Soluble ACE2 as a Risk or Prognostic Factor in COVID-19 Patients: A Cross-sectional Study

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel severe acute respiratory syndrome coronavirus. The first known receptor for this virus in the human body is angiotensin-converting enzyme 2 (ACE2), the same receptor for the SARS virus.

Methods: A total of 38 hospitalized adult (18 years) patients with laboratory or clinically confirmed coronavirus disease 2019 (COVID-19) were identified in the infectious disease ward of Tehran Imam Khomeini hospital complex in this single-center cross-sectional study. A blood sample was taken at the time of hospitalization and a second one was taken 48 hours later. Blood samples are kept frozen at -80 degrees Celsius. After the complete collection of samples, the ACE2 level of the samples was measured using a serum sACE2 detection ELISA kit. The data were analyzed using SPSS v26. P value of 0.05 was considered statistically significant. An analysis of covariance was performed to examine the mean differences in day 7 serum ACE2 concentration among the 2 groups after adjusting for the baseline serum ACE2 concentration. The 1-way multivariate analysis of variance was used to determine whether there were any differences between independent groups (mechanical ventilation yes/no) on serum ACE2 levels at 3 different times.

Results: The mean age of patients was 64.13 ± 16.49 years, 21 patients (55.3%) were men, 16 patients (42%) were polymerase chain reaction test positive, and 15 patients (39.5%) died. A total of 35 individuals (92.1%) had chest computed tomography images that indicated lung involvement. A comparison of the 2 groups of patients who died and were discharged revealed that serum ACE2 at the first (p=0.033) and third (7th day) measurements were statistically different (p=0.026). Patients had a mean of serum ACE2. The results indicated that the day 7 serum ACE2 concentration did significantly differ between the 2 groups after controlling for the baseline serum ACE2 concentration (p=0.023). The model explained about 73.61% of the variance in the 7-day serum ACE2 concentration. Specifically, after adjusting for the baseline concentration, survived patients had the lowest level of serum ACE2 concentration (1 ± 0.65) on the 7th day compared with the deceased patient group (2.83 ± 1.12).

Conclusion: Soluble ACE2 in the serum of COVID-19 patients who died, later on, was significantly higher than the discharged patients when the samples were taken seven days after admission. It is suggested that serum soluble ACE2 level could be used as a prognostic factor for COVID-19 patients’ outcomes and also their need for mechanical ventilation.

Keywords: SARS-CoV-2, Angiotensin-converting enzyme 2, Polymerase chain reaction, Mechanical ventilation, Prognosis, Mortality

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What is “already known” in this topic:
- There have been numerous suggestions for therapeutic options regarding the new coronavirus, among which a significant number are based on the interaction between ACE2 and the viral spike protein.
- For instance, hydroxychloroquine alters a portion of the ACE2 molecule and prevents the binding of spike protein from the virus.
- Blocking the ACE2 receptor and using soluble ACE2 to bind to and neutralize the viral spike protein are further examples of how the mentioned interaction could lead to therapeutic strategies.

What this article adds:
- Although serum soluble ACE 2 on day 7 of patient admission can be a prognostic factor, its levels on the first and third days of patient admission are not significantly different in patients.
- An increase in serum soluble ACE-2 on days 3 and 7 after hospitalization (compared with the first day) can be a predictor of the need for mechanical ventilation.
Soluble ACE2 as a Risk or Prognostic Factor in COVID-19 Patients

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, the causative agent of the coronavirus disease 2019 (COVID-19) pandemic, is now a global problem and has infected more than 180 countries, including Iran. The only known receptor for this virus in the human body is angiotensin-converting enzyme 2 (ACE2), the same known receptor for the SARS virus (1). The spike protein of SARS-CoV-2 tends to bind to the ACE2 receptor, expressed on the surface of human cells, facilitating its entry and thus replication (2). Since the ACE2 gene is most abundantly expressed in the heart, lung, and kidney tissues (3), many of the symptoms and problems of patients with COVID-19 are related to the interaction of the virus with the ACE2 protein in the same sites, including cardiovascular and pulmonary complications (4). There have been numerous suggestions for therapeutic options regarding the new coronavirus, among which a significant number are based on the interaction between ACE2 and the viral spike protein. For instance, hydroxychloroquine, one of the first approved medications for COVID-19, alters a portion of the ACE2 molecule and prevents the binding of the spike protein of the virus (5). Blocking the ACE2 receptor and using soluble ACE2 (sACE2) to bind to and neutralize the viral spike protein (4) are further examples of how the mentioned interaction could lead to therapeutical strategies. Additionally, alterations in ACE2 expression brought on by heart disease (6), kidney disease (7), diabetes (8), and an aging population (9) may also contribute to the greater susceptibility of these patient populations to SARS-CoV-2.

