Comparison of biochemical and immunological biomarker levels of patients with COVID-19 with healthy individuals

Ugur Ercin*, Emel Turk Aribas, Semra Tuncbilek, Canturk Kaya, Aylin Sepici Dincel, Ayse Bilgihan and Mehmet Emin Tekeli

Abstract

Objectives: It was aimed to compare Alpha-1 antitrypsin (AAT), Alpha-1 acid glycoprotein (AGP), Total Immunoglobulin M (Total IgM), Total Immunoglobulin G (Total IgG), Galectin-3 (Gal3), and severe acute respiratory syndrome coronavirus 2 IgG (SARS-CoV-2 IgG) levels in patients with COVID-19 and healthy individuals.

Methods: The study included a total of 86 participants, 44 patients diagnosed with COVID-19 by real-time reverse transcription-polymerase chain reaction (rRT-PCR) test and 42 as the control group. AAT, AGP, Total IgM, and Total IgG levels were measured using the immunoturbidimetric method. Gal3 and SARS-CoV-2 IgG levels were measured using the chemiluminescent microparticle immunoassay method.

Results: AAT, AGP, Total IgG, Gal3, and SARS-CoV-2 IgG levels were found to be significantly higher in the patient group compared to the control group (p<0.001 for all tests). In the patient group, there was a moderate correlation between AAT-AGP and SARS-CoV-2 IgG-AAT (r=0.692; r=0.561, respectively).

Conclusions: High levels of AAT, AGP, Total IgG, Gal3, and SARS-CoV-2 IgG in the patient group and correlations between variables suggest that these parameters may be involved in the pathogenesis of the disease and provide an idea about the prognosis of the disease. However, new studies on this subject are needed in order to clearly reveal the laboratory tests related to the clinical course of the disease.

Keywords: corona virus; COVID-19; pandemic; SARS-CoV-2.

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**Introduction**

A number of unexplained cases of pneumonia rapidly spreading worldwide with a high fatality, though not at the level of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or Middle East respiratory syndrome coronavirus (MERS-CoV), were reported in Wuhan, China at the end of 2019 [1, 2]. Genome sequencing analysis of bronchoalveolar lavage fluid samples has confirmed that the pathogen is a separate class of β-coronavirus associated with human SARS-CoV and MERS-CoV. The novel virus was officially named SARS-CoV-2 and the disease it caused was named COVID-19 [3].

As expected, the clinical features, management, and epidemiology of SARS-CoV, MERS-CoV, and COVID-19 seem similar; however, differences have been noted in the clinical manifestation of COVID-19 since the first reports. There is a need for a complete clinical characterization of this disease as well as a clear demonstration of its laboratory and imaging characteristics [4].

Since the incubation period of SARS-CoV-2 is longer (approximately two weeks) than SARS-CoV and MERS-CoV, while the risk of transmission and the number of cases increases, the number of deaths is also increasing exponentially due to viral sepsis, disseminated intravascular coagulation, and multi-organ failure [5]. Because of these severe clinics, it is very important to determine the severity of COVID-19, investigate potential risk factors, and delay or halt the progression of the disease. Previous studies have shown that the elderly and those with underlying diseases develop much more severe pictures. However, the clinic of the disease emerges with different levels of severity in all age groups. Previous research has also revealed that the cytokine storm resulting from the disease’s abnormal immune-inflammatory response may play a role in the disease’s progression. Cytokine storm is a condition that occurs with the excessive increase in the levels of small protein molecules called cytokines, which provide intercellular communication and are involved in immune modulation, in some infectious diseases. Studies have shown that cytokine storm, which plays a role in severe influenza, SARS-CoV, and MERS-CoV, may cause severe cases such as acute lung damage, acute respiratory distress syndrome (ARDS), and even multi-organ dysfunction during SARS-CoV-2 infection. These studies have shown that patients with severe SARS-CoV-2 infection have higher levels of interleukin-6, interleukin-10, and interferon-gamma (INF-γ) than those with a mild form of the disease [6, 7].

Alpha-1 antitrypsin (AAT), is basically the third most circulating protein synthesized by hepatocytes in the liver. AAT plasma level increases 3–5 times in cases of systemic inflammation and/or infection [8]. AAT is a multifunctional protein that protects tissues from damage caused by enzymes released from cells, is involved in repairing tissue damage, and has anti-inflammatory and immunomodulatory properties [9].

