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ORIGINAL ARTICLE

Evaluation of Antinuclear Antibodies of SLE Panel in COVID-19 Patients: A Cross-Sectional study in a Tertiary Care Hospital

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ABSTRACT

Introduction: COVID-19, caused by SARS-CoV-2, has raised concerns about its potential to trigger autoimmune phenomena and post-infection autoimmune diseases. This study aimed to assess the prevalence and patterns of antinuclear antibodies (ANA) in post COVID-19 patients. **Methods:** A cross-sectional study was conducted from August to October 2021, involving 108 adult post COVID-19 patients with articular and musculoskeletal symptoms. ANA screening was performed using the Indirect Immunofluorescent Test (IIFT) with HEp-2 cell substrate, and positive samples were further analyzed using Line ImmunoAssay (LIA) for specific ANA detection. Demographic data and disease severity information were collected. **Results:** Among the participants, 29% tested positive for ANA by IIFT, and 17% of those with 3 months post COVID-19 and 37% with >6 months post COVID-19 were ANA-positive. LIA confirmed ANA positivity in 18 patients. The most common ANA pattern was nuclear speckled (52%), followed by homogenous (21%), DFS 70, and Nucleolar (10% each), and Cytoplasmic (7%). The prevalence of ANA increased significantly with longer post COVID-19 duration (>6 months vs. 3 months, p = 0.017) U1 snRNP-related speckled pattern was most frequent. However, the study found no correlation between ANA patterns and post COVID-19 duration. **Conclusion:** The findings suggest that COVID-19 may trigger the development of ANA autoantibodies, especially in patients with a longer post-infection duration. Long-term follow-up studies are essential to understand the role of ANA in infection-triggered autoimmune conditions, enabling early diagnosis and treatment.

KEYWORDS: COVID-19, SARS-CoV-2, antinuclear antibodies, autoimmune diseases, indirect immunofluorescence assay, Line Immuno Assay

INTRODUCTION

Coronavirus disease 19 (COVID-19) is an infection caused by a novel coronavirus SARS-CoV-2, which is the current and resolving pandemic. Early reports from COVID-19 pathophysiology suggest that an overt inflammatory response, akin to cytokine release syndrome, could be a major contributing factor in its associated morbidity and mortality. The scientific community is still learning about the risk factors and consequences involving post-COVID-19 conditions.

A recent study by Zhou and colleagues showed that autoimmune phenomena exist in some patients with COVID-19 with the prevalence of anti-52 kDa SSA/Ro antibodies, anti-60kDa SSA/Ro antibodies, and antinuclear antibodies were 20%, 25%, and 50% respectively [1]. Latent autoimmunity with one IgG autoantibody and PolyA with two or more IgG autoantibodies were found in 83% and 62% of post-COVID-19 patients, respectively [2]. The presence of autoantibodies in COVID-19 patients was found to be correlated with increased antiviral humoral immune responses and inflammatory immune signatures [3].

Viral pathogens are known to be one of the most common exogenous factors causing potential autoimmune triggers. Kerr JR has shown that parvovirus B19 infection could give rise to the production of a variety of autoantibodies and be a trigger for the development of a diverse array of autoimmune diseases. Guillain-Barré has also been linked with infections of certain herpes viruses and Zika virus [4].

Infectious diseases have long been considered one of the triggers for autoimmune and auto-inflammatory diseases, mainly via molecular mimicry, epitope spreading, or bystander activation [5]. Several studies suggest severe COVID-19 could decrease self-tolerance by tissue damage and inflammation, leading to the generation of autoantibodies [6]. Even 6 months after acute COVID-19 infection, changes in serum antinuclear antibodies (ANA)-positive individuals were observed, reflecting an ongoing low-grade inflammation [3]. ANA are autoantibodies of different specificity directed against antigens of the cell nucleus. The type of autoantibody formed during the post-COVID-19 phase and the duration of positivity is not clear yet. This may confuse the diagnosis of systemic autoimmune rheumatic diseases (SARD) using Indirect ImmunoFluorescent Test (IIFT) ANA tests.

