



ORIGINAL ARTICLE

Evaluation serum levels of Insulin Growth Factor-1 (IGF-1) and its association with clinical parameters in severe COVID-19

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Abstract

Background Severe coronavirus disease-2019 (COVID-19) is associated with dysregulated immune response and extreme inflammatory injury. Considering the role of insulin growth factor-1 (IGF-1) in immune-mediated and inflammatory reactions, this study was conducted to investigate the IGF-1 contribution to the pathogenesis of severe form of COVID-19.

Material and methods Sixty-two patients with severe COVID-19 and 52 healthy subjects were enrolled in this study. The serum levels of IGF-1 were measured using a solid-phase enzyme-linked chemiluminescent immunoassay on an Immulite 2000 system (Siemens Healthcare Diagnostics).

Result The serum levels of IGF-1 had no significant difference in COVID-19 patients compared to the healthy subjects ($p=0.359$). There was a positive correlation between IGF-1 and age in the severe COVID-19 patients, while a negative correlation was observed for the serum levels of IGF-1 and age in the control group ($r=0.364$, $p=0.036$, $r=-0.536$, $p=0.001$, respectively). Moreover, IGF-1 was remarkably associated with hypertension, neurogenic disease, shock, and nausea in patients with the severe form of COVID-19 ($p=0.031$, $p=0.044$, $p=0.01$, $p=0.03$, respectively).

Conclusion Our results pointed to the complex role of IGF-1 in the severe form of COVID-19, and its association with clinical parameters, and some risk factors in the severe form of COVID-19.

Keywords IGF-1 · Severe COVID-19 · Age · Clinical parameters

Abbreviations

COVID-19	Severe coronavirus disease-2019
IGF-1	Insulin growth factor-1
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus 2
ALI	Acute lung injury
MOF	Multi-organ failure

IGF2R	Insulin-like growth factor II receptor
PI3K/AKT	Phosphatidylinositol-3-kinases/protein kinase B
MAPK	Mitogen-activated protein kinase
ARDS	Acute respiratory disease syndrome
WHO	World Health Organization
BMI	Body mass index
BPD	Blood pressure diastolic
PR	Pulse rate
RR	Respiratory rate

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T Temperature
 CNS Central nervous system

Introduction

Coronavirus Disease 2019 (COVID-19) is an acute viral respiratory infection caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) (Team EE 2020). COVID-19 is associated with a critical and overwhelming impact on the health system and life-threatening medical conditions, particularly pneumonia and acute lung injury (ALI) (Of the International CSG 2020). SARS-CoV-2 has flu-like symptoms ranging from asymptomatic and mild infection to severe ALI and multi-organ failure (MOF), eventually leading to death (Zhu et al. 2020). Studies have shown that the severe consequences in COVID-19 patients do not directly evolve by the replication of the SARS-CoV-2 itself but are relatively due to the destructive inflammatory responses caused by the immense activation of the immune cells. Therefore, the adjusted immune reaction is indispensable to control and eliminate SARS-CoV-2 infection. On the other hand, maladjusted immune responses and the elaboration of the massive number of inflammatory mediators and cytokines can have adverse and sometimes lethal sequelae (Li et al. 2020; Qin et al. 2020; Sinha et al. 2020).

Insulin-like growth factor 1 (IGF1) is a 70-amino acid long polypeptide hormone, belonging to the insulin-like growth factor family [insulin-like growth factor II (IGF2), growth hormone, insulin-like growth factor 1 receptor (IGF1R), insulin-like growth factor II receptor (IGF2R), and insulin-like growth factor binding protein 1–6 (IGFBP1–6)] (Jogie-Brahim et al. 2009) with several functions, including tissue growth and development, insulin-like activity, proliferation, pro-survival, anti-aging, antioxidant and neuro-protective (Martin-Estal et al. 2016). Furthermore, IGF-1 is involved in regulating the biological responses of the immune system through phosphatidylinositol-3-kinases/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK) signaling pathways (Myers et al. 1992). Various studies have proven the role of the IGF-1 signal transduction in lung development, as well as inflammatory diseases like ALI and Acute respiratory disease syndrome (ARDS), asthma, cancer, inflammation, and fibrosis (Stiles and D'Ercole 1990; Ahasic et al. 2012; Mu et al. 2020; Narasaruju et al. 2006; He et al. 2019; Li et al. 2016). IGF-1 is also implicated in the regulation of inflammation in the immune system (DeBoer et al. 2017; Heemskerk et al. 1999). A study conducted by Hoshino et al. showed that IGF-1 mRNA expression in the bronchial cells of asthmatic patients was significantly higher than those of healthy individuals, which was remarkably associated with fibrosis in epithelial cells (Hoshino et al. 1998). Given the evidence for

