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Effect of COVID-19 on ANA positivity in the Indian population

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ABSTRACT

Background: The prevalence of Antinuclear Antibodies (ANA) positivity has increased following Covid-19 infection. This study investigates the ANA positivity rate by comparing ANA data from two distinct years, 2019 (a pre-Covid year) and 2022 (a post-Covid year).

Materials and Methods: This retrospective study analyzes and compares ANA Indirect Immunofluorescence Assay (IFA) data for the years 2019 and 2022 across various parameters, including age, gender, prevalence rate, positivity rate by grade, and patterns of ANA.

Results: In the post-Covid year 2022, there was a notable increase in both the total suspected cases and the ANA-positive cases, amounting to approximately a 30% rise. Positivity rates were observed to increase with age, and a female preponderance was noted in both years. Nuclear speckled patterns remained the most common in both time periods.

Conclusion: The post-Covid pandemic period has witnessed a significant role of immune modulation in the development of autoimmunity. This phenomenon could potentially be attributed to Molecular Mimicry, the production of Autoantibodies upon exposure to Viral epitopes through the generation of Neutrophil Extracellular Traps (NETs), or via Toll-like Receptor (TLR) pathways of immune modulation, which may activate latent autoimmunity.

1. Introduction

Coronavirus Disease 2019 (COVID-19) emerged as one of the deadliest global viral outbreaks by the end of 2019. It garnered this reputation due to its high mortality rates worldwide, primarily owing to the absence of specific therapies and the virus's high virulence. Patients presented with a range of symptoms, including dyspnea, cough, fever, and fatigue, while others developed severe complications such as Acute Respiratory Distress Syndrome (ARDS), sepsis, and multi-organ failure. Notably, severe COVID-19 infection triggered a cross-reactive response against Antinuclear Antibodies (ANA), leading to an increased prevalence of ANA in multiple autoimmune diseases.[1] This phenomenon is in line with the concept of "Molecular Mimicry," where viruses exhibit immune responses against structurally similar self-antigens, activating both B and T cells and inducing cross-reactive immune responses against self and other antigens. Molecular Mimicry has been observed in various viruses, including rotavirus, Coxsackie B virus, respiratory influenza virus, parvo B19, Hepatitis B, and C viruses, well before the emergence of COVID-19.[2,3]

In a study conducted in China in 2020, autoimmune characteristics were observed in 21 COVID-19 patients, with 20% exhibiting anti-52 kDa SSA/RO, 25% showing anti-60 kDa SSA/RO, and 50% displaying ANA antibodies. This finding strongly suggested the activation of autoimmune mechanisms in COVID-19 patients.[4] Another

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study in 2020 reported that 57.5% of their subjects tested positive for ANA antibodies, while 25% had positive ANCA antibodies. Subsequent evaluations indicated a robust ANA positivity for cytoplasmic patterns, followed by centriole patterns.[5] Similarly, a study by Zhou Y et al. in China in the same year revealed detectable ANA in 50% of 21 ICU patients with COVID-19.[4]

Considering this background, our study aims to investigate whether COVID-19 infection has impacted the prevalence of autoimmunity. We assess the autoimmune response in a susceptible population, comparing the pre-COVID era of 2019 to the post-COVID era of 2022. Our study focuses on a population suspected of having autoimmune diseases. A significant proportion of the Indian population has already been infected with or recovered from COVID-19, with official reported figures of approximately 4 crore cases in India by December 2022.[6] As more individuals receive vaccinations, herd immunity develops, providing indirect protection. Mathematical models suggest that over 50% of the Indian population may have developed natural immunity to the virus by now.[7] Although we did not assess the vaccination status or COVID infection history of the study population, our study centers on ANA positivity rates in the population and the emergence of specific autoimmune disease characteristics in the post-COVID era.

2. Material and Methods

2.1. Study design

An observational retrospective study was conducted at a globally recognized diagnostic laboratory in Mumbai, India. This study spanned two distinct years, 2019 and 2022, representing the pre-Covid era and the post-Covid era, respectively. The primary diagnostic test employed for ANA detection in this study was the ANA Indirect Immunofluorescence Assay (IFA).

