Article

Relation between Cytokines Expression and Pulmonary Dysfunction-among a Cohort of COVID-19 Patients

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Abstract: Aim: In individuals with COVID-19, the study assessed the relationship between cytokine expression and pulmonary dysfunction. These correlations may help to suggest strategies for prevention and therapies of coronavirus disease outbreak. **Patients and methods:** 50 healthy participants and 100 COVID-19 patients participated in this study. COVID-19 participants were subdivided into moderate and severe groups based on the severity of their symptoms. In both patients and controls, measurements of white blood cells (WBCs), lymphocytes, C-reactive protein (CRP), interleukin (IL)-1, IL-4, IL-6, IL-18, and IL-35 were estimated. All the patients performed chest CT and CO-RADS score was assessed. **Results:** All patients had increased WBCs count and CRP, IL-1, IL-4, IL-6, IL-18, and IL-35 levels than healthy controls. While WBCs, CRP, and cytokines like IL-1β and IL-6 showed significantly higher levels in the severe group as compared to moderate patients, IL-4, IL-35, and IL-18 showed comparable levels in both disease groups. Furthermore, CO-RADS score was positively connected with WBCs, CRP, and cytokine levels (IL-35, IL-18, IL-6, IL-4 and IL-1β) in both groups, and lymphocyte levels in all patient groups considerably decreased as compared to the controls. CO-RADS score, also demonstrated a positive correlation with lymphocytes in the moderate COVID-19 patients, whereas in the severe patients, it demonstrated a negative correlation with lymphocytes. **Conclusion**: Severe COVID-19 patients, compared to individuals with moderate illness and healthy controls, patients had lower lymphocyte counts and increased CRP with greater WBCs counts. In contrast to moderate COVID-19 patients, severe COVID-19 patients had higher levels of IL-1β and IL-6, but IL-4, IL-18, and IL-35 between both illness categories at close levels. CO-RADS 5 was the most frequent category in both moderate and severe cases. Patients with a typical CO-RADS involvement had a higher CRP and white blood cell count with a lower lymphocyte count than the others. Cytokine levels were considered a surrogate markers of severe lung affection in COVID 19 patients.

Keywords: cytokines; pulmonary; COVID-19; CORADS; moderate; severe

1. Introduction

The coronavirus disease outbreak of 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO) in March 2020. Lung is the primary target organ for the new respiratory and systemic sickness COVID-19, which also causes damage to other organs. Detailed alveolar oedema, proteinaceous exudate, fibrin deposition, and immune cell infiltration were found in the post-mortem lung tissue of COVID-19 patients **[1].** One of the primary processes contributing to ALI (acute lung injury) and disease development was thought to be the cytokine storm, much like other viral infection

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diseases like severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) **[2, 3].** In a previous study, it was discovered that the plasma levels of interleukin (IL)-10, IL-2, IL-7, tumour necrosis factor (TNF), IP-10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1A were higher in COVID-19 patients who were in the intensive care unit (ICU) as compared to those who weren't **[4].** A different investigation with 21 COVID-19 cases found that severe cases had greater levels of IL-2R, IL-6, IL-10, and TNF-α than did moderate cases **[5].** Recent research suggests that when it comes to detecting COVID-19, chest computed tomography (CT) may be more sensitive than real-time polymerase chain reaction (RT-PCR). Based on the imaging results, a chest computed tomography (CT) scan may also be used to assess the disease's severity **[6, 7].** Created by the Dutch Radiological Society, the COVID-19 Reporting and Data System (CO-RADS), is a categorical grading system for chest CT scans that rates the probability of COVID-19 infection in patients with moderate to severe symptoms on a range from 1 (very low) to 5 (very high) **[8].** The correlation between cytokine state and lung injury as determined by chest CT in COVID-19 patients is not well understood. Therefore, our initial goal was to contrast the cytokine profiles, CO-RADS score, and CT patterns in moderate versus severe COVID-19 patients. The second analysis looked at the relationship between laboratory indices and CO-RADS category.