Table 1 Demographic characteristics and IGF-1 serum levels between COVID-19 patients and healthy control groups

Characteristics	Level	COVID-19 (<i>n</i> = 62)	Control (<i>n</i> = 52)	<i>p</i> value
Age (years)	–	60.19 ± 18.56	64.13 ± 15.03	0.221
Sex	Male	30 (48.4%)	28 (53.8%)	0.145
BMI (kg/m ²)	–	26.84 ± 4.24	27.47 ± 5.53	0.497
IGF-1 (ng/mL)	–	83.04 ± 51.96	75.73 ± 31.19	0.359

Data are expressed as mean ± SD or *N* (%)

BMI body mass index, *IGF-1* insulin growth factor

the role of IGF-1 in lung development and its involvement in immune responses, evaluating the IGF-1 levels may further shed light on mechanistic underlying the pathogenesis of COVID-19.

Emerging data from previous studies indicated that the clinical manifestations of COVID-19 are heterogeneous and highly depend on many underlying conditions. Senescence and comorbidities, including hypertension, diabetes, obesity, renal failure, and lung diseases, are significant conditions associated with increased risk of developing ARDS, MOF, and consequently death in patients with COVID-19. Some other variables are also worth mentioning, like ethnicity and sex (Kassir 2020).

Considering immune-mediated inflammatory responses underpinning COVID-19 pathogenesis, involvement of IGF-1 in immunological reactions, and association documented between IGF-1 and underlying conditions such as diabetes, obesity, hypertension, aging (Teppala and Shankar 2010; Spielman et al. 2014; Ounis et al. 2010; Norling et al. 2020; Delafontaine et al. 2004; Salminen and Kaarniranta 2010) this study aimed to investigate the serum levels of IGF-1 and its association with clinical parameters and underlying conditions in the severe form of COVID-19.

Methods and materials

Study design and patient characteristics

Sixty-two patients aged from 19 to 91 years [60.19 ± 18.56, (mean ± standard error of the mean)] with severe COVID-19 and 52 healthy subjects aged from 21 to 90 (64.13 ± 15.03) after matching for age and sex were enrolled in the current study. The diagnosis of COVID-19 was confirmed using RT-PCR (real-time reverse transcriptase-polymerase chain reaction) assay and specialist physician according to the defined clinical and other laboratory detection parameters. The demographic and clinical characteristics of both groups are presented in Table 1. The project was approved by the ethics committee of the Kermanshah and Ardabil

University of Medical Sciences (IR.KUMS.REC.990599, and IR.ARUMS.REC.1399.562), and all defined protocols were done according to the Helsinki declaration. All participants gave written informed consent before taking part in the study.

Blood sample preparation and measurements of IGF-1 serum levels

Blood Samples were taken from the antecubital vein of patients and controls, and they were processed within 1 h after collection, centrifuged for 15 min, aliquot, and stored at -80°C until analysis. IGF-1 was measured in serum using a solid-phase enzyme-linked chemiluminescent immunoassay on an Immulite 2000 system (Siemens Healthcare Diagnostics, Inc).

Statistical analysis

Statistical analysis was performed with SPSS software (version 21.0, SSPS Inc., Chicago, Illinois, USA). Results were presented as mean \pm standard deviation (SD). The distribution Normality in the groups was determined by Kolmogorov–Smirnov test (K–S test). *P* value is based on the independent *t* test/or Mann–Whitney nonparametric test for statistical comparisons between both groups based on the continuous variables. Categorical variables were analyzed through the chi-square/or Fisher exact test between both patients and healthy individuals. The association between two variables was determined by Spearman rank correlation. *p* value indicated as statistically significant at the level of <0.05 .

