Clinical Correlates of Early IgG Response in Patients with Mild COVID-19

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Abstract

Background: We determined the temporal pattern of early SARS-CoV-2 IgG response in patients with mild COVID-19, and sought to identify predictive clinical and laboratory features.

Methods: Serum samples were prospectively obtained from 111 convalescent COVID-19 patients, staying in dedicated Isolation-hotels, and tested for the presence of SARS-CoV-2 IgG by anti-S1 protein ELISA.

Results: SARS-CoV-2 IgG was detected in 78 (70.3%) patients tested within the first month from diagnosis. While highly variable between patients, the rate of antibody detection generally increased with time, from 47.1% to 93.8% at the first and fourth weeks from diagnosis, respectively, with the largest shift observed between the second and third week. Notably, the presence of more profound symptoms at presentation, namely, fever and chills, positively and independently correlated with early antibody response. IgG-positive patients had higher ferritin levels ($p=0.039$). Older age ($p<0.001$) and increased CRP levels ($p=0.001$) were associated with higher SARS-CoV-2 IgG levels.

Conclusions: The identified temporal pattern along with the correlation between inflammation-related clinical and laboratory parameters and early IgG response in patients with mild COVID-19, could provide a basis for better prediction and understating of the immune response to SARS-CoV-2, and inform therapeutic donor-plasma selection.

Background

Since its emergence in Wuhan, China, in December 2019, the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), identified as the etiological agent of coronavirus disease-19 (COVID-19), has caused a rapidly spreading global pandemic associated with significant morbidity and mortality and far-reaching economic and social implications(1, 2). By early June 2020, more than seven million confirmed cases and more than 400,000 SARS-CoV-2-related deaths have been reported worldwide. While the majority of infected patients are asymptomatic or present with mild disease, severe disease associated with acute respiratory distress syndrome (ARDS) and multi-organ failure complicate 5-20% of COVID-19 cases (2-4). The diagnosis of active SARS-CoV-2 infection is based on the detection of viral RNA in nasopharyngeal swab sample by reverse transcription (RT)-real time polymerase chain reaction (PCR) (5). This assay, requiring initial viral inactivation step, skilled laboratory personnel, special laboratory facilities, and large volumes of RNA extraction and RT-PCR kits along with automated liquid handlers (to address the requirement for high throughput performance during the pandemic), has been complicated by diagnostic bottlenecks and reagents' shortage.

SARS-CoV-2 antibody detection assays are currently developed at a rapid pace. Serological studies should enhance the understanding of the immune response to SARS-CoV-2 (6), allow the diagnosis of recent or past infection (when RT-PCR was not performed or was false-negative) (7, 8), support population-based studies and public-health strategies, and inform vaccine development. Additionally,

SARS-CoV-2 IgG detection allows for the initial screening of immune-donor plasma – recently shown to be a promising therapeutic approach in critically ill COVID-19 patients (9).

In Israel, the first cases of SARS-CoV-2 infection were confirmed in mid-February, and were followed by accelerated transmission during late-March through April – due to travel-associated importations, large holiday gatherings, and introductions into the densely populated orthodox-religious neighborhoods. During this period, recovering hospitalized COVID-19 patients with mild disease were routinely discharged into dedicated isolation hotels. The common location of these patients during the early convalescence phase presented us with an opportunity to determine the pattern and clinical correlates of early SARS-CoV-2 IgG response in patients with mild disease – constituting the majority of COVID-19 patients.

Patients And Methods

Study design and patient population.

Included in the study were 111 adult patients who had been hospitalized with mild COVID-19, and were subsequently staying in dedicated isolation hotels in Jerusalem until recovery. The vast majority of patients did not require oxygen support (and none received noninvasive or mechanical ventilation) and no patient was admitted to the intensive care unit. Therefore, the patients were retrospectively defined as representing mild COVID-19 cases. The hospitalization in itself did not preclude the definition of mild disease as at this stage of the pandemic in Israel, all patients were initially hospitalized.

