IgM and IgG Antibody Levels in Patients with COVID-19 in South Andhra Pradesh

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ABSTRACT

BACKGROUND

Coronavirus disease - 19 (COVID-19) is an infectious disease caused by a newly discovered coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Anti-SARS-CoV-2 IgM and IgG antibodies can be detected in almost all patients of COVID-19. We sought to evaluate the antibody responses in COVID-19 patients and also analyse their potential role in disease prognostication.

METHODS

All consecutive COVID-19 patients, between ages 20 - 65 years, encountered between April and July 2020 were included and compared to age-matched controls. Severity of the SARS-CoV-2 infection was categorized as none, mild and severe, based on the presence of symptoms, oxygen saturation and need for respiratory support. Serum levels of IgM and IgG antibody assays were obtained, using chemiluminescence immunoassay, after the 2nd week of presentation (range 14 - 60 days). Antibody titres above 10 AU/ml were taken as elevated.

RESULTS

Of 50 eligible patients, majority (40/50, 80 %) had mild symptoms and oxygen saturations above 94 %. Of the remainder, 10 % (5/50) had severe infection with need for either high flow nasal cannula oxygen or mechanical ventilation while the remainder (10 %; 5/50) were asymptomatic. IgM and IgG seroconversion were noted in almost all COVID-19 patients (46/50, 92 %) compared to healthy controls. While elevated IgG antibody levels were noted in 76 % (38/50), combined elevation of IgM and IgG antibodies is seen in 16 % (8/50) of patients. Seroconversion was markedly profound in patients with severe infection than those with mild infection. Also, greater seroconversion was noted after 21 days of testing compared to 14th day, especially for IgG.

CONCLUSIONS

Antibody seroconversion to SARS-CoV-2 occurred in majority of patients with COVID-19, with most salient increase in the IgG antibody levels. Antibody titres correlated directly to the disease severity, suggestive of the potential value of antibodies not only in diagnosis but also in prognostication.

KEYWORDS

COVID-19, Chemiluminescence Immunoassay, Invasive Mechanical Ventilation, High Flow Nasal Oxygen

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BACKGROUND

COVID-19 is an infectious disease caused by the most recently discovered coronavirus, SARS-CoV-2.[1] First identified in December 2019 in Wuhan, China, the disease has rapidly panned all across the world becoming a public health emergency of international concern by the world health organization (WHO). Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family Coronaviridae and the order Nidovirales.[2] Although most human coronavirus infections are mild, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) – beta coronaviruses are zoonotic in origin – have been associated with potentially fatal disease, particularly during the outbreaks in 2002 and 2012, respectively.[3,4,5]

The diagnosis of COVID-19 is dependent mainly on clinical characteristics and laboratory tests. Clinical manifestations of COVID-19 typically includes fever, dry cough and fatigue but presentation is widely varied, ranging from asymptomatic to fatal pneumonitis.[6] Fortunately, mildly symptomatic patients account for about 80 % of all cases but elderly patients and those with co-morbid conditions like diabetes, cardiovascular disease, cancers and chronic respiratory disease are at risk of succumbing to the illness. Reverse-transcript polymerase chain reaction (RT-PCR), a molecular test, is regarded as the "gold-standard" for diagnosis of SARS-CoV-2;[7,8] however, limitations include potential false negative results,[6,9] changes in diagnostic accuracy over the disease course, and precarious availability of test materials.

Sole reliance on molecular testing also poses the risk of missing the mild or asymptomatic infections that do not require medical attention, making the full extent of infection non-discernible. Seroprevalence studies, on the contrary, can provide a more comprehensive picture of how much of a population has been infected with SARS-CoV-2 and also capture unrecognized cases not identified through molecular testing. Nearly all immune-competent individuals will mount an immune response following SARS-CoV-2 infection. Like infections with other pathogens, SARS-CoV-2 infection elicits development of IgM and IgG antibodies.