Despite the absence of the anchored portion of the ACE2 molecule, soluble ACE2 contains the same functional domain as ACE2 receptors that bind to the spike protein of SARS-CoV-2 (10, 11). This enables the soluble ACE2 molecules to circulate in the bloodstream, while simultaneously neutralizing the virus particles, inhibiting them from entering host cells. Also, with the soluble ACE2 being derived from ACE2 receptors in the body (10), measuring the serum soluble ACE2 would give us a clue about the quantity of ACE2 receptors expressed in different tissues.

With this background in mind, we aimed to monitor the level of soluble ACE2 in recently diagnosed COVID-19 patients.

Measurement of serum soluble ACE2 in this study is performed using the sACE2 ELISA kit. By comparing serum ACE2 levels in newly admitted patients with sACE2 levels within 48 hours of the same patients, the role of sACE2 levels in determining the prognosis of COVID-19 patients could be valued. Therefore, this study aimed to use serum ACE2 levels to determine the prognosis of patients with COVID-19.

Methods

In this single-center cross-sectional study, 38 hospitalized adult (≥18 years) patients with laboratory-confirmed COVID-19 were identified in the infectious disease ward in Imam Khomeini hospital. Sampling was performed from June to December 2020. Eligible patients were included in the study and observed until discharge or death. No costs were imposed on patients, and all laboratory costs were paid by the researchers. Inclusion criteria were as follows: patients aged 18 to 75 years old without organ failure and nonintubation. Exclusion criteria were as follows: critically ill patients, end-stage cancer patients, and patients treated in other clinical trial studies. This study has also been approved by the ethics committee of Tehran University of Medical Sciences (ethic code: 99/11/101/16529). When the patient was admitted to the hospital, one blood sample was obtained, and a second one was taken 48 hours later. Blood samples are frozen at -80 °C. After complete collection of samples, the ACE2 level of the samples was measured using the serum sACE2 detection ELISA kit (Human Angiotensin Converting Enzyme 2 [ACE2] ELISA Kit-Bioassay Technology Laboratory-SHANGH KI KORAIN BIOTECH CO, LTD.)

All serum sACE2 and other lab tests were collected 24, 72 hours, and 7 days after patients' hospitalization.

Data Analysis

The data were analyzed using SPSS 26 (IBM Corp). Descriptive statistical analysis was used to describe items included in the survey. Data were expressed as medians (interquartile ranges [IQRs]) for continuous variables. For bivariate analysis, the Mann–Whitney U test or the t test was used for continuous variables, and the 2 or the Fisher exact test for categorical variables. A P value of 0.05 was considered statistically significant when a 2-tailed test was performed. The Kolmogorov-Smirnove test was used to evaluate the normal distribution of the data. An analysis of covariance (ANCOVA) was performed to examine the mean differences in day 7 serum ACE2 concentration among the 2 groups after adjusting for the baseline serum ACE2 concentration. The 1-way multivariate analysis of variance (1-way MANOVA) was used to determine whether there were any differences between independent groups (mechanical ventilation yes/no) on serum ACE2 levels at 3 different times.

Results

The mean age of the patients was 64.13 ± 16.49 years, 21 patients (55.3%) were men, 16 patients (42%) were polymerase chain reaction test positive, and 15 patients (39.5%) died. The most common presenting symptoms were dyspnea (66.7%), fever (33.3%), cough (26.7%), myalgias (20%), and nausea/vomiting (16.7%). During hospitalization, 13.2% of patients (3 women and 2 men) needed mechanical ventilation. In addition, lung involvement was visible in 35 patients' chest computed tomography scans (92.1%). Underlying diseases and organ failure are listed in Tables 1 and 2.

