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# VEGF, IL-17 and IgG4 levels of patients with lung sequelae in post-COVID-19 period

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## ABSTRACT

### VEGF, IL-17 and IgG4 levels of patients with lung sequelae in post-COVID-19 period

**Introduction:** Although the epidemiological and clinical characteristics of COVID-19 patients have been described; the pathogenesis of the disease and its long-term consequences are still unclear. Pulmonary fibrosis is one of these late outcomes. In this study we evaluated Interleukin-17 (IL-17), vascular endothelial growth factor (VEGF), and immunoglobulin G4 (IgG4) levels of COVID-19 infected patients with different clinical course and their effect on pulmonary fibrosis in post-COVID period.

**Materials and Methods:** In total, 90 patients were evaluated. Among the patients who presented for a control visit between 3-12 weeks after acute infection; patients with signs of pulmonary sequelae radiologically (traction bronchiectasis, interseptal thickening, disorders in parenchyma architecture) were classified as Group I (n= 32), patients who recovered without sequelae radiologically as Group II (n= 32). The Control group included healthy individuals who did not have COVID-19, and was classified as Group III (n= 26).

**Results:** The mean age in Group I was significantly higher than Group II and III ( $p < 0.001$ ). There was a statistically significant difference between the VEGF and IL-17 values based on the patient group they are in ( $p < 0.05$ ). Vascular endothelial growth factor values of Group I and III were significantly

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lower than the patients in Group II ( $p < 0.001$ ). IL-17 values of Group I and II were found to be significantly lower than Group III ( $p = 0.005$ ). There was no statistically significant relationship between groups in terms of IgG4 values.

**Conclusion:** In our study, it was observed that the profibrotic effects of VEGF, IL-17, and IgG4 were not dominant in patients who recovered with pulmonary sequelae after COVID; therefore, it is thought that different mechanisms mentioned or not yet revealed may cause this outcome.

**Key words:** COVID-19; IL-17; VEGF; IgG4; pulmonary sequelae

## ÖZ

### Post-COVID-19 dönemi akciğerde sekel gelişen hastalarda VEGF, IL-17 ve IgG4 düzeyleri

**Giriş:** COVID-19 hastalarının epidemiyolojik ve klinik özellikleri tanımlanmış olmasına rağmen; hastalığın patogenezi, uzun dönem etkiler hala belirsizdir. Pulmoner sekel bu geç sonuçlardan biridir. Bu çalışmada; COVID-19 ile enfekte olan ve farklı klinik seyir gösteren hastaların akut enfeksiyon sonrası dönemde interlekin-17 (IL-17), vasküler endotelial büyüme faktörü (VEGF), immunglobulin G4 (IgG4) düzeylerinin pulmoner sekel gelişimine etkilerini değerlendirmek hedeflenmiştir.

**Materyal ve Metod:** Toplam 90 hasta çalışmaya dahil edildi. Akut enfeksiyon sonrası 3-12 hafta arası kontrol amaçlı başvuran hastalardan; radyolojik olarak pulmoner sekel bulguları (traksiyon bronşektazisi, interseptal kalınlaşma, parankim yapısında bozukluklar) olan hastalar Grup I ( $n = 32$ ), radyolojik olarak sekelsiz iyileşen hastalar Grup II ( $n = 32$ ), COVID olmayan sağlıklı bireyler Grup III ( $n = 26$ ) olarak sınıflandırıldı.

**Bulgular:** Grup I'deki hastaların yaş ortalaması Grup II ve III'e göre anlamlı derecede yüksek saptandı ( $p < 0,001$ ). Vasküler endotelial büyüme faktörü ve IL-17 değerleri arasında, bulundukları hasta grubuna göre istatistiksel olarak anlamlı fark vardı ( $p < 0,05$ ). Grup I ve III'ün VEGF değerleri Grup II'deki hastalara göre anlamlı derecede düştü ( $p < 0,001$ ). Grup I ve II'nin IL-17 değerleri Grup III'e göre anlamlı olarak düşük saptandı ( $p = 0,005$ ). IgG4 değerleri açısından gruplar arasında istatistiksel olarak anlamlı bir ilişki yoktu.