Alpha-1 acid glycoprotein (AGP) is an acute-phase protein synthesized in the liver and secreted in response to inflammation and infection, the synthesis of which is regulated by interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) [10]. Moreover, AGP can be produced in the infection site and has some immunomodulatory properties [11].

Galectins play an extensive role in immune response with their chemokinetic properties. Galectin-3 (Gal3) is one of the best known properties among galectins. The most expressed organ of the Gal3 protein in healthy individuals is the lungs (macrophages, epithelial, and alveolar cells), followed by the gastrointestinal system and the brain. Gal3 has been shown to activate the proinflammatory transcription factor NFκB and induce both IL6 and TNF-α release. The spike protein, which is found in viruses in the β-coronaviridae family including SARS-CoV-2, plays a key role in pathogenesis, and the morphological structure of this protein closely resembles the human Gal3 protein. Spike protein plays a critical role in the entry of the virus into the host cell. A recent study showed that Gal3 inhibitors decrease the levels of inflammatory cytokines such as IL-1, IL-6, and TNF-α in dendritic cells, while increase the level of IL-10 with anti-inflammatory effect. Moreover, it is predicted that by disrupting the binding of the SARS-CoV-2 S1 N terminal domain to GM1 gangliosides on the host cell surface with Gal3 inhibition, the entry of the virus into the cell can be prevented. Consequently, Gal3 inhibition is considered to be beneficial in the treatment by both reducing the host inflammatory response and preventing viral binding to host cells [12]. High serum levels of Gal3 have been shown to be significantly associated with poor prognosis and lower survival in patients with ARDS [13].

Gal3 levels in infected macrophages in the serum of patients with COVID-19 were found to be much higher in patients with severe disease than those with mild disease. At the cellular level, the highest levels of Gal3 have been detected in cells responsible for initiating Cytokine Storm Syndrome (CSS), such as immune system cells, monocytes, and dendritic cells [14].

Recently, detection of the SARS-CoV-2 immunoglobulin M (SARS-CoV-2 IgM) and immunoglobulin G
(SARS-CoV-2 IgG) antibodies is a fast and simple screening method however, these two antibodies are impossible to detect in the window period of about two weeks.

Therefore, detection of these antibodies can only be used as an effective complement and aid to nucleic acid test results [15].

In this study, it was aimed to compare the levels of AAT, AGP, Total IgM, Total IgG, Gal3, and SARS-CoV-2 IgG tests in patients whose COVID-19 was confirmed by rRT-PCR test with healthy individuals.

The aim of selecting these tests is to approach the disease from a different perspective and contribute to the literature with these tests, which are considered to be involved in the inflammatory process in COVID-19 and have been conducted in a small number of studies.

**Materials and methods**

**Study population**

A total of 86 (46 female, 40 male) participants who applied to Ufuk University Faculty of Medicine Dr. Rıdvan EGE Hospital polyclinics between 20/07/2020 and 21/09/2020 were included. The patient group was formed with 44 (19 female, 25 male) participants between the ages of 13–95 who applied to the Fever clinic with complaints of fever, cough, myalgia, and shortness of breath and confirmed to be COVID-19 with the rRT-PCR test result. Control group was formed with 42 (27 female, 15 male) participants who applied to other polyclinics of our hospital between the specified dates, did not show any known symptoms of COVID-19 (fever, cough, myalgia, shortness of breath), did not have any chronic disease, and did not use regular medication.

Blood samples and throat swabs for the rRT-PCR test were collected from all participants on the same day. Blood samples taken from all participants were centrifuged at 1,700 g for 10 min, their serum was separated and stored at −80 °C until the day of analysis.

Exclusion Criteria: Those with negative rRT-PCR test results but findings of disease on chest tomography were excluded from the study. Patients who previously had COVID-19 disease and applied for control were not included in the study.

For the study, permission was obtained from the Non-Invasive Clinical Research Commission of the Gazi University Clinical Research Ethics Committee with the decision number 494 dated 06/07/2020, and the study was carried out in accordance with the Helsinki Declaration (World Medical Association Declaration of Helsinki http://www.wma.net/en/30/publications/10policies/b3/index.html) and prospectively.