For these reasons, serological estimation of these antibodies is becoming one of the critical methods for the diagnosis of suspected COVID-19 patients with negative RT-PCR results and for identification of asymptomatic infections, as well as gaining popularity for epidemiological surveillance. However, the antibody response to SARS-CoV2 currently remains inadequately understood in COVID-19 patients, especially in the South Indian population.

Objectives

Recognizing the stand of serological testing in the current COVID-19 situation, we sought to evaluate the antibody responses in COVID-19 patients of South Andhra Pradesh, Nellore and also analyse their potential role in disease prognostication.

METHODS

We performed a retrospective cohort analysis of patients admitted with diagnosis of COVID-19, at Government General Hospital attached to ACSR Government Medical College, Nellore between April and July 2020. After Institutional Review Board Approval, medical records were reviewed for demographics, severity of illness, oxygen saturation during illness, and treatment received during illness. All COVID-19 patients between age 20-65 years were included for the study. Twenty-five age matched healthy patients served as controls. Patient with pre-existing chronic conditions especially when associated with baseline low oxygen saturations, immune deficiency, cancer or immunosuppressant therapy were excluded from the study.

A positive test with the "gold standard" reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swabs was used for making diagnosis of COVID-19 infection. Severity of the SARS-CoV-2 infection was categorized as none, mild and severe, based on the presence of symptoms, oxygen saturation and need for respiratory support either in form of nasal cannula or mechanical ventilation. Patients with fever, upper respiratory tract illness symptoms and radiological findings of pneumonia were defined as mild cases, while patients meeting any of the following criteria were defined as severe cases: 1) Respiratory distress (≥ 30 breaths/min), 2) oxygen saturation ≤ 94 % at rest, and 3) need for respiratory support in any form, such as nasal cannula or mechanical ventilation.

Blood samples were collected after the 2nd week of presentation, with the majority happening on the 14th day, though some were tested after 21 days. Asymptomatic patients were followed at 60 days. Collections of the blood samples were obtained, under strict aseptic conditions, into plain vacutainers. Strict adherence to all laboratory biosafety guidelines related to COVID-19 were implemented throughout the laboratory processing.

After separation of serum, to avoid haemolysis, SARS-CoV-2 specific IgM and IgG antibody levels were estimated using chemiluminescence immunoassay analyzer (CLIA), YHLO iFLASH 1800. In this immunoassay technique, CLIA the label which is the true indicator of the analytical reaction is a luminescent molecule.[10] In general, luminescence is the emission of visible or near-visible radiation of λ – 300 - 800 nm which is generated when an electron transitions from an excited state to a ground state. The resultant potential energy in the atom gets released in the form of light.[10] CLIA technology permits analytical procedures with lower analyte detection limits than other immunoassay methods.[10] The levels of more than 10 AU/ml were taken as elevated for both IgM and IgG.

Statistical Analysis

Data was recorded using Microsoft Excel (Version 15 - © 2013 Microsoft, products.office.com/en-us/excel). Statistical analyses and graphical presentation were conducted with GraphPad Prism Version 7.0 (GraphPad Software, Inc., CA, USA). Patient characteristics and clinical findings were

summarized using descriptive statistics. Continuous data was expressed as means with standard deviation or medians with interquartile ranges as appropriate. We compared categorical variables of basic clinical characteristics of COVID-19 patients and healthy controls using Fischer's exact test. Differences of antibody response between COVID-19 patients and controls were determined by unpaired t test. Likewise, unpaired t test was also used for determining differences of antibody response among the various severity spectrum in the COVID-19 patients (asymptomatic vs mild vs severe). Throughout the text, figures, and legends, the following terminology was used to show statistical significance: *, P < 0.05; **, P < 0.01; and ***, P < 0.001.