**Sonuç:** Çalışmamızda COVID sonrası pulmoner sekel ile iyileşen hastalarda VEGF, IL-17 ve IgG4'ün profibrotik etkilerinin baskın olmadığı; dolayısıyla bahsedilen veya henüz ortaya konmamış farklı mekanizmaların bu sonuca neden olabileceği düşünülmektedir.

**Anahtar kelimeler:** COVID-19; IL-17; VEGF; IgG4; pulmoner sekel

## INTRODUCTION

The SARS-CoV-2 coronavirus, which is the cause of the COVID-19 infection, first appeared in Wuhan, China in December 2019, and the epidemic it created was declared a pandemic by the World Health Organization (WHO) in March 2020 (1). Significant rates of chronic respiratory symptoms or the development of fibrotic diseases in surviving adults cause increasing concern about the long-term consequences worldwide. Pulmonary fibrosis is one of these late outcomes (2).

Although coronavirus cases have an acute course, acute respiratory distress syndrome (ARDS) cases have been reported to progress to fibrosis within a week (3). It has been reported that hereditary immune response (4), and proinflammatory/profibrotic factors (5) may have an impact on post-COVID fibrosis. Fibrosis is related to the severity of hyperinflammation and cytokine release syndrome (6). Radiologic fibrotic changes depending on the severity of the COVID infection can be defined as traction bronchiectasis, septal thickening, and architectural disorders (7). The pathogenic relation between viral infection and stable or progressive fibrosis, virally activated

pathways, or cellular mechanisms of viral injury in post-COVID period is still unclear (2).

Because the neutrophils are the predominant cells in the course of COVID (6), interleukin 17 (IL-17) which is one of the neutrophil stimulating factors, may be responsible for this inflammation. Interleukin 17 is the best-known member of a multifunctional cytokine family. Tumor progression, chronic inflammation, and tendency to mucocutaneous infections have been shown in the absence or dysregulation of IL-17 (8). The role of the IL-17-induced pathway in the development of fibrosis has been reported, especially in patients with scleroderma and pulmonary fibrosis (9).

Increased vascular permeability as a result of diffuse injury to the alveolocapillary membrane by vascular endothelial growth factor (VEGF) is key in the pathogenesis of ARDS. In the study of Kong et al. (10), VEGF-D was found to be the most important indicator determining the severity of COVID-19 patients. Also, there are studies that mention idiopathic pulmonary fibrosis (IPF) progression and the severity of circulating VEGF-A levels (11,12).

Immunoglobulin G4 (IgG4) is the subtype with the lowest amount of 3-6% of the four IgG subgroups (13). It is released under the control of T-helper 2 cells (Th2) (14) and causes diseases with fibrosis (15). Its role in inflammation is not clear, and it is thought to have anti-inflammatory activity (26). The relationship of the COVID-19 and IgG4 was mentioned in one study (17) but the effect of IgG4 on the course of COVID has not been discussed yet.

We aimed in this study to evaluate effects of IL-17, VEGF and IgG4 on the development of pulmonary sequelae lesions, in COVID-19-infected patients with different clinical course; and potentially make a prediction in terms of targeted treatment.

## MATERIALS and METHODS

### Patient Selection

Patients who applied to the Pulmonary Diseases Polyclinic of the Training and Research Hospital, after being diagnosed with COVID-19 [with positive Polymerase Chain Reaction (PCR)] and came for a control visit within 3-12 weeks, were included in this observational cross-sectional study. Patients with suspected radiology or symptomatic but having negative PCR results or those with active infection were excluded.

To select the optimal number of participants, we implemented statistical power analysis using G\*Power software (18). According to the power analysis, in total,  $n = 90$  samples with 97.3% power for  $\alpha = 0.05$  error level. Post-COVID patients are divided into two groups, those who show computed tomography (CT) findings of pulmonary sequelae (traction bronchiectasis, interseptal thickening, disorders in parenchyma architecture) were classified as Group I ( $n = 32$ ), and those who recovered without sequelae as Group II ( $n = 32$ ). Healthy individuals who did not have COVID-19 and did not have any known chronic diseases were classified as the control group (Group III,  $n = 26$ ).