**Laboratory measurements**

In the serum samples of the participants, AAT (reference range: 0.9–2.0 g/L) and AGP (reference range: 50–120 mg/dL) were measured as inflammatory biomarkers, while Gal3 (cut off value: female: <28.7 ng/mL, male: <26.1 ng/mL), Total IgG (reference range; female: 5.2–16.31 g/L, male: 5.4–18.22 g/L), Total IgM (reference range; female: 0.33–2.93 g/L, male: 0.22–2.4 g/L), and SARS-CoV-2 IgG (cut off value: >1.4 s/co) levels were measured as immunological biomarkers. The obtained results were compared between the patient and control groups. AAT, AGP, Total IgG, Total IgM levels were measured on an Abbott Architect c8000 biochemistry analyzer (Abbott, Abbott Park, Illinois, U.S.A.) using the immunoturbidimetric method. Gal3 and SARS-CoV-2 IgG (qualitative measurement of antibody developed against the nucleocapsid protein) levels were analyzed on an Abbott Architect i2000SR immunoassay analyzer (Abbott, Abbott Park, Illinois, U.S.A.) using the chemiluminescent microparticle immunoassay method.

**Statistical analysis**

Statistical analyses were carried out using the SPSS software (Version 22.0, Armonk, NY, IBM Corp.). The normality of distribution of all groups was first examined using the Shapiro Wilk test. In comparison between groups, Independent Sample t Test was used for normally distributed data, and Mann Whitney U test, was used for data that did not show normal distribution. The results of the normally distributed parameters were expressed as “mean ± standard deviation (SD)”, while the results of the non-normal distributed parameters were given as “median; interquartile range (IQR)”. Spearman’s correlation test, which is used for nonparametric data, was used after the distribution test for correlation analysis between parameters in the patient group.

**Results**

The analysis of the age distribution in the groups revealed that the mean age was 39.3 ± 11.3 years in the control group and 54.6 ± 21.6 years in the patient group (mean ± SD). There was a statistically significant difference between the groups in terms of age (p<0.001). Statistical analysis results for other parameters among groups are given in Table 1, focused by age. The results were expressed as “mean ± SD” for normally distributed Total IgG and as “median; (IQR)” for other parameters not following a normal distribution.

The visual distribution of patient and control group data is shown in Figure 1 as boxplot graphics.

Of the 44 patients in the rRT-PCR positive patient group, 20.46% (9/44) had positive SARS-CoV-2 IgG test results. Of these patients, eight were male and only one was female. The combined positivity of rRT-PCR and SARS-CoV-2 IgG test results in these individuals suggests that these patients are in the late stage of infection or in the recurrence period [16].

The comparison of the ages of the individuals of the same gender in the groups revealed statistically significant differences between both males (Control male: 44.8 ± 12.5 years; Patient male: 66.5 ± 18.4 years; p<0.001) and females (Control female: 41.2 ± 10.8 years; Patient female: 57.4 ± 18.4 years; p<0.001). Table 2 shows the statistical results obtained as a
Table 1: Comparison of test results between groups.

| Tests               | Control (n=42) | Patient (n=44) | P-value |
|---------------------|----------------|---------------|---------|
| AAT, g/L            | 1.28(1.04–1.39) | 1.87(1.65–2.47) | <0.001  |
| AGP, mg/dL          | 72.5(50.28–85.8) | 145.9(110.8–184.9) | <0.001  |
| Gal3, ng/mL         | 11.1(8.5–13.6)  | 16.7(13.2–31.5)  | <0.001  |
| Total IgM, g/L      | 0.74(0.56–1.07)  | 0.71(0.52–1.08)  | 0.369   |
| Total IgG, g/L      | 8.35 ± 2.08     | 10.5 ± 2.57     | <0.001  |
| SARS-CoV-2 IgG      | 0.02(0.02–0.03)  | 0.05(0.03–1.99)  | <0.001  |

*as mean ± SD, the results of other parameters are given as median;(IQR). AAT, Alpha-1 antitrypsin; AGP, Alpha-1 acid glycoprotein; Gal3, Galectin-3; Total IgM, Total Immunoglobulin M; Total IgG, Total Immunoglobulin G; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

result of the age-weighted analysis of the correlations between the studied parameters.

