https://doi.org/10.31925/farmacia.2025.2.6 **ORIGINAL ARTICLE**

THE ROLE OF IL-6 AND IL-1 IN COVID-19 DISEASE PROGRESSION: THE IMPACT OF GENDER-BASED DIFFERENCES, BMI VARIABILITY AND CO-MEDICATIONS

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Abstract

The immune response to COVID-19 has gained significant attention due to its potential association with disease severity. This study assessed the relationship between IL-1 and IL-6 levels and COVID-19 severity, considering factors such as age, gender, BMI, comorbidities and co-medications. A cross-sectional, retrospective study was conducted on 329 patients with confirmed COVID-19, stratified by disease severity. Serum levels of IL-1 and IL-6 were measured at the time of admission. No significant correlation was found between elevated IL-1 levels and disease severity. Conversely, IL-6 levels were significantly elevated in severe cases. The association between IL-6 and disease severity was more pronounced in patients with lower BMI. Gender differences were noted, with men exhibiting more severe outcomes. IL-6 appears to be a more reliable predictor of disease severity than IL-1 in COVID-19 patients, particularly those with lower BMI. Gender-specific immune responses and the impact of age on cytokine production highlight the complexity of immune regulation in COVID-19. Further research is needed to explore the therapeutic potential of targeting IL-6 and other cytokines and the effects of medications on disease severity.

Rezumat

Rolul răspunsului imun și al citokinelor în cadrul infecției cu SARS-CoV-2 a primit o atenție deosebită prin prisma posibilelor corelații cu severitatea bolii. Scopul acestui studiu a fost sa investigheze asocierea dintre nivelurile serice de IL-1 și IL-6 și severitatea bolii, luând în considerare factori precum vârsta, sexul, indicele de masă corporală (IMC), comorbiditățile și tratamente. Am inclus 329 de pacienți cu infecție SARS-CoV-2 . Nivelurile serice de IL-1 și IL-6 au fost măsurate la internare. Nu am identificat corelații statistice între nivelurile crescute de IL-1 și severitatea bolii. Nivelurile IL-6 au fost crescute în cazul formelor severe. Asocierea dintre nivelurile crescute de IL-6 și severitatea bolii a fost evidentă la pacienții cu IMC scăzut. Au fost identificate diferențe între sexe, bărbații prezentând forme severe într-un procent mai mare. IL-6 pare a fi un predictor mai bun al severității bolii comparativ cu IL-1, în special la cei cu IMC mic. Răspunsul imun diferit în funcție de sex și impactul vârstei asupra producției de citokine subliniază complexitatea reglării sistemului imun în COVID-19. Studiile viitoare sunt esențiale pentru a evalua potențialul terapeutic al inhibiției IL-6 și al altor citokine, precum și influența medicamentelor asupra evoluției și severității bolii.

Keywords: IL-1, IL-6, COVID-19

Introduction

As of December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly across the globe, resulting in extensive morbidity and mortality [1, 2]. Usually, patients with severe forms of the disease who are infected with SARS-CoV-2 develop an abnormal immune landscape characterised by an overactivated innate immune response and an impaired protective adaptive immune response [3].

An abnormal process triggers a massive release of cytokines and chemokines, leading to the "cytokine storm" (CRS), which mediates a state of hyper-inflammation [4]. This hyperinflammatory state, also called "COVID-19 hypercytokinaemia" [5], can contribute to the severity of the disease. Similarly, CRS has been recognised as a significant cause of death in COVID-19. Moreover, the exaggerated activation of the inflammatory response triggers endothelial lesions and a state of hypercoagulability [6].

Inflammatory cytokine levels, such as IL-1, IL-6, IL-8, IL-10 and TNF-α, are elevated, but the most significant increase is observed in IL-6 serum levels. Studies have shown that apart from the increase in

the secretion or production of these cytokines in COVID-19 patients, there is also a decrease in CD4+ and CD8+ T cells. These processes lead to bilateral pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ damage [7]. IL-6 is secreted by stromal cells, immune cells, endothelial cells, and others. It plays a crucial role in the differentiation of B-cells and the production of antibodies, as well as in homeostasis in the acute-phase response and haematopoiesis [8, 9]. Additionally, studies have demonstrated that serum levels of IL-6 are superior to ferritin for predicting clinical outcomes. Also, some studies illustrated that liver enzymes (such as transaminases) are less relevant than IL-6 levels [5, 10-12]. Other studies have shown that an inappropriate immune response to SARS-CoV-2 often occurs in patients with different diseases, such as diabetes and heart and kidney disease [13].

