**Original Article**

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# Hypoxia-inducible factor-1α and ischemia-modified albumin levels in intensive care COVID-19 Patients

https://doi.org/10.1515/hmbci-2022-0024
Received February 23, 2022; accepted June 7, 2022;
published online July 18, 2022

**Abstract**

**Objectives:** In this study, it was aimed to evaluate the hypoxia-inducible factor-1α (HIF-1α) and ischemia-modified albumin (IMA) levels of patients diagnosed with COVID-19 in the intensive care unit (ICU) and healthy controls. To our knowledge, this is the first study investigate HIF-1α and IMA levels in COVID-19 patients in ICUs and comparing them with a healthy control group. For this reason, our study is original and will contribute to the literature.
**Methods:** A total of 70 intensive care patients diagnosed with COVID-19, and 72 healthy controls were included in the study.
**Results:** When we compared the patient and healthy control group; there were no statistically significant differences between the groups in terms of age and gender ($p>0.05$). No exitus was observed in the patient group. We found weak correlation between HIF-1α and IMA (r: 0.320). However, there were statistically significant differences in HIF-1α and IMA levels in the patient group. The receiver operating characteristic (ROC) curve demonstrated an area under curve (AUC) value of 0.651 for HIF-1α and 0.937 for IMA.
**Conclusions:** The HIF-1α and IMA levels were significantly higher among COVID-19 patients in ICU compared with healthy controls. HIF-1α and IMA levels can be used as reliable markers for the prognosis of COVID-19.

**Keywords:** COVID-19; hypoxia-inducible factor; ischemia-modified albumin; receiver operating characteristic.

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## Introduction

The new coronavirus disease 2019 (COVID-19) is a highly contagious disease that affects most systems, especially the respiratory system [1, 2]. Although mortality rates differ between countries, increased intensive care unit (ICU) admissions and the presence of comorbid diseases increase mortality rates. During the ICU follow-up of these patients, close monitoring of all systems, clinical and laboratory monitoring, and monitoring of impaired ventilation/perfusion due to tissue ischemia and hypoxia are of great importance [3, 4]. Although radiological imaging and laboratory tests are used in diagnosis, the real-time polymerase chain reaction (RT-PCR) test still remains the gold standard [5, 6].

Hypoxia-inducible factor (HIF) is one of the main proteins that regulate transcription during hypoxia as well as the adaptation of tissue to hypoxia. It consists of two subunits, alpha, and beta. Among these units, HIF-1β remains stable in all cells under normal oxygenation conditions; HIF-1α is rapidly ubiquinone and degraded by the enzyme prolyl hydroxylase. On the contrary, when the amount of $O_2$ in the environment decreases, the destruction of HIF-1α stops, and a stable, non-degradable HIF-1α molecule is formed. HIF-1α is a key transcription factor that actively plays a key role in oxygen deficiency to promote transcription of a large number of genes necessary to adapt to hypoxic conditions. HIF-1α polymorphisms have been extensively studied to identify associations with the onset or progression of hypoxia-related diseases [7, 8]. HIF-1α has demonstrated increased expression in bladder, ovary, lung, and gastrointestinal tumors [9]. Hypoxia is the main cause of death in COVID-19 patients and accompanies all stages of the disease [10, 11]. Viral infections can induce HIF-1α activation [12, 13]. Depending on the changes in oxygen concentration, changes occur in the transcription of HIF-1-regulated genes. After some physiological stimuli other than hypoxia (metabolic events such as glucose, amino acid and pH regulation), HIF-1α can be activated and transcription of hypoxia-induced genes can occur in a non-hypoxic environment [7, 14].

The human body has a natural antioxidant defense system against the increased reactive oxygen species (ROS) production, and oxidative stress occurs when the balance between ROS and the antioxidant defense system shifts in favor of ROS. The increase in oxidative stress and the body's defense against it are important for most diseases. Albumin is a protein synthesized in the liver and is abundant in the blood. Maintaining osmotic pressure, removing free radicals, and ensuring the transport of certain molecules in the blood are among the important functions of albumin [15]. In cases such as acidosis, ischemia, hypoxia, and therefore an increase in reactive oxygen radicals, the structure of albumin changes and its capacity to bind some metals decreases. This newly formed structure is called ischemia-modified albumin (IMA), and is one of the earliest markers of ischemia. In other words, IMA is an oxidatively modified form of the protein [15, 16]. This new molecule has been shown to be a marker of oxidative stress and to increase in blood in various conditions such as hypoxia, ischemia, and acute coronary syndrome [16–18]. Badaway et al. reported that neutrophil-mediated oxidative stress in plasma and structural damage to albumin in serum can predict mortality associated with COVID-19 [19]. In our previous study, we found that the levels of IMA to be higher in COVID-19 patients compared to healthy controls (p:000). Our work is in the publishing phase. We designed this study, considering that IMA height may also be correlated with HIF-1α.