2. Subjects and methods

2.1. Study Population

This cross-sectional study comprised 100 COVID-19 patients (mean age 60.95 years) based on RT-PCR results showing SARS-CoV-2 positive on nasopharyngeal swabs. The viral genome was amplified using the Invitrogen SuperScript™III Platinum ® One-Step qRT-PCR Kit (Catalog number: 11732020, Waltham, MA). From March 2021 to July 2021, all patients were picked up from Misr International Hospital in Cairo, Egypt. Exclusion criteria included patients with thyroid dysfunction, autoimmune disorders, eczema, those known to have a kidney failure, chronic respiratory disease, liver dysfunction, ischemic heart disease, cerebrovascular diseases, lactating women and pregnancy, and patients receiving immuno-modulatory drugs. Fifty healthy volunteers that had no symptoms of COVID-19 were used as a control group. The research procedure was followed in accordance with the principles of ethical conduct and the Helsinki Declaration. All participants provided written informed permission following the institutional review board's ethical committee's approval of this study.

The COVID-19 patients were split into two groups in accordance with the seventh edition of the Guidelines on the Diagnosis and Cure of COVID-19 published by the National Health Commission of China **[9].** Group (I) contained (50) patients with moderate COVID-19, while group (II) contained (50) patients with severe COVID-19. The control group was a part of group (III).

2.2. Laboratory assay

Participants' blood was drawn and placed in simple tubes (4 ml each). Serum was isolated from blood in simple tubes after a 30-minute incubation period at room temperature. Prior to the biochemical analyses, quickly serum samples were separated, aliquoted, and refrigerated at -40°C. According to the manufacturer's instructions, serum levels of interleukins (IL-1, IL-4, IL-6, IL-18, and IL-35) were measured using a standard sandwich enzyme-linked immune-sorbent assay (ELISA) kit from R&D Systems (USA).

2.3. High Resolution CT chest

All the patients had chest CTs utilizing a 16 slice CT scanner (Toshiba, Japan) without contrast. Window setting that allowed observation of the lung parenchyma were used (window level -600 to -700 HU; window width, 1200-1600 HU). A high resolution-method, using thin slice thickness < 1.5 mm was used. All CT findings were evaluated for the following: 1- pattern of lesion (ground glass opacity (GGO), consolidation, crazy paving,

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combined GGO and consolidation). 2- Distribution (peripheral subpleural, central, or both). 3- Location (unilateral, bilateral). 4- CO-RADS category.

2.4. Statistical analysis

Data were analyzed using SPSS version 20 for Windows (IBM Corp., 2011). Numbers, (percentages), and mean SE were used to characterize categorical and quantitative variables, respectively. The one-way analysis of variance (ANOVA) was used to analyse all statistical differences between groups, and Duncan's post hoc analysis was then performed. The Pearson correlation coefficients approach was used to evaluate the correlation analysis between the various analyzed factors. $P < 0.05$ values have been considered statistically significant.

3. Results

The demographics of all subjects at the outset are shown in **Table 1.** There was no discernible difference in age between the COVID patient (moderate and severe) groups and the control group. Regarding oxygen therapy, and the use of non- invasive ventilation, the patients of severe group, had a higher significant use than those of moderate group (P<0.001 for each).

Table 1. Baseline demographics among the studied groups.

Variable	Moderate patients (n=50)	Severe Patients (n=50)	Controls (n=50)	P-value
Age (Year)	60.56±1.15	63.64±1.27	58.48±1.24	0.06
Male, no. (%) Female, no. (%)	25(50%) 25(50%)	33 (66%) 17 (34%)	28(56%) 22(44%)	0.263
Oxygen therapy	11(22%)	50 (100%)	--	<0.001
NIV Yes, no. (%) No, no. (%)	(0%) 50(100%)	34 (68 %) 16 (32%)	------	< 0.001

Results were presented as numbers and percentages. The one-way ANOVA test was used to compare the results, which were shown as mean±SE. The post hoc analysis was carried out using the LSD test if the results were significant. Abbreviations: NIV: Non-invasive ventilation.

As regard the CT findings in the study, it was found that patients of severe disease had a CO-RADS 4 more than patients of moderate disease (42 % vs 16% , p= 0.003), while CO-RADS 5 was significantly more in moderate COVID 19 patients than those of severe illness (74% vs 52%, p= 0.013). Concerning the CT pattern that was found, consolidation was more significantly in severe cases than moderate ones (20% vs 6%, p=0.037). Nevertheless, ground glass opacities were more in moderate cases in comparison to severe cases (80% vs 60%, p= 0.029). Although there was no significant difference in the distribution of lesions between moderate and severe patients (p> 0.05), **Table (2).**

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Table 2. CO-RADS categories, CT pattern, and distribution of lesions in the studied patients.