### Image Acquisition

COVID-19 reporting and data system (CO-RADS) (for use in the standardized assessment of pulmonary involvement of COVID-19 on unenhanced chest CT images) (19) scales of all patients at the beginning of the infection were obtained from the CT reports on the hospital database.

### Laboratory Assay

Human interleukin-17 (IL-17) ELISA kit (Bioassay Technology Laboratory, Shanghai, China), human vascular endothelial cell growth factor (VEGF) ELISA kit (Bioassay Technology Laboratory, Shanghai, China), and human immunoglobulin G4 (IgG4) ELISA kit (Elab science, Texas, USA) were used in this trial. Serum samples of patients were centrifuged at 2000-3000 rpm for 20 minutes and stored at  $-80^{\circ}\text{C}$  until the working day. All reagents, standard solutions, and samples were prepared as instructed. The absorbance of ELISA microplates was measured at 450 nm optic density (OD) using a Microplate reader (Tecan Infinite 200 PRO, Austria). IgG4 titers were evaluated as being below or upper of 7.8 mg/dL.

The trial protocol was approved by the Turkish Ministry of Health and Trakya University Faculty of Medicine Scientific Research Ethics Committee (TUTF-BAEK 2021/66), and informed consent forms were obtained from all patients.

### Statistical Analysis

All statistical analyses were performed with IBM SPSS 22 software. After the frequency analysis applied to the patient groups; normality tests were performed on the basis of patient groups, ANOVA test was performed in case of normality, and the Kruskal-Wallis test was performed where normality was not present. Fisher's test was performed to examine the relationships between categorical data. Spearman correlation analysis was performed to determine the relationships between quantitative variables. In the phase of statistical hypothesis testing, the number of observations for each demographic variable ( $n$ ), the mean of sub-dimension scores ( $\bar{x}$ ), standard deviation (SD), median (Med), the lower limit (Min), the upper limit (Max) and significance values ( $p$ ) were given. Research findings were evaluated at a significance level of  $p < 0.05$ .

## RESULTS

Demographic findings and mean numeric values of indicators, of 90 individuals included in the trial are given in Tables 1 and 2. When COVID patients were evaluated according to the categorical CT assessment Scheme, CORADS 3 and 5 for Group I, CORADS 2 and 3 for Group II were more frequent (Table 3). Table 4 shows demographic findings and mean VEGF, IL-17, and IgG4 values of the patients of all

**Table 1.** Demographic findings of the individuals included in the trial

| Variable            | n                   | %    |
|---------------------|---------------------|------|
| Gender              |                     |      |
| Male                | 45                  | 50.0 |
| Female              | 45                  | 50.0 |
| Groups              |                     |      |
| I. COVID-fibrosis   | 32                  | 35.6 |
| II. COVID           | 32                  | 35.6 |
| III. Control        | 26                  | 28.9 |
| Age (Mean $\pm$ SD) | 53.533 $\pm$ 14.419 |      |

**Table 2.** Mean numeric values of indicators

| Variable                                                         | n                   | %    |
|------------------------------------------------------------------|---------------------|------|
| IgG4                                                             |                     |      |
| Lower 7.8 ng/L                                                   | 87                  | 96.7 |
| Upper 7.8 ng/L                                                   | 3                   | 3.3  |
| VEGF (Mean ± SD)                                                 | 3417.097 ± 2020.937 |      |
| IL-17 (Mean ± SD)                                                | 91.616 ± 94.895     |      |
| IL-17: Interleukin-17, VEGF: Vascular endothelial growth factor. |                     |      |

**Table 3.** CORADS scales of COVID patients

| CORADS   | 2  | 3  | 4 | 5  | Total |
|----------|----|----|---|----|-------|
| Group I  | 2  | 12 | 6 | 12 | 32    |
| Group II | 14 | 14 | 3 | 1  | 32    |

\*CORADS: COVID-19 reporting and data system.

