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Effects of ACEI and ARB on COVID-19 patients: A meta-analysis

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Abstract

Background: The clinical use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) in patients with COVID-19 infection remains controversial. Therefore, we performed a meta-analysis on the effects of ACEI/ARB on disease symptoms and laboratory tests in hypertensive patients infected with COVID-19 virus and those who did not use ACEI/ARB.

Methods: We systematically searched the relevant literatures from Pubmed, Embase, EuropePMC, CNKI, and other databases during the study period of 31 December 2019 (solstice, 15 March 2020), and analyzed the differences in symptoms and laboratory tests between patients with COVID-19 and hypertension who used ACEI/ARB drugs and those who did not. All statistical analyses were performed with REVMAN5.3.

Results: We included a total of 1808 patients with hypertension diagnosed with COVID-19 in six studies. Analysis results show that ACEI/ARB drugs group D-dimer is lower (SMD = −0.22, 95%CI: −0.36 to −0.06), and the chances of getting fever is lower (OR = 0.74, 95%CI: 0.55 to 0.98). Meanwhile, laboratory data and symptoms were not statistical difference, but creatinine tends to rise (SMD = 0.22, 95% CI: 0.04 to 0.41).

Conclusion: We found that the administration of ACEI/ARB drugs had positive effect on reducing D-dimer and the number of people with fever. Meanwhile it had no significant effect on other laboratory tests (creatinine excepted) or symptoms in patients with COVID-19, while special attention was still needed in patients with renal insufficiency.

Keywords

COVID-19, meta analysis, ACEI, ARB, hypertension

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Introduction

ACEI and ARB are considered to be the first choice for the treatment of hypertension, heart failure, post-myocardial infarction status and chronic kidney disease. Hypertension is obviously harmful to patients with COVID-19.[1] However, treatment with RAS inhibitors can increase the expression of ACE2 in tissues and its expression on the cell surface,[2] ACE2 is a membrane-bound aminopeptidase that is widely expressed in the lungs, heart, and other tissues.[3] ACE2 is the primary receptor for COVID-19 virus entry into host cells.[4] Therefore, for COVID-19 patients, whether the use of these drugs will increase or decrease the severity of COVID-19 infection and cause other adverse reactions has become an urgent problem to be solved.

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Table 1. Basic information of cited literature.

NO.	Author	Journal	Sample source	Research period	Sample size
1	Yang et al.[5]	Hypertension	HPHTCM[a]	January 5 to February 22, 2020	126
2	Li et al.[6]	JAMA Cardiology	Wuhan Central Hospital	January 15 to March 15, 2020	362
3	Meng et al.[7]	Emerging Microbes & Infections	Shenzhen Third People's Hospital	January 11 to February 23,2020	42
4	Zhang et al.[8]	Circ Res	Nine hospitals in Hubei Province[b]	December 31, 2019 to February 20, 2020	1128
5	Huang et al.[9]	Ann Transl Med	Renmin Hospital of Wuhan University	February 7 to March 3, 2020	50
6	Tan et al.[10]	Gastroenterology	West Campus of Wuhan Union Hospital	January 28 to April 8, 2020	100

[a]HPHTCM: Hubei Provincial Hospital of Traditional Chinese Medicine.
[b]The nine hospitals in Hubei province include Renmin Hospital of Wuhan University, Zhongnan Hospital of Wuhan University, Wuhan First Hospital, Wuhan Third Hospital, Wuhan Seventh Hospital, Wuhan Ninth Hospital, Thunder Mountain Hospital, Huanggang Central Hospital, and the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture.

Methods

Search strategy

By searching Pubmed, Embase, EuropePMC, medRxiv (https://www.medrxiv.org), SSRN (https://www.ssrn.com), and CNKI databases, this study obtained relevant studies during the study period of April 8, 2020 (solstice, December 30, 2019).We excluded language limitations in the search for the combination of the following keywords: "COVID-19" or "SARS cov-2" or "Corona Virus disease-2019" and "ACEI" or "ARB," and based on the title abstract of the relevant studies, we preliminarily screened the literature that might be relevant to the study content in this paper for full text reading, and included those that met the requirements in the meta-analysis. In addition, we also reviewed the included references, similar references and cited references to ensure a more comprehensive and accurate result.