We set out from the hypothesis that both HIF-1α and IMA levels increase due to ischemia and hypoxia in respiratory failure and lung damage in COVID-19 patients hospitalized in the ICU. We aimed to measure HIF-1α and IMA levels of these patients and compare the results with other laboratory findings in the presence of comorbid disease. To our knowledge, this is the first study investigate HIF-1α and IMA levels in COVID-19 patients in ICUs and comparing them with a healthy control group. For this reason, our study is original and will contribute to the literature.

# Materials and methods

## Study population

The study was carried out between July 1, 2021, and August 10, 2021, at Van Training and Research Hospital. Ethics committee approval was obtained from the university and study permission was obtained from the hospital. A total of 70 patients diagnosed with COVID-19 in the ICU and 72 healthy controls who were admitted to the internal medicine outpatient clinic for follow-up were included in the study. For the patient and control groups, participants between the ages of 18–65 were included in the study. No invasive procedure was applied during the study. The blood samples of the patient and control group, whose laboratory procedures were completed, were used. RT-PCR test positivity was accepted for the diagnosis of COVID-19. Age, gender, laboratory parameters, presence of chronic disease of the patient and control group were scanned from the hospital automation system and recorded. HIF-1α and IMA measurements were made in the blood samples collected from the patient and control groups. The obtained data were saved in excel, and statistical analysis was performed.

Exclusion criteria in the patient group: <18 and 65> years, chronic liver-kidney failure, pregnancy, acute coronary syndrome, malignancy, emergency surgery.

Exclusion criteria in the control group: <18 and 65> years, diabetes mellitus (DM), hypertension (HT), chronic obstructive pulmonary disease (COPD), pregnancy, chronic liver-kidney failure, and malignancy.

## Biochemical analysis

After the routine analyzes of the control group participants were finished, the remaining plasma was taken. For the participants in the patient group, the plasma of their blood taken at the first admission to the intensive care unit was taken. The blood taken for plasma collection was centrifuged at 3,000 rpm for 15 min. The collected samples were stored at −40 °C until the biochemical analysis was performed. Plasma HIF-1α and IMA levels were measured by enzyme-linked immunosorbent assay method (ELISA) and Cloud-Clone Corp brand kit (Catalog No: SEA798Hu for HIF-1α and CEA825Hu for IMA, Cloud-Clone Corp., Export Processing Zone, Wuhan, Hubei, China) in accordance with the manufacturer's protocol and guideline. The Multiskan Sky Thermo (A.B.D.) device was used to read the results in this study. The study employed a Combi wash (Human) washing device. The results were calculated using the percentage of the anticipated calculated concentration. Intra and inter-assay coefficients of variation were <10% and <12%, respectively. The minimum detectable concentration of HIF-1α was 0.059 ng/mL, and the assay diagnostic interval was 0.156–10 ng/mL. The minimum detectable concentration of IMA was 157.2 ng/mL, and the assay diagnostic interval was 370.4–30.000 ng/mL.

## Ethical considerations

Ethics approval was obtained from the ethics committee of the KTO Karatay University, Faculty of Medicine, Non-Pharmaceutical and Non-Medical Device Research Ethics Committee, Konya, Turkey (Ethics Committee No. 2021/008, Number of meetings 5, date: 08 June 2021).

## Statistical analysis

The data obtained during the data collection stage were digitised and analyzed using a computer. The SPSS Statistics 15.0 (SPSS Inc., Chicago, IL, USA) software program for Windows was used for analysis. While arithmetic mean, standard deviation, median (1st quartile-3rd quarter) (IQR) were used in the evaluation of numerical data, frequency distributions and percentages were used in summarizing categorical data. The relationships between non-normally distributed numerical data and categorical data were evaluated with the Mann–Whitney-U test. Correlations of non-normally distributed numerical variables were evaluated with Spearman correlation analysis.

Relationships between categorical data were evaluated with the chi-square test. The diagnostic decision-making properties of HIF-1α and IMA levels in predicting the disease were analyzed by Receiver Operating Characteristics (ROC) curve analysis and the area under the curve (AUC) was calculated. In the presence of significant breakpoints, the sensitivity, specificity, positive predictive value and negative predictive values of these limits were calculated. A $p<0.05$ was considered to indicate statistical significance.

