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ORIGINAL ARTICLE

The effect of the pandemic on autoantibody rates in the general population

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ABSTRACT

Objectives: The study aimed to investigate the possible effects of coronavirus disease 2019 (COVID-19) on autoantibodies.

Patients and methods: Samples of 89,108 individuals (29,033 males, 60,075 females; median: 36 years; range, 0 to 96 years) who underwent autoimmune testing between January 2017 and May 2022 were retrospectively analyzed. The prepandemic period was defined as May 1, 2017, to March 20, 2020, while the pandemic period was defined as March 20, 2020, to May 31, 2022.

Results: Of the participants, 0.55% were of foreign nationality. The positivity rate was 18.12%. Autoantibody positivity rates, when analyzed by sex, were higher in females for antinuclear antibody (ANA), antimitochondrial antibody (AMA), anti-liver kidney microsomal (LKM) antibody, immunoglobulin A (IgA) anti-gliadin antibody, anti-endomysial antibody A, anti-ribosomal P protein antibody, anti-Sjögren's syndrome A (anti-SSA), anti-Sjögren's syndrome B (anti-SSB), anti-Smith/ribonucleoprotein (anti-SM/RNP), anti-SM, and c-ANCA (cytoplasmic antineutrophil cytoplasmic antibody). When the prepandemic period was compared with the pandemic period, AMA, anti-LKM antibody, IgA anti-gliadin antibody, anti-endomysial antibody A, and anti-SM/RNP levels were higher in the prepandemic period, while ANA was higher during the pandemic. Additionally, statistically significant differences were found in the distributions of ANA, AMA, anti-LKM antibody, IgA anti-gliadin antibody, anti-endomysial antibody A, anti-ribosomal P protein antibody, anti-SM, anti-SSA, and c-ANCA across the years.

Conclusion: This study could not establish a cause-effect relationship between the changing autoantibody levels during the COVID-19 pandemic and severe acute respiratory syndrome coronavirus 2 infection due to the lack of results from the same patients across different periods. Nonetheless, we believe the quantitative seroprevalence changes in such a large sample of autoantibody screening results over a five-year period, including the pandemic, are valuable.

Keywords: Antinuclear antibody, autoantibody, COVID-19, indirect fluorescent antibody test, SARS CoV-2.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), broke out in China in late 2019. More than 539 million confirmed cases and more than six million confirmed deaths have been recorded worldwide since it was declared a global public health emergency in 2020. Some infected patients may be asymptomatic or show flu-like symptoms, such as mild to moderate fever, fatigue, and unproductive cough. Headache, muscle pain, sore throat, nausea, and diarrhea may also occur in COVID-19 patients.[1,2] In some severe cases, severe pneumonia can occur, which can lead to multiple organ failure and death.[3] Severe COVID-19 is often associated with an elevated inflammatory response, including persistent fever, sepsis, coagulopathy, multiple organ failure, and cytokine release syndrome.[4]

Autoantibody production is observed in the majority of autoimmune diseases. Autoimmune diseases have complex mechanisms involving many components of the cellular and humoral response in different compositions, and many

of them are not fully elucidated. The fact that infectious agents and humans have some similar molecular structures is thought to be one of the mechanisms of autoimmunity.[5] There are numerous reports of antigenic similarity between viral proteins and human proteins. One of the best-known examples of molecular similarity is the immune response to Epstein-Barr virus in patients with lupus.[6]

Recently, many clinical associations between COVID-19 and autoimmune diseases, such as Kawasaki-like syndrome, multisystem inflammatory syndrome, Guillain-Barre syndrome, immune thrombocytopenic purpura, and chilblain-like lesions, have been described.[7] Immune mechanisms play an important role in the pathogenesis of COVID-19. SARS-CoV-2 infection may trigger autoimmune disease in some patients as a result of cross-reactivity of viral structures.[8,9] Autoantibodies usually target nuclear antigens, and antinuclear antibodies are searched in the differential diagnosis of many autoimmune diseases, including systemic lupus erythematosus.[10]

Small-scale studies in Germany and China demonstrated high incidence of antibodies to nuclear antigens in severe COVID-19.[11,12] Along with nuclear antigens, many other autoantigens may be targets of autoantibodies in various autoimmune diseases, such as vasculitis. Coagulopathy and thrombosis are prominent issues in severe COVID-19, and it is thought that antiphospholipid antibodies may mediate autoimmune thrombosis in this disease.[13] This study aimed to investigate the possible effects of COVID-19 on autoantibodies.