2.2. Procedure

Patient demographic information, including age and gender, was collected, and ANA-IFA tests were performed using automated fluorescence assay processors, either the Euroimmune IF-Sprinter XL or the Euroimmun Mosaic Hep 20-10 liver (monkey) kit. The initial dilution was set at 1:100. Subsequently, fluorescent patterns were examined at 40x magnification using the Eurostar 3+ fluorescent microscope. The ANA patterns were documented, including grades of fluorescence intensity (+, ++, +++, ++++), along with their corresponding estimated titers (1:100, 1:320, 1:1000, 1:3200).

2.3. Statistical analysis

Data were recorded and organized using Microsoft Excel. Continuous variables were expressed as Mean ± Standard Deviation (SD), Median (Interquartile Range) (IQR), and Range. Discrete variables were summarized using frequencies and percentages.

To assess the association between the Time Period (Pre-Covid/Post-Covid) and the presence of Antinuclear Antibodies (Negative/Positive), as well as the association with different Antinuclear Antibody Titers (1:100/1:320/1:1000/1:3200/Negative), the Chi-square test was employed.

To evaluate the association between the Time Period (Pre-Covid/Post-Covid) and Antinuclear Antibodies (Negative/Positive) while considering potential confounding factors such as Age Group and Gender, the Cochran-Mantel-Haenszel test was utilized. Results were presented as odds ratios (OR) across various strata of the confounding factors, along with their 95% confidence intervals and p-values.

The statistical analysis was performed using "R Studio version 1.4.1103." A two-tailed p-value of <0.05 was considered statistically significant.

3. Results

A total of 50,457 cases were registered for ANA testing during the Pre-Covid era, and this number increased to 72,845 cases in the Post-Covid era.

The distribution of cases by age and gender revealed that the majority of cases tested belonged to the late adult age group, specifically the 31 to 45 years age bracket, in both years. Interestingly, it was observed that there has been a consistent increase in the ANA Positivity rate across all age groups in the Post-Covid year, and this increase was found to be statistically significant (p-value < 0.0001). (Table 1)

There was a notable female preponderance in ANA positivity observed in both the Pre-Covid and Post-Covid years. However, it's important to highlight that there was a significant increase in the positivity rate for both females and males in the Post-Covid year (Table 2). This suggests that the impact of Covid-19 on ANA positivity was not limited to a specific gender but affected both genders, albeit with a higher prevalence among females.

A substantial increase of 30.24% in the positivity rate was observed when comparing the Pre-Covid and Post-Covid years. Specifically, the positivity rate increased from 39.31% in the Pre-Covid year to 69.55% in the Post-Covid year (Table 3). This significant increase in ANA positivity rate underscores the potential impact of Covid-19 on the prevalence of ANA antibodies in the population studied.

The highest prevalence of ANA antibodies was consistently observed in the 1+ (1:100) titer category in both the Pre-Covid and Post-Covid years. Notably, there was a significant increase in the percentage of cases with a 1+ (1:100) titer in the Post-Covid year, reflecting a 20.35% increase compared to the Pre-Covid year (Table 4). This finding highlights the specific impact of the Covid-19

Table 1: Age-wise distribution

Age Group	Time Period				OR	95% CI
	Pre Covid		Post Covid			
	Negative	Positive	Negative	Positive		
	N(%)	N(%)	N(%)	N(%)		
1-12	1221(71.36%)	490(28.64%)	1025(47.39%)	1138(52.61%)	2.7665	2.4182 - 3.1651
13-18	1322(63.77%)	751(36.23%)	1178(40.95%)	1699(59.05%)	2.5389	2.2599 - 2.8522
19-30	7043(64.17%)	3932(35.83%)	4774(34.95%)	8884(65.05%)	3.3333	3.1627 - 3.5131
31-45	9839(61.50%)	6160(38.50%)	7145(31.22%)	15744(68.78%)	3.5195	3.3735 - 3.6719
46-60	7256(58.03%)	5248(41.97%)	5041(26.74%)	13811(73.26%)	3.7880	3.6106 - 3.9742
>60	3777(54.53%)	3150(45.47%)	2711(23.77%)	8695(76.23%)	3.8457	3.6073 - 4.0999
p value	<0.00001					

