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Original Research Paper

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EVALUATION OF SARS COVID -19 ANTIBODY STATUS OF INDIVIDUALS IN POST COVID OUT PATIENT DEPARTMENT OF TERTIARY CARE HOSPITAL OF CENTRAL INDIA

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ABSTRACT

Introduction: COVID-19 is caused by the SARS-CoV-2 virus and it was first identified after an outbreak of Pneumonia in Wuhan, China in December 2019. SARS-CoV-2 is an enveloped, positive-strand RNA virus. Several risk factors are associated with the complications of COVID-19. The Immune system produces IgM, IgG, and Neutralizing antibodies which can block the virus from entering cells. Long term humoral response post COVID-19 infection is still not clearly known. Studies related to complete course of IgG antibody in COVID-19 infection are very sparse. The present study was therefore conducted to evaluate SARS COVID-2 COVID-19 antibody status of individuals in post COVID-19 OPD in Central India's population at our tertiary care hospital. **Material and methods:** A prospective study was conducted in the Department of Microbiology of a tertiary health care centre for a period of one year from January 2021 to December 2022. The cases included in the study were individuals attending post COVID OPD and giving written informed consent for COVID-19 Antibody Test (IgG). Cases were studied in relation to their age, sex, relevant clinical history, relevant clinical comorbidities, status of COVID report with date. Blood samples from the study subjects were tested for the presence of IgG antibody. **Results:** IgG antibody is positive in maximum cases in 0-6 months, followed by 7-12 months, then in 13-18 months and then in 19-24 months. IgG antibody was not detected in cases where the time duration between positive COVID-19 test and IgG test was more than 18 months. **Conclusion:** Our study could be a very important footstep towards understanding the long term humoral response in COVID-19 infection.

KEYWORDS : COVID-19; SARS-CoV-2; Humoral immune response; Neutralizing antibodies; IgG antibody.

1. INTRODUCTION:

COVID-19 is caused by the SARS-CoV-2 virus and it was first identified after an outbreak of Pneumonia in Wuhan, China in December 2019. (SARS-CoV-2), is thought to have emerged from a zoonotic source and spread rapidly in humans through respiratory droplets and contact[1]. The World Health Organization (WHO) officially announced that the coronavirus would be identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1] The disease is also referred to as coronavirus disease 2019 (COVID-19). There have been over 640 million confirmed cases and 6.6 million deaths worldwide reported of COVID-19 till recently (as of 2 December 2022)[2].

SARS-CoV-2 is an enveloped, positive-strand RNA virus. SARS-CoV-2 has a diameter in the range of 60 to 140 nm and its morphology is consistent with those of other members of the *Coronaviridae* family. RNA sequence is approximately 30,000 bases in length. The four main structural proteins of coronavirus particles are crown-like spike (S-) glycoprotein, membrane (M-) glycoprotein, envelope(E-) protein on the viral surface, and nucleocapsid (N-) protein .The S-protein is responsible for facilitating entry of SARS-CoV-2 into the target cell, forming protrusions that can bind to receptors on target cells for infection and giving the virus a crown-like shape, hence the name"coronavirus".[3,4]

Several risk factors are associated with the complications of COVID-19, and these include older age (>65), Chronic respiratory diseases, Cardiovascular diseases, Hypertension, Diabetes, and Obesity. Acute Respiratory Distress Syndrome (ARDS) is reported to be the most common complication[5,6]. Detecting SARS-CoV-2 are an integral part of containment and mitigation strategies. Real-time –Polymerase Chain Reaction (RT-PCR) remains the most common method used to identify SARS-CoV-2.

The Immune system produces IgM, IgG, and neutralizing antibodies which can block the virus from entering cells. Serologic data derived from antibody subclass and titre provides a history of infection and can be used to determine the nature of an infection, monitor population-based prevalence of disease, assess disease stage, guide vaccine development and identify an infectious agent such as a virus. This can be assessed through measuring titres of specific antibodies for different antigens and Ig classes over time using serological assays.

Long term humoral response post COVID-19 infection is still not clearly known. IgG antibody is related to long time humoral response. Studies related to complete cousre of IgG antibody in COVID-19 infection are very sparse. So there is a need to study the complete course of IgG antibody in post COVID-19 infection.

The present study was therefore conducted to evaluate SARS COV-2 COVID-19 antibody status of individuals in post COVID-19 OPD in central India's population at our tertiary care hospital.

2. MATERIAL AND METHODS:

A prospective study was conducted in the Department of Microbiology of a tertiary health care centre for a period of one year from June 2021 to June 2022. The cases included in the study were individuals attending post COVID-19 OPD and giving consent for Antibody Test (IgG). Prior permission cum no objection certificate to carry out the study was obtained from local ethics committee. Written Informed consent was obtained from the study subjects. Consent from the study subjects were obtained by informing the subjects all the scope of the present study, the advantages for doing the present study and giving them the option to refuse the participation in the study if they wish so.

