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Antinuclear antibodies (ANAs) detected by indirect immunofluorescence (IIF) method in acute COVID-19 infection; future roadmap for laboratory diagnosis

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A B S T R A C T

Introduction: As in other viral infections, anti-nuclear antibodies (ANAs) are observed in SARS-CoV-2 infection. We investigated the presence of autoantibodies in acute COVID-19 and the association with early laboratory findings.

Materials and methods: We examined 50 sera (>18 years, 25 Female) from patients with acute COVID-19. ANAs (HEp-20 liver biochip), anti-neutrophil cytoplasmic antibody (ANCA, Europlus Granulocyte Mosaic 32) and anti-double stranded DNA were investigated with product of Euroimmune AG (Luebeck, Germany) by indirect immunofluorescence (IIF) method. Also, antibody against cyclic citrullinated peptide (anti-CCP) was examined by a chemiluminisens assay (Euroimmun AG, Luebeck, Germany). Samples from 50 blood bank donors collected before the COVID-19 pandemic were used as controls.

Results: The IIF-ANA test was positive in 18% (N = 9/50) of the patients. The median time of sample collection was 7 days (range: 1–28 days) after diagnosis. ANA was positive in only one (2%) control sample. Five (55.5%) patients were ANA positive with a strong titer (3+). There was no relationship between antibody titration and time of sample collection (p = 0.55). Anti-CCP was detected in a nucleolar (3+) positive patient (2%). ANA was detected in 14.28% (N = 1/7, rods-rings (±); p = 0.78) of patients in the intensive care unit (ICU). Patients treated in the clinic have more and higher titers of ANA, mostly in nucleolar patterns, than ICU patients.

Conclusions: The variety of antibodies detected in acute COVID-19 and the uncertainty of how long they persist can lead to confusion, especially in the diagnosis of systemic autoimmune rheumatic diseases for IIF-ANA testing in immunology laboratories. Improvements in cell lines and methods will facilitate the diagnostic process.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) still continues its effects despite vaccination and isolation applications around the world. The SARS-CoV-2-associated disease, has been named coronavirus disease 2019 (COVID-19) and has reached over 200 million cases worldwide (Zhou et al., 2020b; Gorbalenya et al., 2020; “WHO Coronavirus (COVID-19) Dashboard”, 2021). In this devastating disease, immunological manifestations such as Kawasaki-like syndrome, Guillain Barre syndrome and immune thrombocytopenic purpura are observed in addition to the inflammatory response associated with sepsis, coagulopathy, multi organ failure and cytokine storm syndrome (Ehrenfeld et al., 2020; Günther et al., 2020; Vojdani and Kharrazian, 2020; Salle, 2021). Viral pathogens are known to be one of the most common exogenous factors that can trigger autoimmunity. Antibodies to viral proteins of SARS-CoV-2 infection in susceptible individuals appear as a potential autoimmune trigger as a result of cross-reactivity with autoimmune target proteins (Vojdani and Kharrazian, 2020; Salle, 2021).

Abbreviations: ANA, anti-nuclear antibody; anti-CCP, anti-cyclic citrullinated peptide; anti-dsDNA, anti-double stranded DNA; ANCA, Anti-neutrophil cytoplasmic autoantibody; COVID-19, coronavirus disease 19; ENA, extractable nuclear antigen; IIF-ANA, indirect immunofluorescence anti-nuclear antibody; ICAP, international consensus on ana patterns; ICU, intensive care unit; MPO, myeloperoxidase; SARD, systemic autoimmune rheumatic diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Nuclear antigens are usually the target of autoantibodies and anti-nuclear antibodies (ANA) can be detected in many autoimmune diseases such as systemic lupus erythematosus (SLE), but also in many viral infections (Sener et al., 2014). Although there are several studies in the literature, autoantibodies are commonly seen in COVID-19 patients positive in the healthy population (with a weak titer and prevalence et al., 2021a; Trahtemberg et al., 2021). However, because ANA is also positive in the healthy population (with a weak titer and prevalence ranging from 8% to 15%) and in other clinical conditions, positive results must be interpreted with clinical data (Kakkikaya et al., 2020; Yurtutun Uyar et al., 2017; Damoiseaux et al., 2016).