Inclusion and exclusion criteria

The inclusion criteria for the six articles were as follows: (1) the patients included in each study were confirmed to be infected with COVID-19; (2) the patients included in each study were confirmed to be diagnosed with high blood pressure and taking antihypertensive drugs; (3) patients were divided into ACEI/ARB group and non-ACEI/ARB group; (4) each study included patient signs and symptoms and laboratory tests. Individual case reports, comments, and editorials were excluded.

Data extraction

The two authors of this study (Xue Yang and Sun Shaoqing) reviewed the abstracts or contents of 235 studies, and finally screened six studies that met the requirements. They independently analyzed and extracted the data. Any ambiguity was judged by a third party and finally reached a consensus. We used the Microsoft Excel database to record the following information from the included trials: first author, year of publication, study location, study design, number of people in the ACEI/ARB and non-ACEI/ARB groups, number of primary symptoms, median laboratory test data reflecting the severity of COVID-19, and IQR. The result is shown in Tables 1 and 2. Hypertension was defined as diastolic blood pressure $\geqslant$90 mmHg or systolic blood pressure $\geqslant$140 mmHg or history of antihypertensive drug use, and ACEI/ARB use was defined as continuous use of these drugs upon admission.

Data analysis

In this study, REVMAN5.3 was used for meta-analysis. For the dichotomous variables, we used the Mantel-Haenszel formula for statistics and calculated OR and the 95% CI. For continuous variables, mean, and SD are calculated according to Wan's et al.[11] and Luo's et al.[12] algorithms, and the Inverse Variance formula is used to calculate the SMD and 95%CI. The evaluation of heterogeneity among the studies is realized by I^2 test. If $I^2 \leqslant 50\%$, the results are homogeneous, and the fixed effect model can be used; if $I^2 > 50\%$, and $p < 0.05$, the results are heterogeneous, and we can use the random effect model to analyze. For these studies with heterogeneity, we further conduct sensitivity analysis to explore the source of heterogeneity by successively eliminating individual studies and observing their impact on the overall heterogeneity. When we get a conclusion with a large difference or completely opposite after eliminating a certain research, it shows that the sensitivity is high and the result is not stable. We need to analyze the potential bias factors. The $p < 0.05$ was regarded as statistically significant.

Quality assessment and bias analysis

We used the Newcastle-Ottawa Scale (NOS) to score the quality of the original study, and at the same time made a

Table 2. Basic information of patients.

Author	Follow-up time	ACEI/ARB			Non-ACEI/ARB		
		Number of patients	Age	Males (%)	Number of patients	Age	Males (%)
Yang et al.[5]	2020/3/3	83	65 (57–72)	48.8	43	67 (62–75)	49.4
Li et al.[6]	NA	115	65 (57–73)	59.1	247	67 (60–75)	49
Meng et al.[7]	NA	17	64 (55.5–69)	52.9	25	65 (55–68)	60
Zhang et al.[8]	2020/3/7	188	64 (55–68)	53.2	940	64 (57–69)	53.5
Huang et al.[9]	NA	20	52.65 ± 13.12	50	30	67.77 ± 12.84	56.67
Tan et al.[10]	NA	31	67 (62–70)	45.1	69	67.5 (57–71)	53.6

qualitative assessment of the publication bias included in the study through a visual funnel plot.

Results

According to search strategy, we deleted 198 articles from 235 articles which has nothing to do with the clinical index of literature, by reading the title and abstract and deleted 15 articles after then. After reading the full text of remaining 22 article, we eliminated 12 review that the patient group did not meet the inclusion criteria, 4 articles without laboratory data and symptoms, finally we remained 6 articles with a total of 1808 patients with COVID-19.The sample size of the study subjects ranged from 42 to 1128. The diagram for study selection appears in Figure 1, and the information of each group is shown in Tables 1 to 3. All the studies were retrospective analysis, and all of them were English articles. All the studies had NOS score $\geqslant 7$.