Variable	Moderate patients (n=50)	Severe patients (n=50)	P-value
CO-RADS -CO-RADS 3	5 (10 %)	3 (6 %)	0.480
-CO-RADS 4	8 (16 %)	21 (42 %)	0.003
-CO-RADS 5	37 (74 %)	26 (52 %)	0.013
CT pattern - Consolidation	3 (6%)	10 (20 %)	0.037
- GGO	40 (80 %)	30 (60 %)	0.029
- Consolidation & GGO	7 (14 %)	8 (16 %)	0.779
- GGO & Pleural effusion	---	2 (4 %)	-
CT distribution Subpleural & peripheral Subpleural & peripheral and central	46 (92 %) 4 (8 %)	45 (90 %) 5 (10 %)	0.727
Bilateral lung lesions Unilateral lung lesions	42 (92 %) 8 (8 %)	45 (90 %) 5 (10 %)	0.372

Results were presented as numbers and percentages. The one-way ANOVA test was used to compare the results. Abbreviations: CO-RADS (COVID-19 Reporting and Data System), CT (computed tomography), COVID-19 (coronavirus disease 2019), and GGO (ground-glass opacities).

Table (3) illustrated the correlation between CO-RADS score and blood markers in both moderate and severe cases. Patients with COVID-19 showed a significant positive correlation ($p<0.001$) between their CO-RADS score and their WBCs, CRP, interleukins (IL-1, IL-4, IL-6, IL-18, and IL-35) levels.

Table 3. Correlation between CO-RADS with study parameters and cytokines in moderate and severe groups.

Variable	CO-RADS			
	Moderate patients		Severe patients	
	r	*p*	*r*	*p*
WBCs	.510***0	**<0.001**	.650***0	**<0.001**
CRP	.642***0	**<0.001**	.894***0	**<0.001**
IL1B	0.680***	**<0.001**	0.578***	**<0.001**
IL4	.563***0	**<0.001**	.426***0	**<0.001**
IL6	.812***0	**<0.001**	.924***0	**<0.001**
IL18	.823***0	**<0.001**	.869***0	**<0.001**
IL35	.794***0	**<0.001**	.777***0	**<0.001**

Using a MedCalc statistical programme (Ostend, Belgium), a straightforward linear correlation analysis was done by Pearson's method to determine the level of dependence between variables. * Correlation is significant at the 0.05 level, ** at the 0.01 level, and *** at the 0.001 level. Abbreviations: CO-RADS; COVID-19 Reporting and Data System; WBCs.: white blood cells; CRP: C-reactive protein; IL: Interlukin.

Fig. (1) showed blood indices among the 3 studied groups, WBCs, lymphocyte and CRP. WBCs, CRP in both patient groups revealed a significant (*P<0.001*) elevation compared to the controls. In severe group a significantly (*P<0.001*) higher levels of WBCs and

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CRP, when compared to moderate group, lymphocyte in moderate group was significantly higher (*P<0.05*) than in severe group.