A recent study designed to document the histopathological findings in COVID-19 patients revealed that lung tissue from patients who died within 12 hours of hospitalisation exhibited high levels of IL-6 expression [14]. Glucocorticoids have been shown to improve survival in severe cases, supporting the idea that excessive immune response activation is responsible for severe forms and death from COVID-19 [15].

Studies have also shown significant host genetic variability, which suggests the potential role of genetic, environmental, or lifestyle factors in determining how IL-1 and IL-6 levels influence the progression of SARS-CoV-2 infection. These factors could help explain the variability in disease severity and outcomes [16].

We examined the impact of elevated IL-1 and IL-6 levels on the progression of SARS-CoV-2 infection, including their influence on the inflammatory response, disease severity, and complications. We also explored potential correlations with gender, BMI, co-medication and comorbidities to identify factors contributing to differences in disease outcomes.

Materials and Methods

Participants

We conducted a retrospective, cross-sectional study, which included patients admitted to the Adults III and Children XI Departments of "Prof. Dr. Matei Balș" National Institute of Infectious Diseases (INBIMB), Bucharest, Romania, from December 16, 2020, to October 31, 2021. All patients had a positive rapid diagnostic test or nasal or oropharyngeal RT-PCR. The study protocol was approved by the ethics committee of INBIMB (protocol no C0408/2020). The scope was limited to hospitalised individuals with confirmed SARS-CoV-2 infection, with the mention that the small number of mild cases in our study is explained by the fact that patients with mild forms no longer required mandatory hospitalisation during this period.

We excluded patients who required orotracheal intubation and mechanical ventilation, those needing transfer to the intensive care unit, and pregnant women. These exclusion criteria for ICU patients were necessary to minimise confounding factors that may arise due to the complexity of ICU care and the interventions. ICU patients often present with more advanced stages of disease, comorbidities, and intensive treatments that are not representative of the general population with less severe COVID-19. The exclusion of ICU patients helps ensure that our findings are more specific to those who do not require intensive monitoring. The classification of disease severity was based on criteria commonly used in clinical settings, including the World Health Organisation (WHO) guidelines. Mild cases were defined as individuals with mild symptoms such as fever and cough without evidence of pneumonia or respiratory distress; moderate cases involved patients with pneumonia but no need for supplemental oxygen, and severe cases were characterised by respiratory failure requiring oxygen therapy or mechanical ventilation [17-19].

Measured parameters

The following variables were selected for inclusion in the database and subsequent statistical analysis: gender, age, body mass index (BMI), duration of hospitalisation, co-pathologies, personal medication, signs and symptoms, complete blood count, D-dimer levels and inflammatory markers (IL-1 and IL-6 levels, C-reactive protein, fibrinogen) as well as liver injury marker enzymes (alanine aminotransferase, ALT; aspartate aminotransferase, AST). The serum levels of IL-1 and IL-6 were quantified using the ELISA technique (Quantikine Immunoassay, Human IL-6 HS, Lot342854, catalogue number: HS600B, RD systems, Minneapolis, MN 554113 (800) 343-7475, made in USA).

Moreover, every patient had at least one chest computed tomography scan (CT) during hospitalisation. The results of the CT scans were categorised as mild, moderate or severe, based on specific radiological findings. We classified a case as mild when a patient had minimal or localised ground-glass opacities, unilateral lung involvement, no consolidation, little to no crazy-paving pattern (ground-glass opacities combined with interlobular septal thickening) and low lung involvement on CT scoring, with only small areas of abnormality. A moderate form of the disease is indicated by more widespread ground-glass opacities that affect both lungs, though still with limited distribution.

On CT scoring, limited, patchy areas of consolidation, bilateral involvement, a mild crazy-paving pattern, and moderate lung involvement may be present. The lung involvement typically covers 20 - 50% of the tissue, with minimal or no pleural effusions or fibrosis.

By contrast, a severe case is characterised by widespread ground-glass opacities, dense and opaque consolidation regions, a crazy-paving pattern, diffuse lung involvement, pleural effusions, fibrosis, or architectural distortion.

Statistical Analysis

In the descriptive statistical analysis, we described the parametric variables using the mean ± standard deviation, while non-Gaussian variables were defined using the median and interquartile range. Categorical variables were presented as counts and percentages, and comparisons were made using the Chi-square test.