The calculation of body mass index (BMI)

The calculation of weight and height were done based on standard protocol and the World Health Organization (WHO). BMI is a person's weight in kilograms divided by the square of height in meters. Normal weight: 18.5–24.9, overweight: 25.0–29.9, obese: ≥ 30 .

Results

Demographic characteristics and the serum levels of IGF-1

The demographic characteristics and quantitative determination of the IGF-1 serum concentration and the statistical evaluation of these results are presented in Table 1. The mean BMI in patients and control groups were 26.84 ± 4.24 (kg/m^2) and 26.84 ± 4.24 (kg/m^2), respectively, in which no significant differences were found between the amounts of

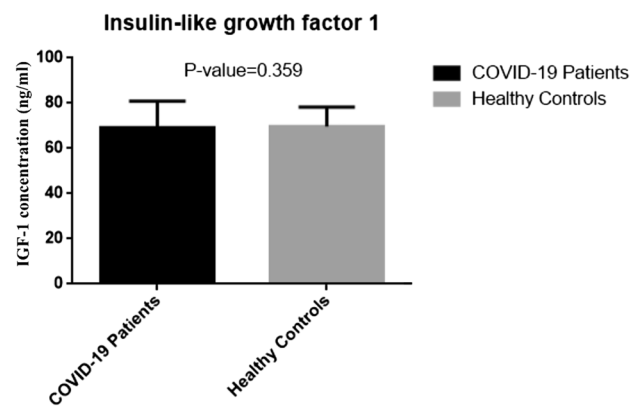


Fig. 1 The serum levels of IGF-1 in the severe patients with COVID-19 and healthy subjects. There was not a significant difference for IGF-1 in severe patients with COVID-19 compared to healthy subjects using a solid-phase enzyme-linked chemiluminescent immunoassay ($p=0.359$)

BMI in studied groups (Table 1). Although the serum levels of IGF-1 in COVID-19 patients (83.04 ± 51.96 ng/mL) was higher than that obtained in controls (75.73 ± 31.19 ng/mL; $p=0.359$), the mean serum concentration of IGF-1 in the patients' group did not significantly differ from that of the healthy group (Fig. 1).

Correlation matrix between IGF-1 serum levels with age and BMI

The age-adjusted mean IGF-1 level was evaluated in each group. The correlation coefficients were calculated between IGF-1 levels, sex, age, and BMI to determine the IGF-1-sex, IGF-1-age, and IGF-1-BMI associations. Statistically significant correlations were observed between IGF-1 levels and age in both studied groups. IGF-1 levels were positively correlated with age in COVID-19 patients ($r=0.364$, $p=0.036$). Conversely, negatively correlated with age in healthy individuals was shown ($r=-0.536$, $p=0.001$) (Table 2, Figs. 2, 3, respectively). In the regression analysis—adjusting for sex and BMI in COVID-19 patient, the relationship was non-significant, ($r=0.082$, $p=0.444$ $r=0.046$, $p=0.725$, respectively). Similar results were observed for the relationship between IGF-1 with sex and BMI in healthy control (Table 2).

Association of the IGF-1 serum levels and clinical characteristics in COVID-19 patients

We next investigated the relationship between IGF-1 level and clinical characteristics of patients. Among co-morbidity in patients with COVID-19, IGF-1 was significantly associated with hypertension ($p=0.031$), Neurogenic diseases ($p=0.044$), shock ($p=0.01$), and Nausea ($p=0.03$)

Table 2 Correlation matrix between IGF-1 serum levels with age and BMI in each group

Group	Variable	Coefficient (<i>r</i>)	<i>p</i> value
COVID-19 patients	Age	0.364	0.036
	BMI	0.046	0.725
	Sex	0.082	0.444
Healthy subjects	Age	-0.536	0.001
	BMI	0.014	0.921
	Sex	0.180	0.121

The given data showed a positive correlation between the serum IGF-1 levels and age in patients with severe COVID-19 and a remarkable negative correlation between IGF-1 levels and the age of healthy controls. There was no significant difference for IGF-1 serum levels with BMI and sex in the severe patients with COVID-19 and the control group. *BMI* body mass index. *p* value was considered statistically significant at the level of < 0.05

(Table 3). Moreover, no significant correlation matrix was observed between IGF-1 levels with blood pressure, blood pressure diastolic (BPD), pulse rate (PR), respiratory rate (RR), and temperature (*T*) in the severe COVID-19 patients (Table 4).