When the relations of the parameters between the genders within the same group were analyzed; no statistically significant difference between the genders in the control group in terms of any parameter (p values for AAT, AGP, Gal3, Total IgM, Total IgG, SARS-CoV-2 IgG, and age, respectively: 0.718*; 0.878*; 0.572; 0.393; 0.386*; 0.535; 0.467*), but a statistically significant difference between the genders in the patient group in terms of the levels of AAT, AGP, Gal3, Total IgM (p values: 0.045*; 0.030; 0.020; 0.003, respectively). Similarly, there was no statistically significant difference between the genders in the patient group in terms of Total IgG, SARS-CoV-2 IgG levels, and age parameter (*as mean ± SD, other parameters are given as median; [IQR]).

The correlation analysis of variables in the patient group showed moderate correlations between AAT and AGP, and SARS-CoV-2 IgG and AAT. There were statistically weak correlations between Total IgM and Total IgG, Gal3 and AAT, SARS-CoV-2 IgG and AGP, Gal3 and SARS-CoV-2 IgG, AGP and Gal3, and Total IgM and SARS-CoV-2 IgG. Correlation graphics of tests showing moderate and low level correlation given in Figure 2.

There were nonsignificant correlations between AAT and Total IgG, AGP and Total IgM, Gal3 and Total IgM, Gal3 and Total IgG, and SARS-CoV-2 IgG and Total IgM. In the patient group, the correlation coefficients and directions obtained as a result of the correlation analysis between variables are given in Table 3.

Discussion

In the study, which we aimed to investigate the relationship between COVID-19 disease and the levels of these tests by comparing the AAT, AGP, Total IgM, Total IgG, Gal3, and SARS-CoV-2 IgG levels in patients with COVID-19 and healthy individuals, we found that AAT, AGP, Total IgG, Gal3 and SARS-CoV-2 IgG levels in the patient group were statistically significantly higher than the control group. When we examine the relationships between variables in the patient group, we determined a moderate correlation between AAT-AGP and SARS-CoV-2 IgG-AAT, while a low level of correlation between Total IgM-Total IgG, Gal3-AAT, SARS-CoV-2-Tot IgM, SARS-CoV-2 IgG-AGP, Gal3-SARS-CoV-2 IgG, and Gal3-AGP.

A cohort study by McElvaney et al. evaluating the acute-phase response of AAT in a total of 40 patients with COVID-19, 20 stable and 20 requiring intensive care support, found high AAT levels in both groups (mean: 2.10 ± 0.51, median: 2.16; mean: 2.89 ± 0.49, median: 2.85 g/L, respectively; reference range: 0.90–1.80 g/L). In our study, the patient group had statistically significantly higher AAT levels than the participants in the control group, which was above the reference range (1.85 ± 0.67; 1.29 ± 0.37 g/L, respectively; p<0.001; reference range: 0.90–1.80 g/L). The study by McElvaney et al. showing increased AAT levels in COVID-19 patients also found that the increase in AAT was directly proportional to the increase in IL-6, which supports the anti-inflammatory function. However, patients with COVID-19 who required intensive care were observed to have a higher ratio of IL-6: AAT compared to stable patients with COVID-19. Furthermore, among intensive care unit (ICU) patients, those with a decreased ratio of IL-6: AAT during the treatment period had clinical improvement, while those with a high ratio during treatment had no clinical improvement. Therefore, the researchers predicted that AAT supportive therapy could be considered a treatment method for COVID-19 [17]. AAT was determined to be a specific SARS-CoV-2 inhibitor when a peptide/protein reserve derived from bronchoalveolar lavage was screened to identify respiratory factors suppressing SARS-CoV-2 [18]. AAT inhibits SARS-CoV-2 infection and the two most important proteases involved in the pathophysiology of COVID-19: transmembrane serine protease 2 (TMPRSS2), and a disintegrin and metalloproteinase 17 (ADAM17). AAT also inhibits the activity of inflammatory molecules such as interleukin-8 (IL-8), TNF-α, and neutrophil elastase. TMPRSS2 is vital for SARS-CoV-2-S protein binding and viral infection. ADAM17 mediates the spreading of angiotensin-converting enzyme 2 (ACE2), interleukin-6 receptor (IL-6R), and TNF-α. ACE2, on the other hand, is an important component of the SARS-CoV-2 entry receptor, the balance of the renin-angiotensin system, inflammation, vascular permeability, and pulmonary homeostasis...
Figure 1: Display of differences between the groups by age-weighted box plots.
Table 2: Relationships between test results of the same gender among groups.