For continuous variables, we first assessed the normality of the data. If the data were normally distributed, independent samples t-tests were used to compare means between men and women. If the data were not normally distributed, the Mann-Whitney U or Kruskal-Wallis tests were used for comparisons. Statistical significance was set at $p < 0.05$.

We used linear and logistic regression models to assess the association of increased serum levels of IL-1 and IL-6 as the dependent variable, with other variables or with different clinical, biological or radiological characteristics. The data was analysed using IBM SPSS Statistics for Windows, IBM Corp., 2011, Version 20.0. Armonk, NY: IBM Corp.

Results and Discussion

We included 329 patients: 136 women (41.3%) with a median age of 65 years (IQR: 52 - 72) and 193 men (58.7%) with a median age of 53 (IQR: 45 - 67) (Figure 1). The median length of hospital stay was 10 days (IQR: 7 - 14) (Figure 2).

A total of 96 women (70.6%) and 154 (79.8%) men had a BMI greater than 25 kg/m^2, while 54 women (39.7%) and 74 men (38.3%) had a BMI greater than 30 kg/m^2.

A number of 169 patients (51.4%) had arterial hypertension. Following hypertension, non-insulin-dependent type II diabetes mellitus was the most prevalent comorbidity among patients, with a total of 48 cases (14.6%) (Table I).

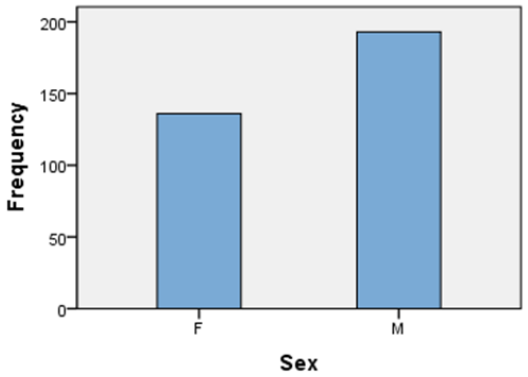

Figure 1.
Gender distribution in our study group

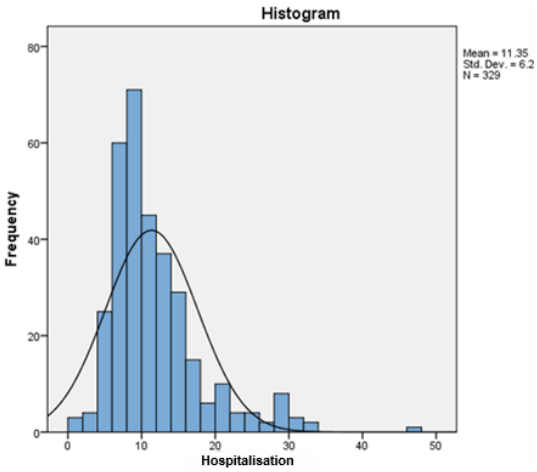

Figure 2.
Median value of the length of hospital stay

Regarding co-medications, 53 (16.1%) of the patients were prescribed an HMG-CoA reductase inhibitor (statin), 47 (14.3%) an angiotensin II receptor antagonist (ARBs), 61 (18.5%) a thiazide-like diuretic and 69 (21%) an angiotensin-converting-enzyme (ACE) inhibitor (Table II).

Table I
Gender distribution of comorbidities in COVID-19 patients

Comorbidities	F	M
	n = 136 (41.3%)	n = 193 (58.7%)
Multiple comorbidities	104 (76.5)	124 (64.2)
Hypertension	84 (61.8)	85 (44)
Diabetes mellitus type II	23 (16.9)	25 (13)
Chronic hepatocellular disease	9 (6.6)	22 (11.4)
History of a neoplasm	16 (11.8)	7 (3.6)
Chronic kidney disease	4 (2.9)	15 (7.84)
Neoplasm	10 (7.4)	8 (4.1)
Diabetes mellitus type I	4 (2.9)	14 (7.3)
Autoimmune diseases	7 (5.1)	5 (2.6)
Chronic obstructive pulmonary disease	3 (2.2)	5 (2.6)
Haematological disorders	2 (1.5)	4 (2.1)
Immunosuppression	2 (1.5)	4 (2.1)