N= Frequency, %= Percentage OR= Odds Ratio, CI= Confidence Interval

Table 2: Gender distribution

Gender	Time Period				OR	95% CI
	Pre Covid		Post Covid			
	Negative	Positive	Negative	Positive		
	N(%)	N(%)	N(%)	N(%)		
Female	19855(56.95%)	15007(43.05%)	13387(26.85%)	36480 (73.15%)	3.6054	3.5023 - 3.7115
Male	10603(69.18%)	4724(30.82%)	8487(38.62%)	13491 (61.38%)	3.5679	3.4152 - 3.7274
p value	<0.00001					

N= Frequency, %= Percentage OR= Odds Ratio, CI= Confidence Interval

Table 3: Percentage positivity across both the years

Antinuclear antibodies	Time Period		p value Chi Square
	Pre Covid	Post Covid	
	N(%)	N(%)	
Negative	30458(60.69%)	21874(30.45%)	< 0.0001
Positive	19731(39.31%)	49971(69.55%)	
Total	50189(100%)	71845(100%)	

N= Frequency, %= Percentage

pandemic on the distribution of ANA titers, with a notable increase in the 1+ titer category.

The most common pattern of ANA antibodies in both the Pre-Covid and Post-Covid years was the "Nuclear Speckled" pattern. However, it's noteworthy that the "Nuclear Homogeneous" pattern showed a significant increase in the Post-Covid year, becoming the second most common pattern. This increase amounted to 9% compared to the Pre-Covid year (Table 5). This shift in the distribution of ANA patterns suggests a potential impact of Covid-19 on the patterns of ANA antibodies observed in the study population.

The age-wise distribution analysis revealed a somewhat similar pattern in the spike in ANA positivity rates post-Covid across different age groups (Table 6). This suggests that the increase in ANA positivity observed in the Post-Covid year was not limited to a specific age group but was relatively consistent across various age groups

The pattern distribution across gender was also somewhat similar. (Table 7)

4. Discussion

4.1. Aging and autoantibodies

Aging is associated with an increased production of autoantibodies, likely stemming from age-related intrinsic changes in immune cells. This mechanism could involve a reduction in self-tolerance and/or senescence, rendering the elderly population more susceptible to autoimmunity.[8,9] Immune dysfunction and imbalances occur with aging due to immune system dysregulation and heightened B cell activity,[10] alongside impaired regulatory functions of the adaptive immune system. As demonstrated by Majka DS et al, aging-associated immune dysfunction is also evident during reduced functional immunity or chronic inflammation.[11] Additionally, age-related increases in cellular damage and inflammatory responses have been

Table 4: Distribution of Grades (Titers) across both the years

Antinuclear Antibodies Grades & Titer	Time Period		p value Chi Square
	Pre Covid N(%)	Post Covid N(%)	
+ (1:100)	14136(28.17%)	34862(48.52%)	
++ (1:320)	3400(6.77%)	9438(13.14%)	
+++ (1:1000)	2088(4.16%)	4365(6.08%)	< 0.0001
++++ (1:3200)	107(0.21%)	1306(1.82%)	
Negative	30458(60.69%)	21874(30.45%)	

N= Frequency, %= Percentage

Table 5: Distribution of ANA pattern Positivity across both the years

Location	Pattern	Time Period			
		Pre Covid		Post Covid	
		N	%	N	%
Nucleus	Speckled	10591	53.68%	21563	43.15%
	Homogeneous	1908	9.67%	6754	13.52%
	Dense Fine Speckled	482	2.44%	746	1.49%
	Centromere	336	1.70%	560	1.12%
	Nuclear Dots	234	1.19%	516	1.03%
	Nuclear Membrane	216	1.09%	807	1.61%
Nucleolus	Nucleolus	2620	13.28%	10678	21.37%
Cytoplasm	Cytoplasmic Speckled	2756	13.97%	8114	16.24%
	Cytoplasmic Filament	1306	6.62%	3299	6.60%
Cell Cycle(mitotic cells)	Centriole	15	0.08%	241	0.48%
	Mid-Body	89	0.45%	1023	2.05%
	Spindle Fibers	93	0.47%	1798	3.60%
Others	Golgi Apparatus	157	0.80%	364	0.73%
	Lysosomal Pattern	81	0.41%	35	0.07%
	Rings & Rods	15	0.08%	34	0.07%
	Spindle Apparatus	0	0.00%	4	0.01%

