



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Candesartan as a tentative treatment for COVID-19: A prospective non-randomized open-label study



Antonia Anna Lukito^{a,b,c,d,*}, Allen Widysanto^{a,b,c}, Theo Audi Yanto Lemuel^{a,b,c}, Ignatius Bima Prasetya^{a,b,c}, Billy Massie^{a,b,c}, Mira Yuniarti^{a,b,c}, Nicolaski Lumbuun^b, Raymond Pranata^{b,c}, Cindy Meidy^b, Eka Julianta Wahjoepramono^{a,b,c}, Irawan Yusuf^{a,b,d}

^a Medical Science Group Team, Tangerang, Indonesia

^b Pelita Harapan University, Tangerang, Indonesia

^c Siloam Hospitals, Tangerang, Indonesia

^d Mochtar Riady Institute of Nanotechnology, Tangerang, Indonesia

ARTICLE INFO

Article history:

Received 26 April 2021

Received in revised form 5 May 2021

Accepted 11 May 2021

Keywords:

Angiotensin
Candesartan
Coronavirus
SARS-CoV-2
Severity

ABSTRACT

Background: This study aimed to investigate whether the addition of candesartan to the standard care regimen improved the outcome in patients with coronavirus 2019 (COVID-19).

Methods: A prospective non-randomized open-label study was undertaken from May to August 2020 on 75 subjects (aged 18–70 years) hospitalized in Siloam Kelapa Dua Hospital. Uni- and multi-variable Cox regression analyses were performed to obtain hazard ratios (HRs). The primary outcomes were: (1) length of hospital stay; (2) time to negative swab; and (3) radiological outcome (time to improvement on chest X ray).

Results: None of the 75 patients with COVID-19 required intensive care. All patients were angiotensin-receptor-blocker naïve. In comparison with the control group, the candesartan group had a significantly shorter hospital stay [adjusted HR 2.47, 95% confidence interval (CI) 1.16–5.29] after adjusting for a wide range of confounders, and no increased risk of intensive care. In the non-obese subgroup, the candesartan group had a shorter time to negative swab (unadjusted HR 2.11, 95% CI 1.02–4.36; adjusted HR 2.40, 95% CI 1.08–5.09) and shorter time to improvement in chest x ray (adjusted HR 2.82, 95% CI 1.13–7.03) compared with the control group.

Conclusion: Candesartan significantly reduces the length of hospital stay after adjustment for covariates. All primary outcomes improved significantly in the non-obese subgroup receiving candesartan.

© 2021 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Coronavirus disease 2019 (COVID-19) is a global public health emergency (World Health Organization, 2021). Hundreds of millions of people have been infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) at the time of writing. Although most patients with COVID-19 are asymptomatic or experience only mild influenza-like illness (Day, 2020), a significant proportion may develop severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure (MOF) and death (Lim et al., 2020). Due to the novelty of the disease, evidence-based treatments remain uncertain, and most studies assessing specific medications for COVID-19 are inconclusive (Cao et al., 2020; Gautret et al., 2020).

The viral surface spike (S) protein of COVID-19 binds to angiotensin-converting enzyme 2 (ACE2) following S protein activation by transmembrane protease serine 2 (Hoffmann et al., 2020). At first, the increase in ACE2 expression in patients receiving ACE inhibitors and angiotensin receptor blockers (ARBs) was thought to increase susceptibility to SARS-CoV-2 infection (Fang et al., 2020). However, studies have shown that COVID-19 downregulates ACE2 expression and hinders its organoprotective effect (Vaduganathan et al., 2020). It has been hypothesized that the unregulated angiotensin II activity leads to multiple organ injury (Gurwitz, 2020; Liu et al., 2020). Furthermore, ACE2 has been shown to protect the lungs from ARDS (Imai et al., 2005). Hence, drugs that increase ACE2 may actually offer protection rather than harm (Cheng et al., 2020; Meng et al., 2020). This is strengthened by recent findings that indicate the potential benefit of ARB use in patients with COVID-19 and hypertension (Pranata et al., 2020b). The present prospective non-randomized study

* Corresponding author at: Pelita Harapan University, Tangerang, Indonesia.
E-mail address: antonia.lukito@uph.edu (A.A. Lukito).

aimed to evaluate the efficacy and safety of candesartan in addition to the standard care regimen in patients with COVID-19 compared with standard care alone.

Methods

Study population and setting

This prospective non-randomized study was coordinated by the Medical Science Group of Pelita Harapan University, Siloam Hospitals and Mochtar Riady Institute of Nanotechnology (MRIN) in Tangerang, Indonesia. Patients were recruited from Siloam Hospitals Kelapa Dua, a COVID-19 referral hospital, from 4 April 2020. All patients with COVID-19 in the hospital received hydroxychloroquine unless contraindicated. Patients were then proposed a treatment regimen comprising standard care and candesartan. Patients who agreed to receive the standard care + candesartan regimen were recruited into the candesartan group. Patients who were treated with standard care without candesartan were recruited into the control group. Hydroxychloroquine was included in the hospital standard treatment protocol at the time of this study. Figure 1 shows the research flowchart.

Patients

Patients included in this study were hospitalized with COVID-19, aged 18–70 years, and had SARS-CoV-2 carriage confirmed by

polymerase chain reaction (PCR) from a nasopharyngeal swab sample at admission, regardless of clinical status.

Patients were excluded if they had a history of allergy to hydroxychloroquine or candesartan, or had another known contraindication to treatment with the study drug, including retinopathy, G6PD deficiency or QT prolongation. Patients with other terminal illnesses were also excluded. Breastfeeding and pregnant patients were excluded based on their declaration and pregnancy test results when required.

