RAS MICROBIOLOGY AND INFECTIOUS DISEASES

Research Article: Quantification of IgG specific antibodies in recovered COVID -19 patients and its association with disease severity

Issue Type: Volume 2 Issue 1

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Citation: Dr Saurabh Srivastava, Quantification of IgG specific antibodies in recovered COVID -19 patients and its association with disease severity

Received Date: 12th Nov 2021

Published Date: 12th Dec 2021

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ABSTRACT

Background: Serological tests for anti-SARS-CoV-2 antibodies can provide valuable information in epidemiologic and public health research. However, the data is limited on serological response post COVID-19 infection.

Objective: To investigate the use of ARCHITECT SARS CoV-2 IgG II Quantitative assay to quantify the IgG antibodies in recovered COVID-19 infections.

Methods: Abbott SARS-CoV-2 IgG assays were performed using the ARCHITECT Quantitative chemiluminescent microparticle immunoassay to detect IgG against SARS-CoV-2 S1 receptor binding domain (RBD) in serum and plasma. Patients having IgG concentrations above ≥ 50 AU/mL were defined as positive. We analyzed 333 COVID-19 patients who were tested negative by RT-PCR not more than three months after testing positive.

Results: The mean age of the population was 34.3 years and 95% were male. About 93% of the patients had mild disease and rest had moderate disease. The mean IgG levels in the entire cohort was 1860.27 AU/mL, the lowest and highest value detected by ARCHITECT SARS CoV-2 IgG II Quantitative Assay (Abbott Laboratories, USA) were 39.8 AU/mL and 43657.4 AU/mL, respectively. While patients with moderate COVID-19 disease had numerically higher IgG levels than patients with mild disease, the difference was not statistically significant (1787.7 AU/mL vs. 2865.39 AU/mL, $p=0.21$). In 97% of the patients, IgG antibodies could be detected up to 95 days after testing negative on RT-PCR.

Conclusion: Patients with moderate COVID-19 disease may develop higher IgG antibodies than in patients with mild disease. Antibodies can be detected in majority of recovered individuals for more than 90 days which may be valuable in developing future vaccination strategy.

Keywords

Abbott ARCHITECT, COVID-19, Chemiluminescent microparticle immunoassay, IgG, SARS-CoV-2, Serology

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease first identified amid an outbreak of respiratory illness of unknown cause in China in December 2019 and now has rapidly spread all over the world [1]. The World Health Organization (WHO) declared the novel COVID-19 outbreak as a pandemic on 11 March 2020. The COVID-19 disease is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2,3]. This novel coronavirus belongs to the betacoronavirus genre of the Coronaviridae family [4]. As of 7 July 2021, more than 184 million people were infected, and more than 3.9 million people died due to COVID-19 disease. [5] In India, the total number of cases crossed more than 30.6 million and more than 400 thousand people died as of July 7 2021. The active cases constitute 1.5% (4,59,920) of total cases and total recoveries across India closing on 3 million with a recovery rate of 97%. The current test positivity ratio is 2.4% [6]. A total of 36.13 crore vaccine doses have been administered so far under Nationwide Vaccination Drive [7].

The spectrum of COVID-19 symptoms ranges from mild respiratory distress to acute respiratory distress syndrome to septic shock [8] and multiorgan failure [9].

In the majority of cases, the COVID-19 infection is mild, and symptoms include fever, cough, sore throat, tiredness, myalgia, and difficulty in breathing. Postexposure, the incubation period is generally within 14 days, and it usually takes 2–8 weeks for recovery [8,10].

Common laboratory characteristics among COVID-19 infected patients include lymphopenia, thrombocytopenia, and leukopenia along with elevated inflammatory markers, such as C-reactive protein, serum ferritin, procalcitonin and erythrocyte sedimentation rate. Increased levels of lactate dehydrogenase, aminotransaminase levels, and D-dimer and abnormalities in coagulation tests have also been reported in hospitalized patients with COVID-19 infection [4,11]. Lymphopenia is especially common, even though the total white blood cell count can vary. Laboratory features, especially elevated D-dimer levels and severe lymphopenia have been linked to morbidity or mortality [12].

As seen with other infections, an adaptive immune response has been observed post SARS-CoV-2 infection among immunocompetent individuals [11]. Further, IgG levels were found to reach the peak from three weeks post symptom onset and persisted thereafter for several months [13,14].

Real-time reverse transcription-polymerase chain reaction (RT-PCR) is considered the gold standard for detecting SARS-CoV-2 infection. However, the risk of false–negative reports is high due to sampling errors during collection, transportation, ribonucleic acid (RNA) extraction, and the presence of enzyme inhibitors. Serological assays have been reported to have a high throughput advantage with minimal risk of false–negative reports [15]. With an increase in the number of recovered patients with COVID-19 disease, understanding immune response post infection is a key to controlling this pandemic and determining and monitoring an individual's immune response to vaccines, as well as determine the duration of response [16].