Meta-analysis showed that compared with patients without ACEI/ARB, the D-dimer was significantly lower in ACEI/ARB group's patients (SMD = −0.22, 95%CI: −0.36 to −0.06; Figure 2(a)), and the probability of fever is also lower (OR = 0.74, 95%CI: 0.55 to 0.98; Figure 2(b)). Meanwhile, laboratory data such as CRP, calcitonin, white blood cells, urea, PT, neutrophil count, lymphocyte count, ALT, AST, LDH, and symptoms, such as diarrhea and dry cough were not statistical difference in two groups (Supplemental Figure S1), but creatinine tends to rise in ACEI/ARB group (SMD = 0.22, 95% CI: 0.04 to 0.41; Figure 2(c)). Sensitivity analysis was carried out and Yang et al.[5] was found to be the source of heterogeneity in PCT statistics. Egger's regression test showed publication bias was not a source of heterogeneity ($p > 0.05$; Figure 3).No obvious source of heterogeneity was found in other indicators. All analysis biases were examined using funnel plots.

Discussion

The COVID-19 epidemic is damaging public health security and causing great distress to people around the world. It has become the largest global health threat. As of May 15, more than 4.6 million people have been infected and 310,000 have died worldwide, Europe and the United States have been at the center of the COVID-19 outbreak. A report shows that the most common comorbidities among COVID-19 patients are hypertension (30%), diabetes (19%), and coronary heart disease (8%).[13] Thus, hypertension is an important risk factor for critical illness and death in COVID-19 patients. ACEI and ARB are the main anti-hypertensive drugs recommended in the current guidelines. How to apply ACEI and ARB reasonably and effectively has become a focal point in the clinical frontline.

ACEI and ARB can reduce the morbidity and mortality of cardiovascular and cerebrovascular diseases in elderly patients with hypertension,[14] and RAS blockers increase the level of angiotensin II, which is the substrate of ACE2. The interaction of ACE-2 and angiotensin II induces conformational changes in the ACE2 receptor binding domain, limiting its ability to bind to SARS CoV.[15] Statistically, we found that patients in the ACEI/ARB groups had lower D-dimer index. There are several explanations: (1) ACEI and ARB can directly reduce d- dimer. The pre-thrombotic state in hypertension is caused by the activation of RAS, which can lead to abnormalities in endothelial and platelet function, coagulation, and fibrinolysis. This abnormal state can be significantly improved by RAS antagonists.[16] (2) ACEI and ARB can reduce D-dimer by reducing inflammatory response. RAS may be involved in the pathogenesis of COPD by participating in the induction of proinflammatory mediators in the lung. Angiotensin II stimulates interleukin 6 and tumor necrosis factor alpha and monocyte chemotactic protein 1 cytokine release,[17] and the increase of cytokines leads to the activation of the coagulation system.[18] This inflammatory response is common in covid-19 patients, so RAS antagonists may have a more positive impact on patient outcomes, and our statistical result which shows the incidence of fever was reduced in the ACEI/ARB group support this hypothesis. Cytokines such as interleukin-6 and tumor necrosis factor-leuplus belong to internal heat source, while RAS antagonists reduce the inflammatory response and the generation of heat source, thus reducing the chance of fever. This assumption requires additional clinical data to support. (3)ACEI and ARB reduced D-dimer by reducing the severity of covid-19 patients. D-dimer was an independent indicator of the severity of covid-19 patients. Studies have shown that the use of ACEI and ARB