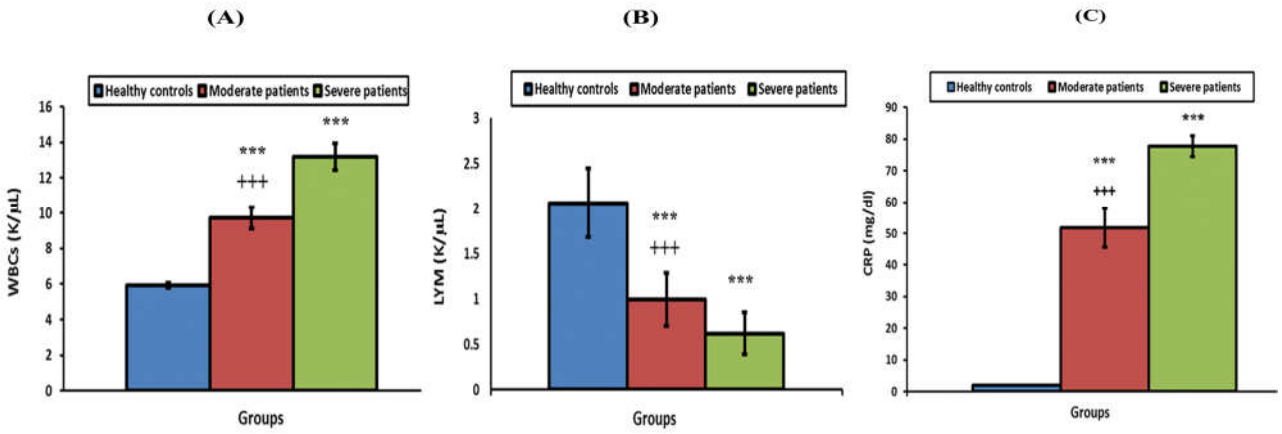

Figure 1. (A) WBCs; (B) LYM; (C) CRP of healthy controls, and moderate and severe groups. *** significant compared to healthy control at p<0.001. +++ significant compared to severe group at p<0.001.

Fig. (2) showed interlukines among the 3 studied groups, when compared to the controls, IL-1β, IL-4, IL-6, IL-18, and IL-35 in moderate and severe COVID patient groups revealed a significant elevation (*P<0.001*). IL-6 levels in the severe group were significantly (*P<0.001*) higher than in the moderate group IL-1β in moderate group was significantly higher (*P<0.05*) than in severe group. When comparing the moderate and severe groups, IL-4, IL-18, and IL-35 did not show any changes that were statistically significant (p>0.05).

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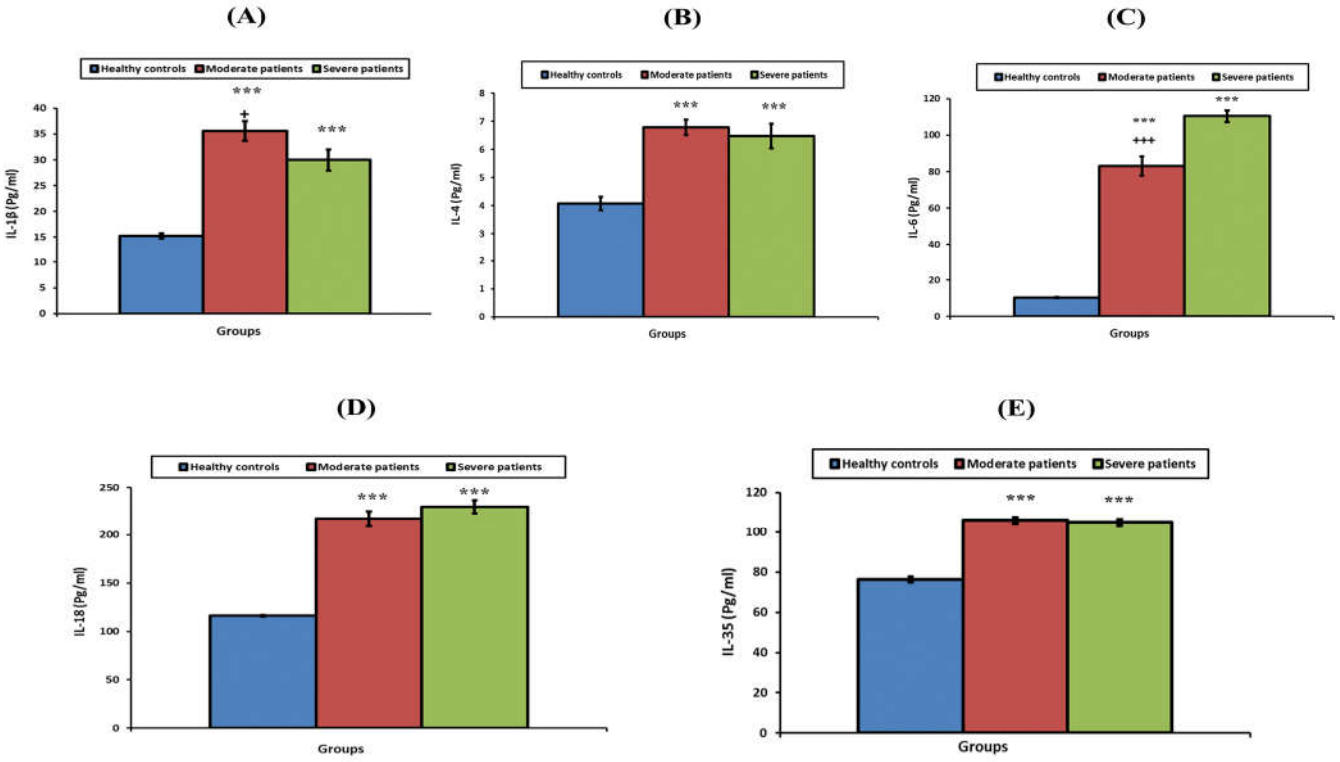