Based on these observations, we investigated the presence and types of autoantibodies in acute COVID-19 patients who were hospitalized and as a secondary outcome we evaluated the association between the presence of autoantibodies and other laboratory findings and poor prognosis (intensive care admission) in the initial phase of SARS-CoV-2 infection.

2. Material and methods

2.1. Study design and participants

The study included 50 patients (>18 years) whose COVID-19 diagnosis was confirmed by a SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test and who had radiological findings of pneumonia associated with COVID-19. After obtaining informed consent from patients hospitalized between March 2021 and April 2021, serum samples were collected and stored at –80 °C in the medical microbiology laboratory of Izmir Katip Celebi University Atatürk Training and Research Hospital until the study day. Fifty samples from healthy blood donors [25 females (F), 25 males (M)] before the COVID-19 pandemic were used as controls.

Patients’ medical records and laboratory test results were taken from the hospital information system. Among the laboratory tests done during hospitalization, complete blood count [white blood cell count (WBC), lymphocytes, monocytes, neutrophils and thrombocyte count, hemoglobin level], C-reactive protein (CRP, mg/dL), D-dimer (μg/L), ferritin (ng/mL), fibrinogen (g/L), procalcitonin (μg/L), international normalized ratio (INR), activated partial thromboplastin time (aPTT, sec), and prothrombin time (PT, sec) tested in the week when study samples were collected were included for the analysis.

2.2. Study group characteristics

Of the 50 patients (25 F, 25 M) who were followed up in the clinic, 7 patients were in the intensive care unit (ICU) at the time of sample collection. Median time from the positive SARS-CoV-2 RT-PCR test to the sample collection was 7 days (range: 1–8 days). During the clinical follow-up, 4 patients (N: 4/50, 8%; 2 F, 2 M) died in due to COVID-19. Patients included in the study did not have not a history of systemic autoimmune rheumatic disease (SARD), oncologic disease, biological agent use and hepatitis B or C virus coinfection.

2.3. IIF testing and evaluation

ANA determination was performed using the indirect immunofluorescence (IIF) method with the HEP-20-10 liver biochip (Monkey) (Euroimmun AG, Luebeck, Germany) kit at a dilution of 1:100 according to the manufacturer’s recommendation in the collected patient and control samples. The evaluation was performed by a laboratory specialist with 20 years of experience using a fluorescence microscope (Eurostar III plus). The fluorescence intensity of the positive control was assumed as 4+, so the titer intensity values were evaluated as ± (borderline), 1+ and 4+ at ×400 objective. In this process, an evaluation was performed considering International Consensus on ANA Patterns (ICAP) standards (Damoiseaux et al., 2016).

2.4. Extractable nuclear antigen (ENA), ANCA and anti-dsDNA testing

The presence of extractable nuclear antigens (ENA) in ANAs positive samples were investigated by a line immunoassay method using the Euroline ANA-profile 1 (IgG) kit (Euroimmun AG, Luebeck, Germany). Each strip consisted of nRNP/Sm (U1-nRNP), Sm, SS-A, recombinant Ro-52 (Ro52, 52 kDa), SS-B, DNA topoisomerase I (ScI-70), PM-ScI, histidyl-tRNA synthetase (Jo-1), centromere protein B (CENP B), dsDNA, nucleosome, histone, and pyruvate dehydrogenase complex antigens and was assayed according to the manufacturer’s protocol. Anti-neutrophil cytoplasmic antibodies (ANCA); cANCA, pANCA, proteinase 3 (PR3) and myeloperoxidase (MPO) were tested with Europlus Granulocyte Mosaic 32 (Euroimmun AG, Luebeck, Germany) kit and anti-double stranded DNA (anti-dsDNA) was evaluated Crithidia luciliae (Euroimmun AG, Luebeck, Germany) test kit at a dilution of 1:10 by IIF method in accordance with the manufacturer’s recommendations.

2.5. Anti-CCP testing

The simultaneously anti-cyclic citrullinated peptide (anti-CCP) IgG antibodies and ANA were investigated in patient samples. Anti-CCP Ig G antibodies were analyzed by a chemiluminescence assay (Euroimmun AG, Luebeck, Germany). Measured serum concentrations were calculated using a five-parameter logistic curve-alignment calculation formula according to the manufacturer’s recommendations (cut-off value >5.0 AU/mL).