Informed consent

Written informed signed consent was obtained from patients who met the inclusion criteria and agreed to participate in the study. An information document that indicated the risks and the benefits associated with study participation was given to each patient. Patients received information about their clinical status during care regardless of whether or not they participated in the study. Regarding patient identification, a study number was assigned sequentially to included participants, according to the range of patient numbers allocated to the study. The study was conducted following the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines of good clinical practice, the Declaration of Helsinki, and applicable standard operating procedures. The protocol and any other relevant documentation were submitted to the MRIN Ethics Committee for review and approval.

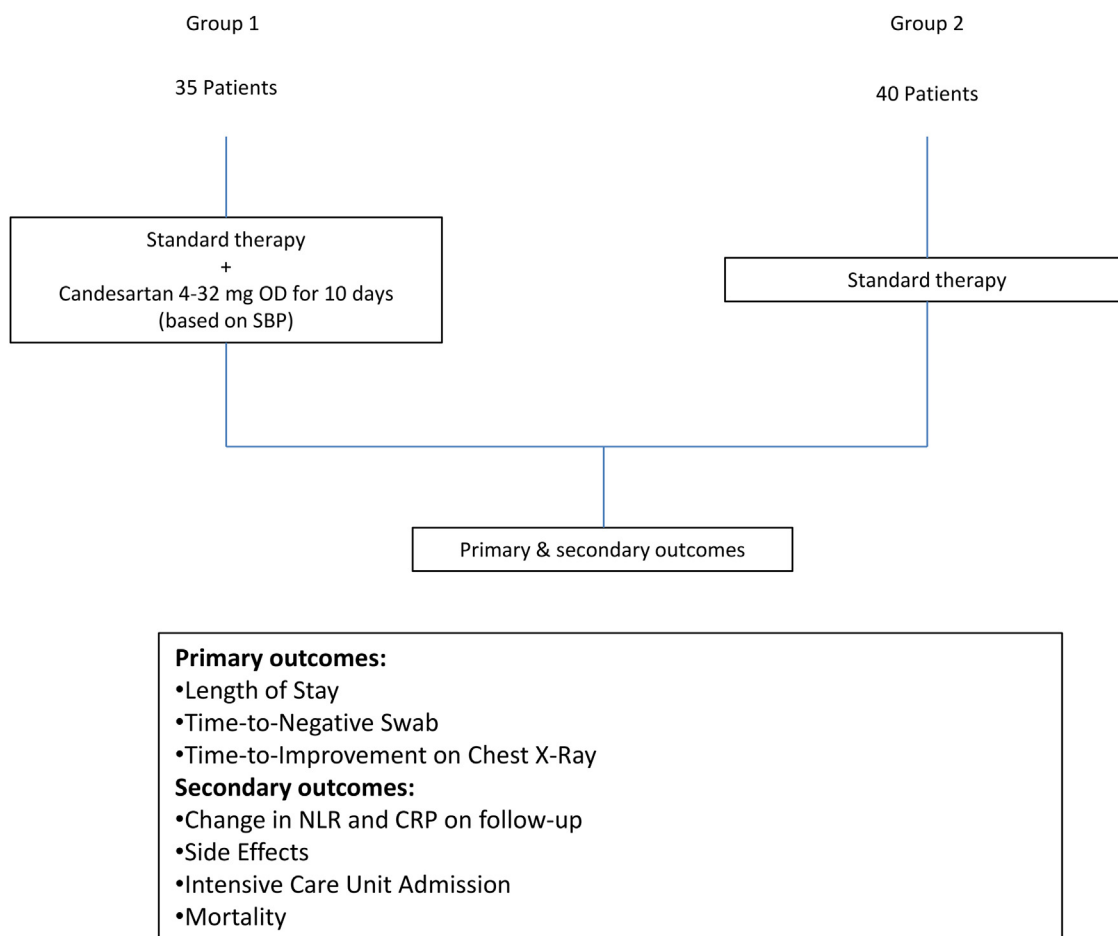


Figure 1. Research flowchart.

Procedure

Patients were seen at enrolment (baseline), initial data collection, treatment on days 0 and 7, and for daily follow-up for 14 days. Each day, patients received a standardized clinical examination. A nasopharyngeal sample was collected on days 0 and 5, and then every 2 days until negative before hospital discharge. Low-radiation-dose thorax computed tomography or chest X ray was performed on days 0 and 14, and then every 5 days. All clinical data were collected using standardized questionnaires. Investigators provided symptomatic treatment and antibiotics as a measure to prevent bacterial super-infection based on clinical judgement.

Clinical presentation

Patients were grouped into two categories: mild–moderate and severe COVID-19. Mild–moderate status was defined as mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain or malaise. Severe status was defined in accordance with the World Health Organization's interim guidance for the clinical management of patients with severe acute respiratory infection. This included patients who had any of the following features at the time of, or after, admission: (1) respiratory distress (≥ 30 breaths per min); (2) oxygen saturation at rest $\leq 93\%$; (3) ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air ≤ 300 mmHg; or (4) critical complication (respiratory failure, septic shock and/or multiple organ dysfunction/failure) (World Health Organization, 2020).

PCR assay

SARS-CoV-2 RNA was assessed by real-time reverse transcriptase PCR.

Intervention group

In the intervention group, patients received candesartan 4–32 mg once daily, titrated according to blood pressure tolerance and not given to patients with estimated glomerular filtration rate < 30 mL/min/1.73 m². Candesartan was postponed if systolic blood pressure (SBP) fell below 90 mmHg, and was restarted when SBP exceeded 100 mmHg. Patients were also given azithromycin 500 mg once daily or levofloxacin IV 750 mg once daily, hydrochloroquine 400 mg once daily, and vitamin C 1000 mg IV. Patients also received symptomatic medications and additional antibiotics at the physician's discretion.

Table 1

Baseline characteristics of the included studies.

