Section: General Medicine

Original Research Article

# STUDY OF VARIOUS CLINICAL PRESENTATION AND OUTCOMES IN COVID 19 PATIENTS DIAGNOSED BY COVID ANTIBODY, PRESENTING LATE IN DISEASE COURSE IN A TERTIARY CARE HOSPITAL

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## Abstract

**Background:** The current study's objectives are to characterise antibody kinetics in hospitalised patients with COVID-19 verified by RT-PCR and to analyse antibody response using various serological techniques in accordance with clinical and laboratory data. This study also aims to investigate the various presentation pulmonary and extrapulmonary in COVID-19 antibody positive patients as well as study of the various clinical presentation, total antibody level and outcome of long COVID. **Materials and Methods:** A retrospective cross-sectional Hospital-based study was Conductd in the General Medicine Department at the Indira Gandhi Institute of Medical Sciences (IGIMS) in Patna, Bihar. At the start of the pandemic, 50 consecutive sera from 18 randomly chosen hospitalised adult patients (aged 25–80) with laboratory-confirmed COVID-19 were analysed. RT-PCR analysis was used to determine the diagnosis of COVID-19. **Results:** There were 18 patients, and 12 of them had comorbid conditions: 7 (38.2%) were over 60, 4 (14.1%) had hypertension, 3 (9.4%) had diabetes mellitus and hypertension, 3 (9.4%) had cardiovascular diseases, 2 (4.9%) had cerebrovascular disease and hypertension, and 1 had a malignant condition. Anti-SARSCoV-2 antibodies were examined in 60 consecutive sera in total. Twelve patients had three consecutive sera, five had two, four had three, and two patients had nine samples analysed. All samples underwent ELISA and ICA tests for IgA and IgG as well as IgM and IgG. Table 3 displays positive antiSARS-CoV-2 antibodies based on the number of days following the commencement of the illness. **Conclusion:** In conclusion, the degree of variation in antibody response in COVID-19 depends not only on the type of test performed but also on the time the serum is drawn and the severity of the illness. Clinical interpretation is essential for COVID-19 diagnosis even with the two-step testing strategy.

## INTRODUCTION

A new SARS-CoV-2-caused severe respiratory virus spread quickly in the end of 2019 and had a high mortality rate in Wuhan, China.[1,2] SARS-CoV-2 infection can manifest clinically in a variety of ways, ranging from asymptomatic and moderate to severe and critical.[1,3-5] Since the first symptoms are identical, mild instances are difficult to distinguish from other respiratory tract infections. For proper treatment and to prevent the transmission of the virus, early identification and recognition of the illness are essential. Each patient should be treated as having COVID-19 during the pandemic if they have a fever, cough, exhaustion, shortness of breath, headache, sore throat, runny nose, or even diarrhoea, and a diagnosis can only be made by targeted microbiological testing.[3-8]

The clinical evaluation of the symptoms and signs in light of the epidemiological information and medical history determines which samples are collected for diagnostic procedures. Nasopharyngeal


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and/or oropharyngeal swabs, as well as sputum, endotracheal aspirates, and bronchoalveolar aspirates, are the primary clinical diagnostic samples. Stool and feco-anal swabs could be used on people who don't have any respiratory symptoms.[4,6,9-11] The mainstay of SARS-CoV-2 diagnosis is molecular diagnostics. The reverse transcriptase quantitative polymerase chain reaction (RT-PCR) nucleic acid test for SARS-CoV2 should be positive in order to confirm COVID-19. Viral load, medical expertise, the specimen, the timing of the sample from the commencement of symptoms, and a PCR process with a low risk of false negatives all play a role in the success of RNA detection.[12,13] Serological diagnostics can be beneficial as an additional diagnostic method, particularly for delayed presentations and the retroactive diagnosis of minor cases,[12-15] Serological diagnostics still lack a gold standard, however studies employing various assays and techniques are the process.[15] It is assumed that the timing of the emergence of specific IgM, IgA, and IgG antibodies will coincide with the data for MERS and SARS. About two weeks following the start of the sickness, antibodies can be anticipated.[16-18]

A number of vaccines have been quickly created in response to the COVID-19 unusual scale and spread, and some of them have even received vaccination approval. Understanding the immunologic response to spontaneous infection and recognising signs of protection are crucial for determining if the immunological response to certain vaccinations is protective. Both humoral immunity and cell-mediated immunity would be involved. A novel pathogen necessitates the development, validation, and application of procedures. The initial worldwide focus has been the antibody response for obvious reasons. Several serological tests were created and used to analyse antibody responses brought on by SARS-CoV-2 infection. These assays utilised recombinant viral proteins or inactivated entire viruses.[19,20]