Table II

Co-medication usage among COVID-19 by gender

Co-medications	F	M
	n = 136 (41.3%)	**n = 193 (58.7%)**
Anticoagulants	10 (7.4)	13 (6.7)
Statin	20 (14.7)	33 (17.1)
ARBs	26 (19.1)	21 (10.9)
Thiazide-like diuretics	33 (24.3)	28 (14.5)
ACE inhibitors	39 (28.7)	30 (15.5)
Other immunosuppressive medications	3 (2.2)	6 (3.1)
Other medications	87 (49.7)	97 (50.3)

Statistically significant correlations between the maximum amount of oxygen supplementation needed and the use of statins (p = 0.010), thiazide-like diuretics (p = 0.031), and ACE inhibitors (p = 0.034) were found in men. No such correlations were observed in women (p = 0.849, p = 0.37, p = 0.10), nor with the use of ARBs in both groups (men: p = 0.847 and women: p = 0.906)**.** Moderate and severe forms of the disease were the most prevalent in our study groups, accounting for 143 (43.5%) and 176 (53.5%) patients, respectively. A total of 10 patients (8 females and two males) had mild forms of the disease, while the total number of moderate forms was 143 (62 women and 81 men). Severe forms of the disease were the most prevalent, with a total number of 176 cases (66 women and 110 men) (Table III).

Table III

Gender comparison of COVID-19 cases by severity

Distribution of COVID-19 cases by severity	F	M
	n = 136 (41.3%)	**n = 193 (58.7%)**
Mild	8 (5,9)	2 (1)
Moderate	62 (45,6)	81 (42)
Severe	66 (48,5)	110 (57)

A total of 10 patients (8 females and two males) had mild forms of the disease, while the total number of moderate forms was 143 (62 women and 81 men). Severe forms of the disease were the most prevalent, with 176 cases (66 women and 110 men) (Table IV). The most identified symptoms were cough (n = 293, 89.1%), asthenia (n = 206, 62.6%), dyspnoea (n = 156, 47.4%), anorexia (n = 143, 43.5%), myalgias (n = 140, 42.6%), and headache (n = 128, 38.9%). The least commonly reported symptoms were conjunctival hyperaemia and cutaneous manifestations (Table IV).

Table IV

Frequency of symptoms in males and females

Symptoms	F	M
	n = 136 (41.3%)	**n = 193 (58.7%)**
Cough	120 (88.2)	173 (89.6)
Asthenia	88 (64.7)	118 (61.1)
Dyspnoea	64 (47.1)	92 (47.7)
Anorexia	67 (49.3)	76 (39.4)
Myalgia	60 (44.1)	80 (41.5)
Cephalgia	58 (42.6)	70 (36.3)
Nausea	41 (30.1)	43 (22.3)
Diarrhoea	34 (25)	47 (24.4)
Arthralgia	35 (25.7)	42 (21.8)
Anosmia	23 (16.9)	40 (20,7)
Thoracic pain	26 (19.1)	31 (16.1)
Ageusia	19 (14)	29 (15)
Vomiting	19 (14)	13 (6.7)
Abdominal pain	15 (11)	13 (6.7)
Dysgeusia	5 (3.7)	11 (5.7)
Nasal congestion	6 (4.4)	7 (3.6)
Confusion	7 (5.1)	5 (2.6)
Rhinorrhoea	5(3.7)	7 (3.6)
Conjunctival hyperaemia	1 (0,7)	7 (3,6)
Irritability	1 (0,7)	2 (1)
Cutaneous manifestations	0 (0)	3 (1.6)
Paraesthesia	1 (0,7)	1 (0,5)

The median value of IL-1 was 5.1 pg/mL in women (IQR: 0,03 - 18,6) and 2.93 pg/mL in men (IQR: 0.15 - 16.6), with a minimum of 1.4 pg/mL and a maximum of 155 pg/mL in women. In men, we identified a maximum of 1903 pg/mL and a minimum of 2 pg/mL. Increased serum levels of IL-1 (> 5 pg/mL) were identified in 68 women (50%) and 78 pg/mL men (40.4%). In our study group, increased levels of IL-1 were identified in 68 women (50%) and 78 men (40.4%). Interestingly, the median value of IL-1 in patients with moderate diseases was more significant than in patients with severe forms (7.30 *vs* 3.22) but less than in mild forms (3.78). Additionally, among men, the highest median value was found in patients with mild forms (74.80), compared to those with moderate forms (3.41) and severe forms (2.53) (Table V).