	Candesartan group (n = 35)	Control group (n = 40)	P-value
Age (years), mean (range)	37 (19–70)	41.5 (23–70)	0.249
Male	24 (68.6%)	29 (72.5%)	0.709
Hypertension	4 (11.4%)	3 (7.5%)	0.334
Diabetes	3 (8.6%)	1 (2.5%)	0.699
BMI, kg/m ² , mean \pm standard deviation	25.7 \pm 4.3	25.0 \pm 3.3	0.437
Obesity (BMI > 25 kg/m ²)	17 (48.6%)	20 (50%)	0.902
Current smoker	3 (8.6%)	6 (15%)	0.489
Prior use of candesartan	0 (0%)	0 (0%)	1.000
Aspirin	3 (8.6%)	3 (7.5%)	1.000
Statin	1 (2.9%)	2 (5%)	1.000
Amlodipine	1 (2.9%)	1 (2.5%)	1.000
Metformin	2 (5.8%)	1 (2.5%)	0.596
DPP-4 inhibitor	0 (0%)	1 (2.5%)	1.000
Severe COVID-19	4 (11.4%)	4 (10%)	1.000

BMI, body mass index; COVID-19, coronavirus disease 2019; DPP-4, dipeptidyl peptidase-4.

Values are n (%) unless otherwise indicated.

Control group

Patients received azithromycin 500 mg once daily or levofloxacin IV 750 mg once daily, hydrochloroquine 400 mg once daily, and vitamin C 1000 mg IV, along with symptomatic medications and additional antibiotics at the physician's discretion.

Outcomes

The primary endpoints were clinical outcomes including: (1) length of hospital stay; (2) time to negative swab; and (3) time to improvement on chest X ray. Secondary outcomes were change in neutrophil–lymphocyte ratio and C-reactive protein on follow-up, occurrence of side-effects, admission to the intensive care unit (ICU) and mortality.

Statistical analysis

Using 85% power, a type I error rate of 5% and 10% loss to follow-up, it was calculated that a total of 60 patients with COVID-19 (i.e., 30 cases in the candesartan group and 30 cases in the control group) would be required for the analysis (Fleiss with CC). Continuous data were tested for normal distribution; *t*-test was used for normally distributed data and Mann–Whitney test was used for non-normally distributed data. Normally distributed data were reported as mean and standard deviation (SD), and non-normally distributed data were reported as median and interquartile range. Chi-squared test or Fisher's exact test was performed for categorical variables. Cox regression was performed to obtain the hazard ratio (HR) for the use of candesartan and length of hospital stay, time to improvement of chest X ray and time to negative swab. Multi-variable Cox regression analysis was performed using age, gender, hypertension and type 2 diabetes mellitus as covariates. To avoid model overfitting, only five covariates were included in the multi-variable Cox regression analysis at a time. Subgroup analysis was performed for non-obese patients. SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

This prospective non-randomized open-label study was conducted in the early months of the COVID-19 pandemic.

Seventy-five subjects were included in this study. Of these, 35 patients were in the candesartan group. The mean age of subjects was 41 (SD 13.65) years, 70.67% were male, 9.3% were hypertensive, 5.3% were diabetic, mean body mass index was 23.35 (SD 3.77

kg/m²), 12% were current smokers, 89.33% had mild–moderate COVID-19 and 10.67% had severe COVID-19. All patients in this study were ARB naïve. One patient in the control group had a history of candesartan use, but had not been actively taking candesartan for months. There were no significant differences in baseline characteristics, including comorbidities, between the two groups (Table 1).

None of the 75 patients with COVID-19 included in this study required ICU admission. Candesartan was not associated with a significant difference in length of hospital stay (unadjusted HR 1.50, 95% CI 0.91–2.48) (Figure 2A), time to negative swab (unadjusted HR 1.41, 95% CI 0.85–2.32) (Figure 2B) or time to improvement on chest X-ray (unadjusted HR 1.60, 95% CI 0.78–3.29) (Figure 2C). Multi-variable analysis indicated that candesartan reduced the length of hospital stay significantly (adjusted HR 1.74, 95% CI 1.01–2.97) (Figure 3A) after adjustment for age, gender, hypertension and type 2 diabetes mellitus, but did not reduce the time to negative swab (adjusted HR 1.55, 95% CI 0.92–2.63) (Figure 3B) or time to improvement on chest X ray (adjusted HR 1.45, 95% CI 0.82–2.55) (Figure 3C) (Table 2).

In the unadjusted analysis of the non-obese subgroup, the use of candesartan was associated with shorter length of hospital stay (unadjusted HR 2.47, 95% CI 1.16–5.29) (Figure 4A), and shorter time to negative swab (unadjusted HR 2.11, 95% CI 1.02–4.36) (Figure 4B), but not shorter time to improvement on chest X ray (unadjusted HR 1.06, 95% CI 0.40–2.80) (Figure 4C). In the adjusted analysis of the non-obese subgroup, the use of candesartan was associated with shorter length of hospital stay (adjusted HR 3.07, 95% CI 1.33–7.12) (Figure 5A), shorter time to negative swab (adjusted HR 2.40, 95% CI 1.08–5.09) (Figure 5B) and shorter time to improvement on chest x ray (adjusted HR 2.82, 95% CI 1.13–7.03) (Figure 5C and Table 2). Time to improvement of chest X ray is a proxy for lung injury resolution in patients with COVID-19.

There was no significant difference in neutrophil–lymphocyte ratio and C-reactive protein between baseline, day 7 and hospital discharge (Table 3). No side effects related to medications were reported in either the candesartan group or the control group. No patients in either group required ICU admission, and there were no deaths.