RESULTS

Fifty consecutive COVID-19 patients met the inclusion criteria. Of these, majority (40/50, 80 %) had mild symptoms such as fever, sore throat, dry cough, fatigue and oxygen saturations above 94 %. Of the remainder, 10 % (5/50) were asymptomatic and 10 % (5/50) had severe infection with need for either high flow nasal cannula oxygen or mechanical ventilation. There was no significant gender discrepancy among the enrolled patients (males : female = 46 % : 54 %). The patients were aged 25 - 63 years (mean 43 years).

	Variables	Mean	S. D	t Value	P Value
IgM	Cases	7.32	14.01	2.27	< 0.025
	Controls	0.91	0.98		
IgG	Cases	72.98	35.85	10.05	< 0.0001
	Controls	0.68	0.67		

Table 1. Various Study Parameter Values Mean, S.D., t & P Values of Control and Test Groups

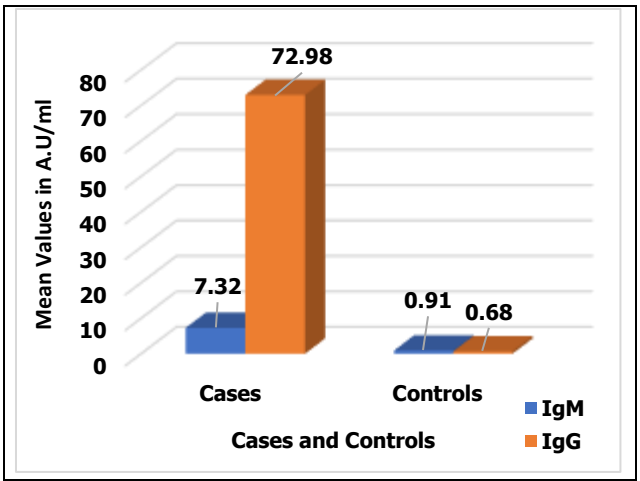

Figure 1. Means of IgM and IgG Levels in Cases vs. Controls

Seroconversion was predominantly in the form of IgG. Increased IgM and IgG antibody levels were appreciated in 16 % (8/50) of cases while 76 % (42/50) had only IgG elevation. About 8 % (4 patients), who were asymptomatic, failed to seroconvert, with no appreciable elevation of either IgM or IgG antibody levels even after day 60 (Figure 2).

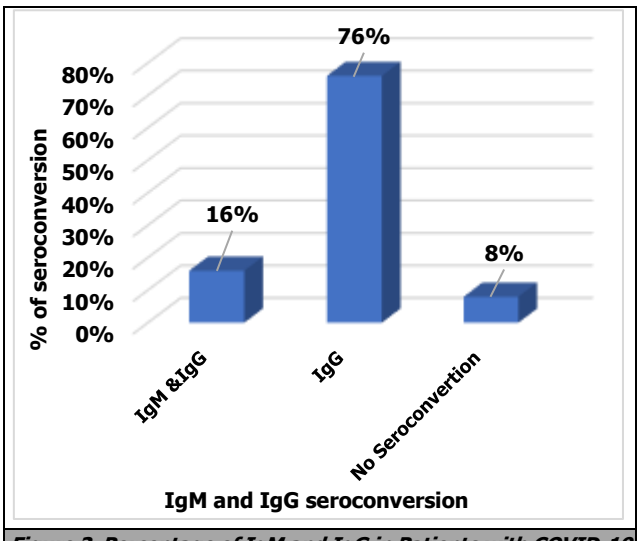

Figure 2. Percentage of IgM and IgG in Patients with COVID-19

Elevated IgM and IgG antibody levels were appreciated in the majority of the COVID-19 patients (46/50, 92 %) compared to healthy controls. All the four patients (8 %) who failed to show any seroconversion had mild symptoms. Majority of the serology tests (44/50, 88 %) were performed on the 14th day of diagnosis, just before discharge, adhering to the hospital's protocol. However, some patients (6/50, 12 %) had testing after 21 days and a few asymptomatic persons (4/50, 8 %) also on day 60. There was a statistically significant increase in the IgM levels in patients with COVID-19 in comparison to healthy persons (IgM 7.32 ± 14.01 versus 0.91±0.98 [P < 0.025]) (Table 1, Figure 1).