Table V

Median values of IL-1 and IL-6 by forms of disease and gender

Sex	Severity forms of disease	No. of cases	%	Median value for IL-1	Median value for IL-6
F	**Mild forms**	8	5.9	3.78	52.050
	Moderate forms	62	45.6	7.30	122.60
	Severe forms	66	48.5	3.22	194
	Total	**136**	100	–	–
M	**Mild forms**	2	1	74.80	85
	Moderate forms	81	42	3.41	133
	Severe forms	110	57	2.53	687.65
	Total	**193**	100	–	–

The median length of hospital stay (LOS) was 5.50 days for mild forms, 8 days for moderate forms, and 12 days for severe forms. The median LOS for patients who did not have an increased level of IL-1 was 9 days, and for those who did, it was 10 days. Statistical correlations were found only in men, with a p-value of 0.025 for a BMI greater than 30 and a p-value of 0.001 for a BMI greater than 25.

Among comorbidities in women, statistically significant associations were found between increased levels of IL-1 and the presence of haematological diseases (p = 0.000), type I diabetes mellitus (p = 0.000) and chronic obstructive pulmonary disease (p = 0.000). In men, we found correlations only with type II diabetes mellitus and increased levels of IL-1 (p = 0.015).In men, increased levels of IL-1 correlated with cough (p = 0.019) and nausea (p = 0.049). In women, increased levels of IL-1interleukins correlated with myalgias, p = 0.039. No correlations were identified between patients who developed at least one complication during hospitalisation and an increased value of IL-1. Regarding IL-6, the median value was 154.25 pg/mL in women (IQR: 49.65 - 391.55) and 121.10 pg/mL in men (IQR: 45.75 - 229.47). The minimum value was 2 pg/mL, and the maximum was 5420 pg/mL in females and 5333 pg/mL in men, with 126 women (92.6%) and 175 men (90.7%) having levels of IL-6 more than 17 pg/mL. The median LOS for those who had normal values of IL-6 was 8.50 and 10 days for those who did not.

Correlations were identified between levels of IL-6 and BMI, with values between 25 and 30 in women (p = 0.006) and between 21 and 32 in men (p = 0.026). However, no correlations were found between increased levels of IL-6 and a BMI greater than 30 in women (p = 0.184) or men (p = 0.25). Increased levels of IL-6 in women correlated with the presence of active neoplasia (p = 0.001) and a history of oncological diseases (p = 0.001). Increased levels of IL-6 correlated with abdominal pain (p = 0.027). In women, increased levels of IL-6 correlated with myalgias p = 0.025.

Patients who developed at least one complication during hospitalisation had a median value of IL-1 and IL-6 of 181 pg/mL and 13.7 pg/mL, respectively, compared to those who did not experience any complications (107 pg/mL and 2.93 pg/mL). In both females and males, high levels of IL-6 directly correlated with bacterial co-infection (p = 0.002 and p = 0.02). Acute respiratory failure was associated with increased levels of IL-6 in women (p = 0.001) but not men (p = 0.56). No statistical correlations were identified between smoking status and increased levels of both interleukins (p = 0.295 and p = 0.841).

Immunomodulatory treatment, consisting of targeted therapy with an IL-6 inhibitor (tocilizumab), was administered to 76 patients (15.8%). Corticotherapy was administered to 285 patients (86.6%), and 240 (72.9%) also received antibiotic treatment.

IL-1

IL-1 is a signalling molecule that plays important roles in the innate and adaptive immune systems. It is part of a family of IL-1-like cytokines, which includes 11 cytokines and 10 receptors (*e.g.*, IL-33, IL-18). All members of the IL-1 cytokine family can promote inflammation, and their activities are influenced by various factors, including gene transcription and how they bind to specific receptors. The binding process can be controlled by cytokines with antagonistic effects, such as IL-1Ra and IL-36Ra [20].

In addition to its role as a potent mediator of inflammation, IL-1 has several other functions: it acts as a lymphocyte-activating factor, mediates fever, enhances the proliferation and differentiation of B

and T cells, and stimulates fibroblast proliferation and collagen production [21]. The IL-1 family likely evolved to improve the effectiveness of adaptive immunity by enhancing the activity of Th1, Th2, Th17 and CD8 T cells, in conjunction with the components of the innate immune system [22].