PATIENTS AND METHODS

In this retrospective study, samples of 89,108 individuals (29,033 males, 60,075 females; median: 36; range, 0 to 96 years) who underwent autoimmune testing at the medical microbiology laboratory of the Necmettin Erbakan University, Meram Faculty of Medicine Hospital between January 2017 and May 2022 were evaluated. Slides were prepared using immunofluorescent antibody (IFA) kits (Euroimmun AG, Lübeck, Germany) and were examined using the EUROStar III Plus immunofluorescence microscope (Euroimmun AG, Lübeck, Germany). Suspicious samples were confirmed using the immunoblotting technique, and the results were evaluated retrospectively. Ten different autoantibodies (antinuclear antibody [ANA], antimitochondrial antibody [AMA], anti-smooth muscle antibody [ASMA], p-ANCA [perinuclear antineutrophil cytoplasmic antibody, MPO-ANCA], c-ANCA (cytoplasmic ANCA, proteinase 3 [PR3]-ANCA, anti-endomysial antibody A, immunoglobulin A [IgA] anti-gliadin antibody, anti-ribosomal P protein antibody, anti-histone antibody, and anti-liver kidney microsomal [LKM] antibody) and six different proteins (anti-JO1, anti-SCL, anti-Smith [anti-SM], anti-SM/anti-ribonucleoprotein [RNP], anti-SSA, and anti-SSB) were tested by immunoblotting techniques. The distribution of autoantibody types and ratios in the results obtained according to age, sex, and seasons was evaluated. Data obtained during the COVID-19 pandemic were included in the study, with the prepandemic period defined as May 1, 2017, to March 20, 2020, while the pandemic period defined as March 20, 2020, to May 31, 2022. The study protocol was approved by the Necmettin Erbakan University Pharmaceutical and Non-Medical Device Research Ethics Committee (date 22.07.2022, no. 2022/3893). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Data were analyzed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Two-way tables of categorical variables were analyzed using the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

Among the participants, 0.55% (n=491) were of foreign nationality. Of the 89,108 individuals undergoing autoantibody testing, 18.12% (n=16,147) tested positive. The median age of individuals with a positive result in the autoantibody test was 39 years (range, 0 to 94 years; IQR, 24-53 years), whereas the median age of individuals with a negative result was 35 years (range, 0 to 96 years; IQR,

18-51 years). The median age of individuals with a positive result in the autoantibody test was statistically higher compared to those with a negative result (p<0.001).

When evaluating the positivity rates of autoantibody tests based on sex, ANA, AMA, anti-LKM, IgA anti-gliadin antibody, anti-endomysial antibody A, anti-ribosomal

Table 1. Positive rates of autoantibodies by sex

Antibodies	Sex	Negative (n)	Positive (n)	Positivity rate (%)	*p*
AMA, ASMA, anti-LKM	Female	26,450	1,376	4.9	<0.001
	Male	20,474	529	2.5	
Anti-nuclear antibody	Female	30,991	17,888	36.6	<0.001
	Male	16,796	5,642	25.1	
Anti-Gliadin	Female	21,955	1,344	5.8	<0.001
	Male	16,360	697	4.1	
Anti-Endomysial antibody A	Female	10,822	851	7.3	<0.001
	Male	8,094	449	5.3	
Anti-histone antibody	Female	8,196	167	2.0	0.838
	Male	2,437	48	1.9	
Anti-JO1 (Immunoblotting)	Female	9,643	84	0.9	0.265
	Male	2,895	19	0.7	
Anti-SM (Immunoblotting)	Female	10,870	218	2.0	<0.05
	Male	3,304	41	1.2	
Anti-SSB (Immunobloting)	Female	8,132	232	2.8	<0.001
	Male	2,453	29	1.2	
Anti-SSA (Immunoblotting)	Female	6,507	493	7.0	<0.001
	Male	2,001	52	2.5	
Anti-SM/RNP (Immunoblotting)	Female	6,785	217	3.1	<0.001
	Male	2,026	28	1.4	
Anti-Scl 70 (Immunoblotting)	Female	6,877	124	1.8	0.113
	Male	2,031	26	1.3	
Anti-ribosomal P protein	Female	6,903	104	1.5	<0.05
	Male	2,038	13	0.6	
Anti-ENA	Female	5,171	2,610	33.5	<0.001
	Male	2,264	436	16.1	
PR3 ANCA (Immunoblotting)	Female	3,035	44	1.4	<0.05
	Male	1,908	44	2.3	
MPO ANCA	Female	3,488	45	1.3	0.842
	Male	2,218	30	1.3	
Anti-Neutrophil cytoplasmic antibody	Female	3,136	212	6.3	0.493
	Male	2,001	146	6.8	