N= Frequency, %= Percentage

linked to a rise in antinuclear antibodies (ANA).[11,12]

In our study, the majority of positive cases were found in the 31 to 45 years age group, followed by the 46 to 59 years group in both years (Table 1). Remarkably, the frequency of suspected autoimmune diseases remained nearly consistent across age groups, while ANA positivity increased with age. Studies have reported adult-onset autoimmune conditions associated with COVID-19 infection in older age groups, such as Kawasaki-like vasculitis and idiopathic inflammatory myopathy.[13] This suggests a heightened susceptibility to age-related autoimmune manifestations in the post-Covid era.

4.2. Gender disparities in autoimmunity

In 2019, only 39.1% of cases were ANA-positive, with 56.95% of these being females. However, in 2022, 69.55% of cases tested positive for ANA, with 73.15% being females (Table 2). Experimental and clinical evidence points to a female preponderance in autoimmunity, potentially attributed to sex hormones like estrogen, progesterone, and prolactin. X chromosomes carry a greater number of immune-related genes and autoimmune regulatory genes, intensifying the immunological response in females and raising their risk of developing autoimmune diseases.[9,14] Factors such as alterations in the menstrual cycle, puberty-related growth spurts, oral contraceptive use, and menopause may contribute to this gender disparity.

4.3. Significant increase in ANA pPositivity post-covid

The prevalence of ANA positivity substantially increased post-Covid. In 2019, the total ANA-positive cases stood at 39.3%, while in 2022, it surged to 69.6% (Table 3). This indicates a higher presence of autoimmune antibodies in patients who were either infected, recovered, or immunized with the SARS Coronavirus (SARS-COV-2) vaccine. Similar findings were reported in 2020 by Zhou Y et al,[4] with a 35.6% ANA detection rate in Covid-19 patients, and by Lerma et al,[15] with a 30% rate. Severe COVID-19 patients in China also exhibited high ANA positivity rates, reaching up to 50% in 2020.[4] Various studies have reported the presence of autoantibodies in Covid-19 patients at different frequencies, including ANA

Table 6: Age Group wise pattern specificity

Pattern	<18				18-60				<60			
	Pre Covid		Post Covid		Pre Covid		Post Covid		Pre Covid		Post Covid	
	N	%	N	%	N	%	N	%	N	%	N	%
Speckled	727	58.58%	1392	49.07%	8389	54.69%	16971	44.15%	1475	46.83%	3200	36.80%
Homogeneous	129	10.39%	313	11.03%	1468	9.57%	5137	13.36%	311	9.87%	1304	15.00%
Dense Fine Speckled	17	1.37%	50	1.76%	384	2.50%	582	1.51%	81	2.57%	114	1.31%
Centromere	4	0.32%	11	0.39%	229	1.49%	378	0.98%	103	3.27%	171	1.97%
Nuclear Dots	10	0.81%	22	0.78%	181	1.18%	397	1.03%	43	1.37%	97	1.12%
Nuclear Membrane	14	1.13%	44	1.55%	164	1.07%	579	1.51%	38	1.21%	184	2.12%
Nucleolus	147	11.85%	541	19.07%	2045	13.33%	8258	21.48%	428	13.59%	1879	21.61%
Cytoplasmic Speckled	136	10.96%	300	10.57%	2023	13.19%	5913	15.38%	597	18.95%	1901	21.86%
Cytoplasmic Filament	104	8.38%	243	8.57%	993	6.47%	2494	6.49%	209	6.63%	562	6.46%
Centriole	0	0.00%	17	0.60%	11	0.07%	195	0.51%	4	0.13%	29	0.33%
Mid-Body	2	0.16%	60	2.11%	73	0.48%	803	2.09%	14	0.44%	160	1.84%
Spindle Fibres	6	0.48%	141	4.97%	69	0.45%	1366	3.55%	18	0.57%	291	3.35%
Golgi Apparatus	9	0.73%	37	1.30%	118	0.77%	245	0.64%	30	0.95%	82	0.94%
Lysosomal Pattern	0	0.00%	4	0.14%	61	0.40%	28	0.07%	20	0.63%	3	0.03%
Rings & Rods	0	0.00%	0	0.00%	13	0.08%	21	0.05%	2	0.06%	13	0.15%
Spindle Apparatus	0	0.00%	0	0.00%	0	0.00%	2	0.01%	0	0.00%	2	0.02%