The IIFT, while widely used and considered a gold standard, has limitations. It can detect various antibodies, leading to potential cross-reactions. False positives may occur in up to 3% of the normal population. Specific autoantibody testing, especially using techniques like Line ImmunoAssay (LIA) allows for a more targeted approach, aiding in the identification and categorization of specific autoantibodies associated with different connective tissue diseases. This can enhance the precision of autoimmune disease diagnosis compared to the broader IIFT [7].

On this background this study was undertaken to detect the prevalence and pattern of ANA by IIFT, to detect the presence of specific ANA by immunoblot in two groups of patients, 3 months and >6 months of post-COVID-19 infection, and to compare both the tests.

MATERIALS AND METHODS

The study employed a cross-sectional descriptive design over 3 months from August to October 2021, with Institutional Ethics Committee approval secured. Following informed written consent, individuals with laboratory-confirmed real-time polymerase chain reaction (RT-PCR) positive post-COVID-19 status meeting inclusion criteria were recruited. The laboratory confirmed COVID-19 is defined as the detection of an exponential amplification curve with a Ct value above a given cut-off threshold of the E gene and RdRp gene by RT-PCR with the appropriate positive control, negative control, no template control, and internal control. Samples with below threshold or no amplification for the E gene and RdRp gene by RT-PCR were reported as negative.

Inclusion Criteria

Willing adult patients experiencing articular and musculoskeletal symptoms, at 3 to >6 months post-COVID-19, of both genders were included in the study as the presence of autoantibodies needs to be interpreted based on the clinical symptomatology.

Exclusion Criteria

Patients with known autoimmune disorders and those undergoing immunosuppressive treatment were excluded.

Data Collection

A standard proforma gathered demographic information, COVID-19 severity details, treatment history, and the presence of rheumatic and musculoskeletal symptoms.

Blood Sample Collection

Under aseptic conditions, 5ml blood samples were collected, and sera were separated through centrifugation at 1000 RPM for 5 minutes.

Laboratory Method

Immunofluorescence testing (IIFT) using HEp-2 cell substrate, acknowledged as the gold standard, was employed for detecting antinuclear antibodies.

Patient sera was diluted using 1:40 (10 µl serum + 390 µl diluent) screening dilution. On the HEp-2 substrate, patient samples demonstrating specific fluorescence reactions at a dilution of 1:40 or greater titer were reported as positive. End dilution titer was done only if indicated. Pattern reporting was done on the same day using an immunofluorescence microscope with LED as a light source by two independent trained microbiologists. The fluorescence intensity of the positive control was considered as 4+, and the titer intensity values of test samples were evaluated as ± (borderline), 1+ to 4+.

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The homogenous pattern on IIFT may be caused by antibodies against double-stranded DNA (dsDNA), histone, and nucleosome. The autoantibody to dsDNA is a specific and diagnostic marker for Systemic Lupus Erythematosus (SLE). When a homogenous pattern is observed on IIFT, additional confirmatory steps are recommended to confirm dsDNA the specific antibody. This algorithmic approach aligns with the recommendation by Kumar et al. and aims to improve the accuracy of the diagnosis of autoantibodies by confirming the specificity of it, through targeted blotting tests [8].

All IIFT-positive samples were subsequently tested by Line ImmunoAssay (LIA) (IMTEC ANA LIA MAXX) with an ANA profile. LIA tests the specific antigens targeted by the immune response rather than immunofluorescence. It provides a differential diagnosis using 17 different autoantibodies. It is an indirect membrane-based enzyme immune assay for the qualitative measurement of IgG class antibodies against dsDNA, Nucleosome, Histones, SmD1, PCNA, ribosomal P0 (RPP), SS-A/Ro 60, SS-A/Ro 52, SS-B/La, CENP-B, Scl70, U1-snRNP, AMA M2, Jo-1, PM-Scl, Mi-2 and Ku in human serum or plasma. The test has an Inbuilt cutoff control for improved validation. The specific bands are arranged on each test strip according to their relevance in dedicated diseases (SLE, Sjögren- Syndrome, CREST-syndrome, Scleroderma, Mixed Connective Tissue Disease, PBC, and Myositis).