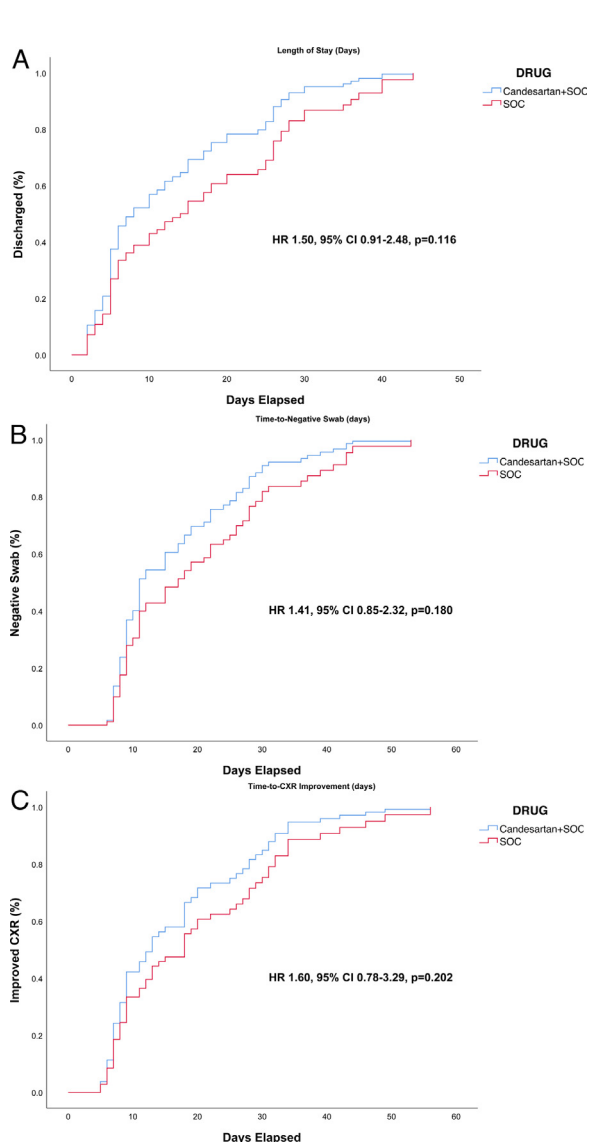


Figure 2. Use of candesartan and primary outcomes (unadjusted model). (A) Length of hospital stay, (B) time to negative swab, and (C) time to improvement on chest X ray. SOC, standard care; HR, hazard ratio; CI, confidence interval.

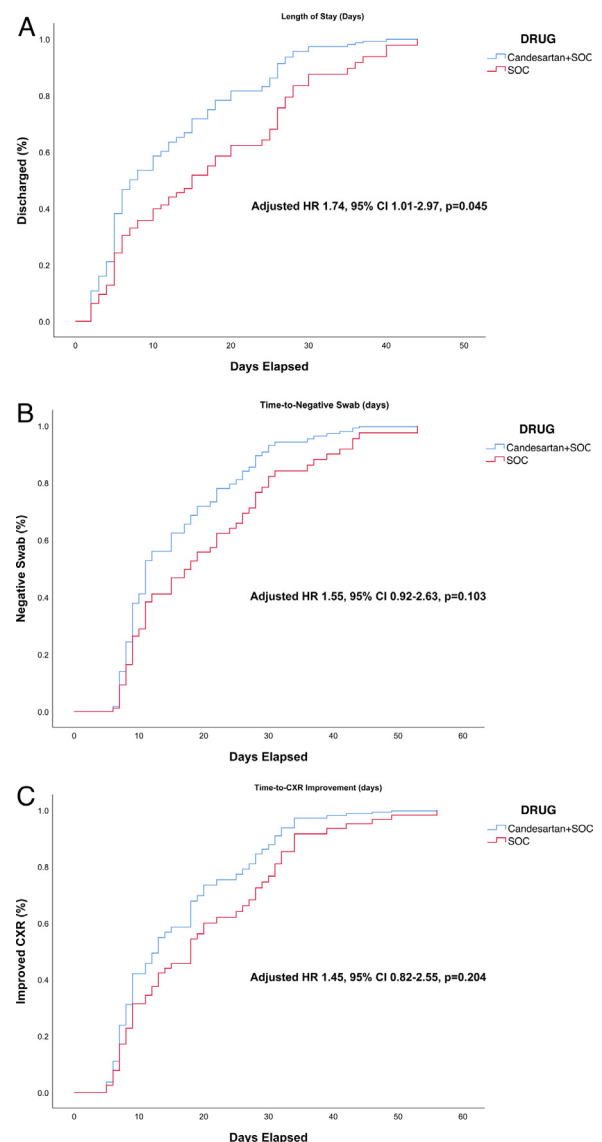


Figure 3. Use of candesartan and primary outcomes (adjusted model). (A) Length of hospital stay, (B) time to negative swab, and (C) time to improvement on chest X ray. SOC, standard care; HR, hazard ratio; CI, confidence interval.

Table 2
Hazard ratio.

	Unadjusted hazard ratio	Adjusted hazard ratio
Primary analysis		
Length of stay	1.50, 95% CI 0.91–2.48, p = 0.116	1.74, 95% CI 1.01–2.97, p = 0.045
Time-to-negative swab	1.41, 95% CI 0.85–2.32, p = 0.180	1.55, 95% CI 0.92–2.63, p = 0.103
Time-to-improvement chest X-ray	1.60, 95% CI 0.78–3.29, p = 0.202	1.45, 95% CI 0.82–2.55, p = 0.204
Non-obese subgroup		
Length of stay	2.47, 95% CI 1.16–5.29, p = 0.020	3.07, 95% CI 1.33–7.12, p = 0.009
Time-to-negative swab	2.11, 95% CI 1.02–4.36, p = 0.044	2.40, 95% CI 1.08–5.09, p = 0.032
Time-to-improvement chest X-ray	1.06, 95% CI 0.40–2.80, p = 0.903	2.82, 95% CI 1.13–7.03, p = 0.026

Adjusted for age, gender, hypertension, and type 2 diabetes mellitus.