However, the performance characteristics of the majority of the SARS-CoV-2 serological tests currently available are reportedly inadequate to be used for the widespread population or clinical testing. This study aimed to quantify IgG antibodies in recovered COVID-19 patients by using ARCHITECT SARS CoV-2 IgG II Quantitative assay and to assess its association with clinical and laboratory parameters.

METHODS

A cohort of 333 COVID-19 patients who had tested negative by RT-PCR was recruited between March to November 2020 at our center. All recovered COVID-19 patients after 28 days and not more than three months after testing positive were included after informed consent. Serum samples of the enrolled patients were collected. The patient records were evaluated for detailed clinical examination, laboratory parameters and comorbidities. Disease severity was grouped into the following:

- Asymptomatic: Individuals who tested positive for SARS-CoV-2 using an RT-PCR, but who had no symptoms that were consistent with COVID-19.
- Mild disease: Mild cases were defined as those who had an oxygen saturation (SpO₂) of >94% on room air at sea level.
- Moderate disease: Moderate cases were defined as those who had an SpO₂ of <94% and >90% on room air at sea level.
- Severe disease: Severe cases were defined as those who had an SpO₂ of <90% on room air at sea level.

Abbott's quantitative IgG antibody test is designed to detect immunoglobulin class G (IgG) antibodies, including neutralizing antibodies, to the receptor binding domain (RBD)

of the S1 subunit of the spike protein of SARS-CoV-2 in serum and plasma. Serum-IgG antibodies against SARS-CoV-2 were analyzed using the quantitative ARCHITECT chemiluminescent microparticle immunoassay (Abbott Laboratories, USA), measuring IgG against SARS-CoV-2 S1 RBD protein; IgG concentrations ≥ 50 AU/mL were defined as positive.

The outcomes included determining disease characteristics of those individuals who had recovered from COVID-19 and the distribution of quantitative COV-2IgG II in the overall cohort and among disease severity types.

STATISTICAL ANALYSIS

Statistical analysis was done using the R software version 4.0.5. The categorical variables were summarized by using frequency and percentage. The numerical variables were presented using mean and standard deviation. The distribution of quantitative COV-2IgG II over the study period was shown using a scatter plot. Quantitative COV-2IgG II values were also shown graphically by using a horizontal histogram as well as a boxplot. SARS-CoV-2 immunoglobulin G antibodies distribution by age category was presented using boxplots. The x-axis of the box plots represented different age categories while the y-axis depicted the log of IgG antibodies

RESULTS

Demographics and clinical characteristics of the study population are reported in Table 1. The mean age of the participants was 34.3 years and 94.9% were male. Hypertension was the most common comorbidity (6%).

Fever was the most common symptom (85%) followed by cough (72.4%) and sore throat (52.9%). About 3% of the patients were asymptomatic (Table 2).

Table 3 presents the disease characteristics of COVID-19–infected patients. The majority of the patients had the mild disease (93%). The mean concentrations of IgG antibodies in the entire cohort was 1860.27AU/mL. The mean concentrations of IgG antibodies were higher in patients with the moderate disease compared to those with mild disease; however, the difference was not statistically significant (1787.7 AU/mL vs.2865.39 AU/mL, $p=0.21$).

Immunoglobulin G antibodies were detected in the majority of the patients up to 95 days after testing negative on RT-PCR (96.7%); even in some cases the antibodies could be detected up to 125 days post RT-PCR testing (3%) (Figs 1a,b& 2).

The mean concentration of IgG antibodies was highest among patients aged ≥ 50 years (3040.12 AU/mL) followed by those aged 30–49 years (2119.45 AU/mL) and 18–29 years (1215.95 AU/mL).

DISCUSSION

The occurrence of antibodies has a direct implication in identifying previous exposure or response to immunization. The presence of antibodies can be used as a surrogate for immune response and help in public health planning to determine individuals who may be immune and hence safe for themselves and the individuals they come into contact with. The use of serology allows the understanding of the incidence of infection; the proportion of severity of infection, and identification of the population who may be protected against infection in the future [16,17].

In this study, we assessed IgG antibody responses in 333 patients after moderate and mild COVID-19 infection. Patients with the

moderate disease had higher maximum concentrations of anti-viral IgG than those with mild disease. Previous studies reported that Abbott ARCHITECT SARS-CoV-2 IgG assay has very high specificity with IgG reactivity detectable by two weeks after symptoms onset [16,18]. In the current study, IgG antibodies could be detected up to 125 days after testing negative on RT-PCR.