Although IL-1 is known to endorse a host-protective antiviral response, more research is still needed regarding its role in SARS-CoV-2 infection. Some studies have identified high levels of IL-1 in lung macrophages and bronchoalveolar lavage fluid in patients who develop severe forms of COVID-19 [23], as well as increased levels of the NLRP3 inflammasome, which triggers the release of IL-1 [24]. However, other studies have shown that high serum levels of IL-1 do not correlate with disease severity [25].

Various factors influence IL-1 levels in individuals with COVID-19, including age, biological differences and comorbidities [26]. Our study's median age of 65 in women and 53 in men may contribute to the lack of a clear correlation between elevated IL-1 levels and disease severity.

Aging is associated with a decline in immune function and reduced cytokine responses, which may explain why IL-1 levels did not predict severity as strongly as expected. The hormonal differences between genders, particularly the protective role of oestrogen in women, could influence the immune response to COVID-19. Previous studies have shown that oestrogen modulates immune cell activity, potentially explaining why in women there are fewer severe cases despite higher IL-1 levels. Our study's findings are that severe forms of disease were more prevalent in men and align with growing evidence that sex hormones can impact the severity of viral infections [27,28], but we should always keep in mind that perhaps these results are influenced by the fact that men are at higher risk of developing cardiovascular events.

IL-6

IL-6 is a pleiotropic mediator of inflammation. It stimulates the production of acute-phase proteins, the differentiation and proliferation of hematopoietic cells and hepatic cells. Additionally, it stimulates the formation of atheromatous plaque and increases muscle sensitivity to insulin [29].

Moreover, IL-6 can function as an anti-inflammatory molecule by inhibiting the apoptosis of intestinal epithelial cells, aiding in the regeneration processes of the liver and pancreas, stimulating the effects of the nonspecific immune system, promoting antibody production, and regulating neutrophil tissue infiltration [30]. Conversely, IL-6 can also exhibit pro-inflammatory activities such as stimulating the hepatocytes to secrete the acute-phase proteins, decreasing the production of fibronectin, albumin, and transferrin, inhibiting T-regulatory cell differentiation, and inhibiting T cell apoptosis [31].

Patients who developed severe forms of COVID-19 or suffered from ARDS had increased levels of IL-6 [32,33], and it has been demonstrated that IL-6 can cause damage to the alveolar membrane. Additionally, IL-6 can alter the structure of the endothelial cells by stimulating the vascular endothelial growth factor (VEGF), resulting in increased permeability and chemotaxis of neutrophils in the alveolar space [34]. Thus, there is a buildup of interstitial fluid in the alveoli, resulting in hypoxia [29].

Given that our study group was predominantly composed of individuals over 65, we can postulate that IL-6 may be a better predictor of severity, as its levels were more significant in severe forms. No such presumptions can be made regarding IL-1.

We also noted that elevated IL-6 levels were identified in patients with a higher BMI. In our study group, most participants of both sexes had a BMI over 25 kg/m^2, with a considerable part exceeding 30 kg/m^2. We found no significant associations between elevated IL-6 levels and higher BMI values in either women or men.

However, a significant relationship was identified between elevated IL-6 levels and lower BMI thresholds in both sexes. For IL-1, statistical correlations were found only in men, with notable associations for both BMI categories.

Co-morbidities and co-medications

Most women and a substantial portion of men in the study had more than one comorbidity. Hypertension emerged as the most prevalent pre-existing condition, affecting a large proportion of women and nearly half of the men. Type II diabetes mellitus was the second most common comorbidity, impacting a notable segment of both women and men. Our findings suggest that ACE inhibitors may have a role in disease progression, particularly in men. Still, our findings may be influenced by the fact that patients who received ACE inhibitors also received other medications and had comorbidities. Further investigations need to be done, as recent studies suggest that ACEIs and ARBs do not significantly increase ACE2 expression [35]. Also, statins showed no significant correlation with increased oxygen needs, aligning with studies suggesting that statins may have a protective role in COVID-19 by modulating immune responses [36]. However, further investigation is needed to clarify whether these medications contribute to the severity or protection against disease.

A nationwide Swedish cohort study illustrated that the prior use of statin drugs was associated with a lower risk of developing severe disease and mortality, suggesting that the use of statins in COVID-19 could have a protective effect [36]. Conversely, another study from Johns Hopkins stated that statins increase the production of ACE2, thereby increasing the cell's sensitivity to SARS-CoV-2 infection, which could result in more severe cases of disease [37]. In

our group, we found a statistical correlation between the use of statins and the need for the oxygen supplementation only in men.