## Results

A total of 70 (31 F, 39 M) intensive care patients diagnosed with COVID-19, and 72 (35 F, 37 M) healthy controls were included in the study. The length of stay of the patients in the ICU was 2.98 ± 4.62 days. No exitus was observed in the patient group. While 56.9% (n: 39) of the patients had at least one chronic disease, 43.1% (n: 31) had no chronic disease. Among the accompanying chronic diseases, DM (n: 21, 30%), and HT (n: 19, 27.14%) were common. In the comparison of two groups with and without at least one chronic disease in COVID-19 patients, the IMA levels of patients with chronic disease (n ≥ 1) were significantly higher than those without chronic disease (p: 0.03). A comparison of some parameters of COVID-19 patients with and without chronic disease is given in Table 1.

When we compared the patient and healthy control group; there were no statistically significant differences between the groups in terms of age and gender (p>0.05). However, there were statistically significant differences in HIF-1α and IMA levels in the patient group. The comparison of the data of the patient and control group is given in Table 2.

When we analyzed the data of all participants (n: 142) in terms of correlations, we observed a moderate positive correlation between age and IMA (r: 0.485, p: 000). We found that the weak correlation between HIF and IMA in the study ((r: 0.320, p: 000). We obtained significant correlations between the laboratory parameters of the patient group, which are given in Table 3.

To study the predictive power of HIF-1α and IMA, we performed ROC curves and AUC analyses. In the ROC analysis made between the groups in terms of HIF-1α, the

**Table 1:** Comparison of some parameters of COVID-19 patients with and without chronic disease.

| Variables | Number of comorbidites: 0 (n: 31) (median ± SD) (IQR) | Number of comorbidites: ≥1 (n: 39) (median ± SD) (IQR) | p-Value |
|---|---|---|---|
| Age | 49.25 ± 13.63 (38–60.5) | 60.96 ± 8.60 (54–63) | 0.00[a] |
| Length of ICU stay (days) | 2.68 ± 3.14 (1–3.5) | 2.21 ± 2.19 (1.0–3.0) | 0.87 |
| Albumin, g/dL | 3.18 ± 0.50 (2.79–3.53) | 3.06 ± 0.42 (2.74–3.39) | 0.39 |
| Na, mmol/L | 138.00 ± 3.36 (135.50–139.50) | 134.93 ± 7.71 (132.00–139.50) | 0.04[a] |
| K, mmol/L | 4.25 ± 0.36 (4.00–4.51) | 4.41 ± 0.59 (4.07–4.56) | 0.43 |
| AST, U/L | 35.64 ± 21.34 (21.50–39.95) | 35.48 ± 31.42 (21.60–35.80) | 0.40 |
| ALT, U/L | 35.09 ± 23.19 (19.30–44.50) | 28.17 ± 28.57 (14.50–32.05) | 0.06 |
| Urea, mg/dL | 34.18 ± 9.82 (27.65–40.50) | 60.23 ± 35.13 (35.85–71.40) | 0.00[a] |
| Creatinine, mg/dL | 1.06 ± 0.23 (0.92–1.20) | 1.55 ± 1.07 (0.95–1.77) | 0.06[a] |
| ProCT, ng/mL | 0.09 ± 0.18 (0.05–0.19) | 0.20 ± 2.98 (0.09–0.34) | 0.03[a] |
| CRP, mg/L | 62.01 ± 39.93 (28.32–98.26) | 64.54 ± 40.36 (21.90–145.50) | 0.52 |
| HIF-1α, ng/mL | 0.62 ± 0.91 (0.20–0.85) | 0.68 ± 0.62 (0.21–0.62) | 0.91 |
| IMA, ng/mL | 12519.64 ± 6787.97 (11046.75–22439.03) | 17588.53 ± 9522.37 (8125.00–17804.89) | 0.03[a] |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ProCT, procalcitonin; CRP, C-reactive protein; [a]p<0.05 statistical significance.

**Table 2:** Comparison of the age, gender, HIF-1α and IMA parameters of the COVID-19 patients and the controls.

| Variables | Patient (n: 70) (Median ± SD) (IQR) | Control (n: 72) (Median ± SD) (IQR) | p-Value |
|---|---|---|---|
| Age[b] | 55.11 ± 9.21 (51–65) | 44 ± 8.14 (18–63) | 0.45 |
| Gender (female/male)[c] | 31/39 | 35/37 | 0.213 |
| HIF-1α, ng/mL[b] | 0.64 ± 0.75 (0.21–0.68) | 0.27 ± 0.16 (0.22–0.31) | 0.003[a] |
| IMA, ng/mL[b] | 13414.50 ± 48936.18 (8524.30–20243.91) | 3962.71 ± 3027.41 (1996.55–4947.91) | 0.000[a] |

n, number of cases; SD, standard deviation; HIF-1α, hypoxia-inducible factor-1α; IMA, ischemia modified albumin; [a]p<0.05 statistical significance; [b]Mann–Whitney U test; [c]Chi-square test.