Recently, Indian government has given an advisory to defer vaccination by three months after clinical recovery from COVID-19 illness [19]. Emerging evidence suggest that a third dose COVID-19 vaccine regimen may offer protection in some immunocompromised patients with inadequate antibody response after two doses [20,21]. France government now recommend a third dose of COVID-19 vaccine for severely immunocompromised patients [22]. The UK government is planning for third vaccine doses in elderly (>70 years of age), frontline and social care workers, and immunosuppressed adults [23]. With long-term follow-up in this study, we were able to detect IgG levels after more than 95 days in 97% of patients with mild and moderate symptoms. Thus, serological testing in current situation can act as an important tool for strengthening vaccination strategy in India. It creates a need for antibody testing who are already infected and in future, the antibody testing might help those who require a third dose of COVID-19 vaccine. Previous studies have reported detectable IgG levels in patients with mild and severe symptoms after more than 75 days [24] and majority of patients (>95%) have detectable IgG levels until five weeks after symptoms onset [25]. The Irish Health Information and Quality Authority has conducted a scoping review to determine the long-term immune responses post COVID-19 disease. The review included five and two studies that examined immune responses at ≥ 6 and ≥ 8 months post infection respectively. The antibody response declined 3–6 months post infection while T-cell and B-cell responses were still present [26].

Several studies confirmed the association between clinical severity and higher SARS-CoV-2-specific serum-IgG antibodies [27,28]. Our findings confirm previous results that the clinical severity of the disease is associated with higher SARS-CoV-2-specific serum-IgG antibodies. Patients with the moderate disease develop higher concentrations of SARS-CoV-2-specific IgG than patients with mild symptoms. It was reported that S-, RBD-, and N-specific IgG levels were gradually increased as age increased, during hospitalization and on discharge ($p < 0.05$)

[29].

The longevity of antibody responses needs to be determined with longitudinal studies. The WHO is conducting a multinational study for COVID-19, Solidarity II, which may provide a deeper understanding of the seroprevalence of SARS-CoV-2 infection [30].

LIMITATIONS

This being an observational study, by design has an internal bias. A larger proportion of patients in the mild group than the moderate group have been not available for late follow-up sampling.

CONCLUSION

In conclusion, patients with moderate COVID-19 disease seem to develop higher concentrations of SARS-CoV-2-specific IgG than patients with mild symptoms. The presence of detectable levels of IgG using Abbott's quantitative IgG antibody test maybe useful for population-level assessment of infection rates over time and can act as an important tool for vaccination strategy. Further, long-term prospective studies are warranted to ascertain these findings.

ETHICS APPROVAL: Study has been approved by GIMS Institutional Ethics Committee.

CONSENT TO PARTICIPATE: Consent was taken from patients before enrolment into the study

HUMAN AND ANIMAL RIGHTS: No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

CONFLICT OF INTEREST:

- Dr Jaganathan Sickan is an employee of Abbott Core Diagnostics, Singapore
- Dr Ajay Darbar, Dr Hussain Ali are employees of Abbott Core Diagnostics, India
- Dr Agim Beshiri is Sr Medical Director Abbott laboratories, USA
- Rest all authors have no conflict of interest

Fig. (1a) Distribution of quantitative COV-2 IgG II with cut-off of <50000 AU/mL.

Fig. (1b) Distribution of quantitative COV-2 IgG II with cut-off of <10000 AU/mL.

Fig. (2) Histogram and box plot for IgG values.

The mean concentration of IgG antibodies was highest among patients aged ≥ 50 years (3040.12 AU/mL) followed by those aged 30–49 years (2119.45 AU/mL) and 18–29 years (1215.95 AU/mL).

Table 1: Baseline patient characteristics

Characteristic	Value (N=333)
Age (years), mean	34.3
Gender, n (%)	
Male	316 (94.9)
Female	17 (5.1)
Comorbidities n (%)	
Diabetes mellitus	13 (3.9)
Hypertension	20 (6.0)
Hypothyroidism	1 (0.3)
Obesity	4 (1.2)
Congenital heart disease	1 (0.3)

Table 2: Symptoms in COVID-19–infected patients

Symptoms, n (%)	Sample (N=333)
Fever	283 (85.0)
Cough	241 (72.4)
Sore throat	176 (52.9)
Breathlessness	36 (10.8)
Asymptomatic	9 (2.7)

Table 3: Disease characteristics

Characteristic	Mild	Moderate	Overall	p-value
Disease severity, n (%)	310 (93.1)	23 (6.9)	-	
SpO ₂ , mean	98.21	93.09	97.86	
Quantitative COV-2 IgG II (AU/mL), mean $\pm$ SD	1785.7 $\pm$ 3782.74	2865.39 $\pm$ 2606.44	1860.27	0.21

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