# Comparison of Severity of COVID-19 Infection among Patients Using RAAS Inhibitors and Non-RAAS Inhibitors

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## Abstract

**Aims and objectives:** The aim of the article was to study the safety profile of renin-angiotensin-aldosterone system (RAAS) inhibitor in COVID-19-affected Indian patients.

**Introduction:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for COVID-19 infection. There has been uncertainty about use of RAAS inhibitors in COVID-19. The association of RAAS inhibitors with severity of infection and clinical outcomes was addressed in this study.

**Materials and methods:** This is a single-center retrospective study from Indian intensive care unit (ICU). A total of 138 were included, who were divided into group A (RAAS inhibitor) and group B (non-RAAS inhibitor). They are followed up till ICU stay during which peak levels of ferritin, D dimer, interleukin-6 were noted (primary outcome). The number of ventilator days, ICU length of stay, and ICU outcome also compared.

**Results:** Of 138 patients, 18 are included in group A and 120, in group B. There is no difference in peak levels (mean) D dimer [5,893 vs 7,710, $p$ 0.46], ferritin [2,388 vs 3,635, $p$ 0.56], interleukin-6 [9,597 vs 3,625, $p$ 0.06]. There is no difference in number of ventilator days (2.2 vs 1.78, $p$ 0.53) and ICU length of stay (6.5 vs 6.1, $p$ 0.74).

**Conclusion:** RAAS inhibitors can be safely continued in COVID-19 infection. It is not associated with an increase in severity of infection, ICU length of stay, and mortality.

**Keywords:** ACE inhibitors, Angiotensin receptor blocker, COVID-19, D dimer, Interleukin-6, Renin angiotensin aldosterone system, Serum ferritin, Serum interleukin-6

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## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first described in December 2019 in Wuhan, China.[1] It is responsible for coronavirus disease-2019 (COVID-19) infection, a global pandemic affecting millions of population worldwide including healthcare workers with a mortality of 16% in intensive care unit (ICU) from Western India.[2] The SARS-CoV-2 is genetically closely related to SARS CoV that emerged in 2002 causing the severe acute respiratory syndrome. It is believed that just like SARS CoV, SARS-CoV-2 also uses angiotensin-converting enzyme 2 (ACE2) receptor located on alveolar epithelial cells for entry into the lungs.[3]

The renin-angiotensin-aldosterone system (RAAS) in a closed-loop mechanism maintains sodium concentration and regulates blood pressure. ACE2 receptor, a transmembrane aminopeptidase, has the highest expression in the heart, lungs followed by endothelium, and kidneys.[4] This receptor counter-regulates RAAS through angiotensin II. Following SARS CoV infection, there is downregulation of ACE2 expression that leads to increased activation of RAAS potentiating acute lung injury.[5,6] In theory, the use of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) collectively called RAAS inhibitors should be protective against the virus causing lung injury. But to the contrary, the use of RAAS inhibitors leads to increased expression of ACE receptors in experimental studies, thereby allowing more virus entry into cells causing fatal outcomes.[7]

This uncertainty about the association of RAAS inhibitors and COVID-19 infection led to few observational studies around the world which found that there is no increased risk of infection, mortality with RAAS inhibitors in COVID-19.[8-11] we aimed to find out the association of RAAS inhibitors in COVID-19 infection among Indian population.

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## Materials and Methods

This is a single-center retrospective observational study from a tertiary care center in Hyderabad. The patients admitted to the ICU from May 2020 to July 2020 with COVID-19 infection based on positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay of the nasopharyngeal assay were included in the study. Admission criteria (from emergency unit or wards) to ICU included patients with respiratory rate >30, SpO$_2$ <90% on the nonrebreather mask, tachycardia >120/minute, and those with multiorgan failure. A total of 172 were admitted to ICU. Following variables were noted from electronic medical records—duration of symptoms,

$PaO_2/FiO_2$ (P/F) ratio at the time of admission to hospital, comorbidities, antihypertensive medication, peak levels of ferritin, D dimer, interleukin-6 (IL-6) during hospitalization, number of ventilator days, length of stay in ICU. The patients using ACEIs or ARBs were included in group A. Group B includes patients on non-RAAS inhibitors, those with no prescription records for hypertension and nonhypertensives.

The primary outcome assessed is the severity of illness based on peak levels of biomarkers—Ferritin, D dimer, interleukin-6, and secondary outcomes are ICU length of stay, mortality.

Patients whose biomarkers are in decreasing trend, off the mechanical ventilator for >24 hours, and requiring less than 10 L/minute of oxygen to maintain $SpO_2$ >94% were shifted out.

