitalization (95% CI: 0.10-2.53, OR = 0.51, $P = .41$) (**Figure 3**).

ICU admission risk:

One study combined data of ICU admission with mortality.[30] We assumed all these patients as requiring ICU admission; however, we did not utilize these data to assess mortality risk. Among ADT (+) patients who were infected with SARS-CoV-2, 18.3% required ICU admission (**Figure 5**)[29-32,34] and ADT did not decrease the likelihood of ICU admission (95% CI: 0.43-2.90, OR = 1.11, $P = .82$) (**Figure 6**).

Mortality risk:

We included five appropriate studies to estimate the mortality rate and association between ADT use and risk of mortality.[29-33] The mortality rate was about 22.7% (**Figure 7**) and was not associated with ADT use (95% CI: 0.34-4.32, OR = 1.21, $P = .77$) (**Figure 3**).

Publication bias

We performed Egger's test and funnel plot to test publication bias of all the four major outcomes. None of the variables had significant publication bias: COVID-19 infection (P for Egger's test = .50, funnel plot as **Supplementary Figure 1**), hospitalization ($P = .59$, **Supplementary Figure 2**), ICU admission ($P = .98$, **Supplementary Figure 3**), mortality ($P = 0.58$, **Supplementary Figure 4**).

DISCUSSION

We found that ADT use could not reduce COVID-19 infection, hospitalization, ICU admission, or mortality risks. On the other hand, they also did not face elevated risks of complications related to ADT.

Prostate cancer patients who are receiving ADT usually suffer from more comorbidities, advanced disease, and higher risk of mortality.[21,35] Three studies that were included in the comparative analysis reported the patients' age and underlying disease status. Overall, patients in the ADT (+) group seemed to have more comorbidities than ADT (-) patients. This may mask the potential protective effects of ADT on COVID-19.[29,30,32]

SARS-CoV-2 infection rate among ADT (+) patients was 2.65%. This rate might be associated with both underestimation and overestimation. Most studies were from Italy and the USA, two of the world's worst-hit countries with the potential to overestimate the risk of infection. On the other hand, missing many patients with milder symptoms who did not seek care might underestimate the true rate of COVID-19 in the ADT (+)

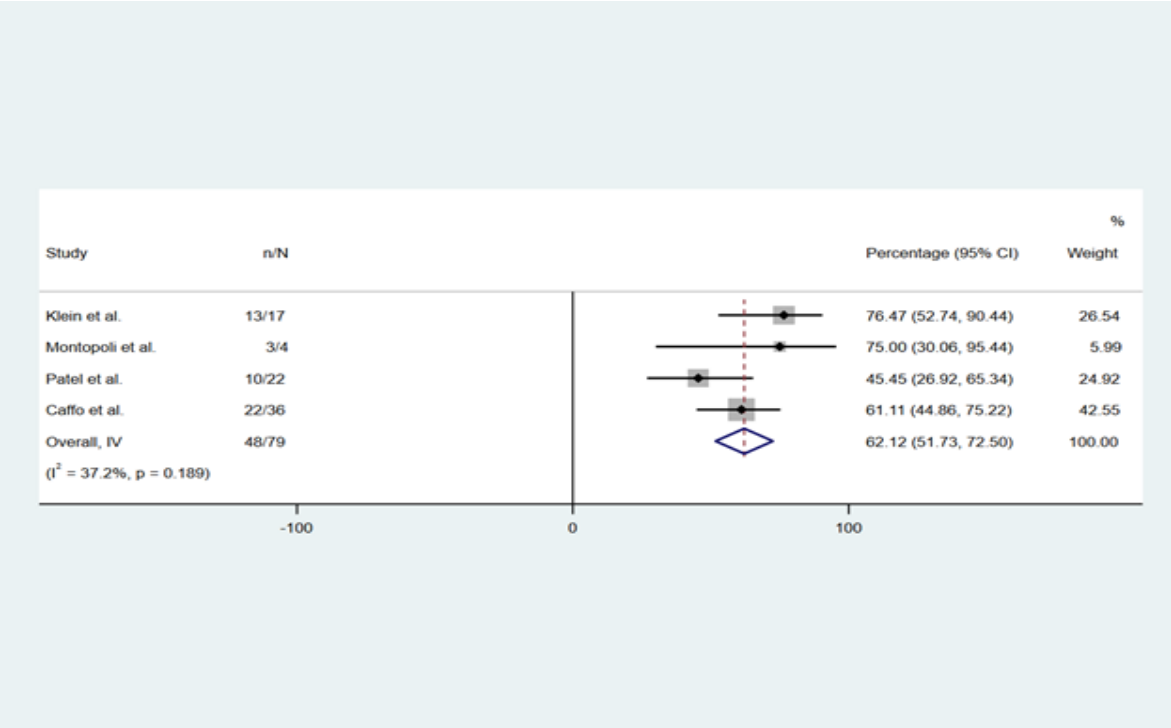

Figure 4. Pooled analysis of hospitalization rate in COVID-19 patients receiving ADT