**Table 4.** Demographic findings of the individuals included in the trial based on patient groups

| Group                                                            | I (n= 32)          |       | II (n= 32)          |       | III (n= 26)        |      |
|------------------------------------------------------------------|--------------------|-------|---------------------|-------|--------------------|------|
| Variable                                                         | n                  | %     | n                   | %     | n                  | %    |
| Gender                                                           |                    |       |                     |       |                    |      |
| Male                                                             | 25                 | 78.1  | 12                  | 37.5  | 8                  | 30.8 |
| Female                                                           | 7                  | 21.9  | 20                  | 62.5  | 18                 | 69.2 |
| IgG4                                                             |                    |       |                     |       |                    |      |
| Lower 7.8 ng/L                                                   | 32                 | 100.0 | 32                  | 100.0 | 23                 | 88.5 |
| Upper 7.8 ng/L                                                   |                    |       |                     |       | 3                  | 11.5 |
| Age (Mean ± SD)                                                  | 63.656 ± 8.450     |       | 54.906 ± 12.790     |       | 39.385 ± 10.346    |      |
| VEGF (Mean ± SD)                                                 | 2996.71 ± 1951.233 |       | 4642.092 ± 1641.413 |       | 2426.81 ± 1819.589 |      |
| IL-17 (Mean ± SD)                                                | 71.302 ± 68.938    |       | 71.819 ± 80.847     |       | 140.983 ± 120.399  |      |
| IL-17: Interleukin-17, VEGF: Vascular endothelial growth factor. |                    |       |                     |       |                    |      |

**Table 5.** Age comparisons of the individuals participating in the trial based on their patient group

| Variable | Group            | $\chi$ | SS     | Min    | Max    | Test statistic | p*      | Significant difference |
|----------|------------------|--------|--------|--------|--------|----------------|---------|------------------------|
| Age      | I <sup>a</sup>   | 63.656 | 8.450  | 50.000 | 83.000 | 37.006         | <0.001* | a,b,c                  |
|          | II <sup>b</sup>  | 54.906 | 12.790 | 27.000 | 79.000 |                |         |                        |
|          | III <sup>c</sup> | 39.120 | 10.469 | 22.000 | 54.000 |                |         |                        |

\*:ANOVA test.

**Table 6.** Comparison of VEGF and IL-17 values of individuals participating in the trial based on their patient group

| Variable | Group            | $\chi$   | SS       | Min      | Max      | Test statistic | p**    | Significant difference |
|----------|------------------|----------|----------|----------|----------|----------------|--------|------------------------|
| VEGF     | I <sup>a</sup>   | 2996.710 | 2869.650 | 644.320  | 6400.000 | 18.649         | <0.001 | c and b<br>a and b     |
|          | II <sup>b</sup>  | 4642.092 | 4690.950 | 1267.500 | 6400.000 |                |        |                        |
|          | III <sup>c</sup> | 2479.154 | 1985.700 | 167.250  | 6400.000 |                |        |                        |
| IL-17    | I <sup>a</sup>   | 71.302   | 52.345   | 6.325    | 389.360  | 10.651         | 0.005  | b and c<br>a and c     |
|          | II <sup>b</sup>  | 71.819   | 53.916   | 5.043    | 449.450  |                |        |                        |
|          | III <sup>c</sup> | 144.388  | 106.160  | 6.239    | 418.680  |                |        |                        |

\*\*: Kruskal-Wallis test.

**Table 7.** Variation of IgG4 levels between groups

| Variable  | IgG4 (mg/dL) |       |           |     | Test statistic | p*    |
|-----------|--------------|-------|-----------|-----|----------------|-------|
|           | Lower 7.8    |       | Upper 7.8 |     |                |       |
|           | n            | %     | n         | %   |                |       |
| Group I   | 32           | 36.80 | 0         | 0   | 5.238          | 0.073 |
| Group II  | 32           | 36.80 | 0         | 0   |                |       |
| Group III | 23           | 26.40 | 3         | 100 |                |       |

\*:Pearson Chi-square test.

three groups participating in the trial. When the patients were compared based on age, the mean age in Group I was significantly higher than Group II and Group III and 78% of them are male (Table 5) ( $p < 0.05$ ).

