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Coronavirus Pandemic

ACE2 and ANGII levels in patients with COVID-19 based on thoracic tomography findings and PCR test results

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Abstract

Introduction: Reverse transcriptase polymerase chain reaction tests and thoracic tomography have been widely employed in the diagnosis of the disease, but doubts about their sensitivity still persist. Also there are controversial results about ACE2 and AngII levels according to the severity of disease. In this study, we aimed to analyze the ACE2 and AngII levels in patients with suspected COVID-19 based on polymerase chain reaction test results and thoracic tomography findings and to examine their relationship with disease severity.

Methodology: Patients with suspected COVID-19 in the emergency department were divided into 4 groups according to thoracic tomography findings and PCR test results. The in-hospital mortality of patients was recorded. ACE2 and AngII levels in patients were analyzed according to groups and severity of the disease.

Results: ACE2 levels for the patients with suspected COVID-19 were significantly lower than in the control group, but AngII levels were higher (not statistically significant). The mean age and male sex ratio of patients who developed acute respiratory distress syndrome (ARDS) and died were significantly higher than those who survived. Whereas there was no difference in ACE2 levels in patients with severe diseases such as ARDS and mortality, their AngII levels were significantly lower.

Conclusions: It can be suggested that decreased ACE2 levels combined with increased AngII levels are determinative at disease onset and in the development of lung damage. However, decreased AngII levels are more determinative in patients with severe diseases such as ARDS and mortality.

Key words: Angiotensin-converting enzyme 2; angiotensin II; acute respiratory distress syndrome; COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which emerged in the Wuhan province of China in December 2019, and was declared as a pandemic by the World Health Organization in March 2020, has caused devastation worldwide [1,2]. Although the reverse transcriptase polymerase chain reaction (RT-PCR) test is routinely used in the diagnosis of the disease, doubts about its sensitivity persist [3,4]. Thoracic tomography has been widely employed in the diagnosis of the disease and examining pulmonary findings, especially during the early stages of the disease [5]. Patients with COVID-19 experience diverse symptoms from asymptomatic/mild to severe and even death. Pneumonia and acute respiratory distress syndrome (ARDS) are the most important findings related to the severity of the disease. The incidence of ARDS in patients was reported to be 15.6%–48%, whereas the intensive care admission rate was 26%–31.7% and the mortality rate was 7.5%–15% [6-10].

The renin angiotensin system (RAS) plays a crucial role in the onset and prognosis of the disease. RAS is composed of the classical and counter-regulatory (non-classical)/vasodilator pathways. The classical pathway is governed by angiotensin-converting enzyme (ACE), angiotensin II (AngII), and angiotensin type I receptors, causing vasoconstriction, cell proliferation, organ hypertrophy, sodium retention, and aldosterone release.

In contrast, the non-classical pathway that causes vasodilation, antiproliferation, anti-hypertrophy, and cardio and renoprotective effects, is governed by angiotensin-converting enzyme II (ACE2), angiotensin (1-7), and the mas-receptor [11]. ACE2 is a member of the membrane-bound carboxypeptidase hormone family and is found in the heart, kidney, small intestine, and lungs. It is released by the lungs from type 2 alveolar cells, macrophages, and tracheobronchial epithelial cells [12,13].

ACE2 has recently attracted attention owing to its role in severe ARDS induced by the severe acute respiratory syndrome coronaviruses (SARS-CoV and SARS-CoV-2) [14,15]. At present, it is established that transmembrane protease serine 2-mediated separation of the spike protein of homotrimeric SARS-CoV-2 and its S1/S2 subunit has a major role in the entry of the virus into the target cell [16]. The binding of SARS-CoV-2 to ACE2 and its entry into the cell are key steps in the initiation of the infection. This process causes a decrease in plasma membrane ACE2 level and an increase in the ACE/AngII/AT1 receptor axis, which is the other pathway of RAS, and thus the harmful effects of the disease are triggered [17].

In our study, we aimed to analyze the ACE2 and AngII levels in patients with suspected COVID-19 according to PCR test results and thoracic tomography findings and to examine the correlation between their expression level and the severity of the disease.

Methodology

Study Population and Design

We conducted prospective observational study of adult COVID-19 patients diagnosed, hospitalized and followed up at Istanbul University-Cerrahpasa Hospital between April 1 and June 1, 2020. All patients aged ≥ 18 years who presented to the emergency department and suspected to have COVID-19 were included in our study.

Data Collection

Nasopharyngeal swab samples of all included patients were processed for detection of SARS-CoV-2 virus by RT-PCR. Samples for total blood count, biochemical tests, and arterial blood gas were collected from the patients at admission. In addition, samples were taken for ACE2 and AngII tests and stored at -80 ^{o}C until the analysis. Patients' age, sex, admission complaints, vital signs, PCR test results, and tomography findings were recorded.