## Statistical Analysis

Quantitative variables were described as mean (±standard deviation) and qualitative variables as sample and percentage. The $p$ value <0.05 is taken as significant. For normal distribution of variables (duration of symptoms), $t$-test is used as a test of significance during comparative analysis, and for rest of variables, Mann-Whitney U test is used for significance due to skewed distribution. Chi-square test is used to compare ICU outcomes. Statistical analysis was performed using SPSS software version 21.

## RESULTS

Of 172 patients admitted to ICU, 138 patients were included in the study due to the nonavailability of biomarkers for few patients. Of these 138, 68% of patients were males and 18 patients categorized to group A. The patients in group A are older than group B (61.9 vs 58.1, $p$ value 0.21). The other clinical characteristics are shown in Table 1. The mean duration of symptoms at the time of hospitalization was 5 - 6 days and a majority of patients are hypertensive, diabetic among chronic conditions.

There is no difference in primary outcome between the two groups. The biomarkers D dimer, Ferritin, IL-6 (mean ± SD) of group A (5,893 ± 4,518, 2,388 ± 1,954, 9,597 ± 22,187) are comparable to group B (7,710 ± 10,396, 3,635 ± 9,015, 3,625 ± 10,898), respectively. In this observation, 8 of 18 patients from group A and 52 of 120 from group B had expired with mortality of 55.6 vs 43.3%, respectively ($p$ value 0.33). Other results are presented in Table 2.

**Table 1:** Baseline characteristics

| | Group A (RAAS inhibitors) | Group B (non-RAAS inhibitors) | p value |
|---|---|---|---|
| Age, mean (±SD) | 61.9 (±9.9) | 58.1 (±12.1) | 0.21 |
| **Sex** | | | |
| Male | 15 (83%) | 80 (67%) | |
| Female | 03 (17%) | 40 (33%) | |
| **Comorbidities** | | | |
| Hypertension | 18 (100%) | 50 (41.6%) | |
| Diabetes mellitus | 11 (61%) | 48 (40%) | |
| Coronary artery disease | 8 (44%) | 13 (10.8%) | |
| Hypothyroid | 1 (5.5%) | 16 (13%) | |
| Airway disease | 1 (5.5%) | 5 (4%) | |
| Nil | 36 (30%) | | |
| Duration of symptoms, mean (±SD) | 6.22 (±2.4) | 5.6 (±2.4) | 0.40 |
| P/F ratio (±SD) | 203.5 (±122.5) | 204.5 (±118.5) | 0.97 |

**Table 2:** Primary and secondary outcomes

| Outcome | Group A (RAAS inhibitors) | Group B (non-RAAS inhibitors) | p value |
|---|---|---|---|
| **Peak levels** | | | |
| D dimer, mean (±SD) | 5893.3 (±4518.7) | 7710.5 (±10395.9) | 0.46 |
| Ferritin, mean (±SD) | 2388.1 (±1954.2) | 3635.3 (±9015.1) | 0.56 |
| Interleukin-6 mean (±SD) | 9597.3 (±22186.9) | 3625.1 (±10897.9) | 0.06 |
| Ventilator days | 2.22 (±3.1) | 1.78 (±2.7) | 0.53 |
| ICU length of stay | 6.5 (±6.4) | 6.1 (±4.0) | 0.74 |
| ICU outcome (mortality) | 55.6% | 43.3% | 0.33 |

## DISCUSSION

In this single-center retrospective study, the use of RAAS inhibitors had not led to increased severity of COVID-19 infection. There is no difference in ICU length of stay, ventilator days (invasive) when compared. The study by Zhang et al. showed that the use of RAAS inhibitors is associated with low mortality, but they have compared results among hypertensive patients only, unlike our study where our control group is cohort of hypertensive and nonhypertensives.[8] The position statements by the European Society of Cardiology and the American Heart Association regarding RAAS inhibitors support our findings. Recent observational studies also proved the safe use of RAAS inhibitors, they do not increase the risk of COVID-19 infection or severity of illness.[9,10]

## CONCLUSION

RAAS inhibitors can be used safely, and there is no increased risk of severity of illness, mortality, and ICU length of stay due to COVID-19 infection.

## LIMITATIONS

A study from single-center retrospective study.

## ABBREVIATIONS

ACE2 - Angiotensin-converting enzyme 2
ACEI - Angiotensin-converting enzyme inhibitor
ARB - Angiotensin receptor blocker
COVID-19 - Coronavirus disease 2019
ICU - Intensive care unit
IL-6 - Interleukin-6
RAAS - Renin-angiotensin-aldosterone system
SARS-CoV-2 - Severe acute respiratory syndrome corona virus-2
SD - Standard deviation

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