Table 6 shows the comparison of the VEGF and IL-17 values of individuals participating in the trial based on their group. According to the results, there is a statistically significant difference between the VEGF and IL-17 values based on the patient group ( $p < 0.05$ ). Table 7 shows the results of the relationship between IgG4 and study groups, based on being higher or lower than 7.8 mg/dL.

## DISCUSSION

In this study, the VEGF, IL-17, and IgG4 levels of patients presented in the post-COVID period were examined to evaluate prominent mechanisms that

cause pulmonary sequela. IgG4 was found below the minimum value in both groups infected with COVID and it was interpreted in favor of not having any impact on the course of the disease. Interleukin-17 which has mucosal barrier, hyper-inflammation, and pro-inflammatory functions, was found to be significantly lower in Group I and Group II compared to the control group. This led us to suggest that its pro-fibrotic effect is not dominant in COVID-19 patients. Vascular endothelial growth factor, which has a significant role in the alleviation of acute inflammation, was found to be significantly higher in the patient group who recovered without sequelae compared to the patients who recovered with sequelae and the control group. It also suggests that this mediator, which is a growth factor, may not be effective on fibrosis in COVID-19 patients, and that other underlying profibrotic pathways should be investigated.

The most severe cases of COVID-19 were observed at older ages (20,21), and this group had the highest risk of developing post-infectious fibrosis in SARS-CoV infections (22). It has also been shown in demographic studies that COVID-19 affects men more (23,24). In our study, similar to these data 78% of Group I, which is an indicator of a more severe disease, was male, and the mean age was found to be statistically significantly higher than the other two groups ( $p < 0.001$ ).

### VEGF

The presence of VEGF receptors on both sides of the alveolocapillary membrane suggests its important in maintaining the structure and function of a normal lung (25). Damage to the epithelial and endothelial cells caused by the uncontrolled release of matrix metalloproteinases during the inflammatory phase, uncontrolled fibroproliferation, and vascular dysfunction induced with cytokines such as VEGF, IL-6, TNF- $\alpha$  play a key role in the pathogenesis of post-infectious fibrosis (26). In the study by Kong et al. which examined 24 COVID patients and the levels of fifteen different cytokines; VEGF-D was found to be the most important indicator in determining the severity of COVID-19 (10). In the study by Chi et al. (27), a weak but positive correlation was found between MCP-1, G-CSF, VEGF levels and viral titer, and 27 serum indicators, including IL-17 and VEGF, were found to be high in symptomatic patients. But in a trial examining the VEGF-A levels of pregnant patients infected with COVID-19; no significant difference was observed compared to healthy pregnant women, and it was not associated with the severity of the disease or obstetric complications (28). The relationship between VEGF-A and IPF is also confusing. While some studies showed decreased VEGF-A levels with BAL in patients with IPF (29); in another trial, values obtained were similar to the control group (30).

In our study; VEGF levels of Group II were found to be significantly higher than Groups I and III. Vascular endothelial growth factor is a cytokine that increases in the process of sedating inflammation. Patients in Group I were mostly those who were discharged after prolonged hospitalization and anti-inflammatory treatment, and presented at a later stage of the disease. With the immunosuppressive treatments they received during this period, the cytokine storm may have subsided and other mechanisms causing sequelae lesions may have become dominant. Group II

were mostly the patients who had a milder disease and came for control in earlier weeks. Therefore, it was thought that VEGF was high due to the fact that it is one of the factors controlling inflammation, which is still active in the earlier stages of the disease.