Statistical Analysis

Continuous data were presented as mean ± standard deviation (SD), number (N), and percentage (%). The categorical variable was compared using the Chi-Square test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 108 post-COVID-19 patients were screened for the presence of ANA autoantibodies with the male patients 22% and female patients 77%. The male-to-female ratio was 1: 4. The total mean age of the patients was 38.14 years, with a range of 16 to 66 years (Table 1). Among male patients, most of the patients were between 20 to 40 years of age (66%) and in females most of the patients were between 20 to 40 and 40 to 60 years of age (51% and 41.6%).

Table 1 Age distribution of study participants (n= 108)

Age groups	Male (%)	Female (%)
16-20	1(4%)	3(3.5%)
21- 40	16(66%)	43(51%)
41- 60	4(16%)	35(41.6%)
61- 80	3(12.5%)	4(4.7%)

Total number of patients -- 108

Among the study participants, 54 (50%) were with 3 months and the rest were >6 months post-COVID-19 infection status. Table 2 shows the prevalence of ANA autoantibodies by IIFT among patients with 3 months and >6 months of post-COVID-19 infection status.

Table 2 Prevalence of ANA autoantibodies among patients with 3 months post COVID-19 status (n= 54)

S.NO	Patient ID	Age, Sex	ANA Pattern (IIFT)	LIA – ANA profile
1	P16	48, F	CYTOPLASMIC	AMA-M2
2	P27	32, F	NUCLEOLAR	PMScL
3	P30	54, F	DFS70	Not done
4	P32	51, F	HOMOGENOUS	PO, dsDNA, Histones, Nucleosome
5	P35	42, F	HOMOGENOUS	Negative
6	P39	35, M	DFS70	Not done
7	P48	19, F	SPECKLED	Negative
8	P50	39, F	SPECKLED	Negative
9	P53	60, F	CYTOPLASMIC	Negative

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Screening of ANA autoantibody was done by indirect immunofluorescence test. It was found to be positive for autoantibodies among 29 participants (27%) and negative for 71 participants (73%). Among these, nuclear speckled pattern was predominantly seen (52%) followed by a homogenous pattern (21%), DFS 70 and Nucleolar (10% each), and Cytoplasmic pattern (7%). Figure 1 depicts the ANA homogenous and nuclear-speckled pattern by IIFT. Further confirmation and specific antigen detection by LIA (Immunoblot) was done. It was found to be positive in 18 patients (Table 3 and Table 4).