In a study on the "association of inflammatory marker with severity of COVID-19" conducted in Hunan, China, Furong Zent and colleagues found a positive correlation between inflammatory markers and COVID-19 severity.[21] Another study by Feng Pan et al. examined different inflammatory markers in the death event group and patients who had been discharged. (22) Another retrospective study carried out in a COVID recognised hospital at Wuhan, China, revealed higher levels of CRP, PCT, IL6, D-dimer, and BNP in the death event group compared to discharge patient group. In order to quickly test for SARS-CoV2 infection at various phases, Li et al. developed a rapid point-of-care lateral flow immunoassay that can detect IgM and IgG levels in less than 15 minutes. As a result, screening for SARS-CoV2 protein-specific antibodies in patient serum samples may be a viable alternative for quick and highly sensitive laboratory diagnosis.[17]

The current study's objectives are to characterise antibody kinetics in hospitalised patients with COVID-19 verified by RT-PCR and to analyse antibody response using various serological techniques in accordance with clinical and laboratory data. This study also aims to investigate the various presentation pulmonary and extrapulmonary in COVID-19 antibody positive patients as well as study of the various clinical presentation, total antibody level and outcome of long COVID.

## MATERIALS AND METHODS

A retrospective cross-sectional Hospital-based study was conducted in the General Medicine Department at the Indira Gandhi Institute of Medical Sciences (IGIMS) in Patna, Bihar. At the start of the pandemic, 50 consecutive sera from 18 randomly chosen hospitalised adult patients (aged 25–80) with laboratory-confirmed COVID-19 were analysed. RT-PCR analysis was used to determine the diagnosis of COVID-19.

During the initial appointment and afterwards in accordance with normal biochemical tests, blood samples were taken for serology. Prior to testing, all samples were kept at 20°C. Using enzyme-linked immunosorbent assays (ELISA; Euroimmun, Germany), the anti-SARSCoV-2 IgA and IgG antibodies were examined. Ratios, which are a relative measurement of the antibody concentration in the serum, were used to express the results. The extinction ratio of the patient samples (S) over the cutoff calibrator value (CO; S/CO) was calculated to ascertain the antibody levels. The manufacturer reported IgA and IgG sensitivity of 44.7% and 22.3% for samples taken 9 days after sickness onset and 99% and 87.4%, respectively, for samples taken after the 9th day of illness.

Using a qualitative lateral flow immunochromatographic assay (ICA) and a SARS-CoV-2 IgM/IgG Antibody Assay Kit, the same samples were also examined for anti-SARS-CoV-2 IgM and IgG antibodies. The manufacturer's guidelines were followed during testing. Anti-SARS-CoV-2 antibodies were determined to be present when an easily seen coloured quality control band and detection line, either IgG or IgM, were present. Two independent researchers always read the final results, which were regarded as preliminary screenings that needed to be interpreted in light of the clinical data. Data from the patients' computerised medical records were retrieved, including clinical, biochemical, and haematological information. We examined demographic information, clinical signs and symptoms, illness severity, and laboratory and radiologic findings. This research was authorised by the ethical committee. The patients involved waived written informed consent.


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**Inclusion Criteria:** All hospitalized patients with COVID 19 RTPCR-negative and antibody-positive cases.

**Exclusion Criteria:** All patients with COVID 19 RTPCR or antigen positive cases

In accordance with the inclusion and exclusion criteria, a sample or case will be chosen from the hospital record for the study.

**Statistical Analysis**

The statistical analysis was descriptive. Quantitative variables' absolute and relative frequencies, medians, interquartile ranges, means, and 94% confidence intervals of the means were computed. The discrepancies between the two serological techniques were compared using the McNemar chi-square test.

## RESULTS

Clinical and demographic characteristics

We examined 18 randomly chosen hospitalised patients who had blood obtained for serology and had SARS-CoV-2 infection verified by RT-PCR. Table 1 displays the demographic information and key clinical traits of the COVID-19 participants. [Table 1]

There were 18 patients, and 12 of them had comorbid conditions: 7 (38.2%) were over 60, 4 (14.1%) had hypertension, 3 (9.4%) had diabetes mellitus and hypertension, 3 (9.4%) had cardiovascular diseases, 2 (4.9%) had cerebrovascular disease and hypertension, and 1 had a malignant condition. The key clinical laboratory findings are listed in Table 2. [Table 2]

**Serological Results**

Anti-SARSCoV-2 antibodies were examined in 60 consecutive sera in total. Twelve patients had three consecutive sera, five had two, four had three, and two patients had nine samples analysed. All samples underwent ELISA and ICA tests for IgA and IgG as well as IgM and IgG. [Table 3]