**Table 3:** Spearman's correlation coefficients within the patient group.

| Correlations | Correlation coefficient, r | Level | p-Value |
|---|---|---|---|
| WBC- lactate | 0.598 | High | p<0.01 |
| AST- ALT | 0.596 | High | |
| Urea- creatinine | 0.588 | High | |
| LDH-albumin | 0.551 | İntermediate | |
| Length of ICU stay-lactate | 0.558 | İntermediate | |
| Length of ICU stay-CRP | 0.519 | İntermediate | |
| APTT- albumin | 0.500 | İntermediate | |
| LDH-CRP | 0.494 | İntermediate | |
| WBC-PLT | 0.490 | İntermediate | |
| Age-urea | 0.460 | İntermediate | |
| HGB-ferritin | 0.420 | İntermediate | |
| HIF-1α-IMA | 0.320 | Weak | |

WBC, white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; APTT, activated partial thromboplastin time; PLT, platelet; HGB, hemoglobin; p<0.05 statistical significance.

serum cut-off value was calculated as 0.295 with 56.9% sensitivity and 68.6% specificity (p=0.003, AUC=0.651, CI=0.49–0.753). In the ROC analysis made between the groups with and without mortality in terms of IMA, the serum cut-off value was calculated as 6,196.42 with 89.7% sensitivity and 82.9% specificity (p=0.000, AUC=0.937, CI=0.898–0.976) (Figure 1).

# Discussion

Coronavirus Disease-19 is a global public health problem. The clinical features and severity of the disease vary between individuals depending on many factors such as age, gender, and comorbidities. Among the accompanying diseases, DM and HT are at the forefront [20]. In a study conducted in 2020, it was reported that HT, ischemic heart disease, and DM are among the most common comorbidities [21]. Kim et al. [22], in their study with 2.491 COVID-19 patients, reported that patients with three or more chronic diseases had a 1.3-fold higher risk of admission to the ICU and a 1.8-fold higher risk of in-hospital death. In a retrospective study of 304 patients who died due to COVID-19, it was reported that 70% of the patients had DM, 69% had HT, and the number of male patients was higher than the number of female patients [23]. In our study, the number of male patients was higher than female patients, and DM and HT were among the common comorbid diseases. Since mortality was not observed in our patient group, we could not evaluate the effect of chronic diseases on mortality.

In our study, mean age, urea, creatinine, procalcitonin and IMA levels were higher in COVID-19 patients with at least one chronic disease compared to those without any chronic disease. An increase in urea creatinine is an expected situation in diseases such as DM and HT [8, 17]. In COVID-19 patients, the addition of chronic diseases caused an increase in the level of IMA. We did not examine all oxidative stress parameters, but a retrospective study