A comparison between the 2 groups of patients who died and were discharged showed that serum ACE2 at first
(p=0.033) and third measurement (7th day) was statistically different (p=0.026). Compared to patients who died, survivors exhibited higher mean serum ACE2 levels (Table 3).

An ANCOVA was performed to examine the mean differences in day 7 serum ACE2 concentration among the 2 groups after adjusting for the baseline serum ACE2 concentration. The results indicated that the day 7 serum ACE2 concentration did significantly differ among the 2 groups after controlling for the baseline serum ACE2 concentration (p=0.023). The model explained about 73.61% of the variance in the day 7 serum ACE2 concentration. Specifically, after adjusting for the baseline concentration, survived patients had the lowest level of serum ACE2 concentration (1 ± 0.65) on the 7th day compared with the deceased patient group (2.83 ± 1.12) (Figs. 1 & 2).

According to a patient’s demand for mechanical ventilation, the results of the MANOVA test (Table 4) revealed a statistically significant difference in soluble serum ACE2 (p=0.029; Wilk’s Λ =0.49; partial η² =0.50). After adjusting for baseline concentration, patients who required mechanical breathing had greater serum ACE2 levels on the second and third measurement days.

### Table 1. Comorbidities and organ failures

| Comorbidity | N (%) |
|-------------|-------|
| Diabetes mellitus | 11 (28.9) |
| Ischemic heart disease | 8 (21.1) |
| Hypertension | 10 (26.3) |
| Hypothyroidism | 3 (7.9) |
| End-stage renal disease/ chronic kidney disease | 3 (7.9) |
| Heart Failure | 3 (7.9) |
| Cerebrovascular accident | 3 (7.9) |
| Asthma | 2 (5.3) |
| Thalassemia | 2 (5.3) |
| HIV/AIDS | 1 (2.6) |
| HCV | 1 (2.6) |
| Cirrhosis | 1 (2.6) |
| Acute Kidney Injury | 3 (7.9) |
| Acute respiratory distress syndrome | 12 (31.6) |
| Liver failure | 4 (10.5) |