The patients were divided into 4 groups according to thoracic tomography findings and PCR test results, as follows: Group 1, or the control group, included patients with a negative PCR test results and normal thoracic tomography findings; Group 2 included patients with a negative PCR test results but with findings indicative of COVID-19 in thoracic tomography [PCR(-)CT(+)]; Group 3 included patients with a positive PCR test results but normal thoracic tomography [PCR(+)CT(-)]; and Group 4 was composed of patients with a positive PCR test results with findings suggestive of COVID-19 in thoracic tomography [PCR(+)CT(+)].

Patients were also divided into two groups according to the development of ARDS and in-hospital mortality. Berlin diagnostic criteria were used for the diagnosis of ARDS in patients.

Patients' ACE2 and AngII levels were analyzed according to tomography findings, PCR results, and severity of the disease.

Serum ACE2 and Angiotensin II Measurement

Human ACE II ELISA kit (Elabscience Biotechnology Inc, Catalog No: E-EL-H0281, Houston, Texas, USA) was used to measure ACE2 levels, which was based on the sandwich enzyme-linked immunosorbent assay (ELISA) method. This method was applied according to the manufacturer's recommendations. The within-study and between-study coefficient of variation (CV) levels were 10.4% and 11.5%, respectively. The results for ACE2 were provided in ng/mL. The detection range of the kit was 0.39–25 ng/mL, and its sensitivity was 0.23 ng/mL.

Human AngII ELISA kit (Elabscience Biotechnology Inc. Catalog No: E-EL-H0326, Houston, Texas, USA) was used to measure serum AngII levels, which was based on the competitive ELISA method. The method was applied according to the manufacturer's recommendations. Within-study and between-study CV were 10% and 95% for AngII, respectively. The values for AngII were provided in pg/mL. The detection range of the test kit was 31.25–2,000 pg/mL, and its sensitivity was 18.75 pg/mL.

Statistical Analysis

SPSS 20.0 software was used for statistical analyses. Frequency (n) and percentage (%) were employed for descriptive statistics. Mean ± standard deviation (SD) was used for numerical data, whereas median and minimum-maximum (min-max) values were used for the basic data elements. Kolmogorov-Smirnov test was used to analyze the normal distribution of data. Student's *t*-test was used for comparison of 2 independent groups that distributed

normally, one-way analysis of variance test for comparison of more than 2 groups, and Tukey's test for posthoc analysis. Mann–Whitney U test was used for comparison of 2 independent groups that did not comply with normal distribution, Kruskal-Wallis test for comparison of more than 2 groups, and Mann–Whitney U test for posthoc analysis. Chi-square test was used for comparison of categorical data. $p < 0.05$ was considered statistically significant.

Ethics approval

This study was approved by the Clinical Research Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine (dated 05/06/2020 and numbered 68359).

Results

Demographics and Clinical Characteristics of the Disease

A total of 243 patients, 18 of whom were grouped as control and 225 were grouped as patients, were included in the study, based on their thoracic tomography findings and PCR test results. The mean age of patients was 60.77 ± 14.90 years, and 52.7% of them were males. The mean age of the PCR(+)CT(-) patient group was found to be significantly lower than that of the others. The most common complaints at presentation were cough (65.3%), weakness (54.5%), and fever (47.9%); shortness of breath was significantly higher in the CT(+) patient groups. Further, respiratory rate (RR) was significantly higher, whereas oxygen saturation (SpO2) was significantly lower in the CT(+) patient groups. Mortality and ARDS observed were the highest in the PCR(+)CT(+) patient group, while mortality and ARDS was not observed in the PCR(+)CT(-) and control group patients (Table 1). While lung involvement was higher in elderly patients, the rate of PCR test positivity was higher in younger patients without lung involvement.

The mean age of the patients with ARDS was higher. Also, male sex ratio was significantly higher in patients with ARDS and patients who did not survive. Whereas the SpO2 levels were significantly lower in patients with ARDS and non-survived, the RR was significantly higher (Table 2). Lung involvement and accordingly ARDS development and mortality rate were found to be higher in older aged patients.

ACE2 and ANGII levels in Diagnosis and Course of the Disease

ACE2 and AngII levels in the control group were 118.49 ± 40.70 ng/mL and 514.30 ± 478.45 pg/mL, respectively. The PCR(+)CT(+) patients group had the lowest ACE2 (93.85 ± 29.95 ng/mL) and the highest AngII (621.86 ± 513.56 pg/ml) levels.

Table 1. Demographics, clinics, and laboratory parameters of patients.