2.6. Statistical analysis

For normally distributed values, the t-test was used for independent samples. Comparisons between groups were performed using Fisher’s exact test for categorical variables and Mann – Whitney U test for continuous variables. Categorical data were compared using the Chi-Square test. Statistical analyzes were performed using IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD), number (N), and percentage (%). P < 0.05 was considered statistically significant.

3. Results

Fifty patients diagnosed with acute COVID-19 pneumoniae were screened for the prevalence of ANAs. The results obtained were analyzed with clinical findings and biochemical laboratory markers.

The mean age of all patients was 58.83 ± 15.25 years (range: 27.23–95.49 years) and the mean ages of males (N:25) and females (N:25) with COVID-19 were 54.84 ± 13.2 years (range: 33.65–85.83 years) and 62.81 ± 16.35 years (range: 27.23–95.49 years), respectively. The mean age of the control group was 35.84 ± 9.75 years (range: 21–60 years) and the mean ages of males and females were 33.12 ± 7.94 years (range: 24–49 years) and 38.56 ± 10.74 years (range: 21–60 years) for the control group, respectively.

The IIF-ANA test was positive in 18% (N: 9/50) of patient sera. The mean age of patients with ANA positive and negative was 62.08 and 58.11 years, respectively (p = 0.29, Mann – Whitney U test). ANA was positive in 20% (N: 5/25) of female and 19% (N: 4/25) of male patients with no statistical difference in terms of gender (p = 0.71, Chi – Square test). Only one control serum was positive for ANA (N: 1/50, 2%, Dense fine speckled: DFS pattern (AC-20 and/or AC-19)). Although the positivity rate of the IIF-ANA test was lower in the control group compared to COVID-19 patients, the difference was not statistically significant (p = 0.63, Chi – Square test).

ANCA (myeloperoxidase; MPO) was positive in one (N: 1/50, 2%) female serum detected as nucleolar (±) (AC-8) pattern by IIF-ANA test.
In addition, one serum from a female patient with a homogenous (3+) (AC-1) pattern was positive for anti-histone antibody by ENA immunoblot assay (N: 1/50, 2%). Table 1 shows the distribution of the patients’ ANA patterns and their titration values. In the IIF-ANA test, strong positivity (3+) was detected in 5 patients’ sera (55.5%).

Anti-dsDNA was not detected in any of the study patients. Anti-CCP antibody was measured positive in one (N: 1/50, %2) male patient’s serum. In addition, a nucleolar (3+) pattern was detected in this patient by the IIF-ANA assay. The rods-rings antibody (±) (AC-23) was positive in one male patient who was monitored in the ICU (N: 1/7, %14.28). During the follow-up period, four patients died due to COVID-19 and IIF-ANA, ANCA, ENA, and anti-CCP test positivity was not detected in any of these patients.

Table 2 shows the relationship between the presence of ANA and patient characteristics, sampling time and clinical findings. There was no correlation between the time of sampling and the presence of autoantibodies. The median time of sample collection in ANA positive and negative patients was 7 and 8 days, respectively (p = 0.67, Mann – Whitney U test). In ANA positive patients, there was no association between antibody titration and sampling time (p = 0.55, Mann – Whitney U test).

Seven patients (2F, 5M) were being monitored in the ICU at the time of sample collection. The ratio ANA positive patients followed in the ICU and the clinic were 14.28% (N: 1/7) and 18.6% (N: 8/43), respectively (p = 0.78, Fisher’s exact test).