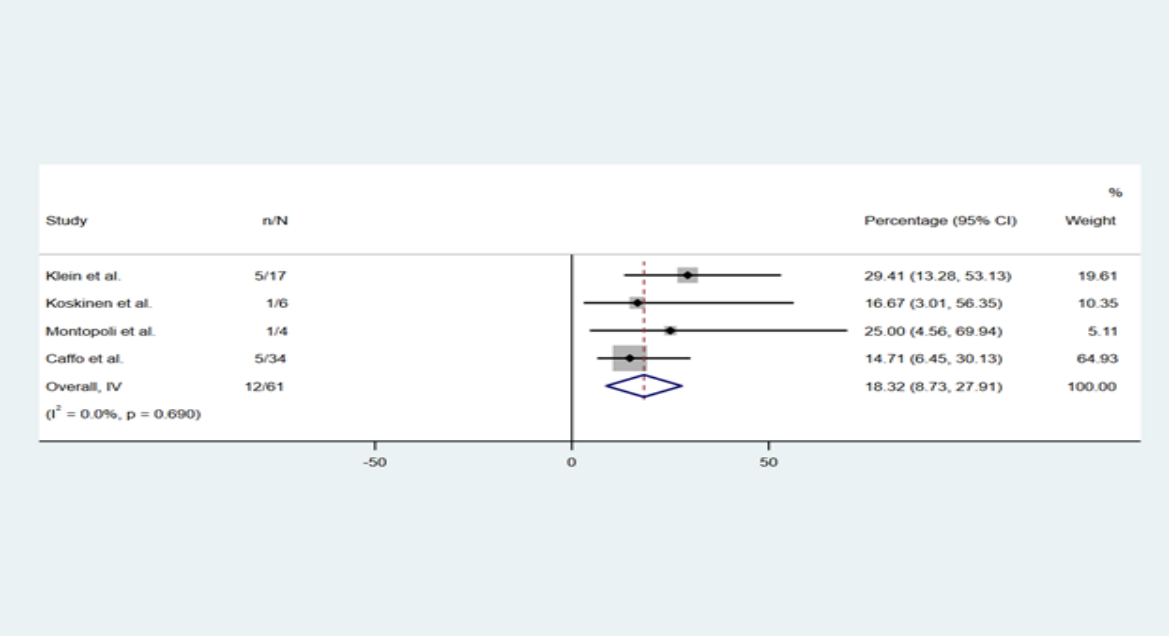

Figure 5. Pooled analysis of ICU admission rate in COVID-19 patients receiving ADT

patients.

The main limitation of this meta-analysis is the limited number of studies and patients due to the novelty of the subject. Results were not adjusted for confounding factors including comorbidities and disease stage. The dosage and duration of ADT was also not mentioned in most of the studies. Our study is the first meta-analysis on this subject, providing valuable information on ADT and the risk of COVID-19 and included studies were relatively homogeneous in terms of methodology. More investigations are needed to better identify the role of ADT in COVID-19.

CONCLUSIONS

ADT showed a modest protective effect on COVID-19 and only one of the five parameters were associated with ADT use. However, ADT did not increase the morbidity and mortality related to COVID-19. Therefore, ADT should be considered safe and physicians should not hesitate to administer this treatment to the candidates during the pandemic. Further studies with larger sample size are necessary to obtain more definitive results.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