| Organ failures | N (%) |
|----------------|-------|

### Table 2. Categorical variables according to patients’ outcome

| Variable | Outcome | N | % | N | % |
|----------|---------|---|---|---|---|
| Sex | | | | | |
| Male | | 9 | 42.9 | 12 | 57.1 |
| Female | | 6 | 35.3 | 11 | 64.7 |
| PCR | | | | | |
| Negative | | 10 | 45.5 | 12 | 54.5 |
| Positive | | 5 | 31.3 | 11 | 68.8 |
| Chest CT scan involvement | | | | | |
| No | | 0 | 0.0 | 3 | 100.0 |
| Yes | | 15 | 42.9 | 20 | 57.1 |
| Diabetes | | | | | |
| No | | 11 | 40.7 | 16 | 59.3 |
| Yes | | 4 | 36.4 | 7 | 63.6 |
| Ischemic heart disease | | | | | |
| No | | 12 | 40.0 | 18 | 60.0 |
| Yes | | 3 | 37.5 | 5 | 62.5 |
| Hypertension | | | | | |
| No | | 11 | 39.3 | 17 | 60.7 |
| Yes | | 4 | 40.0 | 6 | 60.0 |
| Hypothyroidism | | | | | |
| No | | 13 | 37.1 | 22 | 62.9 |
| Yes | | 2 | 66.7 | 1 | 33.3 |
| ESRD_CKD | | | | | |
| No | | 13 | 37.1 | 22 | 62.9 |
| Yes | | 2 | 66.7 | 1 | 33.3 |
| Heart failure | | | | | |
| No | | 13 | 37.1 | 22 | 62.9 |
| Yes | | 2 | 66.7 | 1 | 33.3 |
| Asthma | | | | | |
| No | | 15 | 41.7 | 21 | 58.3 |
| Yes | | 0 | 0.0 | 2 | 100.0 |
| CVA | | | | | |
| No | | 13 | 37.1 | 22 | 62.9 |
| Yes | | 2 | 66.7 | 1 | 33.3 |
| Thalassemia | | | | | |
| No | | 15 | 41.7 | 21 | 58.3 |
| Yes | | 0 | 0.0 | 2 | 100.0 |
| HIV_AIDS | | | | | |
| No | | 15 | 40.5 | 22 | 59.5 |
| Yes | | 0 | 0.0 | 1 | 100.0 |
| HCV | | | | | |
| No | | 14 | 38.9 | 22 | 61.1 |
| Yes | | 1 | 50.0 | 1 | 50.0 |
| Cirrhosis | | | | | |
| No | | 15 | 40.5 | 22 | 59.5 |
| Yes | | 0 | 0.0 | 1 | 100.0 |
| Fever | | | | | |
| No | | 10 | 50.0 | 10 | 50.0 |
| Yes | | 2 | 20.0 | 8 | 80.0 |
| Cough | | | | | |
| No | | 11 | 50.0 | 11 | 50.0 |
| Yes | | 1 | 12.5 | 7 | 87.5 |
| Myalgia | | | | | |
| No | | 12 | 50.0 | 12 | 50.0 |
| Yes | | 0 | 0.0 | 6 | 100.0 |
| Dyspnea | | | | | |
| No | | 3 | 30.0 | 7 | 70.0 |
| Yes | | 9 | 45.0 | 11 | 55.0 |
| Headache | | | | | |
| No | | 12 | 40.0 | 18 | 60.0 |
| Yes | | 0 | 0.0 | 0 | 0.0 |
| Nausea and vomiting | | | | | |
| No | | 11 | 44.0 | 14 | 56.0 |
| Yes | | 1 | 20.0 | 4 | 80.0 |
The results of cross-tabulation (Tables 5 & 6) indicated that diabetic patients are more likely to develop AKI. A history of hypothyroidism significantly increases the odds of liver failure, need for mechanical ventilation, and ARDS. History of kidney diseases (ESRD/CKD) also significantly increased the odds of developing AKI and the
need for mechanical ventilation.

Among the 3 detected organ failures, liver failure and ARDS significantly increased in-hospital mortality. Also, all 3 organ failures significantly increased the risk of the need for mechanical ventilation.