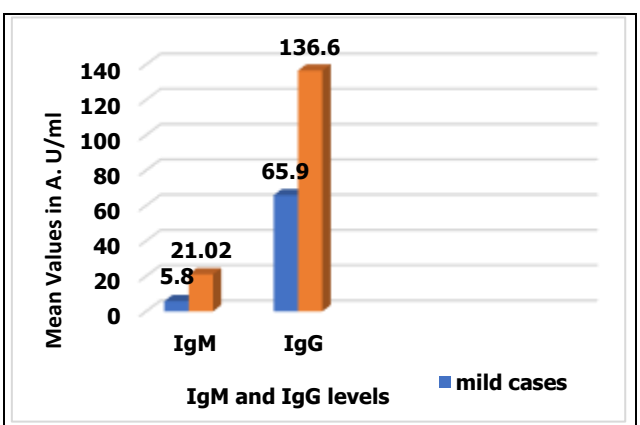

Figure 3. Means of IgM and IgG in Mild and Severe Cases of COVID-19

Likewise, a statistically significant elevation of IgG levels was noted in patients with COVID-19 when compared to the healthy controls (IgG 72.98 ± 35.85 versus 0.68 ± 0.67 [P value < 0.0001]) (Table 1, Figure 1). The mean and S.D. of IgM and IgG of the control group are within established normal values.

Upon further analysis of the serological assay in relation to the day of testing, there was no statistically significant increase in IgM levels when tested after 21 days compared to when tested at 14 days (12.50 ± 17.60 versus 6.6 ± 13.50 [P value = 0.33]). On the contrary, a remarked increase was seen in the IgG levels tested after 21 days in comparison to those at 14th day (118.66 ± 55.31 versus 66.75 ± 27.89 [P

value < 0.005]).

Serocon version was markedly more profound in patients with severe infection than those with mild infection, for both IgM and IgG levels. Statistically significant increase in the antibody levels were noted in severe cases vs mild cases, for both IgM levels (21.02 ± 24.29 versus 5.8 ± 11.89 [P - value = 0.0197]) as well as for IgG levels (136.60 ± 52.78 versus 65.90 ± 25.83 [P - value < 0.0001]) (Figure 3)

DISCUSSION

Our study supports several findings: (1) seroconversion to SARS-CoV-2 is seen in almost all the patients, especially when IgM and IgG are considered together, signifying their role in diagnosis and management of COVID-19 infection (2) positive rates of IgM or IgG in the early stage can be low or delayed, but gradually increases during the disease progression, (3) patients who did not have seroconversion are usually the ones with mild or asymptomatic infections, (4) patients with a higher IgM and IgG serological response had more severe COVID-19 manifestations. Our center was 1 among the 5 centers in Andhra Pradesh with privileges to perform serological assay in patients with COVID-19 and considering the dearth of research in the region, our study is thus novel in its own kind.

Our present study demonstrates that seroconversion to SARS-Cov-2 is noted in the majority (92 %; 46/50) of patients - an elevation of both IgM and IgG in 16 %, and elevation of only IgG in the other 76 %. Only 8 % of the study participants failed to show any seroconversion, even after follow up for 60 days.