	PCR(-)CT(-)	PCR(-)CT(+)	PCR(+)CT(-)	PCR(+)CT(+)	Total	*p*
	n = 18, 7.4%	n = 84, 34.7%	n = 11, 4.5%	n = 129, 53.3	n = 243	
Age, mean ± SD	59.00 ± 16.47	62.58 ± 13.37	44.55 ± 19.84	61.14 ± 14.53	60.77 ± 14.90	0.002*
Sex						
Male	9 (3.7%)	43 (17.8%)	4 (1.7%)	71 (29.3%)	128 (52.7%)	0.674
Female	9 (3.7%)	41 (16.9%)	7 (2.9%)	58 (24%)	115 (47.3%)	
Admission complaint, n (%)						
Fever	10 (4.1%)	37 (15.3%)	4 (1.7%)	65 (26.9%)	116 (47.9%)	0.620
Weakness	11 (4.5%)	50 (20.7%)	4 (1.7%)	67 (27.7%)	132 (54.5%)	0.402
Cough	11 (4.5%)	52 (21.5%)	6 (2.5%)	89 (36.8%)	158 (65.3%)	0.593
Dispnea	2 (0.8%)	31 (12.8%)	5 (2.1%)	66 (27.3%)	105 (43%)	0.026*
Myalgia	7 (2.9%)	29 (12%)	5 (2.1%)	66 (27.3%)	107 (44%)	0.115
Vital Signs, Median (min–max)						
Fever	36.7 (36–38.5)	37 (35.7–40)	36.3 (36–37.7)	37 (35.4–39.1)	37 (35.4–40)	0.070
RR	22 (18–28)	24 (18–40)	22 (16–30)	24 (18–40)	24 (16–40)	0.041*
SBP, mmHg	120 (90–150)	126 (80–200)	110 (87–132)	125 (75–180)	120 (75–200)	0.060
DBP, mmHg	76 (44–110)	80 (45–103)	70 (58–90)	75 (50–120)	76 (44–120)	0.444
SpO2	97 (90–98)	95 (83–99)	97 (88–99)	94 (78–99)	95 (78–99)	0.003*
Laboratory parameters, mean ± SD						
WBC, $10^3/\mu L$	8.70 ± 3.37	7.61 ± 3.64	5.90 ± 2.11	6.97 ± 3.40	7.27 ± 3.47	0.020*
Lymph, $10^3/\mu L$	1.79 ± 0.79	1.42 ± 0.84	1.70 ± 0.94	1.32 ± 0.75	1.41 ± 0.80	0.041*
CRP, mg/L	46.09 ± 55.71	63.51±66.71	32.78 ± 83.07	62.50 ± 67.07	60.28 ± 66.82	0.006*
Ferritin, ng/ml	203.97 ± 225.07	411.45 ± 485.18	164.45 ± 168.84	412.28 ± 435.56	385.20±437.80	0.010*
D-dimer, mg/L	2.90 ± 4.54	3.29 ± 7.90	0.75 ± 0.69	2.28 ± 7.26	2.61 ± 7.15	0.292
Outcome, n (%)						
ARDS	-	12 (27.9%)	-	31 (72.1%)	43 (17.8)	0.015*
Mortality	-	6 (22.2%)	-	21 (77.8%)	27 (11.2%)	0.038*

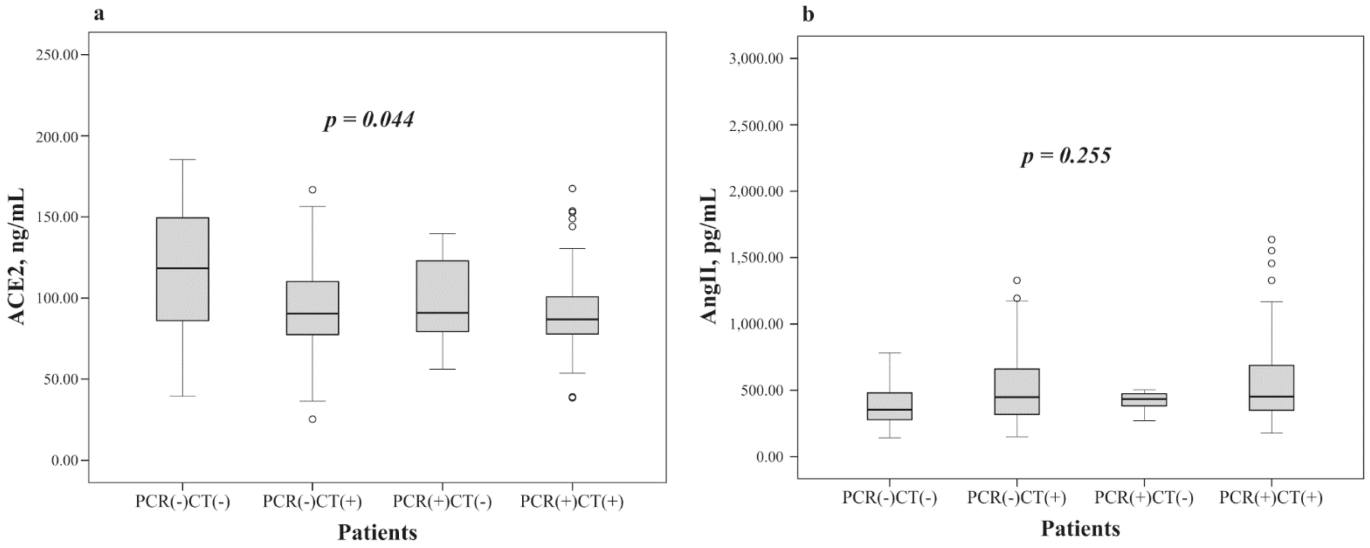
ARDS: acute respiratory distress syndrome; SD: standart deviation; RR: respiratory rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SpO2: oxygen saturation; WBC: white blood cells; Lymph: lymphocyte count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; *: $p < 0.05$.