Experimental animal studies suggest that thiazide-type diuretics could lower the expression of ACE2 compared to statins [38] – using a thiazide-like diuretic correlated with the need for oxygen supplementation in men, not women. Thus, IL-1 and IL-6 blockade could have various positive effects in inflammatory diseases and autoimmune and malignant pathologies. There are several targeted therapies, and one of the most important positive aspects of their use is that they are not known to cause serious adverse reactions, such as lymphoproliferative disorders, as other targeted therapies do.

The most researched approach to ease the pro-inflammatory effects of IL-6 in developing respiratory damage is inhibiting the IL-6 receptor. Different studies have been recently published [29]. Our study highlights the potential utility of IL-1 and IL-6-targeted therapies in treating COVID-19, particularly in patients with elevated IL-1 and IL-6 levels and comorbid conditions. With agents already in development, further studies are warranted to assess their efficacy in reducing cytokine-mediated damage, especially in patients who show high levels of IL-1 or IL-6**.** [39, 40]. Given the safety profile of these therapies, they could offer a promising treatment strategy for severe COVID-19 and other inflammatory conditions.

The median IL-6 serum level was higher in women than in men. Levels above the cut-off were observed in a high percentage of both women and men, with IL-6 elevation more frequent than IL-1 in both sexes. In comparison, elevated IL-1 levels were detected in approximately half of the women and less than half of the men. Our findings suggest that IL-6 may serve as a better predictor of disease severity than IL-1, as its levels were significantly higher in severe cases of COVID-19.

Another key difference between IL-1 and IL-6 levels in our study group is that, in women, the median IL-6 level was highest in severe cases, followed by moderate and then mild cases. Similarly, the median IL-6 level in men was also greater in severe cases compared to moderate and mild cases. As previously discussed, IL-1 levels can be reduced in elderly people, and studies show that IL-6 can also be diminished in elderly people [41].

Increased levels of IL-1 correlated with the presence of cough. A notable study demonstrated that, like *Bordetella pertussis*, IL-1 can induce the production of a muramyl peptide, which acts as an enzyme that can destroy the ciliated epithelium of the respiratory tract [42]. In women, increased levels of both inter-leukins correlated with myalgias. In men, abdominal pain correlated with the increased levels of IL-6. Another study suggests that human parechovirus-3 (HPeV-3) infection could be exacerbated by elevated serum levels of IL-6, as IL-6 induces the production of endothelin 2, which is known to cause pain [43].

Future research

The potential role of predictive biomarkers is still under investigation. So far, we know that elevated levels of these two interleukins may be associated with severe forms of disease. However, whether they could also serve as biomarkers that predict the response to therapy or long-term outcomes remains to be seen. Interestingly, some studies support the idea that high levels of IL-6 could be associated with the development of long COVID-19 or post-acute sequelae of SARS-CoV-2 infection [44]. Understanding the link between cytokine levels during an acute event and subsequent symptoms is also crucial in COVID-19. The question is whether prolonged or dysregulated IL-1 and IL-6 levels play a role in the development of long COVID-19.

Conclusions

In our study, IL-6 levels were more strongly associated with disease severity than IL-1, particularly in severe SARS-CoV-2 infections, suggesting that IL-6 could be a more reliable predictor of disease progression. The weaker predictive value of IL-1 may be linked to age-related immune decline, especially in older individuals.

Hormonal differences, such as the protective effects of oestrogen in women, could explain the gender disparities in disease severity, with men experiencing worse outcomes despite having lower IL-6 levels. Elevated IL-6 was notably associated with lower BMI thresholds in both sexes, while IL-1 correlated with BMI only in men, indicating potential sex- and weight-related variations in cytokine responses. IL-1 was linked to cough, likely due to its role in respiratory epithelial damage. At the same time, IL-6 correlated with abdominal pain in men and myalgias in women, reflecting cytokine-driven differences in symptom expression.

The association between ACE inhibitors and increased oxygen requirements in men raises concerns about their role in modulating disease severity through ACE2 expression. However, further studies are necessary to explore other potential influencing factors like comorbidities, age, or environmental conditions. Statin use showed no significant link to increased oxygen needs, supporting a potential protective effect, but conflicting results warrant further investigation.

Conflict of interest

The authors declare no conflict of interest.

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