Analysis of the receiver operating characteristic curve

Table 3. Continued

| Variable | Outcome | N  | Mean  | SD    | P Value |
|----------|---------|----|-------|-------|---------|
| Cr-1     | Death   | 12 | 2.775 | 2.6718| 0.104   |
| Cr-1     | Survived| 18 | 1.611 | 1.0380|         |
| Cr-2     | Death   | 11 | 2.782 | 1.8362| 0.005   |
| Cr-2     | Survived| 17 | 1.299 | 0.7042|         |
| Cr-3     | Death   | 8  | 2.275 | 1.7153| 0.030   |
| Cr-3     | Survived| 12 | 1.008 | 0.2275|         |
| Na-1     | Death   | 12 | 141.00| 6.325 | 0.241   |
| Na-1     | Survived| 18 | 138.78| 4.052 |         |
| Na-2     | Death   | 11 | 142.18| 8.424 | 0.765   |
| Na-2     | Survived| 17 | 141.47| 3.659 |         |
| Na-3     | Death   | 8  | 137.50| 4.660 | 0.130   |
| Na-3     | Survived| 13 | 140.31| 3.637 |         |
| K-1      | Death   | 12 | 4.592 | 1.0783| 0.580   |
| K-1      | Survived| 18 | 4.411 | 0.7267|         |
| K-2      | Death   | 11 | 4.291 | 0.7204| 0.413   |
| K-2      | Survived| 17 | 4.112 | 0.4241|         |
| K-3      | Death   | 8  | 4.613 | 1.0643| 0.061   |
| K-3      | Survived| 13 | 3.962 | 0.4214|         |
| Mg-1     | Death   | 11 | 2.355 | 0.4803| 0.431   |
| Mg-1     | Survived| 15 | 2.333 | 0.3039|         |
| Mg-2     | Death   | 8  | 2.088 | 0.2588| 0.220   |
| Mg-2     | Survived| 10 | 2.250 | 0.2759|         |
| Mg-3     | Death   | 3  | 2.067 | 0.4509| 0.851   |
| Mg-3     | Survived| 4  | 2.125 | 0.3304|         |
| Ca-1     | Death   | 12 | 7.933 | 0.7278| 0.014   |
| Ca-1     | Survived| 15 | 8.587 | 0.6289|         |
| Ca-2     | Death   | 7  | 7.571 | 0.6873| 0.174   |
| Ca-2     | Survived| 11 | 8.136 | 0.9047|         |
| Ca-3     | Death   | 3  | 7.700 | 0.4000| 0.144   |
| Ca-3     | Survived| 4  | 8.225 | 0.3862|         |
| P-1      | Death   | 12 | 4.458 | 1.1642| 0.570   |
| P-1      | Survived| 15 | 4.217 | 1.7339|         |
| P-2      | Death   | 7  | 4.414 | 1.8942| 0.270   |
| P-2      | Survived| 10 | 3.510 | 1.3747|         |
| P-3      | Death   | 3  | 4.067 | 1.6258| 0.258   |
| P-3      | Survived| 3  | 2.667 | 0.7767|         |
| CRP-1    | Death   | 12 | 38.58 | 26.301| 0.033   |
| CRP-1    | Survived| 18 | 79.11 | 58.415|         |
| CRP-2    | Death   | 3  | 103.67| 50.817| 0.260   |
| CRP-2    | Survived| 14 | 71.00 | 42.863|         |
| CRP-3    | Death   | 4  | 54.75 | 18.626| 0.850   |
| CRP-3    | Survived| 7  | 61.00 | 61.172|         |
| ESR-1    | Death   | 11 | 62.27 | 33.782| 0.860   |
| ESR-1    | Survived| 17 | 64.71 | 38.459|         |
| ESR-2    | Death   | 3  | 84.67 | 49.319| 0.640   |
| ESR-2    | Survived| 11 | 75.45 | 23.624|         |
| ESR-3    | Death   | 1  | 94.00 | 0      | 0.350   |
| ESR-3    | Survived| 4  | 77.25 | 13.598|         |
| BS-1     | Death   | 11 | 117.91| 83.185| 0.005   |
| BS-1     | Survived| 18 | 173.50| 79.394|         |
| BS-2     | Death   | 9  | 132.56| 53.843| 0.068   |
| BS-2     | Survived| 12 | 201.67| 95.989|         |
| BS-3     | Death   | 6  | 136.17| 61.727| 0.521   |
| BS-3     | Survived| 5  | 112.40| 56.880|         |
| ALT-1    | Death   | 12 | 54.83 | 55.604| 0.543   |
| ALT-1    | Survived| 15 | 89.07 | 183.861|        |
| ALT-2    | Death   | 5  | 48.40 | 20.804| 0.880   |
| ALT-2    | Survived| 7  | 53.14 | 56.858|         |
| ALT-3    | Death   | 2  | 151.50| 181.726| N/A     |
| ALT-3    | Survived| 0  | 0     | 0      |         |
| AST-1    | Death   | 12 | 66.67 | 79.529| 0.431   |
| AST-1    | Survived| 15 | 49.40 | 23.018|         |
| AST-2    | Death   | 5  | 58.80 | 34.845| 0.880   |
| AST-2    | Survived| 8  | 54.88 | 54.465|         |
| AST-3    | Death   | 2  | 86.00 | 90.510| N/A     |
| AST-3    | Survived| 0  | 0     | 0      |         |
ROC (Fig. 3) to predict mortality based on patients' serum ACE2 levels showed that serum ACE2 measured in the first and third rounds are most accurate in predicting patient mortality (Table 7).

The cut-off for the serum ACE2 level was found for the first time at 1.405, the second time at 1.375, the third time at 1.755, and the mean of the serum ACE2 level was 2.773.

