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# IL-17A (rs2275913; G197A) gene polymorphism as predictor for disease severity and its correlation with IL-17 serum levels in COVID-19 patients

**Marwa Rushdy[1], Marwa S. Elsayed[2], Rasha Ahmed[3], Amr G. Gaber[4] and Riham El-Asady[2]**

[1]Department of Clinical Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[2]Department of Medical Microbiology & Immunology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[3]Department of Geriatric & Gerontology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[4]Department of Anesthesia, ICU, & Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

**Corresponding author:** Marwa S. Elsayed, Department of Medical Microbiology & Immunology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
Email: marshabban@yahoo.com.

## Abstract

Severity of symptoms in COVID-19 has been shown to result from a cytokine storm. Interleukin (IL)-17 is one of these various cytokines, which results in a proinflammatory response, systemic inflammatory symptoms, inflammatory cell infiltration of lung tissue and thus leads to the massive lung pathology and multiorgan failure. Gene polymorphisms in the regulatory regions of cytokine-encoding genes affect the amounts of cytokines produced and possess a fundamental role in infectious diseases. This study aimed to investigate the role of IL-17A (rs2275913; G197A) gene polymorphism as predictor of disease severity and its correlation with IL-17 serum levels in COVID-19 patients. A group of 70 COVID-19 patients and 17 age and sex-matched control subjects were enrolled in the present work. Patients were classified into two groups moderate, severe and acute respiratory distress (ARDS) cases, defined according to the criteria established by the world health organization. Quantitative real time-polymerase chain reaction was done to detect IL-17A (rs2275913; G197A). Serum IL-17 levels were assessed by an enzyme-linked immunosorbent assay in both patients and controls. The distribution of different IL-17A G/A genotypes among COVID-19 patients were 44.3% for GG genotype, 44.3% for AG genotype and 11.4% for AA genotype. Genotypes among the control group were 43.8% for GG genotype, 50% for AG genotype and 6.3% for AA genotype. G allele distribution was 66.4%, 68.8% in patient and control group, respectively, and A allele was 33.6% and 31.3%, respectively. There was no association between the different genotypes, disease severity or IL-17 serum levels in the patient group. In conclusion, despite the possible role of IL-17 in the pathogenesis of inflammation, there was no association between IL-17 polymorphism and disease severity or IL-17 serum levels among Egyptian COVID-19 patients.

**Keywords:** gene polymorphism, IL-17, and COVID-19.

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## Introduction

The outbreak of the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), firstly found in Wuhan, in the Hubei province of China, in December 2019, has rapidly spread worldwide, resulting in a global public health emergency. On 11th March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. As of 12nd March 2022, there were 452,201,564 confirmed cases of COVID-19, including 6,029,852 deaths, reported to WHO.[1] About 80% of COVID-19 cases were asymptomatic or exhibited mild to moderate symptoms, but approximately 15% progressed to severe pneumonia and about 5% developed acute respiratory distress (ARDS), septic shock and/or multiple organ failure.[2]

Rising clinical evidence from severe COVID-19 patients suggests that major changes in the serum levels of several cytokines play a significant role in the pathogenesis of COVID-19.[3,4] The cytokine storm has been proposed as one of the key leading factors that trigger the pathological processes leading to plasma leakage, vascular permeability, and disseminated vascular coagulation, observed in COVID-19 patients, and accounting for life-threatening respiratory symptoms.[5]

Because there is no specific antiviral therapy for COVID-19, understanding of the cytokine storm mechanisms in this disease could reveal possible therapeutic options. Among the many cytokines involved in the storm, IL-17 is a predominant mediator of inflammation. IL-17A (commonly known as IL-17) is the most studied member of the IL-17 cytokine family that consists of six related proteins. It is produced by T-helper (Th)-17 lymphocytes, and by innate cellular components.[6] For SARS-CoV-2, the severity of disease was shown to positively correlate with levels of IL-17.[7] Delivery of a therapy targeting IL-17 early in COVID-19 may be efficacious in flattening the disease course and improving outcomes such as severe respiratory failure.[8]

Polymorphisms in gene encoding molecules of the host defense system have been targeted as possible genetic markers. The IL-17A gene encodes IL-17A cytokine. The rs2275913 single-nucleotide polymorphism (SNP) is located in the 2KB upstream region of the IL-17A gene on chromosome 6p12. The rs2275913 SNP is located in the promoter region of the IL-17A gene. [9] Polymorphism of the gene IL-17A (rs2275913 G/A) can affect the activity of interleukin by modifying the role of cytokine and regulation of its expression.[10] A preliminary work was conducted to investigate the association between IL-17 gene polymorphisms and COVID-19 prevalence and mortality.[11] Based on their results, the authors suggested that the genetic variations in IL-17 gene may be linked to the distribution of COVID-19 infection among nations.[11]

Consequently, this study aimed to investigate the role of IL-17A (rs2275913; G197A) gene polymorphism as predictor of disease severity in Egyptian COVID-19 patients. Moreover, serum IL-17 levels among COVID-19 patients and a control group, and the relationship between the IL-17A SNP and IL-17 serum levels were also explored. The results could potentially provide an explanation for the predominance of a mild disease versus a severe, often fatal outcome. Additionally, it could open novel avenues in the search of therapeutic interventions.