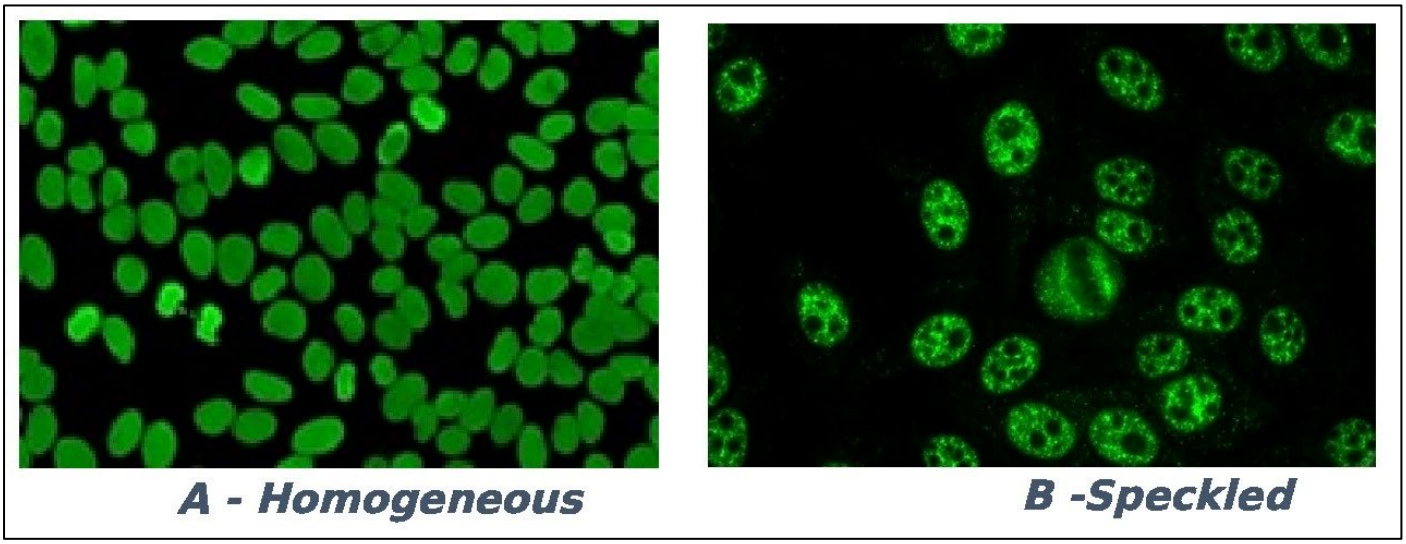

Figure 1 depicts the ANA homogenous and nuclear-speckled pattern by IIFT

Table 3 Prevalence of ANA autoantibodies among patients with >6 months post COVID-19 status (n= 54)

S.NO	Patient ID	Age, Sex	ANA Pattern (IIFT)	LIA – ANA profile
1	P58	58, F	HOMOGENOUS	Negative
2	P59	49, F	SPECKLED	U1 snRNP
3	P62	23, F	HOMOGENOUS	DSDNA
4	P65	38, F	SPECKLED	Negative
5	P67	29, F	SPECKLED	U1snRNP
6	P72	26, F	SPECKLED	SSA(RO52)
7	P73	36, F	NUCLEOLAR	Negative
8	P75	38, F	SPECKLED	SSA(RO52), U1 snRNP
9	P79	47, F	SPECKLED	U1 snRNP
10	P82	38, F	SPECKLED	U1 snRNP
11	P83	27, F	HOMOGENOUS	Negative
12	P86	23, F	SPECKLED	SSA (RO60, RO52)
13	P89	25, F	SPECKLED	U1 snRNP
14	P90	35, F	SPECKLED	SnRNP
15	P92	50, F	DFS 70	Not done
16	P93	40, F	NUCLEOLAR	PMScL
17	P95	40, F	SPECKLED	PMScL
18	P98	46, F	SPECKLED	U1 snRNP
19	P99	28, F	HOMOGENOUS	dsDNA
20	P102	23, F	SPECKLED	U1 snRNP

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Table 4 Comparison of IIFT test ANA pattern with LIA –ANA profile among post COVID-19 study participants (n= 108)

IIFT pattern (number, %)	LIA – ANA profile (number)
Nuclear speckled (15, 52)	U1 snRNP (7)
	SSA(RO52) (1)
	SSA(RO52), U1 snRNP (1)
	SSA(RO60, RO52) (1)
	SnRNP (1)
	PMScL (1)
Homogenous (6, 21)	dsDNA (2)
	Ribosomal PO, dsDNA, Histones, Nucleosome (1)
Nucleolar (3, 10)	PMScL (2)
DFS 70 (3, 10)	Not done
Cytoplasmic pattern (2, 7)	AMA-M2 (1)
Total 29	Total 18

DISCUSSION

This study delves into the presence of ANA post-COVID-19 infection, to recognize the potential link between post-COVID-19 infection and autoimmune conditions. Previous studies, like Zhou et al. and others, have highlighted the prevalence of antinuclear antibodies (ANA) and autoimmune markers in patients with COVID-19 infection, indicating a broader autoimmune response [1,2].

In the present study, serum samples were collected from 108 post-COVID-19 infected patients and subjected to ANA autoantibody tests by IIFT. All the samples with positive IIFT were further confirmed by LIA blot test with ANA profile which can detect 17 autoantibodies simultaneously.

The prevalence of ANA autoantibody tested by IIFT among post-COVID-19 patients in this study was 29 (27%). LIA blot test was positive for 18 patients. Among the patients with 3 months post-COVID-19 infection status, 9 (17%) of them showed positive IIFT (Table 2). This is less compared to a study on antinuclear antibodies in individuals infected with COVID-19 by Bossuyt X et al, in which ANA was detected in 17% of individuals within 10-34 days after positive RT-PCR COVID-19 at 1:80 cutoff and in 6% (n = 14) at 1:320 cutoff [9].

The prevalence of ANA autoantibodies among patients with >6 months post-COVID-19 status was 37% (20 patients in 54) (Table 2). Among them, a specific autoantibody was identified in 15 patients by LIA. The increase in prevalence of ANA autoantibodies with >6 months duration of post-COVID-19 infection status, compared with 3 months of post-COVID-19 infection status was found to be significant with p value of 0.017.