Table 3 shows the relationship between the presence of ANA and inflammatory biomarkers, tests for coagulation and blood count parameters. The changes in procalcitonin (50%, elevated) and CPR (92%, elevated) values in relation to ANA positivity were not statistically significant (p = 0.17, and p = 0.12, Mann – Whitney U test). Elevated ferritin levels were found in 42.8% of patients and the difference was not statistically significant (p = 0.12, Mann – Whitney U test) in relation to the presence of ANA. Fibrinogen levels were detected in the reference range in 28.2% (N: 13/46) of patients. In addition, fibrinogen levels were lower in ANA positive patients than in negative patients (mean: 4,11, ±0,99 SD, range: 2,43–5,15, p = 0.03, Mann – Whitney U test). Although D-dimer levels were elevated in 78% (N: 39/50) of patients, this was not statistically significant with respect to the presence of ANA (p = 0.63, Mann – Whitney U test). There was no statistically significant difference between the patient groups with D-dimer values below and above 1000 μg/L in the presence of ANA (p = 0.66, Mann – Whitney U test). In multivariate analysis for fibrinogen, D-dimer and WBC, no significant difference was found with respect to ANA positivity (p = 0.054, p = 0.410, p = 0.439, respectively). In terms of coagulation parameters, prolonged aPTT and PT values and increased INR values were observed. The association between coagulation values and the presence of ANA was not statistically significant (p = 0.69, p = 0.80, p = 0.71, Mann – Whitney U test).

Table 2
The relevance between the presence of ANA and the characteristics of patients.

| Parameter | ANA negative (n = 41) | ANA positive (n = 9) | p-value |
|-----------|-----------------------|----------------------|---------|
| Age       | Median (range)         | Median (range)       |         |
|           | 58.11 (27.74–95.49)    | 62.08 (27.23–85.83)  | 0.29    |
| Gender    | F (M)                  | n (%)                |         |
|           | 21 (84)                | 21 (84)              | 0.71    |
| Sampling timea | Median (range)       | 8 (1–28)             | 0.67    |
| C / ICU   | n (%)                  | 35 (81.4) / 6        | 0.78    |
| COVID-19 related death | n (%)             | 4 (9.75)             | NA      |

Table 3
The relevance between the presence of ANA and laboratory findings.

| Parameter | ANA negative | ANA positive | p-value |
|-----------|--------------|--------------|---------|
| CRP, mg/L (0–5) | 41/ 73.86 ± 75.90 | 9/ 35.38 ± 43.47 | 0.12    |
| Procalcitonin, μg/L | 41/ 1.31 ± 3.11 | 9/ 0.06 ± 0.05 | 0.17    |
| Fibrinogen, g/L (2.0–4.0) | 38/ 5.58 ± 2.04 | 8/ 4.11 ± 0.99 | 0.03    |
| D-dimer, μg/L (243) | 41/ 819.82 ± 1093.17 | 41/ 450.55 ± 331.65 | 0.63 |
| PT, sec (9.4–12.5) | 41/ 12.98 ± 2.19 | 9/ 12.51 ± 0.71 | 0.80    |
| aPTT, sec (25–36.5) | 41/ 28.76 ± 4.79 | 9/ 29.28 ± 4.41 | 0.69    |
| INR (0.8–1.2) | 41/ 1.11 ± 0.19 | 9/ 1.06 ± 0.06 | 0.71    |
| Ferritin, μg/L (10–290) | 40/ 586.32 ± 558.97 | 360/ 66 ± 528.32 | 0.12    |
| WBC, 109/L (4–10) | 41/ 9.01 ± 4.63 | 9/ 8.32 ± 4.92 | 0.55    |
| Lymphocyte, 109/L (0.8–4) | 41/ 1.38 ± 0.87 | 9/ 1.40 ± 0.83 | 0.82    |
| Monocyte, 109/L (0.12–1.2) | 41/ 0.45 ± 0.27 | 9/ 0.56 ± 0.28 | 0.27    |
| Neutrophil, 109/L (2–7) | 41/ 7.09 ± 4.52 | 9/ 6.26 ± 4.24 | 0.50    |
| Thrombocyte, 109/L (150–400) | 41/ 263.78 ± 127.29 | 276.55 ± 98.02 | 0.92    |
| Hemoglobin, g/dL (12–16) | 41/ 12.15 ± 1.85 | 9/ 12.32 ± 1.80 | 0.80    |

Table 1
Demographic characteristics and distribution of autoantibody patterns of ANA positive patients.