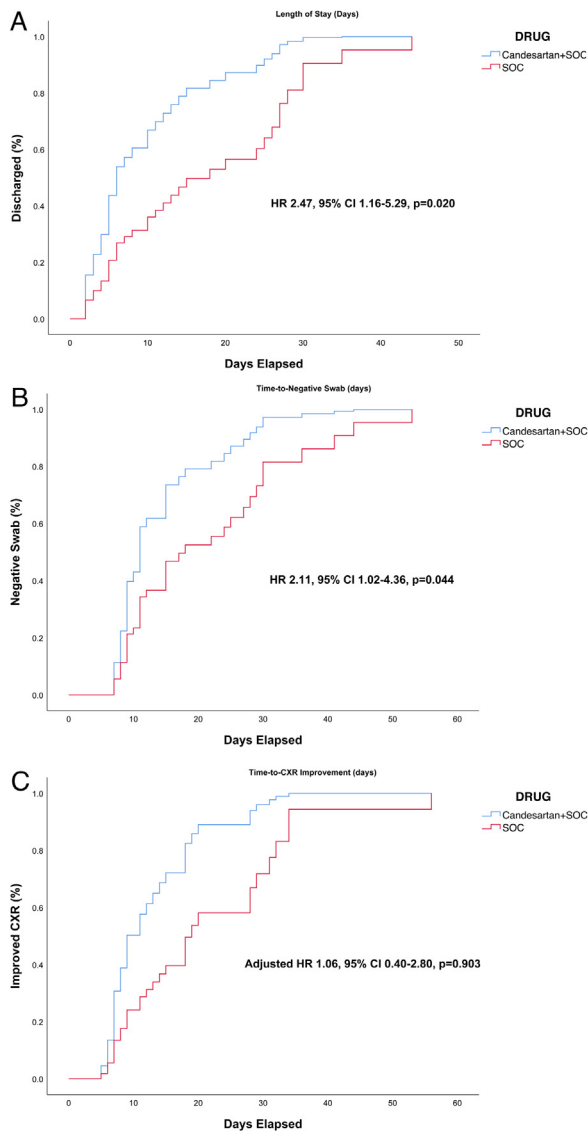


Figure 4. Use of candesartan and primary outcomes in non-obese patients (unadjusted model). (A) Length of hospital stay, (B) time to negative swab, and (C) time to improvement on chest X ray. SOC, standard care; HR, hazard ratio; CI, confidence interval.

Discussion

This prospective non-randomized open-label study showed that the use of candesartan resulted in a trend towards reduced length of hospital stay, time to improvement on chest X ray and time to negative swab, although the findings were not significant.

The lower CI for the reduction in length of hospital stay was close to 1, and it is possible that significance could be achieved with a larger sample size. Multi-variable analysis showed that candesartan reduced the length of hospital stay significantly after adjustment for age, gender, hypertension and type 2 diabetes mellitus. Additionally, subgroup analysis in non-obese patients found that length of hospital stay, time to improvement on chest X-ray and time to negative swab were significantly improved in patients receiving candesartan. None of the patients in this study required ICU admission and there were no deaths, possibly because most of the patients had mild–moderate COVID-19.

Candesartan is widely used to treat hypertension, and there is abundant clinical experience with its use. All representatives of this group are characterized by their excellent tolerance.

Candesartan is a selective antagonist of AT1 receptors that exerts an inhibitory effect on the ACE–AngII–AT1 axis in the renin-angiotensin system (RAS), a known molecular pathway for end-organ fibrosis. Thus, candesartan may be suggested as a potential agent for protection from lung damage induced by COVID-19. Candesartan may also have a protective function against lung fibrosis through other molecular mechanisms, such as the down-regulation of transforming growth factor-beta1.

ACE2 reduces the expression of interleukin (IL)-6 by converting angiotensin II into angiotensin 1–7, thus promoting antioxidant function, increasing the concentration of alveolar surfactants and triggering vasodilation (Pal and Bhansali, 2020; Rossi et al., 2020). These potentially protect the lungs from ARDS (Imai et al., 2005). Additionally, the use of ACEI/ARB increases the number of CD3 and CD8 T cells, with a decreased peak viral load, compared with other antihypertensive drugs (Meng et al., 2020). SARS-CoV-2 down-regulates ACE2 expression, eventually causing unregulated angiotensin II activity (Vaduganathan et al., 2020), which is one of the possible mechanisms that may incite multiple organ injury (Gurwitz, 2020; Liu et al., 2020) (Figure 6). Cardiovascular injuries, pre-existing or new, are commonly encountered in patients with COVID-19 (Pranata et al., 2020a; Martha et al., 2021; Wibowo et al., 2021a,b); prescribing ARBs in these patients may help to mitigate the pathology. The present study supports the use of ARBs in patients without comorbidities such as hypertension or diabetes, in view of the fact that ARBs provide protection against lung injury or cardiovascular complications.

In this study, the non-obese subgroup receiving candesartan in the adjusted model had a shorter length of hospital stay, shorter time to negative swab and shorter time to improvement on chest X ray compared with patients receiving standard care. While the exact mechanisms are unclear, there are several possible explanations. This phenomenon is in line with the findings of Ecelbarger et al. (2010), who evaluated the inflammation profile of lean and obese Zucker rats. The rats were fed with candesartan for 14 weeks, and candesartan was shown to decrease renal IL-1, IL-2, IL-4, IL-6 and IL-10, tumour necrosis factor-alpha and interferon-gamma in obese Zucker rats. However, the levels of growth-