AMA: Antimitochondrial antibody; ASMA: Anti-smooth muscle antibody; LKM: Liver kidney microsomal; SM: Smith; SSB: Sjögren's Syndrome B; SSA: Sjögren's Syndrome A; RNP: Ribonucleoprotein; Scl 70: Skleroderma 70; ENA: Extractable nuclear antibody; PR3: Proteinase 3; ANCA: Anti-neutrophil cytoplasmic antibody; MPO: Myeloperoxidase.

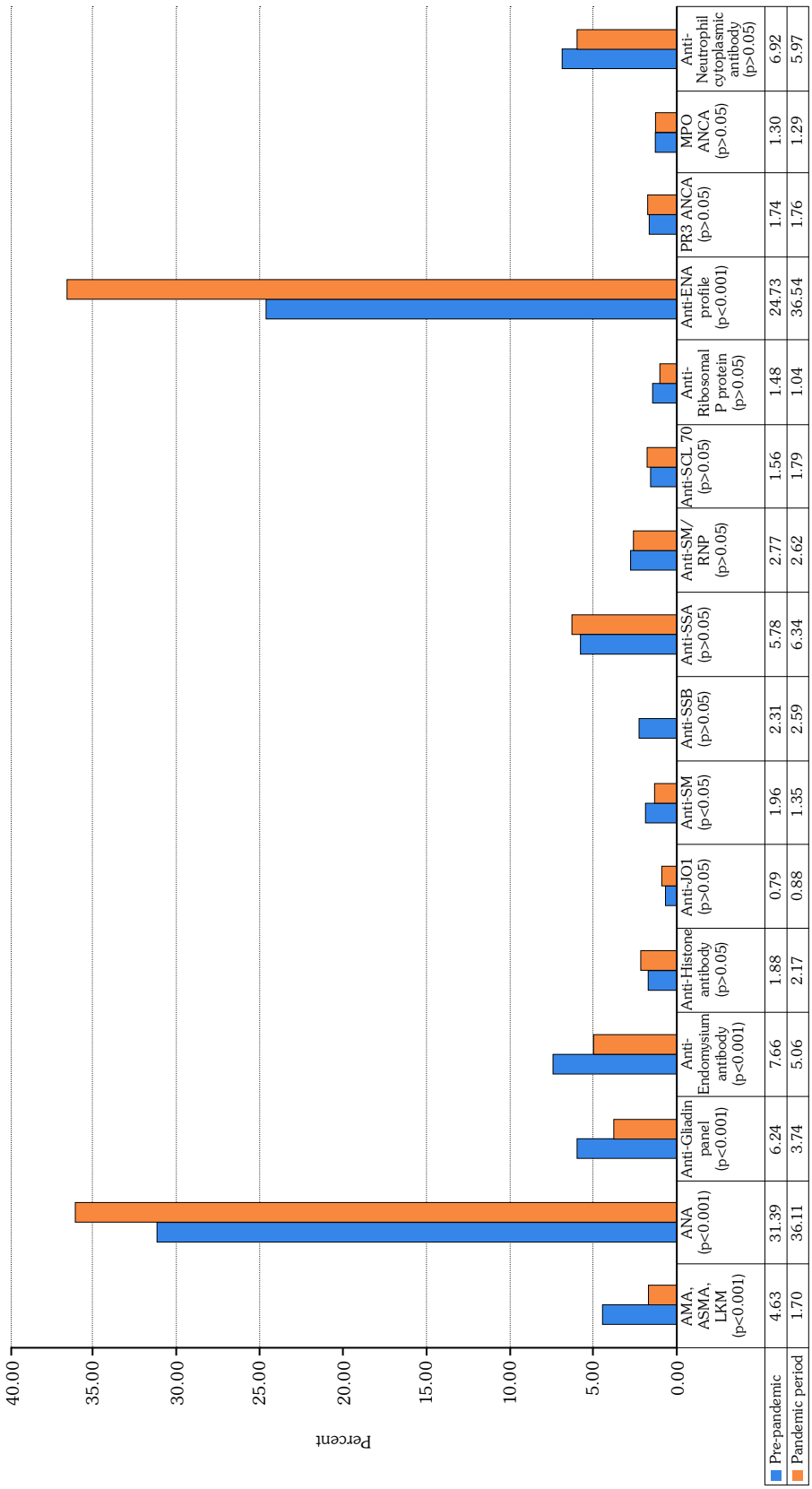
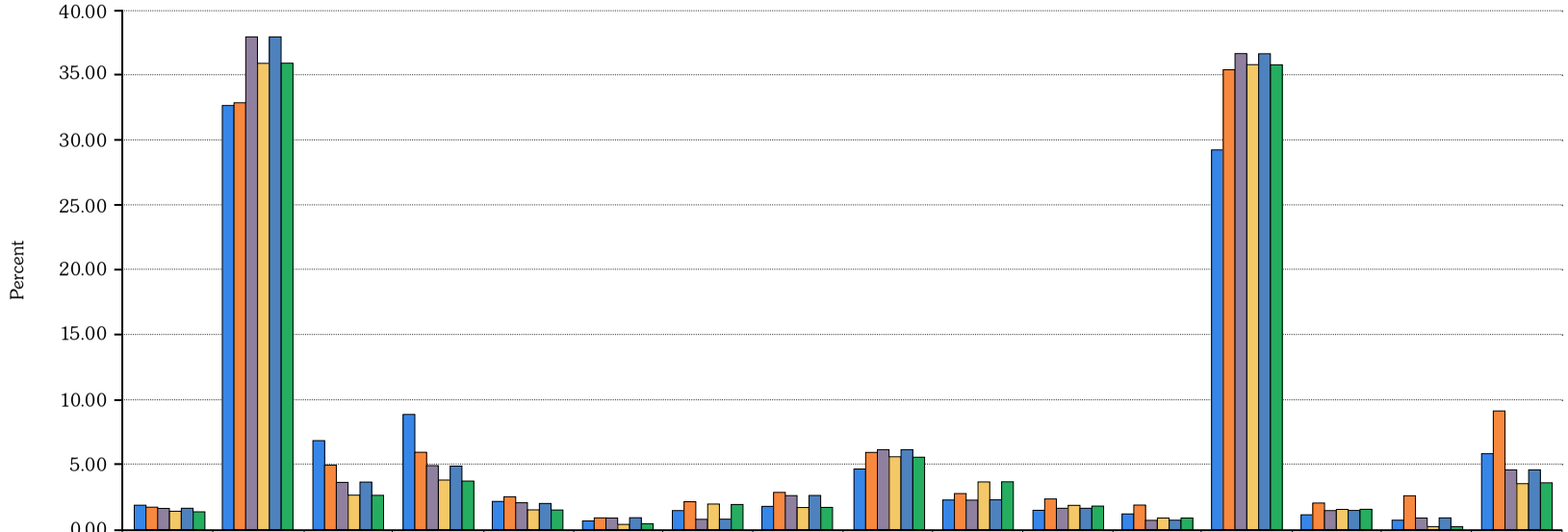


Figure 1. Comparison of autoantibody percentages between pre-pandemic and pandemic period.

AMA: Antimitochondrial antibody; ASMA: Anti-smooth muscle antibody; LKM: Anti-liver kidney microsomal; SM: Smith; SSB: Sjögren's Syndrome B; SSA: Sjögren's Syndrome A; RNP: Ribonucleoprotein; Scl 70: Skleroderma 70; ENA: Extractable nuclear antibody; PR3: Proteinase 3; ANCA: Anti-neutrophil cytoplasmic antibody; MPO: Myeloperoxidase.