Unsurprisingly, all of these patients had mild symptoms. Similar findings were validated by several studies (Table 2).[11,12-16] In the study by Fafi-Kramer et al. all but one (99.4 %) participant had detectable levels of anti-SARS-CoV-2 antibodies from 13 days after onset of symptoms.[13] Also, Yu et al. demonstrated in a cohort of 37 COVID-19 patients that the humoral response rate for IgA, IgM or IgG was 100 % 32 days after symptom onset.[17] Nonetheless, several studies highlight that not everyone who has SARS-Cov-2 infection test positive for antibodies. Liu et al. analysed 32 patients and found that 92.8 % of patients seroconverted while 7.1 % failed to mount any significant antibody response.[15] Likewise, Marklund et al. evaluated 47 patients and found that 9.4 % did not show the expected antibody response.[11] Expectedly, in both the studies, these patients had mild symptoms. Staines et al. in a research led by St George's, University of London and St. George's University Hospitals NHS Foundation found that a proportion (2 - 8.5 %) of the 177 patients do not have detectable antibodies up to 60 days post infection.[16] It is a known fact that humoral response to antigens is diverse with production of IgM, IgA and IgG. Possible postulation for this phenomenon is that these relatively mild infections could have been confined to the mucosal cells of the respiratory and hence elicit a predominant secretory immune response in form of IgA and little, if any, IgG.

Variation in the detection rates of antibodies, especially IgM, have been noted during disease stage in several studies. It is a known fact that seroconversion occurs within the second week following symptom onset, with a median time of 5 - 12 days for IgM antibodies and 14 days for IgG and IgA.[18] So, predictably, the positive rates of IgM or IgG in the early stage was relatively low and gradually increased during the disease progression.

Study	Time of Study	Place of Study	Patients Enrolled	Severe Cases	Test Used	Seroconversion Details	Patients Seronegative
Marklund E et al.[11]	Feb 25 - Mar 25, 2020	Gothenburg, Sweden	47 (Males 52 %)	15	CLIA and CMIA	IgG: 93.6 % (mild 90.6 %, severe 100 %)	3 (6.4 %)
Liu X et al.[15]	2020	Chongqing, China	32 (Males 66.7 %)	18	Quantum dot immunofluorescence assay	IgM and IgG: 96.8 % (mild 92.8 %; severe 100 %)	1 (3.1 %)
Zhao J et al.[18]	Jan 11 - Feb 9, 2020	Guangdong Province, China	173 (Males 48.6 %)	32	ELISA	Total Ab: 93.1 % IgM: 82.7 % IgG: 64.7 %	12 (6.9 %)
Lou B et al.[12]	Jan 19 - Feb 9, 2020	Hangzhou, China	80 (Males 61.3 %)	15	ELISA, CLIA, CMIA	>2 weeks Total Ab: 100 % IgM: 96.7 % IgG: 93.3 %	1 (1.2 %; using IgM and/ or IgG)
Ma H et al.[20]	Jan 26 - Mar 5, 2020	Anhui, China	87	22 (17 severe, 5 critical)	CLIA	IgA: 98.6 % IgM: 96.8 % IgG: 96.8 %	2 (2.3 %; using IgA kit); 4 (4.6 %; using IgM and/or IgG)
Staines HM et al.[16]	Mar 29 - May 22, 2020	London	177 (Males 57 %)	63 (required ICU)	ELISA	IgG: 91.5 %	15 (8.5 %)
Fafi-Kremer S et al.[13]	Apr 6 - Apr 8, 2020	Strasbourg, France	160 (Males 31.2 %)	None	CE-Marked lateral flow assay by Biosynex, S-Flow assay	IgM and IgG: 95.6 % by rapid immunodiagnostic assay & 99.4 % by S-Flow assay	1 (0.6 %)
Yu HQ et al.[17]	2020	China	37 (Males 67.6 %)	20	CLIA	IgA: 98.9 % IgM: 93.4 % IgG: 95.1 % IgA or IgM or IgG: 100 %	None (using IgA or IgM or IgG)
Hou H et al.[21]	Feb 16 - Feb 25, 2020	Wuhan, China	338 (Males 50.6 %)	199 (severe), 75 (critical)	CLIA	IgM: 81.3 % (mild), 82.9 % (severe), 82.7 % (critical) IgG: 90.6 % (mild), 92.7 % (severe), 88 % (critical) IgM and IgG: 79.7 % (mild), 77.9 % (severe), 80 % (critical)	~25
Pan Y et al.[8]	Feb 6 - Feb 21, 2020	Shanghai, China	105 → 67 (Males 45.7 %)		Colloidal gold-based ICG strip	>15 days IgM: 74.2 % IgG: 96.8 %	