Figure 2. (A) IL-1β; (B) IL-4; (C) IL-6; (D) IL-18 ; (E) IL-35 of healthy controls, moderate and severe groups. *** significant compared to healthy control at p<0.001. +++ significant compared to severe group at p<0.001.

Furthermore, CO-RADS score of COVID-19 patients had a significant negative correlation (p<0.001) with lymphocyte in the severe group **(Fig. 3a)**, while demonstrating a significant positive correlation (p<0.01) in the moderate group **(Fig. 3b).**

(a) (b)

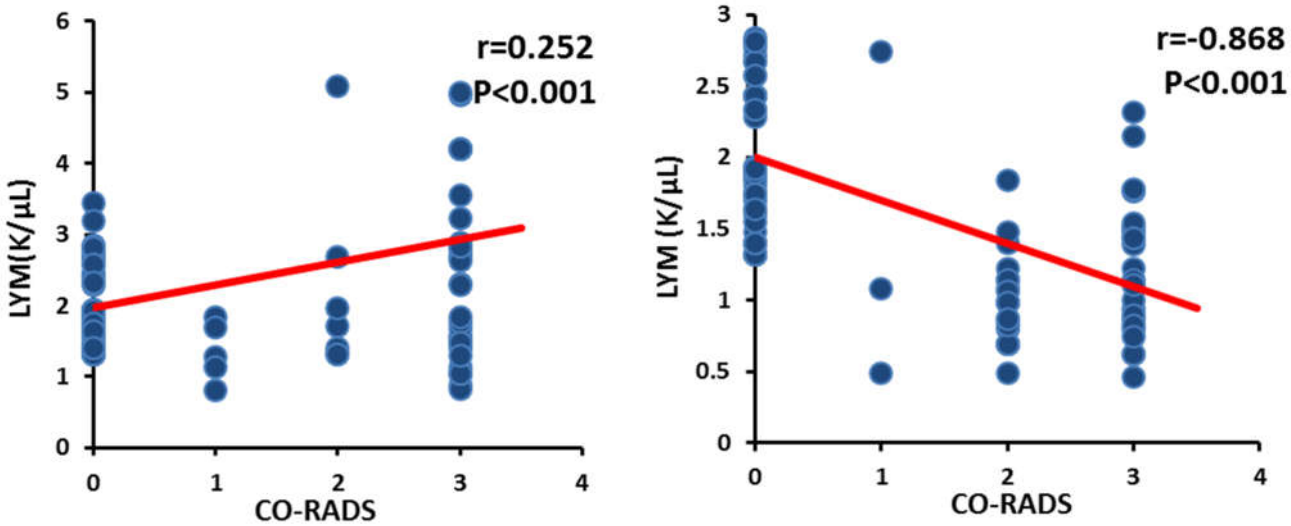

Figure 3. Correlation between CO-RADS with lymphocyte **(a)** in moderate group; **(b)** in severe group.

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4. Discussion

"Cytokine storm" event, which is brought on by the aggressive secretion of pro-inflammatory cytokines, due to COVID-19 infection. An excessive amount of inflammation results from the human immune system's hyperactive response to the SARS-CoV-2 virus. Studies looking at the cytokine profiles of COVID-19 patients have shown that the cytokine storm (CS) is closely related to lung injury, multiorgan failure, and a poor prognosis for severe COVID-19 **[10-11].** Adaptive immune cells and innate immune cells both produce cytokines. According to a study by **Ishikawa,** CS patients had high blood levels of IL-1, IL-6, and TNF-α are examples of pro-inflammatory cytokines, and IL-10 and IL-1 receptor antagonist are examples of anti-inflammatory cytokines **[12].** That agree with our data where IL-1β, IL-4, IL-6, and IL-18 as a pro-inflammatory cytokines and IL-35 as an anti-inflammatory cytokines are elevated in the serum of all patients in our study. Interleukin-6 can act as pro-inflammatory and anti-inflammatory mediator [**13**]. The anti-inflammatory cytokines IL-10 and GDF-15 levels were likewise enhanced throughout ICU treatment, according to **Notz *et al.*** [**14**] study, which also found that IL-6 levels were elevated at every time-point. That is in line with our results, which demonstrated higher levels of all cytokines in the study (IL-35, IL-18, IL-6, IL-4, and IL-1β). In parallel, **Chen *et al.*** reported higher levels of TNF-α, IL-6, and IL-10 in severe instances (n = 11 patients) compared to moderate cases (n = 10 patients) in their research of data from 21 patients in China **[15].**