### IL-17

Interleukin-17 is a significant factor that protects cells on mucosal surfaces from extracellular factors and has a profibrotic effect by stimulating the production of TGF- $\beta$  and collagen proteins (31). After stimulation of CD4+ cells with TGF- $\beta$ , Th17 and T regulatory (Treg) cells emerge and then activate chemokines, provide chemoattraction of neutrophils, and increase inflammatory cytokines. Treg cells play a key role in anti-inflammatory/immunosuppressive control by inhibiting Th1 and Th17 (32). The balance between Treg/Th17 has a significant role in the severity of lung injury. Elevated IL-6 and Th17 levels in COVID-19 disrupt this balance and cause conditions such as ALI/ARDS (33).

In our study, IL-17 levels of Groups I and II were significantly lower than control group. Our study population consisted of COVID-19 patients who survived the exacerbation of the disease and were discharged home. It was thought that Treg's ability to control inflammation predominated, therefore, there was no active inflammation during the recovery period. In addition, profibrotic effects of Th17 through stimulating the production of GMCF induction, apoptosis inhibition, TGF- $\beta$  and collagen proteins, may not be effective in COVID-19 patients with sequelae of this study group; and other mechanisms may be responsible.

### IgG4

Immunoglobulin G4 is one of the IgG subgroups whose structure and function are the least understood. Elevated levels of IgG4, rheumatoid factor and IgG4 antibodies against anti-citrulline have been detected in patients with rheumatoid arthritis, as well as chronic autoimmune and inflammatory diseases (34). Some conditions in COVID-19 patients, such as the development of lung fibrosis in a short time, lack of clear pathogenesis, response to steroid therapy, and eosinophil miscarriage (35), enabled us to investigate the role of IgG4 in COVID fibrosis. No significant IgG4 elevation was detected in any of the patient groups included in the study, therefore, it can be suggested that IgG4 has no effect on post-COVID fibrosis; however, it should be noted that serum ele-

vation of IgG4-RD can be detected in only 50% of patients (15).

The most obvious limitation of this study is the absence of samples that were collected in the acute phase of the disease to evaluate individual differences and changes in cytokines. In this way, we may assess the relation between CORADS scale and cytokine levels.

## CONCLUSION

Based on the experience with MERS and SARS-CoV, it can be predicted that COVID-19 may result in fibrotic disease (36,37). The profibrotic factors that occur after coronavirus infections are still unclear. In our study; the profibrotic effects of VEGF, IL-17, and IgG4 were not dominant in patients who developed pulmonary sequelae after COVID; it is believed that different mechanisms mentioned or not yet revealed may cause this result. We think that investigating other profibrotic factors and planning targeted treatments will be a significant step forward in pandemic management in order to control the disease earlier and prevent permanent damage.

**Ethical Committee Approval:** This study was approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (Decision no: TUTF-BAEK 2021/66, Date: 01.02.2021).

## CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

## AUTHORSHIP CONTRIBUTIONS

Concept/Design: NGA, ŞA

Analysis/Interpretation: NGA, ŞA

Data acquisition: SG

Writing: NGA, ŞA

Clinical Revision: NGA

Final Approval: NGA

## REFERENCES

1. World Health Organization. Pneumonia of unknown cause-China (Online), 2020; Available from: <https://www.who.int/csr/don/05-january-2020-pneumonia-of-unknown-cause-china/en/>.
2. McDonald LT. Healing after COVID-19: Are survivors at risk for pulmonary fibrosis? *Am J Physiol Lung Cell Mol Physiol* 2021; 320(2): L257-L265. <https://doi.org/10.1152/ajplung.00238.2020>