Discussion
There are numerous facts linking ACE2 to SARS-CoV-2, with the first and most important of them being that ACE2 is the receptor for the spike protein of SARS-CoV-2, which facilitates the virus entry into the host cell. This very fact, which has been revealed in the early months of the COVID-19 pandemic (12), has made ACE2 a perfectly suitable therapeutical target for developing an effective...
Researchers have been able to examine a variety of aspects of this global health problem, including the susceptibility to COVID-19 based on ACE2 receptor polymorphism (14) and the pattern of COVID-19 complications using the distribution of ACE2 among tissues (15). They have also been able to demonstrate an association between ACE2 expression and COVID-19 mortality (16). Soon enough, the physiologically relevant soluble ACE2 gathered attention. Soluble ACE2 has been suggested to be of great importance in the fields of therapy and prognosis of COVID-19 (17). It is simpler and more practical to test the soluble form of the ACE2 receptor since it may be broken down into soluble ACE2 and circulate in the bloodstream (10).
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The equation between the ACE 2 receptor and its soluble form, which possibly plays an important role in the pathogenesis of COVID-19, is yet to be fully understood. However, the measuring is not the only advantage of soluble ACE2 over the ACE2 receptor; many suggested therapies for COVID-19 are based on the fact that SARS-CoV-2 tends to attach to soluble ACE2 the same way it attaches to ACE2 receptors. Additionally, despite the ACE2 receptors, attachment of the spike protein of SARS-CoV-2 to soluble ACE2 would not result in cell entry. Thus, it could drain the viruses of the bloodstream, helping to prevent the infection or expedite the healing process of COVID-19 patients.

![ROC Curve](image)

**Fig. 3.** Analysis of the receiver operating characteristic curve for predicting death based on the level of serum ACE2.

| Table 4. Result of MANOVA |
|---------------------------|
| Variable                  | MV |
| Second ACE2               | Yes | 4.43±0.26 | No | 1.2±0.78 |
| Third ACE2                | Yes | 4.16±0.12 | No | 1.39±0.83 |

| Table 5. Cross tabulation of comorbidities and clinical complications |
|---------------------------------------------------------------|
| Risk factors | Mortality (Death) | Mechanical Ventilation | AKI | ARDS | Liver Failure |
|---------------|-------------------|------------------------|-----|------|---------------|
| Diabetes mellitus | OR=1.2, p=0.805 | OR=1.7, p=0.601 | OR=1.37, p=0.020 | OR=2.3, p=0.201 | OR=0.8, p=0.307 |
| Ischemic heart disease | OR=1.1, p=0.948 | OR=3, p=0.210 | OR=2, p=0.545 | OR=1,4, p=0.685 | OR=1.2, p=0.966 |
| Hypertension | OR=0.97, p=0.935 | OR=2, p=0.546 | OR=1.4, p=0.955 | OR=3, p=0.275 | OR=0.92, p=0.945 |
| Hypothyroidism | OR=1.8, p=0.508 | OR=21.3, p=0.041 | OR=0.91, p=0.900 | OR=n/a, p=0.021 | OR=33, p=0.020 |
| End-stage renal disease/chronic kidney disease | OR=1.8, p=0.301 | OR=21.3, p=0.041 | OR=68, p=0.013 | OR=5, p=0.201 | OR=0.8, p=0.900 |

| Table 6. Cross of organ failures with mortality and mechanical ventilation |
|---------------------------------------------------------------|
| Death (n=15) | Mechanical ventilation (n=5) |
| AKI (n=3) | P value | Mechanical ventilation (n=5) | P value |
| OR=n/a | 0.054 | OR=21.3 | 0.04 |
| Liver failure (n=4) | OR=n/a | 0.018 | OR=48 | 0.005 |
| ARDS (n=12) | OR=3.07 | 0.004 | OR=1.74 | 0.002 |

| Table 7. Area Under the receiver operating characteristic Curve |
|---------------------------|
| Variable                  | Area Cut-off | P Value | 95% CI |
| First ACE2            | 0.938         | 1.405   | <0.001 | 0.802 | 1.073 |
| Second ACE2           | 0.854         | 1.375   | 0.001 | 0.644 | 1.064 |
| Third ACE2            | 0.917         | 1.755   | <0.001 | 0.767 | 1.066 |
| Mean ACE2             | 0.875         | 2.773   | <0.001 | 0.683 | 1.067 |

Table 6. Cross of organ failures with mortality and mechanical ventilation

Table 7. Area Under the receiver operating characteristic Curve

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SARS-CoV-2 to neutralize it (18).