ANA prevalence significantly increased over 6 months post-COVID-19 infection, aligning with findings suggesting ongoing low-grade inflammation even 6 months after acute infection. In a study by Son et al, circulating ANA autoantibodies were detected in patients with COVID-19 up to 12 months post-recovery and were found to be associated with persisting symptoms and inflammation [10].

In this study, several HEp-2 IFA patterns were detectable and classified according to the international consensus on ANA pattern nomenclature including Nuclear speckled (AC-4,5), Homogenous (AC-1), Dense Fine Speckled (DFS 70) (AC-2), Nucleolar (AC-8,9,10) and Cytoplasmic (AC-15-23) (Table 3) [11].

The most frequently detected pattern was nuclear speckled which was reported in 15 patients (52%) among 29 positive patients by IIFT. This is in contrast to the study by Chang et al. in which nucleolar pattern being the most commonly reported [12]. Speckled pattern was found to be most commonly associated with U1 small nuclear ribonucleoprotein (U1 snRNP) by LIA blot test (8 patients, 44%).

U1 snRNP complexes have 11 associated proteins that are immunogenic in patients suffering from SLE or mixed connective tissue disease. Studies have reported that the antibody response to snRNP gives a speckled immunofluorescence pattern [13]. Autoimmune responses to U1 small nuclear ribonucleoprotein (U1 snRNP) have been reported to be associated with post-viral infections especially in cytomegalovirus infection [14].

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Homogenous pattern was reported in 6 patients (21%), and anti-dsDNA which is specific for SLE, was positive in 2 of them by LIA. Along with anti-dsDNA, PO, Histone, and Nucleosome were positive in one patient. LIA has a fair agreement with IIFT assay in the detection of anti-dsDNA may be due to the different antigen sources and preparation and coating system [15].

Among the 3 nucleolar pattern positive patients in this study 2 were positive for PMScL by LIA. Nucleolar ANA pattern can be a serological marker of systemic sclerosis and its antigenic target is the topoisomerase I protein (or scl70) [16].

As the LIA ANA panel done in this study does not contain the specific autoantibody for the dense fine speckled (DFS70) pattern, the same was not tested for the 3 patients with the DFS70 pattern. In DFS, fine-granular fluorescence of the nuclei in the interphase and the metaphase chromatin is the characteristic pattern. It is not associated with any systemic autoimmune rheumatic diseases and its biological and clinical significance remains enigmatic [17]. Cytoplasmic pattern was reported in 2 patients, one among them was positive for AMA-M2 antibody by LIA. AMA-M2 was found in 20% of SLE patients.

The study highlights a higher prevalence of ANA in post-COVID-19 infected patients after 6 months, emphasizing the need for recognizing clinical and laboratory features associated with autoimmune antibodies. However, there was no correlation between the ANA pattern and the duration of the post-COVID-19 infection status was found. As per the study by Zhao-wei Gao et al., the existence of auto-antibodies may hint towards an increased risk of autoimmune disorders in some patients with COVID-19 infections [18].

The study lacks a control group, hindering the specificity of observed effects of COVID-19; it also excludes analysing the impact of COVID-19 infection on pre-existing autoimmune conditions like SLE. Future plans include longitudinal follow-ups and universal autoantibody screening for COVID-19 infected patients, aiming to investigate autoimmunity comprehensively.

CONCLUSION

The study's indirect immunofluorescence assays indicated a higher prevalence of ANA autoantibodies in patients with post-COVID-19 infection status lasting over 6 months compared to those of 3-month duration. Recognizing the clinical and laboratory features associated with these autoimmune antibodies post-COVID-19 will enable prompt diagnosis and treatment. However, long-term follow-up studies are essential to confirm whether ANA presence is causative in infection-triggered autoimmune conditions.

Conflict of interest

Authors declare none.

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Authors' Contribution

UK contributed to conception and design, acquisition of data, analysis and interpretation of data and involved in drafting the manuscript. TM did analysis and interpretation of data, manuscript revising for critically. TR did data analysis and interpretation. AK did the data collection and initial analysis. All the authors contributed to critical revisions of the manuscript. All authors approved the final submission of the manuscript to the journal.

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