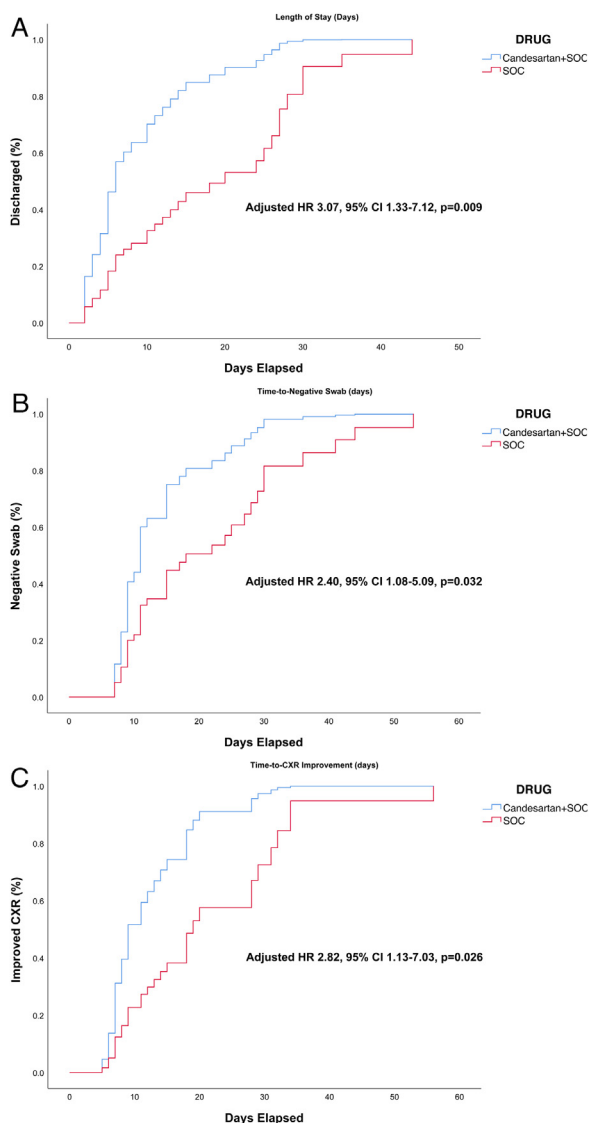


Figure 5. Use of candesartan and primary outcomes in obese patients (adjusted model). (A) Length of hospital stay, (B) time to negative swab, and (C) time to improvement on chest X ray. SOC, standard care; HR, hazard ratio; CI, confidence interval.

regulated oncogene, transforming growth factor-beta1 and IL-18 were elevated in obese Zucker rats compared with lean Zucker rats. This phenomenon remains unclear and further study is needed; however, it may indicate a different response to candesartan in lean and obese subjects (Ecelbarger et al., 2010).

Obesity increases the severity of COVID-19. In a dose–response meta-analysis, Pranata et al. (2021) showed that obesity was associated with composite poor outcome, mortality and severity of COVID-19. The pro-inflammatory state in obese subjects may reduce the benefit of candesartan. Additionally, obese patients express more ACE2 receptors compared with non-obese subjects, which may increase the risk of severe COVID-19 in obese subjects (Al Heialy et al., 2020; Iannelli et al., 2020). A higher number of ACE2 receptors may translate to an increased candesartan dose requirement, explaining why the benefit is observed more readily in non-obese patients. These hypotheses need to be confirmed in larger randomized controlled trials.

The candesartan group had a shorter length of hospital stay compared with the control group, after adjusting for age, gender, hypertension and type 2 diabetes mellitus. This finding supports

Table 3
Laboratory outcomes.

	Candesartan (n = 35)	No Candesartan (n = 40)	p-Value
NLR			
Baseline	2.07 (1.97)	2.39 (2.32)	0.457
Day 7	1.87 (0.81)	2.26 (1.39)	0.169
Discharge	1.84 (0.99)	1.85 (1.08)	0.780
CRP			
Baseline	2.15 (6.38)	3.07 (28)	0.342
Day 7	2.25 (4.45)	2.15 (8.55)	0.761
Discharge	1.90 (3.68)	2.40 (3.68)	0.623

NLR and CRP were reported in median (interquartile range).

the studies which reported that RAS inhibitors may prevent lung injury due to COVID-19 (Imai et al., 2005; Chen et al., 2020; Cheng et al., 2020; Gurwitz, 2020; Liu et al., 2020; Vaduganathan et al., 2020; Zhang et al., 2020). Moreover, in a systematic meta-analysis, Pranata et al. (2020b) reported that administration of a RAS inhibitor was not associated with increased mortality or severity of COVID-19 in patients with hypertension, and specifically, the use of ARBs rather than ACEI was associated with lower mortality (Pranata et al., 2020b).

Recently, Gurwitz (2020) proposed the tentative use of agents such as losartan and telmisartan as alternative options to treat patients with COVID-19 prior to the development of ARDS. Interestingly, Zhang et al. (2020) found that among patients with hypertension hospitalized with COVID-19, inpatient treatment with ACEI/ARB was associated with lower risk of all-cause mortality compared with non-users (Rothlin et al., 2020).

In accordance with these studies, a randomized open-label controlled trial has begun enrolling patients at Hospital de Clínicas ‘José de San Martín’ (School of Medicine, University of Buenos Aires, Argentina). The proposed intervention in the clinical trial setting will be telmisartan (Bertel, Laboratorio Elea Phoenix, Buenos Aires, Argentina), 80 mg twice daily p.o., following a positive PCR test for COVID-19 in comparison with standard care (NCT04355936) (Rothlin et al., 2020).

In line with the present findings, a large population-based study by Hippisley-Cox et al. (2020) found that although ARB prescription was associated with a shorter COVID-19-positive PCR recovery time in a hospital setting after adjusting for a wide range of demographic factors, potential comorbidities and other medication, ARBs were not associated with increased or decreased risk of ICU admission.

Inflammatory markers are usually associated with prognosis in patients with COVID-19 (Huang et al., 2020). The lack of improvement in inflammation markers may indicate that the inflammation process had not subsided entirely after an average hospital stay of 2 weeks. Heywood et al. (2021) reported that that biochemical and inflammatory pathways within the body could remain perturbed long after SARS-CoV-2 infection has subsided, even in asymptomatic and moderately affected patients, for 40–60 days after viral infection.