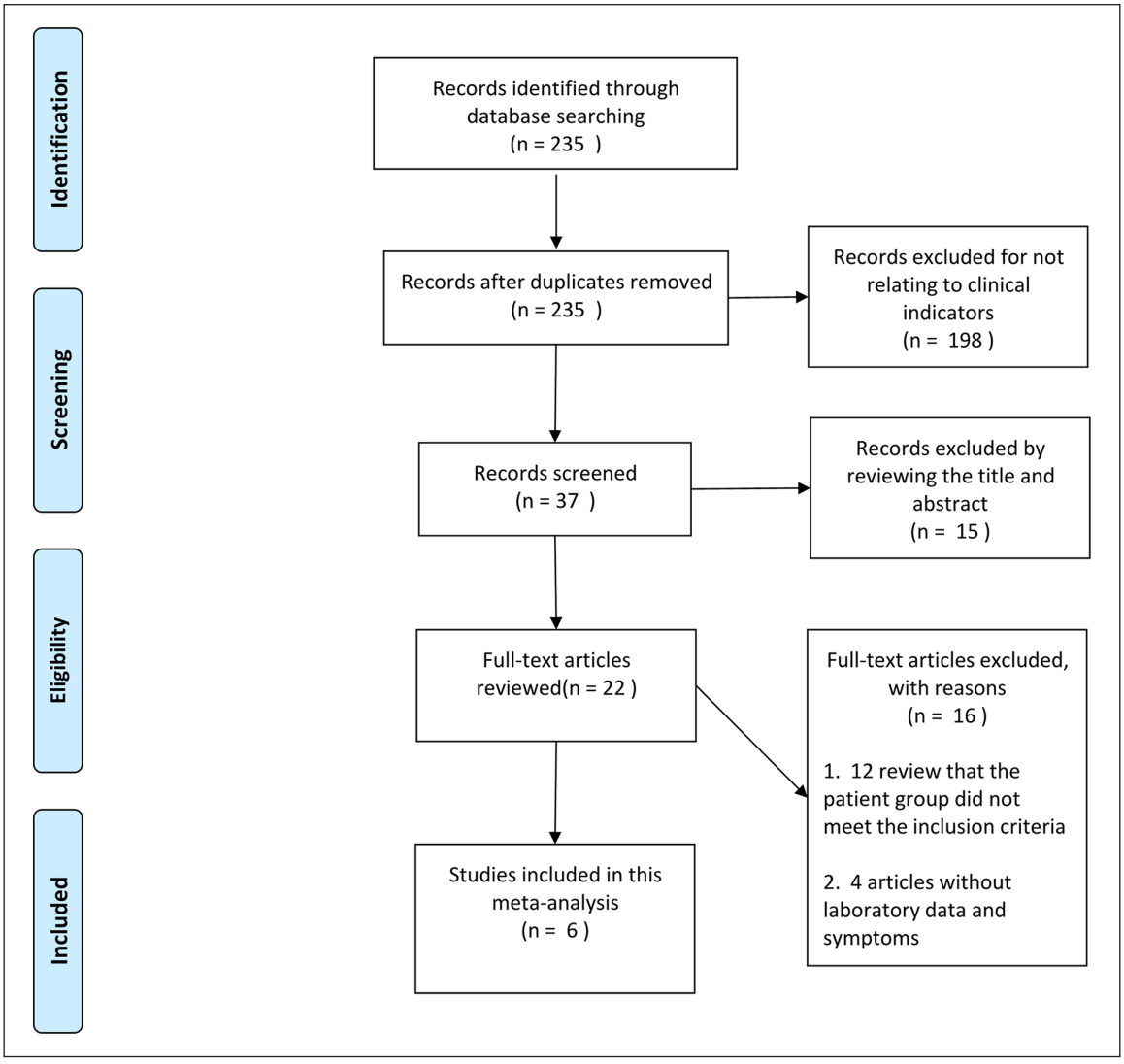

Figure 1. Literature search and selection process.

Table 3. Newcastle-Ottawa scale scores to assess methodological quality of included studies.