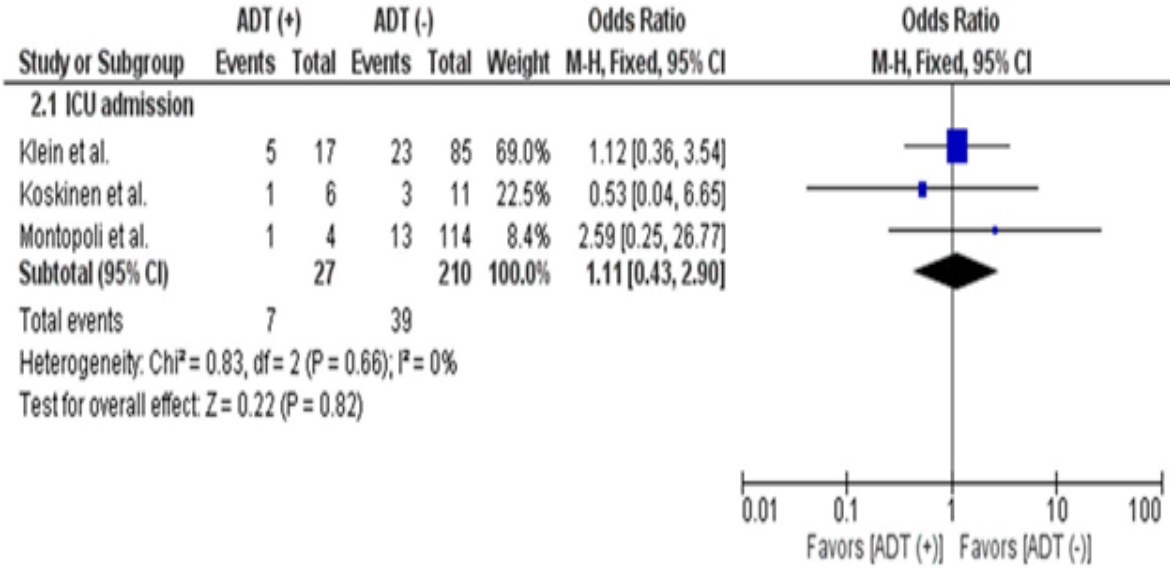

Figure 6. Meta-analysis of the subgroups with low heterogeneity

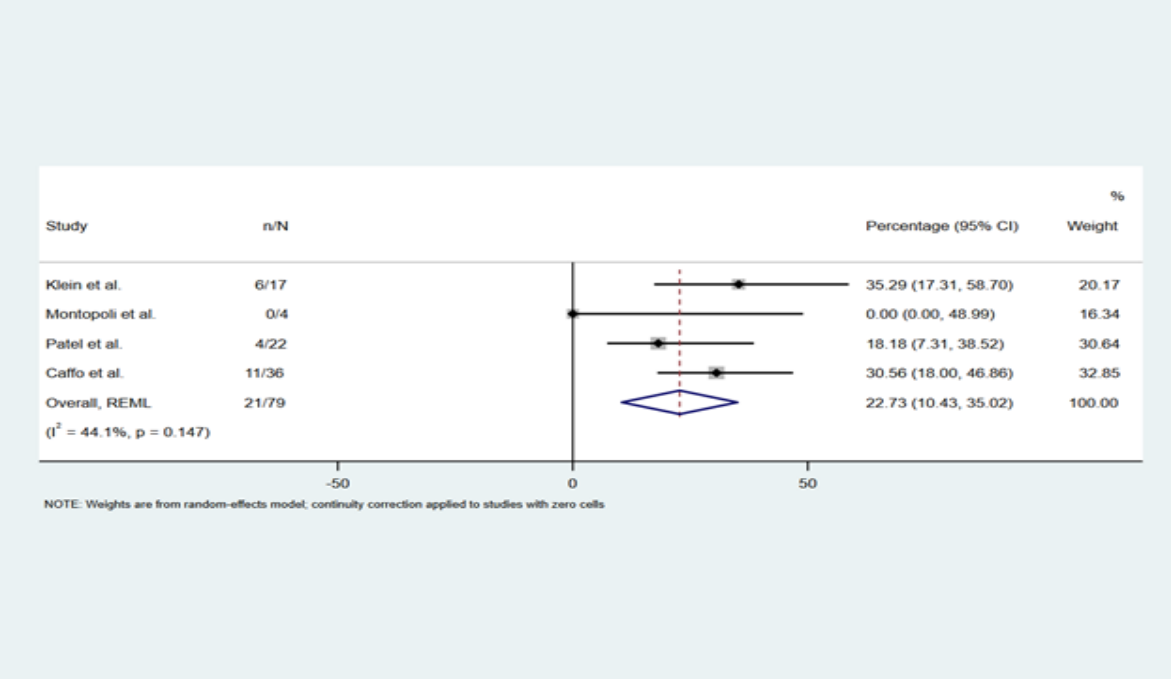

Figure 7. Pooled analysis of mortality rate in COVID-19 patients receiving ADT

APPENDIX

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