Table 2. Comparison of patients data according to the disease course.

	ARDS			Mortality		
	Yes n = 43 (19.2%)	**No n = 181 (80.8%)**	***p***	**Yes n = 27 (12.1%)**	**No n= 197 (87.9%)**	***p***
Age	69.51 ± 11.06	58.81 ± 14.88	< 0.001*	70.15 ± 9.58	59.59 ± 14.97	< 0.001*
Sex						
Male	30 (69.8%)	88 (48.6%)	0.020*	19 (70.4%)	99 (50.3%)	0.046*
Female	13 (30.2%)	93(51.4%)		8 (29.6%)	98(49.7%)	
Vital Signs						
RR	26 (18–40)	22 (16–40)	< 0.001*	28 (18–40)	22 (16–40)	< 0.001*
SBP, mmHg	136 (75–180)	120 (80–200)	0.080	130 (75–180)	120 (80–200)	0.473
DBP, mmHg	70 (45–100)	77 (50–120)	0.368	70 (45–100)	76 (44–120)	0.160
SpO2	89 (78–95)	95 (84–99)	< 0.001*	87 (78–95)	95 (84–99)	< 0.001*
Laboratory Parameters, mean ± SD						
WBC, $10^3/\mu L$	7.60 ± 3.79	7.05 ± 3.64	0.196	7.96 ± 4.24	7.04 ± 3.34	0.156
Lymph, $10^3/\mu L$	0.91 ± 0.61	1.49 ± 0.80	< 0.001*	0.83 ± 0.71	1.45 ± 0.78	< 0.001*
AST, IU/L	70.16 ± 86.68	33.06 ± 29.02	< 0.001*	79.64 ± 105.41	34.78 ± 30.16	< 0.001*
ALT, IU/L	39.03 ± 47.86	30.06 ± 32.66	0.593	45.28 ± 54.87	29.93 ± 32.51	0.139
Urea, mg/dL	46,97±18,79	33,65±16.12	< 0.001*	48,37±19.90	34.54±16.44	0.006*
Creatinine, mg/dL	1.09 ± 0.35	0.93 ± 0.30	0.002*	1.12 ± 0.36	0.94 ± 0.30	0.018*
CRP, mg/L	103.48 ± 75.49	51.43 ± 61.92	< 0.001*	112.01 ± 73.89	54.48 ± 64.01	< 0.001*
Ferritin, ng/mL	804.01 ± 618.31	303.77 ± 333.29	< 0.001*	751.54 ± 611.37	351.59 ± 399.17	< 0.001*
D-dimer, mg/L	5.44 ± 12.34	1.90 ± 5.38	< 0.001*	6.58 ± 15.08	2.03 ± 5.26	< 0.001*

ARDS: acute respiratory distress syndrome; SD: standard deviation; RR: respiratory rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SpO2: oxygen saturation; WBC: white blood cells; Lymph: lymphocyte count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; *: $p < 0.05$.

Figure 1. a: Mean ACE2 levels in patients with PCR(-)CT(-), PCR(-)CT(+), PCR(+)CT(-), and PCR(+)CT(+) were 118.49 ± 39.94 ng/mL, 94.01 ± 27.28 ng/mL, 99.38 ± 27.08 ng/mL, and 93.85 ± 29.95 ng/mL, respectively. **b:** Mean AngII levels in patients with PCR(-)CT(-), PCR(-)CT(+), PCR(+)CT(-), and PCR(+)CT(+) were 514.30 ± 465.30 pg/mL, 566.94 ± 445.69 pg/mL, 530.63 ± 339.78 pg/mL, and 621.86 ± 513.56 pg/mL, respectively.