Study subjects:

Subjects who had COVID-19 infection in the recent past and who had recovered from it. Such post COVID-19 patients coming to Post COVID-19 Out patient department of our tertiary health care centre.

Inclusion criteria:

- All cases who had COVID-19 infection in the recent past and came to post COVID-19 OPD of our college.

- Co-operative patients who had willingly given consent to participate in the study and given necessary details.

Exclusion criteria:

- Patients unable to give details with regards to COVID-19 infection and without its signs and symptoms, incomplete history and not giving necessary details.

After applying above mentioned inclusion and exclusion criteria a total of 370 subjects coming to Post COVID-19 Out patient department were studied in relation to SARS COVID-19 antibody status. Such post COVID-19 patients coming to Post COVID Out patient demographic details were studied in relation to their age, sex, relevant clinical history, relevant clinical comorbidities, status of COVID-19 report with date. Blood samples were collected from the study subjects and were tested for the presence of IgG antibody.

Various data obtained from test results of Enzyme linked Immunosorbent Assay(ELISA) from blood samples of study subjects and study controls were noted. Cut off values of ELISA from blood samples of study subjects and study controls were noted.

3. RESULTS:

3.1. Gender-wise Distribution of cases. (Table No. 01)

Out of the total 370 cases, 236 cases were males while 134 cases were females.

Table No. 01: Gender-wise Distribution of cases.

Gender	No of cases	% of cases
Male	236	63.8
Female	134	36.2
Total	370	100

3.2. Age-wise distribution of cases. (Table No. 02)

Out of the total 370 cases, maximum cases were in the age group 21 to 30 yrs, 51 to 60 yrs, 41 to 50 yrs, 31 to 40 yrs, 11 to 20 yrs and 61 to 70 yrs accounting for 93 (25.1%) cases, 69 (18.7%) cases, 61 (16.5%) cases, 48 (13%) cases, 38 (10.3%) cases and 30 (8%) cases respectively.

Few cases were found in the age group 0 to 10 yrs, 71 to 80 yrs and 81 to 90 yrs accounting for 11 (3%) cases, 15 (4%) cases and 5 (1.4%) cases respectively.

Thus minimal cases were in the extreme age groups i.e mostly the dependent age group of less than 10 years and more than 70 years age. While majority of the cases were in the active age group of 11 to 70 years.

Table No. 02: Age-wise distribution of cases.

Age in years	No of cases	% of cases
0 to 10 yrs	11	3
11 to 20 yrs	38	10.3
21 to 30 yrs	93	25.1
31 to 40 yrs	48	13
41 to 50 yrs	61	16.5
51 to 60 yrs	69	18.7
61 to 70 yrs	30	8
71 to 80 yrs	15	4
81-90 yrs	5	1.4
Total	370	100

3.3. IgG Test result of cases. (Table No. 03)

Out of the total 370 cases, 199 (53.8 %) cases showed positive IgG test results while 168 (48.4 %) cases showed negative IgG test results. 03 (0.8 %) cases showed equivocal IgG test results.

Table No. 03: IgG Test result of all cases.

Gender	No of cases	% of cases
Positive	199	53.8
Negative	168	45.4
Equivocal	03	0.8
Total	370	100

3.4. Time Duration in Months between COVID-19 positive test and positive IgG test. (Table No. 04)

Of the total 199 cases that showed positive IgG test results; 97 (48.7 %) cases were found in 0-6 months duration, 64 (32.2 %) cases were found in 7-12 months duration, 33 (16.6 %) cases were found in 13-18 months duration and only 5 (2.5%) cases were found in 19-24 months duration.There were no positive IgG test cases where the time duration between positive COVID-19 test and IgG test was more than 24 months. About 97.5 % cases of positive IgG antibody tests were found in 0-18 months time duration between positive COVID-19 test and IgG Antibody test. Hence maximum cases where IgG antibody was found were cases where the time duration between positive COVID-19 test and IgG test was less than 18 months.Also IgG antibody is positive in maximum cases in 0-6 months, followed by 7-12 months, then in 13-18 months and then in 19-24 months. Hence we can conclude that IgG antibody increases to its maximum in 0-6 months and then its level decreases gradually till 24 months. And also after 24 months IgG antibody is not detected.

Table No. 04: Time Duration in Months between COVID-19 positive test and positive IgG test.

Time Duration	No of cases	% of cases
0-6 Months	97	48.7
7-12 Months	64	32.2
13-18 Months	33	16.6
19-24 Months	05	2.5
25-30 Months	00	0
31-36 Months	00	0
Total	199	100

3.5. Time Duration in Months between COVID-19 Positive and Negative IgG test. (Table No. 05)

Of the total 168 cases that showed negative IgG test results; 107 (63.7 %) cases were found in 25-30 months duration and 47 (28 %) cases were found in 19-24 months duration.