Several drugs such as metformin and dipeptidyl peptidase-4 inhibitor may affect the prognosis in patients with COVID-19 (Lukito et al., 2020; Rakhmat et al., 2021). The present study found no demonstrable difference between the candesartan group and the control group.

This study has several limitations. Firstly, it had an open-label design, which is not as robust as a randomized controlled trial. Secondly, although the sample size was calculated based on the formula for sample size requirement in analytical studies, it seemed that the study was underpowered and it may be possible to reach statistical significance with a larger sample size. Finally, despite potential self-selection bias, there was no significant

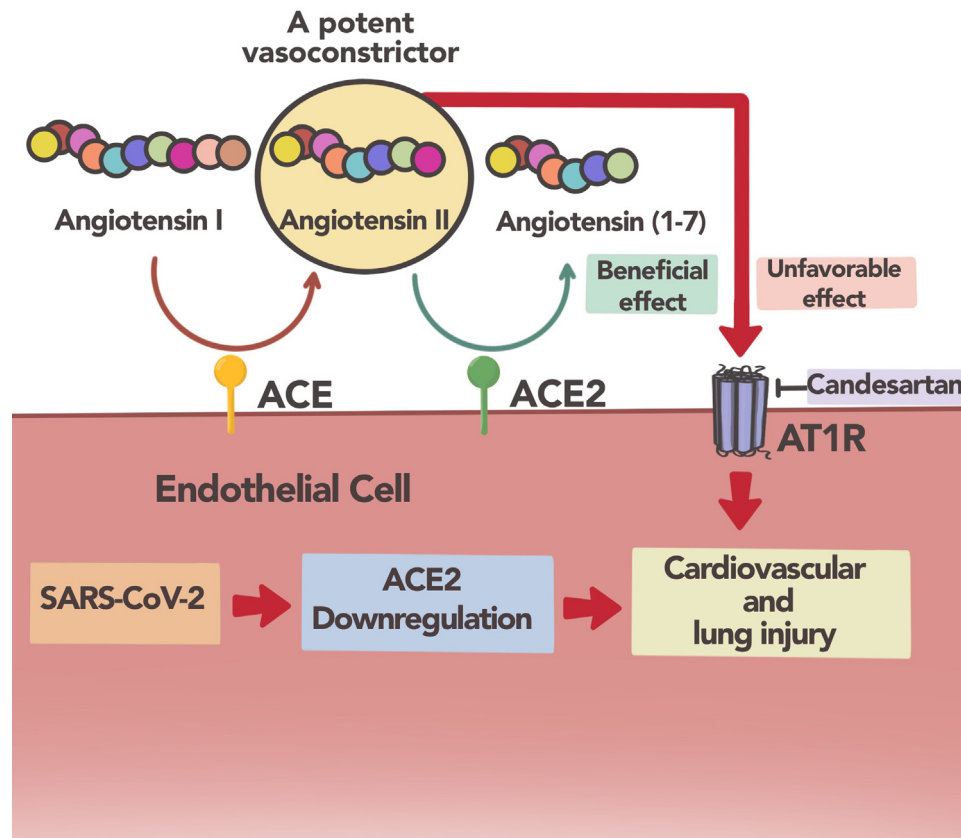


Figure 6. Central illustration: The possible mechanism of angiotensin receptor blockers in mitigating cardiovascular and lung injury in patients with coronavirus disease 2019. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ACE2, angiotensin-converting enzyme 2.

difference between the baseline characteristics of the two groups. Randomized controlled trials should be conducted in patients with severe COVID-19 to evaluate the benefit of candesartan in terms of mortality and ICU admission.

Conclusion

To the authors' knowledge, this is the first prospective non-randomized open-label study to investigate the use of candesartan, an ARB, as a tentative treatment for COVID-19. Use of candesartan was found to have a non-significant trend towards shorter length of hospital stay, shorter time to improvement of chest x ray, and shorter time to negative swab. Interestingly, candesartan reduced the length of hospital stay in the non-obese subgroup after adjustment for age, gender, hypertension and type 2 diabetes mellitus. Candesartan reduced the length of hospital stay in the entire group and the non-obese subgroup, and reduced the time to improvement of chest X ray (a proxy of lung injury resolution) in the non-obese subgroup compared with the standard care regimen. Candesartan was also associated with a shorter time to negative PCR swab in the adjusted model.

Author contributions

Antonia Anna Lukito: conceptualization, methodology, data curation, formal analysis, investigation, validation, writing – original draft, writing – review and editing.

Allen Widysanto: data curation, investigation, writing – review and editing.

Theo Audi Yanto Lemuel: data curation, investigation, writing – review and editing.

Ignatius Bima Prasetya: data curation, investigation, writing – review and editing.

Billy Massie: data curation, investigation, writing – review and editing.

Mira Yuniarti: data curation, investigation, writing – review and editing.

Nicolaski Lumbuun: data curation, investigation, writing – review and editing.

Raymond Pranata: data curation, formal analysis, investigation, writing – original draft, writing – review and editing.

Cindy Meidy: data curation, investigation, writing – review and editing.

Eka Julianta Wahjoepramono: data curation, investigation, writing – review and editing.

Irawan Yusuf: data curation, investigation, writing – review and editing.

Conflict of interest

None declared.

Funding

The open access fee for publication was covered by Siloam Hospital-Medical Science Group, Tangerang, Indonesia.

Ethical approval

This research was approved by Mochtar Riady Institute for Nanotechnology Ethics Committee (Ref. 004/MRIN-EC/ECL/V/2020, Protocol No. 2005003).