Discussion

The majority of patients with COVID-19 have a self-limiting infection and recover, but in some cases, it leads to severe symptoms and death (Azkur et al. 2020). It is worth mentioning, the abruptly worsening conditions of these patients are mainly due to systematic inflammatory assault caused by the uncontrolled or dysregulated immune responses, considered as the cytokine storm, leading to ARDS and multiple organ failure (Ye et al. 2020). To the best of our knowledge, this study is the first to assess the serum levels of IGF-1 in severe COVID-19 patients compared to healthy individuals. Our results showed that the serum levels of IGF-1 in severe COVID-19 patients did not differ significantly compared to healthy subjects.

Previous studies have revealed controversial results regarding the impact of IGF-1 on lung pathology. The research performed by Krein PM et al. showed the increased IGF-1 immunostaining in lung biopsy specimens from patients with fibro-proliferative ARDS (Krein et al. 2003). Interestingly, elevated IGF-1 levels also have been reported in the bronchoalveolar lavage (BAL) fluid of patients with early ARDS (Schnapp et al. 2006). Besides, IGF-1 contributed to Influenza A virus-mediated acute inflammatory lung injury, which can be considered a novel approach to influenza treatment (Li et al. 2019).

Conversely, reduced levels of IGF-1 have been found in ARDS cases compared to the control group with no

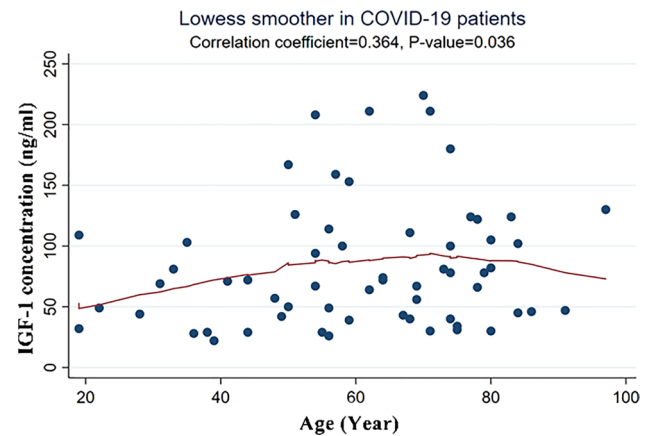


Fig. 2 Correlation of IGF-1 serum levels and age in the patients with COVID-19. The provided graph depicts a significant positive correlation between the serum IGF-1 levels and age in severe patients with COVID-19 using the LOWESS smoothing method ($r=0.364$, $p=0.036$)

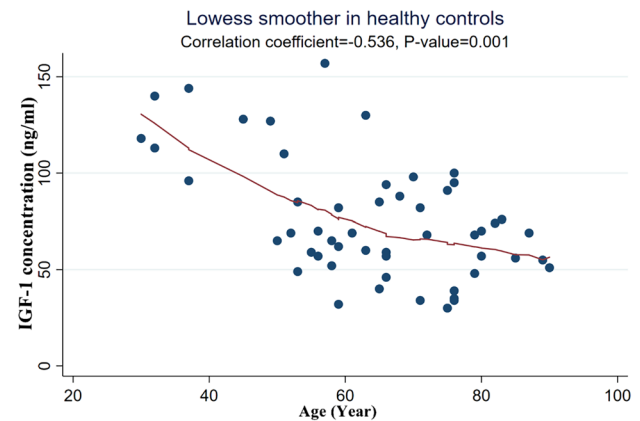


Fig. 3 Correlation of IGF-1 serum levels and age in the healthy subjects. The shown graph depicts a remarkable negative correlation between IGF-1 levels and age of healthy controls using the LOWESS smoothing method ($r=-0.536$, $p=0.001$)