| Patient no | Gender | Age | Unit | ANA pattern (Titer) | ANCA | ENA | Anti-dsDNA |
|------------|--------|-----|------|---------------------|------|-----|-----------|
| P3         | F      | 60,81 | C    | Nucleolar (±)       | –    | –   | –         |
| P6         | M      | 85,83 | C    | Nucleolar* (3–+)    | –    | –   | –         |
| P7         | F      | 65,53 | C    | Midbody/nucleolar (3+) | –    | –   | –         |
| P15        | M      | 61,39 | C    | Nucleolar (3+)      | –    | –   | –         |
| P20        | M      | 56,18 | C    | Nucleolar (3+)      | –    | –   | –         |
| P36        | F      | 27,23 | C    | Midbody (±)         | –    | –   | –         |
| P42        | M      | 59,34 | ICU  | Rods-rings (±)      | –    | –   | –         |
| P47        | F      | 76,19 | C    | Homogeneous (3+)    | –    | –   | Anti-histone |
| P50        | F      | 66,24 | C    | Nucleolar (±)       | –    | –   | MPO       |

ANA: anti-nuclear antibody, ANCA: anti-neutrophil cytoplasmic, Anti-CCP: anti-cyclic citrullinated peptide, Anti-dsDNA: anti-double stranded DNA, C: clinic, ENA: extractable nuclear antigen, F: female, ICU: intensive care unit, M: male, Midbody pattern (AC-27), MPO: myeloperoxidase.

a Anti-CCP IgG antibody was determined positive.
4. Discussion

There are several studies on autoantibody response in COVID-19 patients that are not yet at satisfactory level. We evaluated the ANA and patterns of autoantibodies associated with COVID-19. ANA was detected in 18% (N: 9/50) of COVID-19 patients by IF test in our study. Analyses were performed to determine the relevance between the presence of ANA and other laboratory tests used routinely for the follow-up COVID-19 patients.

In a study conducted with blood bank donors, the ANA positivity in our region was 1.57% (Peker et al., 2019). The mean age of the control group was lower than that of the patients (35.84 years) and ANA positivity was low (2%). Low prevalence of ANA in healthy population in our country and the limited size of the control group might explain the lack of an association between age and ANA positivity.

ANAs, which are usually not associated with an autoimmune disease have been reported to occur in transient autoreactive B and plasma cell reactivation secondary to infection (Litwin and Binder, 2016). In the observation with the context of severe COVID-19, numerous antibody secreting cells are produced as a result of upregulation of extracellular B cells, including clonotypes that are autoreactive (Woodruff et al., 2020). Considering these data in cellular structuring, ANA was detected in 18% of COVID-19 patients in our study, but this was lower than the data in the literature (21.3%-64%) (Pascolini et al., 2021; Gazzaruso et al., 2020; Sacchi et al., 2020; Chang et al., 2021a; Chang et al., 2021a). None of the patients in our study group had a history of a SARD or oncologic disease in which biological agents were used. In long-term follow-up, the persistence of this autoantibody formation and the uncertainty of its clinical response remain unclear.

Although various ANA patterns have been detected in the initiation of COVID-19, the presence of patterns directed mainly against nuclear antigens has been reported (Lerma et al., 2021; Chang et al., 2021b; Chang et al., 2021a). In agreement with the literature, mainly nucleolar antibody patterns were detected in our study. When ANA positive samples are examined, multiple autoantibody patterns that are targeting more than one nuclear antigen are also observed in several studies. While a cooccurrence of ANA with RNP has been reported (Lerma et al., 2020), the presence of anti-SS-A/Ro-52 was also been detected in a study and an anti-histone antibody was found simultaneously with ANA in one patient in our study (Gazzaruso et al., 2020).

There are only a limited number of studies showing vasculitis associated autoantibodies in COVID-19 patients (Gazzaruso et al., 2020; Sacchi et al., 2020; Vlachoyiannopoulos et al., 2020; Chang et al., 2021a). In ANCA associated vasculitis, the most common ANCA targets MPO and PR3 which are closely related with small vessel vasculitis (Sundqvist et al., 2020). Vasculitis associated MPO antibody was detected only in one patient. These data should be evaluated comprehensively, because both the limited number of cases in the study and the differences in background acquired immune responses of patients might have an effect on the condition.

In COVID-19 patients, detectable anti-CCP levels with ANA positivity have been reported up to limited series of patients and with wide ranges (2.1%-20%) (Chang et al., 2021b; Vlachoyiannopoulos et al., 2020; Roongta et al., 2021). It has been reported that a patient who developed arthritis after COVID-19 infection and had anti-CCP positivity became seropositive for rheumatoid factor (Roongta et al., 2021). Besides we have reported only in one patient has an anti-CCP positivity without existence of arthritis and the ratio (2%) was similarly low as in the literature (2.1%) (Chang et al., 2021b; Roongta et al., 2021).