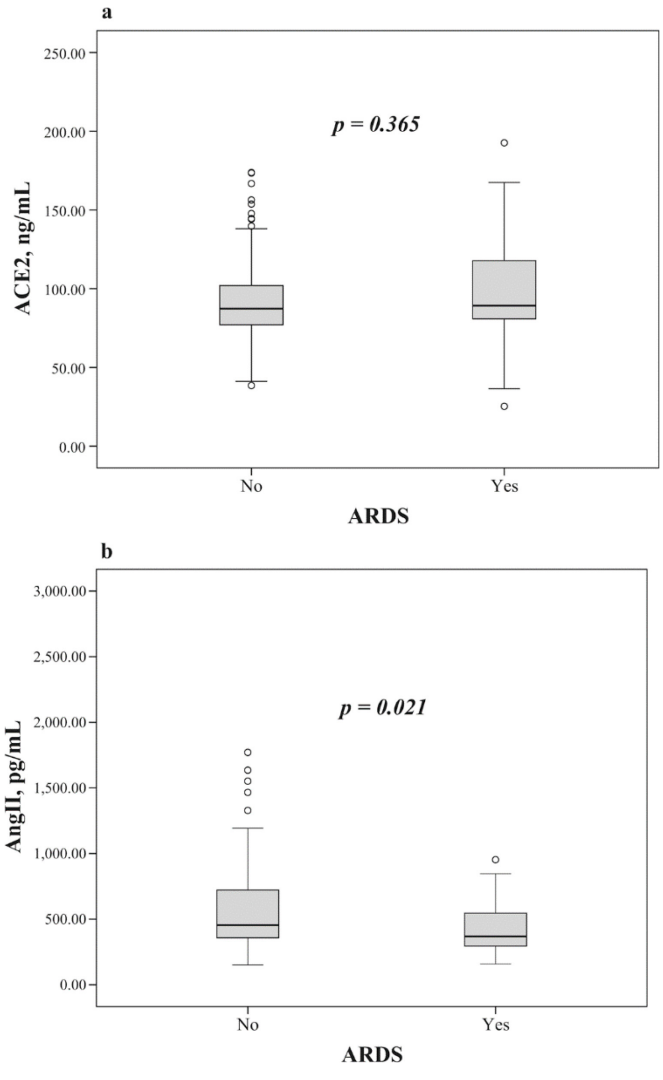


Low ACE2 levels were significant ($p = 0.044$), but higher AngII levels were not significant ($p = 0.244$) in patient groups (Figure 1). Low ACE2 levels in patients with CT positive may provide important information about the lung involvement of the disease.

ACE2 levels of patients with ARDS was higher, but was not significant. However, AngII levels of patients with ARDS were significantly lower than those without ARDS (Figure 2). Low AngII levels in patients who develop ARDS may be due to factors such as protein degradation or multi-organ involvement in these patients.

ACE2 levels in non-survived patients were higher, but were not significant. However, AngII levels in non-survived patients were significantly lower than in patients who survived (Figure 3).

Figure 2. a: Mean ACE2 levels of patients with and without ARDS were 97.74 ± 33.93 ng/mL and 95.60 ± 29.55 ng/mL. **b:** Mean AngII levels of patients with and without ARDS were 467.21 ± 278.24 pg/mL and 617.18 ± 509.03 pg/mL.

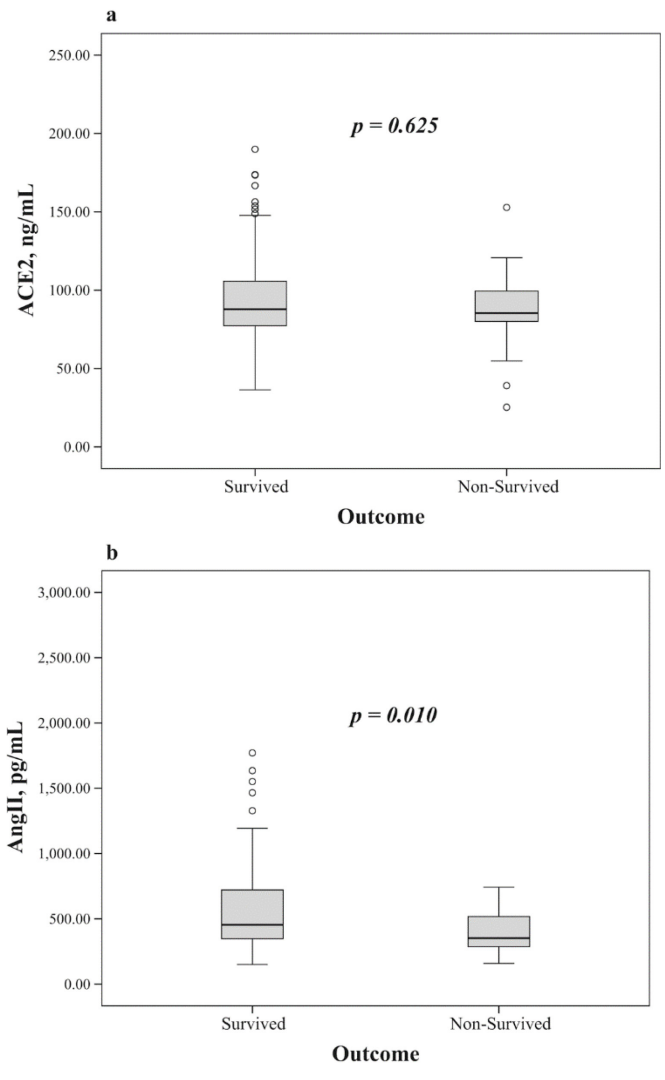


Discussion

In our study, ACE2 levels were significantly lower and AngII levels were higher, although not significant, in patients with findings consistent of COVID-19 in thoracic tomography and/or patients with a positive PCR test when compared with the control group. Whereas there was no significant difference in ACE2 levels of patients who developed ARDS and died, their AngII levels were significantly lower.