NO.	Author	S1	S2	S3	S4	C1	E1	E2	E3	Total
1	Yang et al.[5]	A*	A*	B	A*	A**	A*	A*	A*	8
2	Li et al.[6]	A*	A*	B	A*	A**	A*	A*	A*	8
3	Meng et al.[7]	A*	A*	B	A*	A**	A*	A*	C	7
4	Zhang et al.[8]	A*	A*	B	A*	B*	A*	A*	A*	7
5	Huang et al.[9]	A*	A*	B	A*	A**	A*	A*	A*	8
6	Tan et al.[10]	A*	A*	B	A*	B*	A*	A*	A*	7

Each study can be awarded a maximum of one star for each numbered item within the Selection (S) and Exposure (E) categories. A maximum of two stars can be given for comparability (C).
*One point for each quality evalution.
S1: Adequate case definition.
S2: Representativeness of the cases.
S3: Selection of controls.
S4: Definition of controls.
C1: Comparability of cases and controls.
E1: Ascertainment of exposure.
E2: Same method of ascertainment for cases and controls.
E3: Non-response rate.

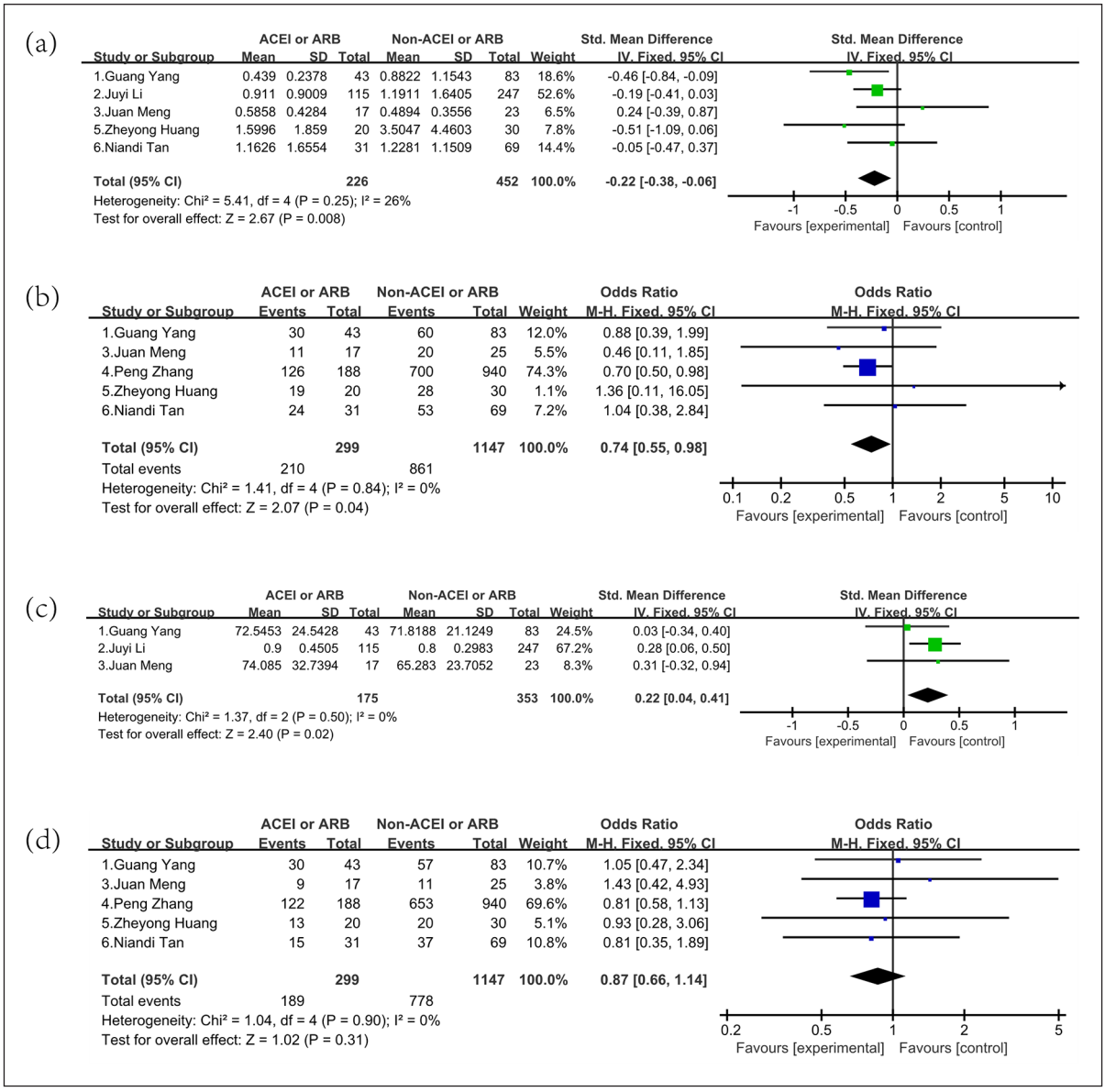

Figure 2. Forest plot of outcomes: (a) D-dimer, (b) fever, (c) creatinine, and (d) dry cough.
The experimental group: ACEI or ARB The control group: Non-ACEI or ARB.
ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers; CI: confidence interval.

can reduce mortality and critical illness in covid-19 patients,[19] and the overall remission of the disease reduced the D-dimer index in the ACEI/ARB group. The decrease of D-dimer has a very positive effect on the prognosis of covid-19 patients, which can reduce the occurrence of myocardial infarction, cerebral infarction, pulmonary embolism and other serious complications, and ACEI and ARB can significantly improve the prognosis of patients with severe limb ischemia.[20] which is significantly related to the decrease of D-dimer. Therefore, we boldly speculate that the main reason for the positive effect of ACEI and ARB on patients with covid-19 may be that they reduce the effect of d dimer. A lot of clinical data, especially on cytokines, will be needed to confirm this hypothesis.

However, studies have shown an increased risk of AKI in hypertensive patients with ACEI/ARB, patients with chronic renal insufficiency and patients with poor cardiac function,[21] which is similar to what we found statistically. An increase in creatinine was observed in patients taking ACEI and ARB, which may be associated with COVID-19 virus attack on the kidneys.Covid-19 can directly invade renal tubules,[22] leading to acute kidney injury [16]. ACE2 is the carrier of covid-19 virus into host cells, and ACEI and ARB can up-regulate the expression of ACE2, which may be the cause of renal injury in patients taking ACEI and ARB. Therefore, ACEI and ARB should be used with more caution in COVID-19 patients with chronic renal insufficiency or renal impairment. For patients without kidney damage, there was no statistically significant