When compared with patients followed in the ICU, ANA titers were higher in those followed in the clinic. Pascolini et al. (2021) reported that the presence of ANA was significantly higher in cases with poor prognosis and death. Trahtemberg et al. (2021) reported a very high rate of ANA positivity (64%) in patients who were in the ICU, and they found that there was a correlation between cytoplasmic dense fine speckled (AC-20 and/or AC-19) IIF ANA patterns and clinical severity. However, no association was found between disease severity and the presence of any ANA patterns in our study. This result might be related to the patient inclusion criteria and the small number of patients in our study. Additionally, severe COVID-19 cases followed in clinic might have effected the results since data on asymptomatic or mild symptomatic outpatients are not included.

Although increases in inflammatory biomarker levels (procalcitonin, CRP, ferritin) and results outside the range in complete blood count values were detected in our study similar to earlier reports, no association was found between the presence of ANA and the inflammatory biomarker levels and complete blood count values (Lerma et al., 2020; Zhou et al., 2020b). In addition, elevated D-dimer and fibrinogen levels were also found in our study group in agreement with the literature (Gazzaruso et al., 2020; Lerma et al., 2020; Zhou et al., 2020a). In our study, fibrinogen levels were lower in ANA negative patients and it was statistically significant. This result might be due to patient inclusion criteria, disease severity and higher number of patients in the ANA negative group in our study. This correlation might become more evident in the chronic inflammatory process after the acute course of the COVID-19 disease, immune structure of the patient and evaluation of long term follow-up data.

A limitation of our study is that only a single sample was collected during follow-up and therefore, antibody responses could not be assessed in the long term. The data in our article belong to a preliminary study. It is planned to reanalyze the obtained results using the clinical records of the patients with future clinical data. Although there is no agreed definition of “Long COVID” yet, it is defined as a series of new or ongoing symptoms that last longer than expected, and may last weeks or months after the initial illness. Long COVID symptoms include fatigue, shortness of breath, cough, arthralgia, chest pain, depression, etc. Different combination of findings can be followed (Davis et al., 2021). In this disease, which differs from the course flu, ANA positivity be an additional laboratory indicator to explain the variety and duration of symptoms, suggestive of Long COVID. Although, antibody responses in the acute phase vary depending on the individual’s immune constitution, epitope spread, bystander activation, crypt antigen presentation, polyclonal B cell activation and viral superantigens are the causes of all autoimmune responses and molecular mimicry being with the main effect that has not yet been proven (Salle, 2021). In response to this question, the detection of autoantibody patterns that occur as a consequence of the immune response due to COVID-19 infection will contribute to the literature. SARS-CoV-2 PCR was performed using the detection kits provided by the Ministry of Health of our country. All patients were PCR positive but variant analysis could not be done in all of them. The influence of strain-specific virulence on the induction of autoimmunity is unknown.

5. Conclusions

In our study, a similar rate of autoantibody positivity was detected in acute COVID-19 patients, which is consistent with the limited data in the literature. The contribution of our results to the clinicians might become clearer in future. Future evaluations will reveal whether the recorded autoantibody patterns in COVID-19 patients during and especially after the pandemic would lead to a confusion in diagnosing SARD using IIF-ANA tests in the immunology laboratories. The type of autoantibody formed during the acute phase of infection and the duration of positivity is not clear yet. Improvements in the cell lines and methods will facilitate the diagnostic process.
Ethical approval

This study was approved by the Izmir Katip Çelebi University ethics committee of clinical research (March 11, 2021, Approval Number 29) and conducted in accordance with the guidelines of 1964 Helsinki Declaration.

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None.

Author contribution statement

Bilal Olcay Peker: Writing of original draft, preparation of manuscript in data collection, assay setup, software and reviewing. Aslı Gamze Şene: Conceptualization, methodology, reviewing and revision of the manuscript. Figen Kaptan Aydoğan: Selection of patients, interpretation and reviewing of data clinically.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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