| Tests                  | Gender | Control Female (n=27), male (n=15) | Patient Female (n=19), male (n=25) | p-Value |
|------------------------|--------|-----------------------------------|-----------------------------------|---------|
| AAT, g/L               | Female | 1.24 ± 0.26<sup>a</sup>           | 1.82 ± 0.38<sup>a</sup>           | <0.001  |
|                        | Male   | 1.23 ± 0.17<sup>a</sup>           | 2.16 ± 0.62<sup>a</sup>           | <0.001  |
| AGP, mg/dL             | Female | 65.4±(49.7–85.8)                  | 115.2;(96.6–146.4)                | <0.001  |
|                        | Male   | 73.6 ± 20.93<sup>a</sup>          | 164.7 ± 46.86<sup>a</sup>         | <0.001  |
| Gal3, ng/mL            | Female | 11.1;(8.5–13.8)                  | 14.8;(11.8–21.1)                 | <0.001  |
|                        | Male   | 10.5;(9.2–13.6)                  | 18.9;(14.3–32.4)                 | <0.001  |
| Total IgM, g/L         | Female | 0.82;(0.55–1.26)                | 0.92;(0.67–1.2)                  | <0.001  |
|                        | Male   | 0.64;(0.56–0.88)                | 0.58;(0.48–0.9)                  | 0.011   |
| Total IgG, g/L         | Female | 8.65 ± 2.08<sup>a</sup>          | 10.39 ± 2.21<sup>a</sup>          | <0.001  |
|                        | Male   | 7.84 ± 1.97<sup>a</sup>          | 10.63 ± 2.77<sup>a</sup>          | <0.001  |
| SARS-CoV-2 IgG, s/co   | Female | 0.03;(0.03–0.02)                | 0.04;(0.02–0.09)                 | <0.001  |
|                        | Male   | 0.02;(0.03–0.01)                | 0.36;(0.03–6.75)                 | <0.001  |

<sup>a</sup>as mean ± SD, the results of other parameters are given as median(IQR). AAT, Alpha-1 antitrypsin; AGP, Alpha-1 acid glycoprotein; Gal3, Galectin-3; Total IgM, Total Immunoglobulin M; Total IgG, Total Immunoglobulin G; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

In the light of this knowledge, increasing AAT levels in our COVID-19 patients may be an indicator that the disease will progress better.

As a result of a retrospective study conducted by Chen et al. with 113 patients who died due to COVID-19; they decided that immunoglobulin levels were not specific markers of CSS, and as a result of analyzing the small number of data they obtained, they did not observe a clinically significant difference between patients who died and who recovered [20]. Zhang et al. found a link between SARS-CoV-2 specific IgG responses and increased disease severity in 222 COVID-19 patients in a retrospective study [21].

A study conducted by Xie et al. with 56 patients, 40 (71.43%) patients with negative rRT-PCR and 16 (28.57%) patients with positive rRT-PCR, found positive IgG antibody test results in all 56 patients [22]. A study by Liu et al. with 111 patients with positive rRT-PCR found that the median IgG levels were lower in the asymptomatic group compared to the symptomatic group (p<0.01) [23]. In our study, the number of specific IgG positive patients in the patient group of 44 participants was nine. The differences in antibody positivity in these studies may be due to the varying times of infection with the coronavirus.