risk of ARDS, which is positively associated with mortality among ARDS cases (Ahasic et al. 2012). A retrospective study conducted by Xikang Fan et al. demonstrated a significant reduction in IGF-1 and IGFBP3 levels in the non-survivor patients with COVID-19, which were mainly older than survivors. For instance, the IGF-1 serum levels in the COVID-19 patients with a mean age of 70.55 ± 7.72 was 4.79–17.09 (nmol/L), while they were 24.53–58.00 (nmol/L) in COVID-19 patients with a mean age of 65.11 ± 9.34 . Also, in the study mentioned above, a positive correlation between COVID-19 mortality and IGF-1 further supported the role of the IGF pathway in COVID-19-related ARDS (Fan et al. 2020).

Table 3 Association between IGF-1 levels and clinical characteristics of 62 severe COVID-19 patients

Characteristics	Level	IGF-1	<i>p</i> value
Hypertension	Negative	89.17 ± 56.43	0.031
	Positive	64.26 ± 28.87	
CKD	Negative	85.54 ± 53.58	0.338
	Positive	66.50 ± 38.19	
IHD	Negative	86.14 ± 59.99	0.605
	Positive	79.14 ± 40.43	
Neurogenic diseases	Negative	82.40 ± 52.15	0.044
	Positive	122.0 ± 44.17	
Diabetic Mellitus	Negative	83.60 ± 52.68	0.899
	Positive	81.72 ± 51.66	
Affected person	Negative	80.33 ± 49.50	0.361
	Positive	96.90 ± 64.28	
Exposure history	Negative	80.51 ± 51.09	0.489
	Positive	91.57 ± 55.90	
Fever	Negative	79.0 ± 48.18	0.663
	Positive	85.17 ± 54.31	
Vomiting	Negative	85.89 ± 56.27	0.459
	Positive	74.33 ± 35.85	
Abdomen pain	Negative	83.62 ± 54.17	0.858
	Positive	87.25 ± 41.86	
Rhinorrhea	Negative	83.06 ± 54.34	0.988
	Positive	82.5 ± 55.86	
Cough	Negative	81.47 ± 55.97	0.856
	Positive	84.0 ± 50.13	
Loss of appetite	Negative	73.11 ± 35.73	0.119
	Positive	95.55 ± 66.72	
ARDS	Negative	81.45 ± 43.09	0.859
	Positive	83.94 ± 56.87	
Distress	Negative	79.87 ± 40.58	0.779
	Positive	84.17 ± 55.82	
Renal pain	Negative	82.62 ± 52.79	0.833
	Positive	87.80 ± 46.29	
Shock	Negative	84.0 ± 51.86	0.001
	Positive	26.19 ± 11.19	
Anosmia	Negative	82.67 ± 50.58	0.866
	Positive	86.5 ± 68.96	
Pharyngitis	Negative	84.75 ± 54.33	0.753
	Positive	80.41 ± 49.11	
Agitation	Negative	85.23 ± 53.33	0.324
	Positive	63.0 ± 33.87	
Nausea	Negative	89.91 ± 55.97	0.030
	Positive	63.75 ± 32.75	
Diarrhea	Negative	85.06 ± 54.46	0.546
	Positive	74.83 ± 41.13	
Myalgia	Negative	83.92 ± 41.61	0.908
	Positive	82.35 ± 59.53	
LOC	Negative	84.33 ± 52.98	0.471
	Positive	64.75 ± 33.51	

Table 3 (continued)

Characteristics	Level	IGF-1	<i>p</i> value
Chest pain	Negative	84.19 ± 53.68	0.766
	Positive	79.53 ± 47.88	
Fatigue	Negative	84.51 ± 50.77	0.756
	Positive	80.05 ± 55.55	
Weakness	Negative	87.03 ± 55.13	0.415
	Positive	79.66 ± 49.72	
Sputum	Negative	82.15 ± 50.55	0.749
	Positive	88.22 ± 62.65	
Headache	Negative	87.92 ± 57.43	0.203
	Positive	72.26 ± 36.16	

The provided table represented a significant correlation between IGF-1 with hypertension, neurogenic diseases, shock, and Nausea in severe patients with COVID-19. Bold *p* value indicated as statistically significant at the level of 0.05