Acknowledgements

The authors wish to thank the following groups for their support: Siloam Hospitals Kelapa Dua, Siloam Hospitals Lippo Village, Pelita Harapan University and Mochtar Riady Institute of Nanotechnology. The authors also wish to thank: Nana Hasan, MD, MM, MMRS; Wahyuni Purwanti, MD; resident medical officers from Siloam Hospitals Kelapa Dua, Aryasena A. Wiedjaja and medical students from Pelita Harapan University; Alvin A. Thengker, MD, and Marco Wirawan, MD, from Siloam Hospitals Lippo Village; Veli Sungono, M Epid from Pelita Harapan University; Rusli Muliadi, MD, PhD, Head of Siloam Radiology Department; David Rustandi, MD, Head of Siloam Laboratory Department; Professor Eka J Wahyupramono, MD, PhD, Dean of Pelita Harapan University; Professor Irawan Yusuf, MD, PhD, and Ivet Suryapranata, PhD, Head and Researcher of Mochtar Riady Institute of Nanotechnology; Grace Frelita Indradjaja, MD, MM, Managing Director of Siloam Hospitals Group; and Caroline Riady, CEO and Deputy President Director of Siloam Hospitals Group.

References

- Al Heialy S, Hachim MY, Senok A, Gaudet M, Abou Tayoun A, Hamoudi R, et al. Regulation of angiotensin-converting enzyme 2 in obesity: implications for COVID-19. *Front Physiol* 2020;11:555039, doi:<http://dx.doi.org/10.3389/fphys.2020.555039>.
- Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med* 2020;382:1787–99.
- Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun* 2020;525:135–40.
- Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol* 2020;92:726–30.
- Day M. COVID-19: four fifths of cases are asymptomatic, China figures indicate. *BMJ* 2020;369:m1375.
- Ecelbarger CM, Rash A, Sinha RK, Tiwari S. The effect of chronic candesartan therapy on the metabolic profile and renal tissue cytokine levels in the obese Zucker rat. *Mediators Inflamm* 2010;841343, doi:<http://dx.doi.org/10.1155/2010/841343>.
- Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?. *Lancet Respir Med* 2020;8:e21.
- Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;56:105949.
- Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020;81:537–40.
- Heywood WE, Doykov I, Hällqvist J, Gilmour KC, Grandjean L, Mills K. “The long tail of COVID-19” – the detection of a prolonged inflammatory response after a SARS-CoV-2 infection in asymptomatic and mildly affected patients. *F1000Research* 2021;9:1349.
- Hippisley-Cox J, Young D, Coupland C, Channon KM, Tan PS, Harrison DA, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart* 2020;106:1503–11.
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–280.e8.
- Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis* 2020;14:
- Iannelli A, Favre G, Frey S, Esnault V, Gugenheim J, Bouam S, et al. Obesity and COVID-19: ACE 2, the missing tile. *Obes Surg* 2020;30:4615–7.
- Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;436:112–6.
- Lim MA, Pranata R, Huang I, Yonas E, Soeroto AY, Supriyadi R. Multiorgan failure with emphasis on acute kidney injury and severity of COVID-19: systematic review and meta-analysis. *Can J Kidney Health Dis* 2020;7:, doi:<http://dx.doi.org/10.1177/2054358120938573>.
- Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020;63:364–74.
- Lukito AA, Pranata R, Henrina J, Lim MA, Lawrensia S, Suastika K. The effect of metformin consumption on mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *Diabetes Metab Syndr Clin Res Rev* 2020;14:2177–83.
- Martha JW, Pranata R, Wibowo A, Lim MA. Tricuspid annular plane systolic excursion (TAPSE) measured by echocardiography and mortality in COVID-19: a systematic review and meta-analysis. *Int J Infect Dis* 2021;105:351–6.
- Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020;9:757–60.
- Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. *Diabetes Res Clin Pract* 2020;162:108132.
- Pranata R, Huang I, Lim MA, Wahjoeparamono PEJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 – systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis* 2020a;, doi:<http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2020.104949>.
- Pranata R, Permana H, Huang I, Lim MA, Soetedjo NNM, Supriyadi R, et al. The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Diabetes Metab Syndr Clin Res Rev* 2020b;14:983–90.
- Pranata R, Lim MA, Yonas E, Vania R, Lukito AA, Siswanto BB, et al. Body mass index and outcome in patients with COVID-19: a dose–response meta-analysis. *Diabetes Metab* 2021;47:101178, doi:<http://dx.doi.org/10.1016/j.diabet.2020.07.005>.
- Rakhmat II, Kusmala YY, Handayani DR, Juliastuti H, Nawangsih EN, Wibowo A, et al. Dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in coronavirus disease 2019 (COVID-19) – a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr Clin Res Rev* 2021;15:777–82.
- Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. *eLife* 2020;9:e57278, doi:<http://dx.doi.org/10.7554/eLife.57278>.
- Rothlin RP, Vetulli HM, Duarte M, Pelorosso FG. Telmisartan as tentative angiotensin receptor blocker therapeutic for COVID-19. *Drug Dev Res* 2020;81:768–70.
- Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med* 2020;382:1653–9.
- Wibowo A, Pranata R, Akbar MR, Purnomowati A, Martha JW. Prognostic performance of troponin in COVID-19: a diagnostic meta-analysis and meta-regression. *Int J Infect Dis* 2021a;105:312–8.
- Wibowo A, Pranata R, Astuti A, Tiksnadi BB, Martanto E, Martha JW, et al. Left and right ventricular longitudinal strains are associated with poor outcome in COVID-19: a systematic review and meta-analysis. *J Intensive Care* 2021b;9:9.
- World Health Organization. Report of the WHO–China Joint Mission on Coronavirus Disease 2019 (COVID-19). Geneva: WHO; 2020.
- World Health Organization. Weekly epidemiological update – 2 March 2021. Geneva: WHO; 2021.
- Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;126:1671–81.