	AMA, ASMA, LKM (p<0.001)	ANA (p<0.001)	Anti-Gliadin panel (p<0.001)	Anti-Endomysium antibody (p<0.001)	Anti-Histone antibody (p>0.05)	Anti-JO1 (p>0.05)	Anti-SM (p<0.05)	Anti-SSB (p>0.05)	Anti-SSA (p>0.05)	Anti-SM/ RNP (p>0.05)	Anti-SCL 70 (p>0.05)	Anti-Ribosomal P protein (p>0.05)	Anti-ENA profile (p<0.001)	PR3 ANCA (p>0.05)	MPO ANCA (p>0.05)	Anti-Neutrophil cytoplasmic antibody (p>0.05)
2017	1.83	32.66	6.87	8.95	2.14	0.75	1.47	1.86	4.80	2.30	1.54	1.31	29.23	1.22	0.81	5.84
2018	1.75	32.85	5.01	6.06	2.54	0.99	2.17	2.91	6.00	2.78	2.41	1.86	35.49	2.04	2.63	9.11
2019	1.66	37.97	3.60	4.95	2.07	0.90	0.80	2.64	6.27	2.26	1.60	0.80	36.68	1.48	0.94	4.70
2020	1.3496	35.88	2.63	3.76	1.55	0.52	1.94	1.69	5.70	3.63	1.82	0.91	35.84	1.65	0.23	3.48
2021	1.66	37.97	3.60	4.95	2.07	0.90	0.80	2.64	6.27	2.26	1.60	0.80	36.68	1.48	0.94	4.70
2022	1.34	35.88	2.63	3.76	1.55	0.52	1.94	1.69	5.70	3.63	1.82	0.91	35.84	1.65	0.23	3.48

Figure 2. Positivity rates of autoantibodies by years.

AMA: Antimitochondrial antibody; Anti-ASMA: Anti-smooth muscle antibody; Anti-LKM: Anti-liver kidney microsomal; Anti-SM: Anti-Smith; Anti-SSB: Anti-Sjögren's Syndrome B; Anti-SSA: Anti-Sjögren's Syndrome A; RNP: Ribonucleoprotein; Scl 70: Skleroderma 70; ENA: Extractable nuclear antibody; PR3: Proteinase 3; ANCA: Anti-neutrophil cytoplasmic antibody; MPO: Myeloperoxidase.

P protein antibody, and anti-Sjögren's syndrome A (anti-SSA), anti-Sjögren's syndrome B (anti-SSB), anti-SM/RNP, anti-SM, and c-ANCA levels were statistically higher in females (Table 1). When comparing the positivity rates of autoantibody tests between the prepandemic and pandemic periods, AMA, anti-LKM, anti-gliadin IgA, anti-endomysial antibody A, and anti-SM/RNP levels were statistically higher in the prepandemic period, while ANA was significantly higher during the pandemic period ($p<0.001$ and $p<0.05$, respectively; Figure 1). When examining the distribution of positivity rates of autoantibody tests across years, statistically significant differences were observed in the distributions of ANA, AMA, anti-LKM antibody, IgA anti-gliadin antibody, anti-endomysial antibody A, anti-ribosomal P protein antibody, anti-SM, anti-SSA, and c-ANCA (Figure 2).

DISCUSSION

In this study, the five-year indirect fluorescent antibody test results were divided into two periods, the prepandemic period and the pandemic period, and the seroprevalence was evaluated. Strong immune responses and the existence of a wide variety of complications involving multiple organs and systems in severe cases are interesting features of COVID-19, but the mechanisms that lead to such a strong immune response and the resulting damage have not yet been fully explained. It is known that the proinflammatory process is more effective and damaging in the pathogenesis of SARS-CoV-2 compared to the general inflammatory responses observed in viral infections.[14] The level of interleukin-6, which has an important place in the cytokine storm, is directly proportional to the severity of COVID-19 symptoms. Another possible mechanism of inflammatory damage caused by viral infections is the triggering of an autoimmune response. Viruses, as infectious agents, can induce autoimmunity in many complex ways, including several well-known mechanisms such as having molecular similarity to host antigens.[15] Likewise, it has been suggested that autoimmunity triggered by the similarity of epitopes between SARS-CoV-2 and the host is responsible for tissue damage.[16] Severe COVID-19 is associated with hypertension and diabetes, which cause chronic stress on endothelial cells and may predispose to molecular similarity. Homology between microbial antigens and self-proteins abnormally expressed on the plasma membrane of endothelial cells under stress has been shown to trigger molecular mimicry.[17] In our study, when we examined the positivity rates of autoantibody tests based on sex, it was significantly higher in females. The complex issue of why autoantibody levels are higher in females compared to males has not been fully elucidated. It is known that the immune system exhibits sex-based differences, and females generally have a stronger immune response. It is believed that estrogen in females has an influence on the immune system and can regulate autoimmune reactions. Therefore, when encountering a virus such as SARS-CoV-2, it is thought that the immune system of females may respond more rapidly and effectively. Additionally, autoimmune reactions are believed to arise as a result of the uncontrolled responses of the immune system during the fight against the virus. In this context, the immune responses triggered by COVID-19 may lead to an increased production of autoantibodies in females.