CKD Chronic kidney disease, *COPD* Chronic obstructive pulmonary disease, *IHD* Ischemic heart disease, *ARDS* Acute Respiratory Distress Syndrome, *LOC* Loss of Consciousness. Data are expressed as mean ± SD

Table 4 Correlation matrix between IGF-1 serum levels with BP, BPD, PR, RR, and *T* in the severe COVID-19 patients

Group	Variable	Coefficient (<i>r</i>)	<i>p</i> value
Severe patients with COVID-19	BP	0.015	0.970
	BPD	0.082	0.529
	PR	0.096	0.460
	RR	0.128	0.329
	<i>T</i>	0.017	0.899

The supplied data demonstrated no remarkable differences between the serum levels of IGF-1 with BP, BPD, PR, RR, and *T*. Data correlation analysis by Spearman rank correlation. Blood Pressure Diastolic (BPD), Pulse Rate (PR), Respiratory Rate (RR), and Temperature (*T*). *p* < 0.05 was considered statistically significant.

Given the importance of aging as a critical risk factor in the pathogenesis of severe form of COVID-19, we evaluated the association between IGF-1 and age in patients and control groups. Although Secretion of IGF-1 drops over time with senescence (Junnila et al. 2013), there was a positive correlation between the IGF-1 serum levels and age in severely affected COVID-19 patients. In contrast, there was a negative association between the IGF-1 serum levels and age in healthy subjects. Aging is the main contributor to pulmonary physiology, function, and pathology during lung infection. Consequently, age-related differences may be associated with immune system responses and tolerance, leading to worse clinical outcomes in elderly individuals (Miller and Linge 2017). In addition, it has been

demonstrated that age-related cellular and tissue function changes are associated with reducing the anabolic hormones, growth hormone, and IGF-1, which may lead to longevity (Sonntag et al. 2000, 2005; Shimokawa et al. 2003). Regarding the positive correlation between age and IGF-1 in severe COVID-19 patients, IGF-1 can be considered an inflammatory factor that may implicate the severity of COVID-19. Likewise, an increase in IGF-1 and IGFB-1 binding protein (IGFBP-3) was reported in the damage and death of lung epithelial cells, as well as early ARDS, while a decrease in IGFB-1 and IGFBP-3 has been reported in late ARDS (Ahasic et al. 2015).

In the following, we investigated the correlation of IGF-1 and some crucial clinical characteristics in COVID-19 patients. The IGF-1 levels were significantly higher in patients without hypertension, shock, and nausea than severe COVID-19 patients with hypertension, shock, and nausea. In line with our finding, various studies showed an inverse correlation between circulating IGF-1 levels and blood pressure among type 1 and type 2 diabetic patients and patients with borderline hypertension (Capoluongo et al. 2006; Sesti et al. 2005; Brismar 1998). Besides, another study revealed the serum levels of IGF-1 were remarkably declined in patients with septic shock compared to healthy subjects (Xu et al. 2017). Our data also showed a positive association between elevated IGF-1 levels with neurogenic diseases in patients with COVID-19.

Neurological complications are one of the essential findings in COVID-19. Several studies have demonstrated the elevated levels of IGF-1 in the central nervous system (CNS) following an injury, which may act as an endogenous protective mechanism (Kizhakke Madathil et al. 2010; Nordqvist et al. 1996). Regarding our finding and existing data about the role of IGF-1 in neurological disorders, it can be hypothesized that IGF-1 may contribute to the neurologic manifestation of COVID-19.

Considering the current and previous studies, the IGF-1 may have a role in the pathogenesis of severe form of COVID-19, and unraveling its exact contribution warrant further investigation.

Conclusion

In sum, our data imply the complex role of IGF-1 in COVID-19 patients. Further studies are warranted to confirm our findings and elucidate underlying mechanisms.

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Author contributions MT contributed to the idea design, checked the final results, and performed the final revision of the manuscript. ES performed the experiments and contributed to the idea design. SM provided patients samples and clinical data. ShM and SAR summarized and analyzed the data. PF drafted and wrote the manuscript. All authors reviewed and approved the final manuscript.

Declarations

Conflict of interest The authors have no conflict of interest and they alone are responsible for the content and writing of the paper.

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