The binding of SARS-CoV-2 virus to ACE2 receptors in the airway epithelium and its entry into the cell is the most important step in the onset of COVID-19, lung damage, and the spread of the infection in the body [16,18,19]. Although it has been suggested that a decreased ACE2 level, impaired RAS functioning, and

Figure 3. a: Mean ACE2 levels of patients who non survived and survived were 92.63 ± 34.98 ng/mL and 96.42 ± 29.71 ng/mL. **b:** Mean AngII levels of patients who non survived and survived were 432.08 ± 251.81 pg/mL and 611.29 ± 498.14 pg/mL.



an increased AngII level in patients with COVID-19 are associated with respiratory failure symptoms, lung damage, and virus load, conflicting results have been obtained in previous studies [20-24]. In studies by Liu Y *et al*. involving 12 patients and by Wu Z *et al.* involving 82 patients, higher plasma AngII levels were found in patients infected with SARS-CoV-2 when compared to the control group. In addition, a relationship between AngII levels and viral load and lung damage was found in these patients [20,21]. In contrast, in a study by Henry BM *et al.* on 30 patients, which was presented as a preliminary report, there was no difference between AngII levels of patients with COVID-19 and that of the control group. Moreover, there was no difference between AngII levels of patients with and without ICU admission [22]. In a study by Rieder M *et al.* on 24 patients the difference was not significant when compared with the control group values, although ACE2 levels were lower and the AngII levels were higher in the patients with COVID-19 [23]. Kintscher *et al.* did not find any difference in the AngII/AngI ratio [24]. Consistent with the aforementioned differences, ACE2 levels were lower in patients with positive PCR tests and/or findings suggestive of COVID-19 in thoracic tomography in our study, supporting that the SARS-CoV-2 virus binds to ACE2 receptors. However, the values of the PCR(+)CT(+) and PCR(-)CT(+) patient groups were significantly lower than levels of the others showing that ACE2 also plays an important role in lung damage. Furthermore, in PCR(+) patients and/or patients with findings consistent with COVID-19 in thoracic tomography, AngII levels were not significantly higher, indicating that AngII is not a strong marker as ACE2 in the early stages of the disease.

ARDS, a destructive inflammatory lung disease causing hypoxia, decreased lung compliance, multiple organ failure, and high mortality is the most important cause of mortality in SARS-CoV and SARS-CoV-2 infections. The condition is pathologically characterized by diffuse alveolar damage, increased alveolar-capillary permeability, pulmonary endothelial dysfunction, and epithelial damage and increased cytokine and interleukin release [25-27]. In experimental studies in which ARDS was induced with viruses, liposaccharides, and endotoxins, it was found that acute lung injury and ARDS were more severe in cases of reduced ACE2 release and ACE2 deficiency [26,28-30]. Even recombinant human ACE2, rhACE2, have been reported to be beneficial [31]. AngII level reportedly increases due to the hike in ACE activity in some studies and decrease in ACE2 in some others, and this is associated with poor prognosis [26,29-30]. Studies have documented that ACE insertion/deletion polymorphism might be associated with ARDS severity [32]. Researchers have identified that endothelial damage in sepsis, vasodilator shock, and ARDS causes decreases in ACE activity and its capacity of converting AngI to AngII, and an increase in the AngI/AngII ratio. Nevertheless, lower AngII levels are related to increased mortality [33-37]. AngII was approved by the American Food and Drug Administration in 2017 for vasodilator shock therapy and was considered effective in treating vasodilator shock and reducing the duration of renal replacement therapy in patients in the ATHOS-3 study [38]. It has been reported in the treatment of vasodilator shock in patients with COVID-19 that the target mean arterial pressure was achieved faster and oxygenation was improved [39-41]. In our study, whereas there was no significant difference in the ACE2 levels in patients with severe disease including ARDS and mortality, AngII levels were found to be significantly lower in these patients. ACE1 and ACE2 are cell-associated enzymes released from the lung endothelial and epithelial cells. Also, cell-associated ACE has a significantly higher catalytic activity than ACE in circulation [42]. In patients with ARDS, the endothelial dysfunction and epithelial damage were higher in the lung, resulting in affected the ACE1 and ACE2 level. A decrease in ACE1 level with ACE2 level can lead to decrease in AngII level. Also, measuring angiotensin II levels is difficult because of the protein degradation. However, sampling time and strategy, measuring technique, and use of ELISA kits may be a contributing factor for different AngII levels in literature. All of these reasons may have been a confronting factor of our results in patient with ARDS and non-survivors. We suggest that multi-organ involvement and effect of ACE release in patients with a severe prognosis of the disease are responsible for the decrease in AngII levels.