## Subjects and Methods

*Subjects*

This case control study included 70 confirmed cases of SARS-CoV-2, with positive nasopharyngeal swab as determined by real-time polymerase chain reaction (RT-PCR). They were recruited from the quarantine isolation hospitals among Ain Shams University Hospitals, during the period from December 2020 to September 2021, based on their hospital records. The laboratory parameters of the patients including total leukocytic count, serum ferritin, C-reactive protein, and D dimer were obtained from patients' hospital records.

The patients were classified into moderate, severe and ARDS according to WHO criteria. Moderate cases were defined as having fever and other respiratory symptoms with

pneumonia manifestation through image results. Severe cases were defined as meeting any one of the following: respiratory distress, hypoxia (SpO2 ≤ 93%), abnormal blood gas analysis: (PaO2 < 60mmHg, PaCO2 > 50mmHg). And, ARDS cases were defined as meeting any one of the following: new or worsening respiratory symptoms within one week of a known clinical insult; chest radiograph or computed tomography (CT) scan showing bilateral infiltrates not fully explained by effusions, pulmonary or lobar collapse, or pulmonary nodule. Subjects with radiologic findings of pulmonary edema, heart failure, or other causes such as fluid overload, they were excluded before assessing it to be ARDS. Also, the ratio of arterial partial pressure of oxygen (PaO2) to fraction of inspired oxygen (FiO2), called the P/F ratio, of at most 300 mmHg and positive end-expiratory pressure (PEEP) of at least 5 cm $H_2O$.[12] Seventeen age and sex matched apparently healthy subjects were included as a control group.

Laboratory work was conducted in the Department of Clinical Pathology, Ain Shams University Hospitals. Prior to initiation, the study protocol was reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Ain Shams University, Egypt (approval number FAMSU R92/2021) and all participants provided a written informed consent.

*Methods*

*Sample collection*

Six milliliters of venous blood were collected under complete aseptic conditions and divided in two aliquots. The first aliquot was placed in a sterile EDTA vacutainer tube and the second aliquot in a plain vacutainer tube. Clotted blood samples (second aliquot) were centrifuged at 300 xg for 10 minutes and serum samples separated and stored at -80◦C until used.

*Enzyme-linked immunosorbent assay (ELISA) for assessment of serum IL-17*

The assessment was carried out using *IL-17* double-antibody sandwich ELISA kit (Cat. No E0142Hu, provided by Bioassay Technology laboratory, 218 Ningguo Rd. Yangpu Dist. Shanghai, China) according to the manufacturer's instructions. The kit sensitivity was 1.06 ng/L.

*Detection of IL-17 A gene polymorphism rs 2275913 by Real-Time PCR technique*

Genomic DNA was isolated from human blood cells using QIAamp DNA Mini extraction Kit (Cat. No. 217184, QIAGEN Strasse 1 40724 Hilden, Germany) according to the manufacturer's instructions. The allelic discrimination of the IL-17A rs 2275913 gene intron polymorphism was assessed with quantitative real time PCR kit (Cat. No. 4351379, Applied Biosystems, Thermos Fisher Scientific, Singapore), the assay ID (C_15879983_10), according to the manufacturer's instructions.

The reaction mix (20 µl) contained 2 µl of the DNA template, 10 of TaqMan Universal PCR Master Mix,1 µl of TaqMan working stock of SNP genotyping assay (20×), and 7 µl nuclease-free water. Thermal cycling profile was hold at 95 °C for 10 min and then, 45 cycles of 15 s at 95 °C and 60 s at 60 °C were performed. The reaction was performed using PCR detection system (5 Plex Rotor Gene Real-Time PCR Analyzer, Qiagen, Germany). Allelic discrimination plot to discriminate types of IL-17A gene rs2275913 SNP to three genotypes AA, AG or GG was according to the detected dye VIC or FAM as implemented by the company.