A study by Long et al. compared the virus-specific IgG levels of asymptomatic patients (n=37) and symptomatic patients (n=37) who were diagnosed with SARS-CoV-2 infection confirmed by rRT-PCR in the Wanzhou Region but did not have clinical symptoms of the disease during the previous 14 days and throughout their hospital stay. This study found that the asymptomatic group significantly lower levels of virus-specific IgG levels (median s/co: 3.4; IQR, 1.6–10.7) than the symptomatic group (median s/co: 20.5; IQR, 5.8–38.2) (p=0.005) [24]. A study by Hou et al. evaluating IgG antibody levels of 338 COVID-19 patients with the chemiluminescence immunoassay method found that 81.1% of the asymptomatic group and 83.8% of the symptomatic group had virus-specific IgG positivity [25]. In our study, specific IgG positivity was found in 20.46% of the patient group. This difference may be due to not knowing whether the symptomatic and asymptomatic individuals in our patient group had enough time to develop virus-specific IgG after infection.

In their study, Zeng et al. divided 331 patients with COVID-19 (127 male and 204 female) into four groups as mild (n=22), general (n=87), severe (n=22), and recovering (n=200), and found the rates of male and female patients as 36.4 and 63.6% in the mild group, 42.5 and 57.5% in the general group, respectively. The number of male and female patients was equal in the severe group. In the recovering group, the rates of male and female patients were 35.5 and 64.5%, respectively, and the mean age was almost the same [26]. In our study, the rates of male and female patients in the patient group were 56.81 and 43.18%, respectively. While our findings appear to contradict those of Zeng et al., it is thought that this is due to the small sample size of our study.

A study by De Biasi et al. with a total of 34 participants, including 13 healthy controls and 21 patients with COVID-19 found statistically significantly higher Gal3 levels in the patient group than in the control group.
In our study, the results we obtained about Gal3 are consistent with the results of the study conducted by De Biasi et al., and we also found that the Gal3 levels in the patient group were higher than the control group. Serum Gal3 levels have been shown to be significantly associated with prognosis in patients with ARDS [28]. As a result of our study, there was a statistically significant difference between the patient and control groups between the

Figure 2: Correlation graphics of the relationships between parameters in the patient group.
Table 3: Results of correlation analysis between tests in the patient group.

| Tests             | Correlation coefficient (r value) | p-Value |
|-------------------|-----------------------------------|---------|
| AAT, g/L – AGP, mg/dL | 0.692                             | <0.001  |
| AAT, g/L – SARS-CoV-2 IgG, s/co | 0.561                             | <0.001  |
| Gal3, ng/mL – AGP, mg/dL | 0.499                             | <0.001  |
| AGP, mg/dL – SARS-CoV-2 IgG, s/co | 0.447                             | <0.001  |
| Gal3, ng/mL – AAT, g/L | 0.344                             | <0.001  |
| Total IgG, g/L – Total IgM, g/L | 0.497                             | <0.001  |
| Total IgG, g/L – SARS-CoV-2 IgG, s/co | 0.362                             | <0.001  |
| Total IgM, g/L – Gal3, ng/mL | –0.222                            | <0.001  |
| Total IgG, g/L – Gal3, ng/mL | –0.240                            | <0.001  |
| AGP, mg/dL – Total IgG, g/L | –0.077                            | <0.001  |
| Total IgM, g/L – AGP, mg/dL | –0.062                            | 0.002   |

AAT, Alpha-1 antitrypsin; AGP, Alpha-1 acid glycoprotein; Gal3, Galectin-3; Total IgM, Total Immunoglobulin M; Total IgG, Total Immunoglobulin G; SARS-CoV-2 IgG, Severe acute respiratory syndrome coronavirus 2 IgG.

Gal3 levels, the statistically significant correlation between AAT, which was determined to be a specific SARS-CoV-2 inhibitor, and AGP, which was known to be an immunomodulator, and correlations of Gal3-AAT and Gal3-AGP could give an idea about the prognosis of this disease as well.

Since there are few studies in the literature on the parameters studied in our analysis, it is possible that our findings will inform future research.

Our study has limitations; the day of the symptoms could be specified at the time of sample collection from the patients and the time of SARS-CoV-2 IgG development could be discussed.

In conclusion; The statistically significantly higher levels of AAT, AGP, Total IgG, Gal3, and SARS-CoV-2 IgG in the patient group compared to the control group, and the correlations between variables in the patient group, can be effective in the pathogenesis processes of the disease and give an idea about the prognosis of the disease. However, new studies on this subject are needed to clearly reveal the levels and changes of these markers in the course of COVID-19 disease.

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