Anti-SARS-CoV-2 IgA and IgG were detected in 41.8% and 8.2% of the samples taken within the first six days of sickness, respectively, while anti-SARS-CoV-2 IgM and IgG were found in 24% and 11.6%, respectively, in the samples analysed with ELISA and ICA. From day 7 after the commencement, 90.7% and 68.9% of individuals tested positive for anti-SARS-CoV-2 IgA and IgG by ELISA, respectively, while 84.5% and 74% tested positive for IgM and G by ICA. In general, ELISA IgA and IgG sensitivity were 68.2% and 41%, respectively, whereas ICA IgM and IgG sensitivity were 56.6% and 45.1%, respectively. Table 4 represents the combordities that were linked with the COVID-19 patients at the time of their admission to the hospital. [Table 4]

Patients suffering from breathlessness was highest (46.2%), followed by patients suffering from cough (44.6%) and fever (2%). Other factors such as asthma, etc., made up to 7.2%.

The vital parameter depicted 3 patients (7.5%) were suffering from blood pressure, 9 (30.6%) had a respiratory rate greater than 25 breaths/minute, and 4 (12.3%) had pulse that was lower than 92 beats per minute. and 2 (5.5%) patients showed SpO2 below 90% as shown in Table 5. [Table 5]

Only 4 patients (23.7%) had detectable IgM within the first 6 days of the beginning, according to seroprevalence results, while 10 patients (43.0%) had IgA. Another 7 individuals were shown to have anti-SARS-CoV-2 IgG from day 7 by ELISA, while 11 patients were found to have it by ICA. Despite one patient having ELISA IgA on the seventh day of illness, antibodies for IgM/IgG ICA were negative in 3 individuals whose subsequent serums were collected 7 or 8 days after the illness began. The antibody titre ratio (S/COV) was used to present the data. Anti-SARS-CoV-2 antibodies are deemed reactive when the ratio is more than 0.9. IgG and IgA had mean ratio antibody titres of 2.2 (94% CI 2.8-4.1) and 4.6 (94% CI 3.9-5.7), respectively. Anti-SARS-CoV-2 IgA first appeared before IgG and grew to greater antibody titres faster. None of the comparisons between ELISA and ICA ($p = 0.091$), early anti-SARS-CoV-2 IgA ELISA and IgM ICA ($p = 0.091$), or anti-SARS-CoV-2 IgG S1 antigen ELISA and IgG N/S antigen ICA ($p = 0.452$) revealed any statistically significant differences. There was a strong association between the anti-SARS-CoV-2 IgG and IgA antibody titres (p 0.04; $r = 0.866$). There were statistical differences between the positive and negative anti-SARS-CoV-2 antibody distributions found by each approach ($p = 0.015$ between ICA IgM and IgG; p 0.001 between ELISA IgG and IgA). [Table 6]

**Table 1: General features and clinical results in 18 patients with confirmed COVID-19**

| Characterisitic | No. of Patients = 18 (%) |
|---|---|
| Age Median (range) years | 55 (25-80) |
| Male/ Female | 12 ( 60.8)/ 8 (40.2) |
| Minimal disease | 7 (29.5) |
| Moderate disease | 8 (47.5) |
| Severe Disease | 3 (23%) |
| Combordities | 12 |
| **Systematic Symptoms** | |
| Headache | 6 (23.9) |
| Fever ( > 37°C) | 18 (90.4) |
| Myalgia and arthlagia | 8 (33.2) |
| Nausea or vomiting | 4 (14.4) |
| Diarhhoea | 5 (19.2) |


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| | |
|---|---|
| New loss of taste and smell | 2 (4.9) |
| Chills | 7 (38.0) |
| **Respiratory Symptoms** | |
| Fatigue | 10 (42.8) |
| Cough | 19 (94.1) |
| Sore throat | 4 (14.4) |
| Nasal Congestion | 1 (9.4) |
| Shortness of breath | 10 (42.8) |
| Sputum production | 6 (23.4) |
| **Anti-viral treatment** | |
| Yes | 13 (80.8) |
| Hydroxychloroquine + Azithromycin | 7 (42.8) |
| Lopinavir/ ritonavir | 2 (9.4) |
| Hydroxychloroquine | 4 (28.5) |
| No | 5 (19.2) |
| **Imaging** | |
| Chest radiography abnormalities | 15 (76.1) |
| Chest radiography | 22 (100) |
| Chest computed tomography | 4 (14.4) |