*Statistical methods*

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS-25). The results were expressed as frequencies, medians, means and standard deviations. Heredity equilibrium was assessed by Hardy–Weinberg test. Comparisons of genotype and allele frequencies between the case and control groups were evaluated by chi-square test. Kruskal-Wallis was used to evaluate the statistical significance among the laboratory results of the different genotypes in patient group. A p value of <0.05 was considered significant.

## Results

The study involved 70 COVID-19 patients; they were 36 (51.4%) males and 34 (48.6%) females. Their mean age was 59.9±13.7. In addition, 17 age and sex-matched apparently healthy individuals [5 (29.4%) males and 12 (70.6%) females] were included as a control group. Their mean age was 41.4± 13.27 years. The patients were classified into 2 groups: moderate [12 (57.1%) males and 9 (42.9%) females], severe and ARDS [24 (49%) males and 25 (51%) females]. The descriptive data and laboratory characteristics of the patients are illustrated in Table 1. There was a statistically significant difference between the severity of the disease and total leukocytic count, serum ferritin, C-reactive protein, and D dimer.

The mean (±SD) serum titer of IL-17 was 152.8 ±89.6 ng/L in the patient group and significantly higher (29.4± 17.3 ng/L) than in the control group ($p < 0.001$). Although the mean serum titer of IL-17 was higher in the severe and ARDS cases compared to the moderate cases (155.8 ng/L vs 145.7 ng/L), but the difference did not reach statistical significance (*P*=0.67) Table 1. Significant correlations were found between IL-17 serum levels, total leukocytic count, C-reactive protein, and D dimer (Table 2).

**Table 1.** Descriptive and laboratory characteristics of COVID-19 patients.

| | Moderate | Severe and ARDS | *P value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Age | 50.62 ± 16.27 | 63.96 ± 10.1 | 0.002 |
| Total leukocyte count ($X10^3$) | 7.94 ± 3.89 | 11.13 ± 5.25 | 0.015 |
| Absolute lymphocyte count ($X10^3$) | 0.91 ± 0.32 | 0.89 ± 0.55 | NS |
| Serum ferritin (ng/ml) | 628.55 ± 529.84 | 1177.22 ± 832.1 | 0.008 |
| C-reactive protein (mg/dl) | 21.46 ± 26.21 | 96.68 ± 97.4 | <0.001 |
| D-dimer (mg/L) | 0.79 ± 0.38 | 1.38 ± 0.99 | 0.001 |
| Lactate dehydrogenase (IU/L) | 339.33 ± 121.65 | 424.35 ± 286.05 | NS |
| IL-17(ng/L) | 145.71 ± 107.03 | 155.82 ± 82.04 | NS |

*$P \geq 0.05$ is not significant (NS).

**Table 2.** Correlations between IL-17 and different laboratory parameters among COVID-19 patients.

| Variables | | Total leukocyte count | Absolute lymphocyte count | Serum ferritin | C-reactive protein | D-dimer | Lactate dehydrogenase |
|---|---|---|---|---|---|---|---|
| *IL-17* (ng/L) | rs | 0.366 | -0.099 | 0.213 | 0.355 | 0.352 | 0.001 |
| | *P* value | 0.002 | NS | NS | 0.003 | 0.003 | NS |

*$P \geq 0.05$ is not significant (NS).

The genotype distribution of the rs2275913 polymorphism was in accordance with the Hardy-Weinberg equilibrium in both COVID-19 the patient group (*P*=0.998) and the control group (*P*=0.807) Table 3. The results of the genotype and alleles analyses are shown in Table 4. Regarding genotypes distribution, in the patient group, the genotype frequencies of the IL-17A rs2275913 polymorphism were GG (44.3 %), AG (44.3%), and AA (11.4%), and in the control group, GG (48.3%), AG (50%), and AA (6.3%). The difference in genotypes distribution (GG, AG, AA) was not statistically significant (*P*= 0.807).

The G allele was observed in 66.4% and 68.8% of the patient and control groups, respectively, whereas the A allele was observed

in 33.6% and 31.3% of the patients and the controls, respectively. There was no significant difference between patients versus control group regarding both G and A allele frequencies (*P* =0.8).

**Table 3.** Observed and expected frequencies of the IL17A gene (rs2275913 SNP) genotypes and their Hardy-Weinberg equilibrium (HWE) in COVID-19 patients and controls.

| Genotype | COVID-19 patients (N=70) | | Control (N=17) | |
|---|---|---|---|---|
| | O (%) | E (%) | O (%) | E (%) |
| GG | 31(44.29) | 30.9(44.13) | 7(43.75) | 7.6(47.27) |
| AG | 31(44.29) | 31.2(44.6) | 8(50) | 6.9(42.97) |
| AA | 8(11.43) | 7.9(11.27) | 1(6.25) | 1.6(9.77) |
| HWE **P*-value | NS | | NS | |

N: Number, O: Observed, E: Expected. **P* ≥ 0.05 is not significant (NS).