There are several limitations in our study. The most important is that ACE and AngI enzyme values, which are key parameters of the RAS system, were not measured. Other limitations include the fact that medications and comorbidities were not specified in detail and that the time elapsed since the onset of the disease could not be fully determined, as well as the limited number of patients due to limited funding, and the fact that it was a single-center study.

Conclusions

Based on the findings, we suggest that decreased ACE2 levels at the onset of the disease and in the

development of lung damage are more effective when compared to increasing AngII levels. However, decreased AngII levels are more determinative in patients with severe disease, including ARDS and mortality. Therefore, further studies, in which all factors in the RAS mechanism are collectively evaluated, are required to fully understand the mechanisms related to COVID-19 and its severity.

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Authors' Contributions

Conception: all authors; design: all authors; supervision: AI, AK, SO, FC, SB, IMB, II, DK; fundings: all authors; Materials: AI, SU, SB, IMB, AK, YSA; data collection and/or processing: AI, SO, FC, DK, II, IMB, YSA; analysis and/or interpretation: AI, FC, SO, YSA, SB, DK, IMB, II, AK, SU; literature review: AI, SU, SB, DK; writing: AI, SO, IMB, AK, II, FC; critical review: all authors

References

1. Johns Hopkins University and Medicine (2021) COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE). Available: https://coronavirus.jhu.edu/map.html. Accessed 25 January 2021.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W (2020) China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 382: 727-733.
3. Cassaniti I, Novazzi F, Giardina F, Salinaro F, Sachs M, Perlini S, Bruno R, Mojoli F, Baldanti F (2020) Members of the San Matteo Pavia COVID-19 Task Force. Performance of VivaDiag COVID-19 IgM/IgG rapid test is inadequate for diagnosis of COVID-19 in acute patients referring to emergency room department. J Med Virol 92: 1724-1727.
4. Liu R, Han H, Liu F, Lv Z, Wu K, Liu Y, Feng Y, Zhu C (2020) Positive rate of RT-PCR detection of SARSCoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clin Chim Acta 505: 172-175.
5. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, Tao Q, Sun Z, Xia L (2020) Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 296: E32-E40.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506.
7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395: 507-513.
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323: 1061-1069.
9. Dreher M, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, Daher A, Stöhr R, Kleines M, Lemmen SW, Brokmann JC, Müller T, Müller-Wieland D, Marx G, Marx N (2020) The characteristics of 50 hospitalized COVID-19 patients with and without ARDS. Dtsch Arztebl Int 117: 271-278.
10. Immovilli P, Morelli N, Antonucci E, Radaelli G, Barbera M, Guidetti D (2020) COVID-19 mortality and ICU admission: the Italian experience. Crit Care 24: 228.
11. Nunes-Silva A, Rocha GC, Magalhaes DM, Vaz LN, Salviano de Faria MH, Simoes E Silva AC (2017) Physical exercise and ACE2-Angiotensin-(1-7)-mas receptor axis of the renin angiotensin system. Protein Pept Lett 24: 809-816.
12. Turner AJ, Hiscox JA, Hooper NM (2004) ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci 25: 291-294.
13. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 203: 631-637.
14. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q (2020) Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 367: 1444-1448.
15. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426: 450-454.
16. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181: 271-280.
17. Verdecchia P, Cavallini C, Spanevello A, Angeli F (2020) The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 76: 14-20.
18. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, Alvarado-Arnez LE, Bonilla-Aldana DK, Franco-Paredes C, Henao-Martinez AF, Paniz-Mondolfi A, Lagos-Grisales GJ, Ramírez-Vallejo E, Suárez JA, Zambrano LI, Villamil-Gómez WE, Balbin-Ramon GJ, Rabaan AA, Harapan H, Dhama K, Nishiura H, Kataoka H, Ahmad T, Sah R (2020) Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 34: 101623.
19. Costa LB, Perez LG, Palmeira VA, Macedo E Cordeiro T, Ribeiro VT, Lanza K, Simões E Silva AC (2020) Insights on SARS-CoV-2 molecular interactions with the renin-angiotensin system. Front Cell Dev Biol 8: 559841.

20. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L (2020) Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 63: 364-374.
21. Wu Z, Hu R, Zhang C, Ren W, Yu A, Zhou X (2020) Elevation of plasma angiotensin II level is a potential pathogenesis for the critically ill COVID-19 patients. Crit Care 24: 290.
22. Henry BM, Benoit S, Lippi G, Benoit J (2020) Letter to the Editor - Circulating plasma levels of angiotensin II and aldosterone in patients with coronavirus disease 2019 (COVID-19): a preliminary report. Prog Cardiovasc Dis 63: 702-703.
23. Rieder M, Wirth L, Pollmeier L, Jeserich M, Goller I, Baldus N, Schmid B, Busch HJ, Hofmann M, Kern W, Bode C, Duerschmied D, Lother A (2021) Serum ACE2, angiotensin II, and aldosterone levels are unchanged in patients with COVID-19. Am J Hypertens 34: 278-281.
24. Kintscher U, Slagman A, Domenig O, Röhle R, Konietschke F, Poglitsch M, Möckel M (2020) Plasma angiotensin peptide profiling and ACE (Angiotensin-Converting Enzyme)-2 activity in COVID-19 patients treated with pharmacological blockers of the renin-angiotensin system. Hypertension 76: e34-e36.
25. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342: 1334-349.
26. Wösten-van Asperen RM, Lutter R, Specht PA, Moll GN, van Woensel JB, van der Loos CM, van Goor H, Kamilic J, Florquin S, Bos AP (2011) Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. J Pathol 225: 618-627.
27. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 180: 934-943.
28. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436: 112-116.
29. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 11: 875-879.
30. Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, Ju X, Liang Z, Liu Q, Zhao Y, Guo F, Bai T, Han Z, Zhu J, Zhou H, Huang F, Li C, Lu H, Li N, Li D, Jin N, Penninger JM, Jiang C (2014) Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun 5: 3594.
31. Treml B, Neu N, Kleinsasser A, Gritsch C, Finsterwalder T, Geiger R, Schuster M, Janzek E, Loibner H, Penninger J, Loeckinger A (2010) Recombinant angiotensin-converting enzyme 2 improves pulmonary blood flow and oxygenation in lipopolysaccharide-induced lung injury in piglets. Crit Care Med 38: 596-601.
32. Marshall RP, Webb S, Bellingan GJ, Montgomery HE, Chaudhari B, McAnulty RJ, Humphries SE, Hill MR, Laurent GJ (2002) Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 166: 646-650.
33. Zhang W, Chen X, Huang L, Lu N, Zhou L, Wu G, Chen Y (2014) Severe sepsis: low expression of the renin-angiotensin system is associated with poor prognosis. Exp Ther Med 7: 1342-1348.
34. Rice CL, Kohler JP, Casey L, Szidon JP, Daise M, Moss GS (1983) Angiotensin-converting enzyme (ACE) in sepsis. Circ Shock 11: 59-63.
35. Orfanos SE, Armaganidis A, Glynos C, Psevdi E, Kaltsas P, Sarafidou P, Catravas JD, Dafni UG, Langleben D, Roussos C (2000) Pulmonary capillary endothelium-bound angiotensin-converting enzyme activity in acute lung injury. Circulation 102: 2011-2018.
36. Chawla LS, Busse LW, Brasha-Mitchell E, Alotaibi Z (2016) The use of angiotensin II in distributive shock. Crit Care 20: 137.
37. Bellomo R, Wunderink RG, Szerlip H, English SW, Busse LW, Deane AM, Khanna AK, McCurdy MT, Ostermann M, Young PJ, Handisides DR, Chawla LS, Tidmarsh GF, Albertson TE (2020) Angiotensin I and angiotensin II concentrations and their ratio in catecholamine-resistant vasodilatory shock. Crit Care 24: 43.
38. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT, Boldt DW, Chock S, Young PJ, Krell K, Wunderink RG, Ostermann M, Murugan R, Gong MN, Panwar R, Hästbacka J, Favory R, Venkatesh B, Thompson BT, Bellomo R, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Deane AM (2017) Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 377: 419-430.
39. Chow JH, Mazzeffi MA, McCurdy MT (2020) Angiotensin II for the treatment of COVID-19-related vasodilatory shock. Anesth Analg 131: 102-105.
40. Zangrillo A, Landoni G, Beretta L, Morselli F, Neto AS, Bellomo R (2020) COVID-BioB Study Group. Angiotensin II infusion in COVID-19-associated vasodilatory shock: a case series. Crit Care 24: 227.
41. Ofosu-Barko K, Liu Y, Alkhatib Tamimi F, Al Husami W, Ganatra S, Resnic F, Shah SP (2021) Angiotensin II administration in patients with COVID-19 shock. Crit Pathw Cardiol 20: 100-102.
42. Flores-Munoz M, Work LM, Douglas K, Denby L, Dominiczak AF, Graham D, Nicklin SA (2012) Angiotensin-(1-9) attenuates cardiac fibrosis in the stroke-prone spontaneously hypertensive rat via the angiotensin type 2 receptor. Hypertension 59: 300–307.

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