Few cases were found in 13-18 months, 7-12 months and 0-6 months duration accounting for 7 (4.2 %) cases, 5 (3%) cases and 2 (1.2%) cases respectively. There was no case found in 31-36 months duration.

Thus maximum cases where IgG antibody was not found were cases where the time duration between positive COVID test and IgG test was more than 18 months.

Table No. 05: Time Duration in Months between COVID-19 Positive test and negative IgG test.

Time Duration	No of cases	% of cases
0-6 Months	02	1.2
7-12 Months	05	3.0
13-18 Months	07	4.2
19-24 Months	47	28.0
25-30 Months	107	63.7
31-36 Months	0	0
Total	168	100

3.6. Table showing statistical significance of time duration between Positive COVID-19 Test and IgG Test (0-18 months). (Table No. 09)

Maximum cases of positive IgG antibody was found in 0-18 months which was found to be highly significant statistically with $p < 0.001$, Chisquare test value 294.884** and odds ratio value 426.800.

Similarly maximum cases of negative IgG antibody was found in 19-36 months which was found to be highly significant statistically with $p < 0.001$, Chisquare test value 294.884** and

odds ratio value 426.800.

Table No. 06: Table showing statistical significance of time duration between Positive COVID-19 Test and IgG Test (0-18 months).

Duration	Positive IgG Test	Negative IgG test	Total	Chisquare test	P-value	Sig. at 5% level
0-18 months	194	14	208	294.884**	0.000	Yes
19-36 months	5	154	159			
Total	199	168	367			
OR#	426.800	95% (150.433 to 1210.893)				

OR# = Odds Ratio i.e. 0-18 months
** Statistically highly Significant at 0.1% level i.e. P<0.001.

4. DISCUSSION:

4.1. Gender-wise Distribution of cases

There are higher number of male cases of post COVID-19 patients in our study.

Males being the main earning member go outside for doing jobs and business for earning. Also males are more likely to roam in outside places and are less likely to follow the containment rules required in COVID-19 cases as compared to females.. Hence this could be the reason for higher number of male cases of post COVID-19 patients in our study. Chen X et al[7] also found higher male cases just like our study.

4.2. Age-wise Distribution of cases

In our study maximum cases were in the age group 11 to 70 years i.e active age group.

Few cases were found in the age group 0 to 10 yrs, 71 to 80 yrs and 81 to 90 yrs accounting for 11 (3%) cases, 15 (4%) cases and 5 (1.4%) cases respectively.

Chen X et al [7] also found findings similar to our study. Chen X et al[7] found that young individuals (<20 years) and older individuals (>65 years) were less likely to be seropositive than individuals in 21-64 years of age group.

Kening Li et al[9] found that the RBD-specific IgG levels are 4-fold higher in older patients than in younger patients during hospitalization.

Bruna Lo Sasso et al[8] found that Anti S-RBD IgG levels were lower in older than younger subjects.

4.3. IgG Test result of cases.

In our study (53.8 %) cases showed positive IgG test results while (48.4 %) cases showed negative IgG test results. 03 (0.8 %) cases showed equivocal IgG test results.

Lou B et al[10] said that Immunological responses take longer to appear in COVID-19 infection, with antibodies typically beginning to appear 6 days after symptom onset, as viral RNA levels begin to decline.

Long Q-X et al[11] said that typically, the first detectible antibody in human blood is Immunoglobulin M (IgM), followed by Immunoglobulin G (IgG). However, concomitant increases of the IgM and IgG Immunoglobulin classes as well as IgG first seroconversion have also been observed.

Moncunill G et al[12] found that the median seroconversion times for total antibody, IgM, and IgG were 9, 10, and 12 days after symptom onset (or 15, 18, and 20 days after exposure), respectively. Isho B et al[13] concluded that it is unclear how long IgG responses last or whether they confer protection against subsequent SARS-CoV-2 reinfection. They also said that longest antibody dynamics tracked IgG up to 115 days in sera and saliva after onset of symptom in sera and saliva.

4.4. Time Duration in Months between COVID-19 Positive test and Positive IgG test.

In our study of the total 199 cases that showed positive IgG test results; 97 (48.7 %) cases were found in 0-6 months duration, 64 (32.2 %) cases were found in 7-12 months duration, 33 (16.6 %) cases were found in 13-18 months duration and only 5 (2.5%) cases were found in 19-24 months duration.

About 97.5 % cases of positive IgG antibody tests were found in 0-18 months time duration between positive COVID-19 test and IgG test.