An unregulated immune response that results in ongoing activation and cell growth in immune cells including lymphocytes and macrophages, as well as their production of copious amounts of cytokines, is the cause of CS. According to **Shimizu (2019) [16],** IL-1, IL-6, IL-18, IFN-γ, and TNF-α are responsible for the clinical findings associated with CS. The diagnosis, therapy, and follow-up of patients with COVID-19 pneumonia all depend heavily on thin slice CT. Chest CT can detect infection in its early stages and aid in patient isolation **[17].**

According to **Prokop *et al.*,** the degree of suspicion for pulmonary involvement is indicated by the CO-RADS categorical grading scheme for pulmonary involvement of COVID-19 on non-enhanced chest imaging [**8**]. The present study found that CO-RADS 5 score was the most encountered one in moderate and severe cases of COVID 19 (74% and 52% respectively). Notably, **Kwee *et al.*** [**18**] meta-analysis, found that the frequency of COVID-19 infections was higher in patients with higher CO-RADS classifications, which was in agreement with our study, the CO-RADS was significantly higher with severity. Regarding the CT pattern that was found in the current study, ground glass opacities were more frequent pattern that was detected in both moderate (80%) and severe groups (60%), while consolidation was more among patients of severe COVID 19 (20%). In a meta-analysis of 13 research, **Bao *et al.*** discovered that GGO was the most prevalent manifestation, being recorded in 83.31% of patients. There were 13 papers included in the meta-analysis and GGO was the key finding in 11 of them **[19].** In a series of 83 individuals, **Li *et al.*** also described consolidation in patients with severe or advanced illness **[20].** In a research by **Song *et al.*** individuals who had symptoms for more than four days and those who were older (> 50 years) had considerably greater incidences of consolidation **[21].** As regard the anatomical distribution of lesions in the current study, it was found that subpleural, peripheral and bilateral affections were the most frequent sites of involvement in both moderate and severe cases with no significant difference. This coincides with other studies **[21, 22].**

The second goal of this research was to determine the correlation between the CO-RADS severity and several laboratory markers. It was found that there was a significant positive correlation between CO-RADS score and both of white blood cell count and CRP in both moderate and severe cases. However, a negative correlation was found between CO-RADS and lymphocyte count in severe group only. There are limited studies on the correlation of CO-RADS and blood count, one study found that there was no correlation between CO-RADS score and different CBC parameters; neither lymphopenia nor high

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neutrophil lymphocyte ratio **[23].** Another study found that the highest CRP value was also observed in the CO-RADS score 5 **[24].** The severity of the disease at the time of diagnosis and lung lesions were frequently connected with elevated CRP levels, according to earlier investigations **[25].**

Our study found a significant positive correlation between CO-RADS groups category and all measured cytokines of cytokine release syndrome, which imply that the more CT affection, the more for cytokine storm. **Ramadan *et al.*** investigated cytokine profile in patients with COVID-19 and found a correlation between it and the severity of the disease as determined by the CO-RADS score. They discovered that the level of intercellular adhesion molecule 1 and CO-RADS score were significantly positively correlated **[26].**

5. Conclusion

Severe COVID-19 compared to individuals with moderate illness and healthy controls, patients had lower lymphocyte counts and increased CRP with greater WBCs counts. IL-1β and IL-6 levels were greater in severe instances compared to moderate COVID-19 patients, but IL-4, IL-18, and IL-35 between both illness categories at close levels. CO-RADS 5 was the most frequent category in both moderate and severe cases. Patients with a typical CORADS involvement had a higher CRP and WBCs count with a lower lymphocyte count than the others. Cytokine levels were considered a surrogate markers of severe lung affection in COVID 19 patients.

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Conflicts of Interest: The authors declare no conflict of interest.

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