**Table 2: Clinical laboratory results of 18 COVID19 patients**

| Data (reference of range) | Findings |
|---|---|
| Creatine kinase (CK) U/L: median (IQR) (< 152 U/L) | 100 (35-162) |
| C-reactive protein mg/L: median (IQR) (< 6.0 mg/L) | 25.1 (6.8-63.9) |
| Lactate dehydrogenase U/L: median (IQR) (< 241 U/L) | 226 (175-291) |
| Alanine aminotransferase (ALT) U/L: median (IQR) (10–34 U/L) | 30 (15-69) |
| Aspartate aminotransferase (AST) U/L: median (IQR) (8–28 U/L | 35 (21-54) |
| Lymphocyte count: median (IQR) × $10^9$ (1.18–3.36 × $10^9$ ) | 1.2 (0.9-1.5) |
| White cell count: median (IQR) × $10^9$ (3.3–9.6 × $10^9$ ) | 5.6 (4.5-6.6) |
| Lymphocyte relative percent: median (IQR) % (20–46%) | 20.4 (13.3-26.3) |

**Table 3: Displays positive antiSARS-CoV-2 antibodies based on the number of days following the commencement of the illness**

| Days after | Samples (N) | Anti SARS CoV-2 positive antibodies | | | |
|---|---|---|---|---|---|
| | | ICA | | ELISA | |
| | | IgM, N(%) | IgG, N (%) | IgA, N (%) | IgG, N (%) |
| 0-2 | 9 | 3 (18.3) | 1 (1.1) | 5 (36.5) | 1 (1.1) |
| 3-6 | 15 | 4 (29.3) | 4 (17.8) | 7 (47.0) | 2 (11.7) |
| 7-10 | 19 | 12 (72.1) | 10 (61.0) | 14 (82.3) | 10 (49.9) |
| ≥ 11 | 7 | 13 (99.0) | 12 (92.8) | 13 (99.0) | 12 (92.8) |
| Total | 50 | 32 (56.6) | 27 (44.9) | 39 (68.2) | 25 (40.1) |

**Table 4: Distribution of Combordities**

| Combordities | | |
|---|---|---|
| **Presentation** | **No.** | **Percentage** |
| Cough | 6 | 44.6 |
| Fever | 2 | 2% |
| Breathlessness | 7 | 46.2% |
| Other | 3 | 7.2% |

**Table 5: Vital parameters**

| Parameters | No. | Percentage |
|---|---|---|
| Blood Pressure | 3 | 7.5% |
| Pulse | 4 | 12.3% |
| SpO2 | 2 | 5.5% |
| Respiratory rate | 9 | 30.6% |

## DISCUSSION

Since COVID-19 is a novel disease, it is important to look into the antibody kinetics (5, 8, 16–18, 24, 25). We provide the findings of antibody dynamics in randomly chosen COVID-19 hospitalised patients who were tested for anti-SARS-CoV-2 IgM and IgG with ICA and IgA and IgG with ELISA at the start of the pandemic. The study highlights the significance of further serum testing and the use of several serological techniques as auxiliary diagnostic tools while demonstrating the wide variation in antibody response. The timing of serum collection, the procedures utilised, the host's immunity, and other factors all affect antibody detection. It was discovered that the average sensitivity for ELISA anti-SARS-CoV-2 IgA and IgG was 68.2% and 41, and for ICA IgM and IgG, it was 56.6% and 45.1%.

Both anti-SARS-CoV-2 IgM and IgA levels were thought to be crucial indicators of the disease's early stage.[8,17] IgA was found more frequently than IgM


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within the first six days following onset (24% and 11.6%, respectively). Additionally, some patients exhibited either IgM or IgA, indicating the necessity to simultaneously test for both criteria. IgG detection during the first 6 days of sickness was sporadic (24% by ELISA and 11.6% by ICA, respectively). Most patients had anti-SARS-CoV-2 antibodies by day 7 following onset: IgM and IgA in 56.6% and 45.1%, and IgG by ELISA and ICA in 68.2% and 41%, respectively.

As a first line of defence against the virus, it targeted respiratory mucous membranes, which quickly produce a large number of secretory anti-SARS-CoV-2 IgA antibodies and promote significant mucosal immunity. Since the ICA approach only considers qualitative data, IgA could not be matched to the quantitative IgM trend. Depending on the severity of the illness, anti-SARS-CoV-2 IgG emerged later than IgA and displayed various linear progressive tendencies. Zhao also noted a relationship between IgG antibody levels and illness severity that was favourable.[16] As a result, it might be a helpful indicator of COVID-19 development. Further research is required to determine the function of IgG in long-term immunity. Treatment and the execution of epidemiological interventions require an accurate COVID-19 diagnosis.[7, 25, 26]

## CONCLUSION

In conclusion, the degree of variation in antibody response in COVID-19 depends not only on the type of test performed but also on the time the serum is drawn and the severity of the illness. Although they cannot be substituted for one another, IgM and IgA antibodies are equivalent as early-stage illness indicators. It is advised to conduct simultaneous IgM, IgG, and IgA antibody testing, followed by a second test to confirm any anti-SARS-CoV-2 positive results. Clinical interpretation is essential for COVID-19 diagnosis even with the two-step testing strategy.

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