Table 2. Comparison of the Various Studies Analysing Serological Response to SARS-CoV-2 Infection

Abbreviations: CLIA = chemiluminescence immuno-analysis; CMIA = chemiluminescence microparticle immunoassay; ELISA = enzyme linked immunosorbent assay; Ab = antibody; ICU = intensive care unit; ICG = immunochromatographic

Liu et al. reported IgM antibody response to SARS-CoV-2 occurred earlier and peaked earlier than IgG antibody response.[15] IgM antibody response was noted to begin declining at 3 weeks of the illness while IgG antibody response persisted and was maintained in patients with COVID-19. The timing of appearance of IgM and IgG antibodies was also noted to be greatly variable, and likely associated with age as well as co-morbidity. In our study, 44 samples were tested on the 14th day and 6 samples were tested after 21 days. The IgM levels were elevated, though not statistically significant, in patients tested on the 14th day and after 21 days (IgM 6.6 ± 13.5 versus 12.5 ± 17.6 [P value 0.33]). IgG levels were significantly elevated in patients when tested after 21 days compared to patients tested on the 14th day (IgG 118.66 ± 55.31 versus 66.75 ± 27.89 [P value < 0.005]). IgG levels are significantly elevated as post symptom onset in the late stages. These findings mirror those of Pan et al. who observed in their analysis of 134 samples from 105 patients that the positive percentages of IgM at early, intermediate, and late stages were 22.2 %, 33.3 % and 57.1 %, respectively while the positive rate of IgG at early, intermediate and late stages were 44.4 %, 66.7 % and 71.4 % respectively.[8]

Our findings also substantiate the notion that clinical severity of disease is associated with higher SARS-CoV-2 specific antibodies.[11,17,12-16,19,20,21] IgM levels were significantly elevated in patients with severe infection compared to those having mild infection (IgM 21.02 ± 24.29 versus 5.8 ± 11.89 [P value 0.0197]). Likewise, IgG values were also significantly elevated in severe cases as compared to mild cases (IgG 136.60 ± 52.78 [P value < 0.0001]). Our findings resonate with the study by Marklund et al. and many others, as depicted in table 2.[8,11,17,12,15,16,18,21] A prudent findings in the studies by Markland et al. and Liu et al. were a seroconversion rate of 100 % in severe cases.[11,15] In the early stage of infection, serum IgG antibody levels did not statistically correlate with clinical severity, but from day 15 onward, the difference in IgG antibody level between mild and severe cases were statistically significant in Liu et al. study (day 15 (N = 17), day 20 (N = 6) and day 21 (N = 11), all P < 0.05).[15] Likewise, higher titres of total antibodies was independently associated with a worse clinical classification in study by Zhao et al.[18] Our findings, nevertheless, were in contrast to those of Hou et al. who noted that positive rates of IgM and/or IgG antibody detections were not significantly different among the mild, severe and critical disease groups.[21]

CONCLUSIONS

In summary, serology-based antibody tests can provide an estimate of the SARS-CoV-2 incidence, when complemented with nucleic acid amplification test (NAAT). As the majority of COVID-19 patients have elevation in IgM and IgG, serological assay should be considered for COVID-19 epidemiology. Clinical severity of disease is associated with higher SARS-CoV-2 specific antibodies. Thus, quantitative estimation of both IgM and IgG antibodies has a potential value in diagnosis and prognosis of COVID-19 infection.

Limitations

Our study has many limitations. Most importantly, the sample size that has been analysed is very small and further analysis of a much larger sample is required before extrapolation of our findings to the general COVID-19 population. Majority of our cases were mild and hence this could have potentially confounded the results. Analysis of a larger sample consisting of severe patients would likely yield stronger results.

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