3. Thille AW, Esteban A, Fern ndez-Segoviano P, Rodr guez JM, Aramburu JA, Vargas-Err zuriz P, et al. Chronology of histological lesions in acute respiratory distress syndrome with diffuse alveolar damage: A prospective cohort study of clinical autopsies. *Lancet Respir Med* 2013; 1: 395-401. [https://doi.org/10.1016/S2213-2600\(13\)70053-5](https://doi.org/10.1016/S2213-2600(13)70053-5)
4. Sheahan T, Morrison TE, Funkhouser W, Uematsu S, Akira S, Baric RS, et al. MyD88 is required for protection from lethal infection with a mouse-adapted SARS-CoV. *PLoS Pathog* 2018; 4(12): e1000240. <https://doi.org/10.1371/journal.ppat.1000240>
5. Wong CK, Lam CW, Wu AK, Ip WK, Lee NLS, Chan HIS, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 2004; 136: 95-103. <https://doi.org/10.1111/j.1365-2249.2004.02415.x>
6. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: The perspectives on immune responses *Cell Death & Differentiation* 2020; 27: 1451-4. <https://doi.org/10.1038/s41418-020-0530-3>
7. Kalchiem DO, Galvin JR, Burke AP, Atamas SP, Todd NW. interstitial lung disease and pulmonary fibrosis: A practical approach for general medicine physicians with focus on the medical history. *J Clin Med* 2018; 7(12): 476. <https://doi.org/10.3390/jcm7120476>
8. McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 family of cytokines in health and disease. *Immunity* 2019; 50(4): 892-906. <https://doi.org/10.1016/j.immuni.2019.03.021>
9. Ahmed S, Misra DP, Agarwal V. Interleukin-17 pathways in systemic sclerosis-associated fibrosis. *Rheumatology international* 2019; 39(7): 1135-43. <https://doi.org/10.1007/s00296-019-04317-5>
10. Kong Y, Han J, Wu X, Zeng H, Liu J, Zhang H. VEGF-D: A novel biomarker for detection of COVID-19 progression. *Crit Care* 2020; 24(1): 373. <https://doi.org/10.1186/s13054-020-03079-y>
11. Simler NR, Brenchley PE, Horrocks AW, Greaves SM, Hasleton PS, Egan JJ. Angiogenic cytokines in patients with idiopathic interstitial pneumonia. *Thorax* 2004; 59: 581-5. <https://doi.org/10.1136/thx.2003.009860>
12. Ando M, Miyazaki E, Ito T, Hiroshige S, Nureki S, Ueno T, et al. significance of serum vascular endothelial growth factor level in patients with idiopathic pulmonary fibrosis. *Lung* 2010; 188: 247-52. <https://doi.org/10.1007/s00408-009-9223-x>
13. Cheuk W, Chan JK. IgG4-related sclerosing disease: A critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol* 2010; 17(5): 303-32. <https://doi.org/10.1097/PAP.0b013e3181ee63ce>
14. Keren GM, Shira BR, Ilan A, Guri KM. Immunglobulin G4 and related disease, *Isr Med Assoc J* 2012; 14(10): 642-5.
15. Martinez-Valle F, Orozco-Galvez O, Fernandez-Codina A. Update in ethiopathogeny, diagnosis and treatment of the IgG4 related disease. *Med Clin (Barc)* 2018; 151(1): 18-25. <https://doi.org/10.1016/j.medcle.2018.05.005>