While antibodies against nuclear antigens were detected in 84% of patients with some form of immunoreactivity, a similarly high ANA seroprevalence was observed in patients with severe COVID-19.[12,18] In our study, when we compared the pre-COVID-19 period with the COVID-19 pandemic, it was observed that the seroprevalence of AMA, ASMA, anti-LKM antibody, IgA anti-gliadin antibody, and anti-endomysial antibody A decreased during the pandemic compared to the prepandemic period. Conversely, ANA and extractable nuclear antigen antibodies (anti-SSA, anti-SSB, anti-SM, anti-SM/RNP, and anti-Scl-70) showed a significant increase during the pandemic compared to the prepandemic period.

It is known that some viral infections induce autoantibodies, and this is confirmed by studies conducted during the pandemic period. This study sought to determine whether the increase in autoantibody rates observed with SARS CoV-2 is truly due to the effects of the

disease and, if so, the possible mechanisms underlying this increase. However, there was not enough information about the presence of autoimmune serological markers in patients who had COVID-19.

COVID-19 is often associated with interstitial pneumonia. In a study investigating the presence of autoantibodies in patients with COVID-19 pneumonia, 33 patients with COVID-19, of whom 31 (94%) developed interstitial pneumonia, and 25 patients with fever or pneumonia of etiologies other than COVID-19 as the control group were prospectively evaluated. Among patients with COVID-19, 15 (45%) were positive for at least one autoantibody, and 11 (33%) of these 15 patients were ANA positive. During hospitalization, six (40%) of 15 patients with positive autoantibodies died due to complications from COVID-19, while only one (5.5%) of 18 patients with negative autoantibodies died.[19] In our study, ANA (36.11%) stood out among the autoantibodies that increased during the COVID-19 pandemic, in parallel with the aforementioned study. Based on these findings, it can be suggested that autoantibodies in COVID-19 exacerbate the effects of the disease; however, more data are still needed.

In a case study of two patients, a high anti-SSA/Ro antibody titer and severe respiratory failure due to COVID-19 was reported.[20] Although the increase in extractable nuclear antigen antibodies we observed in our study during the pandemic period is consistent with this study, more comprehensive studies of patients with COVID-19 are needed to reach a clear conclusion. In a study of patients with severe COVID-19, it was reported that a large number of antibody-synthesizing cells were produced due to the increase of extrafollicular B cells, including autoreactive clonotypes.[21] Some of the autoantibody increases we observed during the pandemic period in our research may result from polyclonal activation and proliferation of B cells. It remains unclear whether the increased autoantibody seroprevalence in the pandemic is due to COVID-19 or is linked to autoimmunity. Autoantibodies, particularly ANA and rheumatoid factor, have been associated with the C-reactive protein levels in COVID-19.[22]

This study had some limitations. The study struggled to establish a strong cause-effect relationship between the changing frequency of autoantibody rates during the COVID-19 pandemic and SARS-CoV-2 infection due to the absence of results from the same patients across different periods. On the other hand, we believe that the quantitative power of thousands of indirect fluorescent antibody test results analyzed over a five-year period, including the pandemic period, is valuable in evaluating changes in seroprevalence. More comprehensive studies are needed to understand the long-term clinical effects of these autoantibodies and to establish a more concrete cause-effect relationship.

In conclusion, it is clear that the pandemic has had an effect on autoantibodies; however, it is quite difficult to explain the extent of this effect. More comprehensive studies are needed to clarify the clinical impact of the COVID-19 pandemic on autoantibodies.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Planning the research, analyzing and interpreting the data, writing the article: M.K.; Planning the research, analyzing and interpreting the data: H.K.; The research, analyzing and interpreting the data: A.C., K.K.; Analyzing and interpreting the data, final check of the prepared text: M.Ö.; Planning the research, analyzing and interpreting the data, final check of th prepared text: B.F.

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