N= Frequency, %= Percentage

(35.6%), anti-Ro/SSA (25%), rheumatoid factor (19%), and lupus anticoagulant (11%).[13] Moreover, there was a notable 20.35% rise in grade 1+ (1:100) ANA positivity in 2022 compared to 2019. Increases of 6.37%, 1.92%, and 1.61% were observed for 2+, 3+, and 4+ positive results, respectively (Table 4). These findings align with those of Lerma L A et al and Garcia et al, where Covid-19 patients exhibited detectable weekly positive ANA in 88% and over 50% of cases, respectively.[13,15] These studies concluded that new-onset autoimmune diseases (NOAD) may develop following a Covid-19 diagnosis. Therefore, it is conceivable that exposed or vaccinated individuals may develop an entirely new autoimmune profile. Our study also indicates an increase in symptomatic autoimmune disorder cases, resembling NOAD. However, given the sensitivity of ANA IFA, false positivity can occur even at low titers like 1+ (1:100).[16] A 2011 study by Maria et al. reported ANA positivity in low to moderate titers (12.9%) in a healthy study population of 918 individuals.[17] This raises the possibility of latent autoimmunity emerging in otherwise healthy individuals without autoimmune disease symptoms, potentially triggered by Covid-19 infection.

4.4. ANA patterns and molecular mimicry

The most common ANA pattern observed in both years was nuclear speckled. However, there was a 10% decrease in the prevalence of the nuclear speckled pattern in 2022. This pattern is typically associated with disease-restricted antibodies, such as anti-SM/anti-U1 snRMP, SSA/Ro & La, Cyclin1 & 2. These target antigens are significantly linked to systemic lupus erythematosus (SLE), drug-induced lupus, rheumatoid arthritis (RA), dermatomyositis (DM), Sjogren syndrome, and overlap syndromes. The second most common ANA pattern in both years was nucleolar, with a 4% increase in the post-Covid year (Table 5). Studies conducted in Greece and Italy in 2021 reported ANA positivity rates of 34.5% and 33.3%, respectively, in smaller populations of Covid-positive individuals, with the nucleolar speckled pattern being the most common in both studies. This pattern is associated with PM-SCL, SCL-70, RNA polymerase, and Fibrillarin, clinically linked to Progressive Systemic Sclerosis (Diffuse). In the post-Covid year, there was approximately a 9% increase in the nuclear homogeneous pattern. Its target antigens are anti-double-stranded DNA, RNA, single-stranded DNA, anti-nucleosome, and Histone, again clinically associated with SLE, drug-induced lupus, RA, mixed connective tissue disorder, dermatomyositis, and systemic sclerosis. The remaining target antigens remained similar in both years. Additionally, ANA patterns showed no significant differences among age groups (Table 6) or between genders (Table 7). This data suggests a molecular similarity between common target antigens and the SARS-COV-