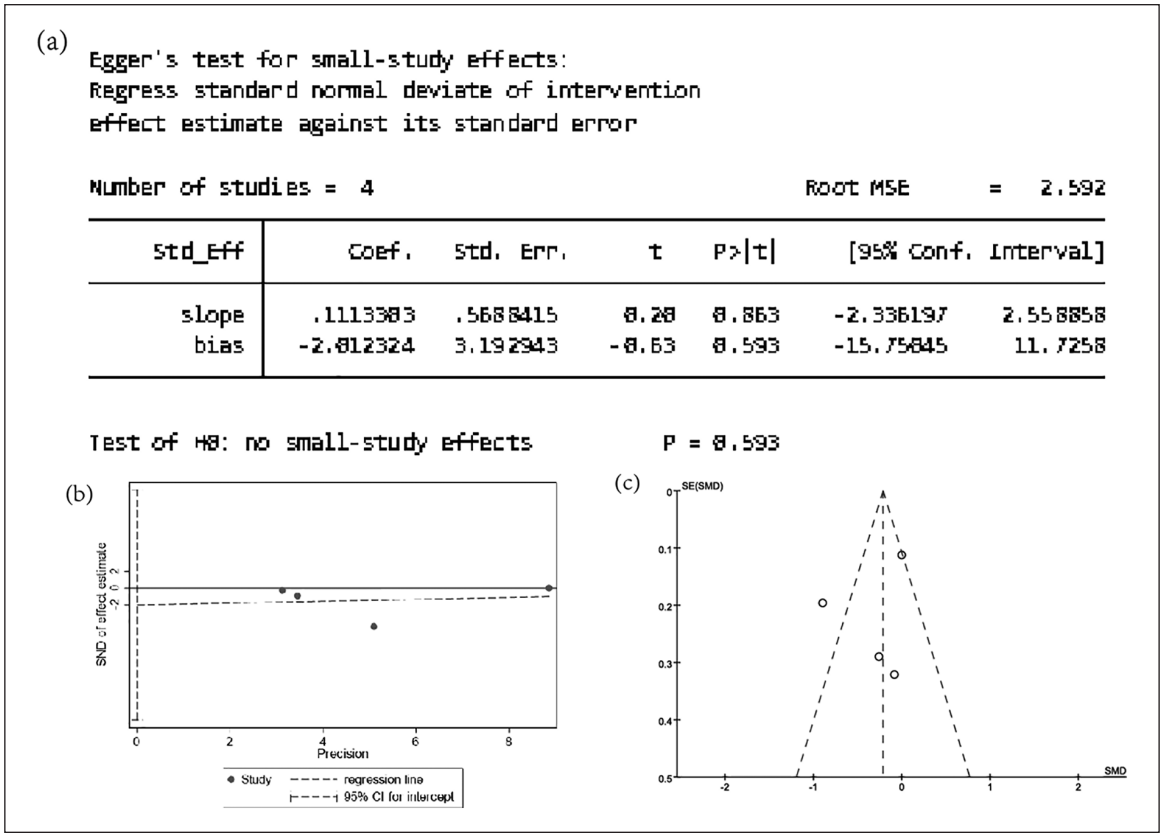

Figure 3. Egger's publication bias plot and Funnel plot on PCT: (a) and (b): Egger's test: $p = 0.593$ and (c) funnel plot.
PCT: procalcitonin.

difference in the severity of COVID-19 pneumonia between patients with ACEI/ARB and those with other anti-hypertensive drugs, and there was no statistically significant difference between the two groups in dry cough (Figure 2(d)), a significant side effect of ACEI.As mentioned above, the application of ACEI and ARB drugs is worth trying for COVID-19 patients with hypertensive.

Limitations

This study has some limitations. First of all, there are still incomplete statistical data in the literature cited as the statistics of the epidemic outbreak in the special period. Second, the original studies included are all retrospective studies, lacking critical RCTs, which are slightly insufficient in statistical significance. Thirdly, limited publications and limited data may lead to biased results, so more articles with a larger sample size are needed to supplement the results. Finally, the collected data are mostly from China, not excluding geographical and ethnic differences.

Conclusion

ACEI and ARB might have a potential positive effect on the remission of COVID-19 patients, because it can reduce the D-dimer in COVID-19 patients, and there was a corresponding decrease in the number of people with fever, not to mention its own antihypertensive effect. There was no increased risk of taking ACEI or ARB drugs in other laboratory data and clinical symptoms. However, ACEI and ARB should be used more carefully in patients with renal insufficiency. More clinical trials are needed to provide evidence for this study.

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Declaration of conflicting interests

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Patient consent

Not required.

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Supplemental material

Supplemental material for this article is available online.

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Notation

Abbreviations

ACEI	angiotensin-converting enzyme inhibitors
ACE2	angiotensin converting enzyme 2
AKI	acute kidney injury
ALT	Alanine transaminase
ARB	angiotensin-receptor blockers
AST	Aspartate transferase
CI	confidence interval
CK	Creatine kinase
COPD	chronic obstructive pulmonary disease
COVID-19	2019 novel coronavirus disease
CRP	C-reactive protein
LDH	Lactate dehydrogenase
NOS	Newcastle-Ottawa Scale
OR	odds ratio
PCT	procalcitonin
PT	Prothrombin time
RAS	Renin-angiotensin-aldosterone system
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMD	standard mean difference