**Table 4.** Genotype and allele frequency of IL-17A (rs2275913 A>G) polymorphisms in patients with COVID-19 and controls.

| | | Control (No.=17) | | Cases(No.=70) | | **P* value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| Genotype | GG | 7 | 43.8% | 31 | 44.3% | NS |
| | AG | 8 | 50.0% | 31 | 44.3% | |
| | AA | 1 | 6.3% | 8 | 11.4% | |
| Alleles | G | 22 | 68.8% | 93 | 66.4% | NS |
| | A | 10 | 31.3% | 47 | 33.6% | |

*Chi square test. **P* ≥ 0.05 is not significant (NS).

No association was found between the frequencies of different genotypes and severity of COVID-19 disease in the studied cases (*P*=0.28) Table 5. We observed a significant association between the studied genotypes and total leukocytic count and serum ferritin levels (*P*=0.04 and 0.002, respectively). However, when we further summarized the average serum concentration of IL-17 in each genotype, there was no significant difference among all three genotypes for this SNP in patients Table 6.

**Table 5.** Association between genotypes and disease severity of the cases.

| Disease severity | IL-17A | | | | | | **P* value |
|---|---|---|---|---|---|---|---|
| | GG (No.=31) | | AG (No.=31) | | AA (No.=8) | | |
| | No. | % | No. | % | No. | % | |
| Moderate | 8 | 25.8 | 12 | 38.7 | 1 | 12.5 | NS |
| Severe and ARDS | 23 | 74.2 | 19 | 61.3 | 7 | 87.5 | |

*Chi square test. **P* ≥ 0.05 is not significant (NS).

**Table 6.** Association between genotypes and laboratory characteristics of the cases.

| Among cases | GG | | AG | | AA | | *P value |
|---|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR | |
| Total leukocyte count ($X10^3$) | 11.00 | 9 - 14 | 7.70 | 4.2 12.3 | 11.25 | 8.6 -13.25 | 0.042 |
| Absolute lymphocyte count ($X10^3$) | 0.90 | 0.6 - 1 | 0.90 | 0.7 - 1 | 0.80 | 0.7 - 0.9 | NS |
| Serum ferritin (ng/ml) | 1150.00 | 659 - 1500 | 570.00 | 300 990 | 1340.00 | 1100 -1443.5 | 0.002 |
| C-reactive protein (mg/dl) | 36.00 | 12 - 115 | 50.00 | 5 - 106 | 71.00 | 17.5 - 120 | NS |
| D-dimer (mg/L) | 1.00 | 0.8 - 1.8 | 0.80 | 0.4 -1.4 | 1.00 | 0.73 - 1.435 | NS |
| Lactate dehydrogenase (IU/L) | 366.00 | 244 - 514 | 326.00 | 277-400 | 352.50 | 339.5 - 520 | NS |
| IL-17(ng/L) | 140 | 90 - 230 | 110 | 80 -180 | 103 | 90 - 130 | NS |

*Kruskal Wallis test. *$P \geq 0.05$ is not significant (NS).

## Discussion

The rs2275913 SNP is the nucleotide variant of the IL-17A gene associated with several pathologies.[13] IL-17 gene polymorphisms in COVID-19 have not been fully investigated. This study aimed to investigate the role of IL-17A rs2275913 gene polymorphism as a predictor of disease severity and its correlation with IL-17A serum levels in COVID-19 patients.

The study enrolled 21 patients with moderate disease and 49 with severe disease and ARDS. We observed that the different laboratory parameters e.g., total leukocytic count, serum ferritin, C-reactive protein, and D dimer differed significantly between moderate cases compared to severe and ARDS cases. Comparable results were published by previous studies.[14,15]

IL-17 is a cytokine contributing to the pathogenesis of several immune-mediated diseases.[16] In the context of COVID-19, some studies suggested that IL-17 may be involved in the pathogenesis of severe COVID-19.[3,17] In this work, the mean serum titers of IL-17 differed significantly between COVID-19 patients and the control group. This agreed with findings of previous studies.[18,19,20] In contrary, a study by Burgos-Blasco et al., 2020, did not find a difference between COVID-19 patients and control subjects.[21] In the current study, by analyzing the mean IL-17 serum levels among the moderate and severe cases, we observed that although the mean serum titers of IL-17 were higher in the severe group compared to the moderate group, but the difference did not reach statistical significance. Similarly, other studies reported no differences in IL-17 levels between severe and non-severe COVID-19 cases[22] or mild and severe COVD-19. [23] On the other hand, a study by Huang et al., 2020, found a significant difference in plasma levels of IL-17 when compared COVID-19 patients attending intensive care unit (ICU) to those not attending ICU.[2] It is known that the overproduction of IL-17 stimulates the T-cell response and increases the production of other inflammatory mediators – IL-1β, IL-6, TNFα, growth factors (G-CSF, GM-CSF), and various chemokines.[24] This increases the recruitment of neutrophils and prevents their apoptosis, which consequently increases the damage to the lung parenchyma, and results in the development of pulmonary edema.[25,26] These factors gave hope to consider