Table 7: Gender wise pattern specificity

Location	Pattern	Female				Male			
		Pre Covid		Post Covid		Pre Covid		Post Covid	
		N	%	N	%	N	%	N	%
Nucleus	Speckled	8118	54.09%	15700	43.04%	2473	52.35%	5863	43.46%
	Homogeneous	1613	10.75%	5650	15.49%	295	6.24%	1104	8.18%
	Dense Fine Speckled	390	2.60%	615	1.69%	92	1.95%	131	0.97%
	Centromere	301	2.01%	502	1.38%	35	0.74%	58	0.43%
	Nuclear Dots	194	1.29%	419	1.15%	40	0.85%	97	0.72%
	Nuclear Membrane	165	1.10%	558	1.53%	51	1.08%	249	1.85%
Nucleolus	Nucleolus	1879	12.52%	7189	19.71%	741	15.69%	3489	25.86%
Cytoplasm	Cytoplasmic Speckled	2022	13.47%	6197	16.99%	734	15.54%	1917	14.21%
	Cytoplasmic Filament	871	5.80%	2129	5.84%	435	9.21%	1170	8.67%
Cell Cycle(mitotic cells)	Centriole	12	0.08%	144	0.39%	3	0.06%	97	0.72%
	Mid-Body	63	0.42%	682	1.87%	26	0.55%	341	2.53%
	Spindle Fibers	64	0.43%	1080	2.96%	29	0.61%	718	5.32%
Others	Golgi Apparatus	96	0.64%	221	0.61%	61	1.29%	143	1.06%
	Lysosomal Pattern	67	0.45%	22	0.06%	14	0.30%	13	0.10%
	Rings & Rods	7	0.05%	17	0.05%	8	0.17%	17	0.13%
	Spindle Apparatus	0	0.00%	2	0.01%	0	0.00%	2	0.01%

N= Frequency, %= Percentage

2 virus. It is postulated that the SARS-COV-2 RNA genome and self-molecules physically interact, initiating an initial immune response against viral proteins in a highly inflammatory microenvironment. This immune response expands through linked recognition and intermolecular epitope spreading.[18] Furthermore, viral epitopes or proteins may cross-react with self-proteins, leading to loss of tolerance and the development of autoimmunity, known as Molecular Mimicry. Historically, viral agents such as coxsackievirus, parvovirus, enterovirus, HTLV, and HIV have been proposed as triggers for autoimmune responses. Viruses like human endogenous retrovirus, Epstein Barr virus, parvovirus, cytomegalovirus, and HIV have long been considered triggers for SLE.[19] A recent study from Switzerland found a transient increase in ANA titer in acute Covid-19 patients. Some severe Covid-19 patients also displayed extrafollicular B cell expansion, loss of germinal centers, and loss of Bcr-6 expression through the Toll-like Receptors 7 (TLR-7) pathway, resembling SLE flares.[20,21] The genomic RNA of SARS-COV-2 could serve as a costimulatory TLR-7 ligand to which many autoantigens bind, including sRNAs like U1-snRNA (found in Sm/RNP complexes), 7SRNA (a component of SRP), and tRNAs (like Jo-1, PL-7, PL-12), activating dendritic cells through a TLR-7-dependent inflammatory pathway (22,23). This may explain the persistence of autoantibodies even after Covid-19 infection subsides. In particular, severe Covid-19 patients with increased neutrophil extracellular trap (NET) formation expose shielded intracellular self-antigens, leading to the production of ANA and ANCA.[22]

5. Limitations and Future Directions

It's important to note that while ANAs are a hallmark of several autoimmune diseases,[23] they can also be found in acute illnesses and infections.[24,25] Our study explores these possibilities in a population already affected or vaccinated against Covid-19 but does not evaluate clinical symptoms of autoimmune diseases. The study focuses on the overall effect of positive prevalence in a population suspected of autoimmune diseases in the pre-Covid and post-Covid scenarios, excluding detailed infection and vaccination information. A comprehensive approach, including clinical and pathological correlation and specific Covid-19 infection and vaccination details, would further enhance the study's credibility. Furthermore, the assessment of specific ANAs using monospecific immunoassays could help identify antigens that exhibit increased levels following Covid-19

infection.

6. Conclusion

In conclusion, our study highlights the significant role of immune modulation in the development of autoimmunity during the post-Covid pandemic period. This modulation may occur through mechanisms such as Molecular Mimicry, the production of autoantibodies upon exposure to viral epitopes through the formation of neutrophil extracellular traps (NET), or Toll-like receptor (TLR) pathways of immune modulation. These factors may activate latent autoimmunity, yield false positive results, or lead to new-onset autoimmune diseases (NOAD). Distinguishing between these scenarios presents a promising avenue for the diagnosis and management of true ANA-positive cases.

7. Source of Funding

None.

8. Conflict of Interest

None.

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