16. Stylianou E, Ueland T, Borchsenius F, Michelsen AE, Øvstebø R, Mollnes TE, et al. Specific allergen immunotherapy: Effect on IgE, IgG4 and chemokines in patients with allergic rhinitis *Scand J Clin Lab Invest* 2016; 76(2): 118-27. <https://doi.org/10.3109/00365513.2015.1110856>
17. Chen Y, Dong Y, Cai S, Ye C, Dong L. Clinical characteristics of IgG4-RD patients infected with COVID-19 in Hubei, China. *Semin Arthritis Rheum* 2020; 50(4): 559-63. <https://doi.org/10.1016/j.semarthrit.2020.04.015>
18. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G\*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009; 41: 1149-60. <https://doi.org/10.3758/BRM.41.4.1149>
19. Prokop M, van Everdingen W, van Rees Vellinga T, Ufford HQ, Stöger L, Beenen L, et al. CO-RADS: A categorical ct assessment scheme for patients suspected of having COVID-19 definition and evaluation. *Radiology* 2020; 296: E97-E104. <https://doi.org/10.1148/radiol.2020201473>
20. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. *Int J Infect Dis* 2020; 94: 91-5. <https://doi.org/10.1016/j.ijid.2020.03.017>
21. Li X, Xu S, Yu M, Pu K, Chen Z, Guo Q, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020; 146(1): 110-8. <https://doi.org/10.1016/j.jaci.2020.04.006>
22. Chan TY, Miu KY, Tsui CK, Yee KS, Chan MH. A comparative study of clinical features and outcomes in young and older adults with severe acute respiratory syndrome. *J Am Geriatr Soc* 2004; 52(8): 1321-5. <https://doi.org/10.1111/j.1532-5415.2004.52362.x>
23. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020; 395: 507-13. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7)
24. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475-81. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5)
25. Kaner RJ, Crystal RG. Compartmentalization of vascular endothelial growth factor to the epithelial surface of the human lung. *Mol Med* 2001; 7: 240-6. <https://doi.org/10.1007/BF03401843>
26. Collins BF, Raghu G. Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis. *Eur Respir Rev* 2019; 28(154): 195022. <https://doi.org/10.1183/16000617.5022-2019>
27. Chi Y, Ge Y, Wu B, Zhang W, Wu T, Wen T, et al. Serum cytokine and chemokine profile in relation to the severity of coronavirus disease 2019 in China. *J Infect Dis* 2020; 222(5): 746-54. <https://doi.org/10.1093/infdis/jiaa363>
28. Yazihan N, Tanacan A, Erol SA, Anuk AT, Sinaci S, Biriken D, et al. Comparison of VEGF-A values between pregnant women with COVID-19 and healthy pregnancies and its association with composite adverse outcomes. *J Med Virol* 2021; 93(4): 2204-9. <https://doi.org/10.1002/jmv.26631>
29. Meyer KC, Cardoni A, Xiang ZZ. Vascular endothelial growth factor in bronchoalveolar lavage from normal subjects and patients with diffuse parenchymal lung disease. *J Lab Clin Med* 2000; 135: 332-8. <https://doi.org/10.1067/mlc.2000.105618>
30. Murray LA, Habel DM, Hohmann M, Camelo A, Shang H, Zhou Y, et al. Antifibrotic role of vascular endothelial growth factor in pulmonary fibrosis. *JCI Insight* 2017; 2(16): e92192. <https://doi.org/10.1172/jci.insight.92192>
31. Zhou X, Loomis-King H, Gurczynski SJ, Wilke CA, Konopka KE, Ptaschinski C, et al. Bone marrow transplantation alters lung antigen-presenting cells to promote TH17 response and the development of pneumonitis and fibrosis following γherpesvirus infection. *Mucosal Immunol* 2016; 9: 610-20. <https://doi.org/10.1038/mi.2015.85>
32. Candia P, Prattichizzo F, Garavelli S, Matarese G. T cells: Warriors of SARS-CoV-2 infection. *Trends Immunol.* 2021; 42(1): 18-30. <https://doi.org/10.1016/j.it.2020.11.002>
33. Muyayalo KP, Huang DH, Zhao SJ, Xie T, Mor G, Liao AH. COVID-19 and Treg/Th17 imbalance: Potential relationship to pregnancy outcomes Ai-Hua Liao *Am J Reprod Immunol* 2020; 84: e13304. <https://doi.org/10.1111/aji.13304>
34. Altindış M. A new marker for the diagnosis of rheumatoid arthritis: Cyclic citrullinated peptide antibodies (anti-CCP). *Mikrobiyol Bul* 2003; 37(4): 313-8.
35. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020; 75(7): 1730-41. <https://doi.org/10.1111/all.14238>
36. Das KM, Lee EY, Singh R, Enani MA, Dossari KA, Gorkom KV, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. *Indian J Radiol Imaging* 2017; 27: 342-9. [https://doi.org/10.4103/ijri.IJRI\\_469\\_16](https://doi.org/10.4103/ijri.IJRI_469_16)
37. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology* 2010; 15: 543-50. <https://doi.org/10.1111/j.1440-1843.2010.01720.x>