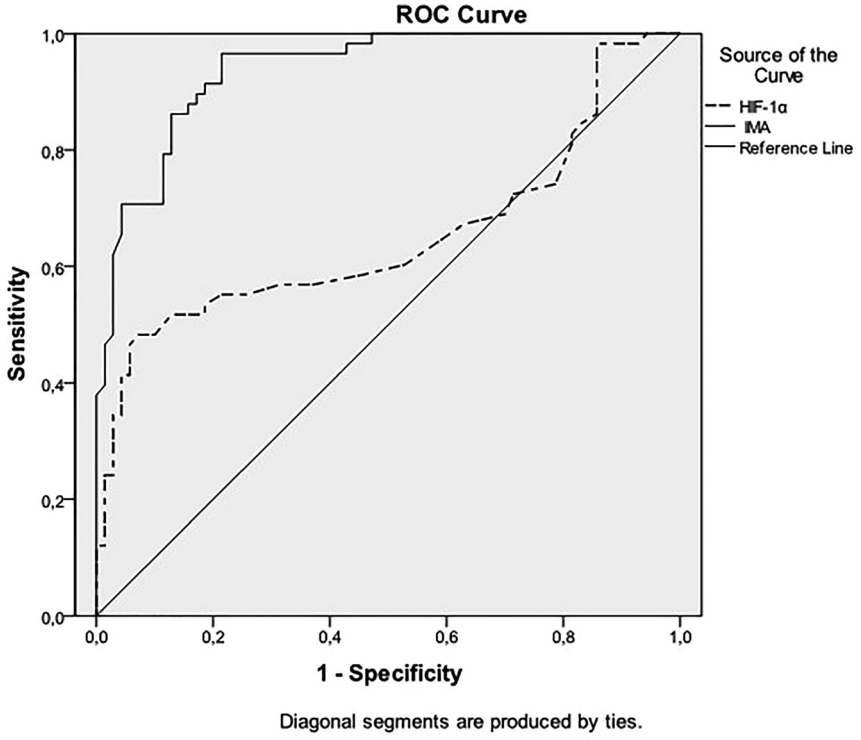


**Figure 1:** The ROC analysis for HIF-1α and IMA.

reported that IMA and IL-6 levels increased and thiol levels decreased in correlation with disease severity [24]. Many studies also reported that IMA levels increase in chronic diseases [17, 18, 25, 26]. The results of our study also support the studies in the literature.

One of the complications of COVID-19 is hypoxia due to respiratory failure. Many organisms have developed mechanisms to adapt to hypoxic conditions [1, 3, 10]. The cellular response to hypoxia is a multistep process, and most transcriptional responses are regulated by HIFs [13]. HIF-1α is an oxygen-dependent protein and has a very short half-life [11, 27]. In a review, it was suggested that HIF-1α stabilization could reduce hypoxia, ferritin level and adverse outcomes in COVID-19 infection by various mechanisms, and improve outcomes in COVID-19 infection [28]. In our study, although HIF-1α levels were high in the COVID-19 patient group with at least one comorbid disease, this difference was not significant. However, when we compared the patient and healthy control group, the HIF-1α level in the patient group was statistically significantly higher than in the control group, and the AUC value was 0.651 in the ROC analysis. We could not find any study in the literature comparing HIF-1α levels in COVID-19 patients, and we could not compare our results for this reason.

The hypoxia and tissue hypoperfusion seen in COVID-19 play a major role in the occurrence of multi-organ failure and increase in oxidative stress and ROS in patients [24, 29, 30]. The presence of chronic disease also contributes to the increase in ROS and oxidative stress, causing IMA elevation [17]. In a study conducted with children with type 1 DM, it was reported that even though acidosis improved in children after diabetic ketoacidosis, IMA levels still remained high [31]. In a study in which 35 non-HT patients with T2DM and 35 patients with T2DM and HT were compared with 35 healthy controls, it was reported that IMA levels were significantly higher in the patient group compared to the control group [32]. In another study, it was emphasized that IMA levels are an important marker in determining the early complications of diabetes [33]. In our study, we found that IMA levels were significantly higher in COVID-19 patients with at least one chronic disease compared to those without chronic disease. There is no study in the literature comparing the COVID-19 patient and control groups in terms of IMA levels. However, there is only one study in which the IMA level was evaluated retrospectively according to the severity of the disease in the patient group. In this study by Ducastel M et al. [24], the data of 160 COVID-19 patients were retrospectively scanned and it was reported that the severity of the disease and the increase in the level of IMA were parallel. In the same study, they found the AUC value for IMA to be 0.634. In our study, we found that IMA levels were significantly higher in the patient group with an obvious increase in oxidative stress compared to healthy controls. In the ROC analysis, the AUC value was quite high (0.937). We found a weak correlation between HIF-1α and IMA levels. We think that the difference in half-lives (especially the short half-life of HIF-1α) is an important factor in this weak correlation level.

### Limitations of the study

The limitations of our study are the lack of information about the factors (serum albumin concentration, inflammation, etc.) that may affect IMA levels and the inability to access blood gas data. In addition, we could not evaluate the effect of HIF-1α and IMA levels on mortality, since there was no mortality in the patient group.

## Conclusions

This is the first study investigating HIF-1α and IMA levels in patients with COVID-19. The increase in ischemia, hypoxia and oxidative stress adversely affects the intensive care processes of COVID-19 patients. DM and HT are also in the first place among the chronic diseases seen in COVID-19. In COVID-19 patients in the ICU the HIF-1α and IMA levels were considerably higher compared to healthy controls. As a result, the HIF-1α and IMA levels were significantly higher among COVID-19 patients in ICU compared with healthy controls. HIF-1α and IMA levels can be used as reliable markers for the prognosis of COVID-19.

**Research funding:** None declared. A brief summary of this article was presented as an oral presentation at the 7th UTSAK congress, 28/29 August 2021.

**Author contributions:** KY performed or analyzed serological tests. AFG obtained clinical data. KY, AFG performed statistical analysis. KY, AFG designed the study and wrote the paper. KY sent the article to the journal. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013). Ethics approval was obtained from the ethics committee of the KTO Karatay University, Health Sciences Institute, Konya, Turkey (Ethics Committee No. 2021/008, date: 08 June 2021).

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