Also IgG antibody is positive in maximum cases in 0-6 months, followed by 7-12 months, then in 13-18 months and then in 19-24 months. Hence we can conclude that IgG antibody increases to its maximum in 0-6 months and then its level decreases gradually till 24 months. And also after 24 months IgG antibody is not seen.

4.5. Time Duration in Months between COVID-19 Positive and Negative IgG test.

In our study of the total 168 cases that showed negative IgG test results; 107 (63.7 %) cases were found in 25-30 months duration and 47 (28 %) cases were found in 19-24 months duration.

Few cases were found in 13-18 months, 7-12 months and 0-6 months duration accounting for 7 (4.2 %) cases, 5 (3%) cases and 2 (1.2%) cases respectively. There was no case found in 31-36 months duration.

Long et al. [11] noted that there was a decline in neutralising antibodies over time in both asymptomatic and symptomatic individuals. The proportion of patients with positive virus-specific IgG reached 100% approximately 17–19 days after symptom onset.

Bin Lou et al [14] The first detectible serology marker was neutralising antibodies, followed by IgM and IgG, with a median seroconversion time of 15, 18 and 20 days post exposure (d.p.e) or 9, 10 and 12 days post onset (d.p.o), respectively. The antibody levels increased rapidly beginning at 6 d.p.o. and were accompanied by a decline in viral load.

Current researches related to IgG are unclear as to how long IgG responses last.

Isho B [13] found that antibodies to S protein were detected in 90% of cases approximately 10 days after symptom onset and neutralising antibodies persisted up to 105 days. Isho B et al [13] found the longest duration of positive IgG tests and concluded that antibody dynamics tracked IgG up to 115 days after symptom onset in sera and saliva. They also said that as the study is not directed for more longer duration it could not have said how long post COVID-19 infection IgG is detected.

SARS-CoV-2 structure and function informations are also derived from research on SARS-CoV-1, MERS-CoV and seasonal Coronaviruses as it shares significant genetic sequences.

As researches related to IgG antibodies beyond 115 days post COVID -19 infection is not available, a practical aspect would be to look for the Humoral response in COVID-19 closely related virus infections i.e against SARS-CoV 1 and MERS-CoV infection

Li-Ping Wu et al. [15] found patients who had Severe Acute Respiratory Syndrome (SARS), SARS-specific antibodies

were maintained for an average of 2 years, and significant reduction of Immunoglobulin G positive percentage and titres occurred in the third year. Thus, SARS patients might be susceptible to reinfection >3 years after initial exposure.

Daniel C. Payne et al. [16] found patients who had Middle East respiratory syndrome coronavirus Antibodies, including neutralizing antibodies, were detectable in 6 (86%) of 7 persons for at least 34 months after the outbreak.

Xiaoqin Guo et al. [17] found that Anti SARS-CoV IgG was found to persist for up to 12 years. IgG titres in SARS-CoV-infected healthcare workers remained at a significantly high level up to 12 years.

Yeon-Sook Kim et al. [18] found that Anti-spike-specific IgG responses, including neutralizing activity and antibody-secreting memory B cells, persisted for up to 3 years, especially in MERS patients who suffered from severe Pneumonia.

Considering all the reviewed literature related to COVID-19 infection we can say that IgG tests can be positive till 115 days post infection[13].

4.6. Statistical correlation significance of time duration between Positive COVID-19 Test and IgG Test (0-18 months).

In our study maximum cases of positive IgG antibody was found in 0-18 months which was found to be highly significant statistically with $p < 0.001$, Chisquare test value 294.884** and odds ratio value 426.800. Similarly maximum cases of negative IgG antibody was found in 19-36 months which was found to be highly significant statistically with $p < 0.001$, Chisquare test value 294.884** and odds ratio value 426.800.

There is a very high statistical correlation of IgG antibody in serum of post COVID-19 patients with the time duration of 18 months. Cases less than 18 months post infection have very high chances of having a positive IgG COVID-19 antibody. Similarly cases more than 18 months post infection have very high chances of having a negative IgG COVID-19 antibody.

Considering all the reviewed literature related to COVID-19 infection we can say that IgG tests can be positive till 115 days post infection[13].

5. CONCLUSION:

Hence we can conclude that IgG antibody increases to its maximum in 0-6 months and then its level decreases gradually till 24 months. And also after 24 months IgG antibody is not seen. IgG antibody was not found in cases where the time duration between positive COVID-19 test and IgG test was more than 18 months.

Considering all the reviewed literature related to COVID-19 infection we can say that IgG tests can be positive till 115 days post infection[13]. As data beyond 115 days is not available we can take help of studies in COVID-19 related infections i.e SARS and MERS.

Our study could be a very important footstep towards understanding the long term humoral response in COVID-19 infection. More such studies with larger number of study samples would definitely help to better understand long time humoral response and the protective effects of IgG antibody against subsequent infection.

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