IL-17 inhibitors as a potential therapeutic target in COVID-19.[27,28]

According to this study, the IL-17A gene was amplified via real time PCR, and there were different IL-17A genotypes (GG type, AG type and AA type). The distribution of different IL-17A genotypes among COVID-19 patients were 44.3% for GG genotype, 44.3% for AG genotype and 11.4 % for AA genotype otherwise, genotypes among control group were 43.8% for GG genotype, 50% for AG genotype and 6.3% for AA genotype. The difference in genotypes distribution (AG, AA, GG) was not statistically significant. Furthermore, there was no statistical difference between the allelic distributions (A allele, G allele) in the studied groups, where the mutant allele frequency (A) was 33.6% and 31.3% in patients and control groups, respectively. In a study conducted by Batur & Hekim, 2021, the diversities of IL-17A gene polymorphism at rs2275913 locus showed that the populations of China, Japan, Iran, Finland, Czechia, India, Norway, and Poland mostly have the AG genotype, while populations of Spain, Mexico, Netherlands, Turkey, Brazil, Germany, Tunisia, Egypt, and Croatia the GG genotype.[11]

We investigated the association of the IL-17A genotypes with the disease severity of COVID-19. There was no significant association between the frequencies of the genotypes and the disease severity. Similarly, the study by Batur & Hekim, 2021, observed that the frequencies of IL-17 gene polymorphisms may not directly correlate with the course and severity of COVID-19 infection.[11] On the other hand, a study by Xie et al., 2019, reported that compared with individuals carrying the wild-type GG genotype of rs2275913 at IL-17, the AA-homozygous and GA- heterozygous individuals were protected from the development of ARDS. Consistently, a decreased 30-day mortality risk was found among A-allele carriers of rs2275913 at IL-17.[29]

In this study, there was no association between genotypes of the studied SNP of IL-17A with its serum levels. This goes in line with other studies that found no evidence of polymorphism effect on cytokine expression.[30,31] On the contrary, other authors reported a significant effect of this SNP on the serum levels of IL-17. A study by Xie et al., 2019, observed decreased IL-17 levels in A-allele carriers of IL-17 rs2275913. They suggested that rs2275913 was a functional polymorphism that can affect IL-17 expression. Located in the regulatory domain of IL-17, SNP of rs2275913 can reduce IL-17 expression and relieve severe inflammatory reaction.[29] However, a study by Rolandelli et al., 2017, observed elevated levels of IL-17A in patients with active tuberculosis carrying the AA genotype as compared to individuals that carry the GG genotype.[32] Based on these data, it seems that IL-17A G197A does not influence protein secretion in some diseases and may be functional in others, reinforcing that each clinical situation should be carefully evaluated.[33]

There was no detailed information about the association between the allele frequencies of IL-17A, and disease severity, as well as the IL-17 serum levels in COVID-19 patients, except for one report that explored the association between the allele frequencies of IL-17A gene, and the prevalence and mortality rates of COVID-19 patients among the populations.[11] Our study has certain limitations including the relatively small sample size, enrolled in a single study center and, IL-17 was measured in serum with no involvement of bronchoalveolar lavage fluid. Therefore, our findings need to be interpreted with caution.

In conclusion, our study findings could be considered novel as they, to the best of our knowledge, were not previously reported in Egyptian populations. Despite the possible role of IL-17 in the pathogenesis of inflammation, we did not find a significant association between IL-17 polymorphism and disease severity or IL-17 serum levels among Egyptian COVID-19 patients.

## Author Contributions

AG, RA, AN, and NO assisted in the collection of samples and patients' data. MR and MS contributed to laboratory work and analysis of data. MS and RE assisted in manuscript drafting and revision. All authors contributed significantly to the study's conception, design, and final approval of the manuscript.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical approval

The study protocol was reviewed and approved by the Research Ethical Committee of Ain Shams University Hospitals (approval No. FAMSU R92/2021).

## Informed consent

A signed consent form was obtained from each study participant.

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