We conducted this study to evaluate the possible correlation between serum soluble ACE2 levels of COVID-19 patients and their prognosis. Some studies hypothesized that a significant increase in serum ACE2 activity may act as an endogenous nonspecific protective mechanism against SARS-CoV-2 infection that preceded the recovery of patients (19, 20). A study by Emilsson et al (21) suggested that the upregulation of ACE2 expression may reflect the severity of the outcome in COVID-19. Besides, it was reported that serum ACE2 activity on admission does not reflect disease severity (22). Clarifying the physiological balance between ACE2 receptors and soluble ACE2 would simplify the interpretation of these findings. Another aspect that is yet to be discussed is the reason causing the serum soluble ACE2 to rise. The most probable sources would either be the upregulated expression of ACE2 receptors (20) in different tissues or extra cleavage of ACE2. In each case, a bold connection is to be noticed between the rise of soluble ACE2 in serum and the susceptibility to COVID-19 or immunity against it.

As the most important result of this study, the soluble ACE2 samples of the third day (taken 7 days after admission) showed a significant difference between discharged and expired groups, despite the first- and second-day samples (taken on the day of admission and 3 days later). This makes a relatively reliable background, upon which the predictive value of soluble ACE2 in COVID-19 would be assessed. The measured soluble ACE2 in the serum of patients in the deceased and discharged group had a mean of 2.6457 and 1.8764 pg/mL, respectively. It is obvious that the higher levels of soluble ACE2 found in the serum of patients who later died do not rule out or disprove the potential neutralizing or protective effects of therapeutic and synthetic soluble ACE2. Nevertheless, it is helpful to have a clearer understanding of how soluble ACE2 levels might be used as a tool in the management of COVID-19 patients.

The fact that soluble ACE2 level changes in patient’s bloodstream in a specific way that leads to this phenomenon, raises the question of how the virus affects the ACE2 receptors so that a significant change appears after this interval; one would look at the pathophysiological changes during the course of COVID-19 to answer this question.

Align with this change, other measured biochemical and clinical indicators measured in our study have also responded to the course of the disease. Patients’ calcium levels showed a significant difference between the 2 groups on day 1, but not on days 2 or 3. Similar to this, the blood sugar of patients was only significantly different between the deceased and discharged group on day 1. Moreover, the creatin level was more significantly higher in the deceased group on day 3 compared with day 2. Among the clinical items, the respiratory rate of patients followed the same pattern as described for creatin levels; the respiratory rate of expired patients has been higher than the discharged group each day, but the difference gradually increased from day 1 to day 3; interestingly, both discharged and deceased groups had lower respiratory rates in each day compared with the last measuring. These statistically different values could be useful in the management of critically ill COVID-19 patients. Since many of the markers measured in this study are covered in routine laboratory data of hospitalized patients, it would be more practical to screen the patient’s soluble ACE2 level while considering how it changes compared with other biochemical and clinical markers.

Given that the soluble ACE2 was much greater in those who were intubated, it is fair to prepare the patient for intubation in addition to closer monitoring for patients who have a higher risk of developing critical conditions based on their soluble ACE2 levels. What seems to be the most practical is having a cut-off level for soluble ACE2. Monitoring both the soluble ACE2 level in the serum of COVID-19 patients and its changes after a certain interval simultaneously could provide a new clinical approach, through which those patients at higher risk would be treated accordingly. However, to come across a reliable cut-off for this purpose, greater sample size is required, which we recommend be taken into account for future studies.

Conclusion

Our data showed that soluble ACE2 in the serum of COVID-19 patients who died, later on, were significantly higher than the discharged patients when the samples were taken 7 days after admission. We suggest that the serum soluble ACE2 level be used as a prognostic factor for COVID-19 patients’ outcomes and also their need for mechanical ventilation. To overcome the limitations we encountered in this study, additional investigations are required to determine the appropriate cut-off and time interval for soluble ACE2 monitoring in COVID-19 patients.

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Conflict of Interests

The authors declare that they have no competing interests.

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