The time from diagnosis was defined as the time from the first recorded positive nasopharyngeal swab. Serum samples and concurrently obtained nasopharyngeal swab samples were prospectively collected once per each patient during April 2020 and analyzed for the presence of SARS-CoV-2 IgG and RNA, respectively. Blood samples were also analyzed for blood count, C-reactive protein (CRP) and ferritin levels.

The demographic and clinical data were collected from the medical files, and analyzed retrospectively (see Table 1 for analyzed parameters). The study was approved by the Institutional review board and was performed according to the Human-Experimentation Guidelines of the Israeli Ministry of Health. All patients provided an informed consent.

SARS-CoV-2 IgG and RNA detection.

Enzyme-linked immunosorbent assay (ELISA) for SARS-CoV-2 IgG (EUROIMMUN Corp., Germany), measuring IgG against the viral spike protein S1, was used in accordance with the manufacturer's instructions. Ratios (sample/calibrator readings at 450 nM) of <0.8, 0.8-1.1, and >1.1 were determined as negative, intermediate, and positive IgG results, respectively. Antibody levels in this assay did not exceed

10.0, therefore, based on the observed range of antibody levels (semi-quantitatively defined by the ratios), a cutoff ratio of 5.0 was chosen to distinguish between high and low antibody levels.

Nasopharyngeal swab samples were collected in 2 ml Viral Transport Medium and mixed 1:1 with a 2X concentrated lysis buffer (DNA/RNA Shield; Zymo Research). Viral RNA was extracted using the QIAAsymphony DSP Virus/Pathogen kit on a QIAAsymphony platform (Qiagen) in accordance with the manufacturer's specifications. RNA was eluted into 60 µl, and 10 µl of the eluted RNA was used for a 30 µl RT-PCR reaction, using Real-Time Fluorescent RT-PCR kit with primers and probe targeted to the SARS-CoV-2 ORF1ab gene (BGI).

Statistical analysis.

The Chi-square test and Fisher's exact test were used to determine the association between two categorical variables. Comparison of continuous variables between two independent groups was carried out using two-sample t-test for normally distributed data and Mann-Whitney non-parametric test for non-normally distributed data. In order to simultaneously assess the effect of several variables on the dependent variable (i.e., positive/negative serology), while correcting for confounders, the multivariate logistic regression model was applied using the stepwise, forward, likelihood ratio method. All tests applied were two-tailed, and a p-value of 0.05 or less was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics, version 25.

Results

Temporal pattern of IgG response in convalescent COVID-19 patients.

Within a month from the first positive nasopharyngeal swab, SARS-CoV-2 IgG was detected in 78 (70.3%) of 111 recovering COVID-19 patients, 6 (5.4%) patients had intermediate IgG results, and 27 (24.3%) patients were found to be negative for SARS-CoV-2 IgG

Figure 1 presents the rate of SARS-CoV-2 IgG detection by the time from diagnosis, ranging from 47.1% to 93.8% among patients tested during the first and fourth week from diagnosis, respectively ($p=0.006$). Five of six intermediate IgG results were obtained in patients tested during the second week (days 8-14), with the greatest antibody detection shift noticed between the second and third week post diagnosis. The mean time from diagnosis was significantly longer for patients with positive SARS-CoV-2 IgG (15.6 ± 6.0 vs. 11.0 ± 4.9 days in IgG negative patients; $p<0.001$), as also demonstrated for the mean time from symptoms onset (21.3 ± 8.9 vs. 13.6 ± 8.3 days; $p<0.001$). The longest time from symptoms onset during which a patient remained IgG negative was 44 days, while the shortest time from symptoms onset to IgG positivity was 8 days.

Comparison of demographic, clinical, and laboratory features between IgG-positive and IgG-negative patients.

Comparison of IgG-positive and IgG-negative patients revealed no significant differences in demographic characteristics and in the presence of underlying medical conditions (Table 1). Smoking and hypertension were the most common comorbidities in both groups. Only three patients had underlying

immunosuppression (kidney transplantation, multiple sclerosis, and chronic inflammatory demyelinating polyneuropathy).

Table 1: Comparison of demographic and clinical characteristics between SARS-CoV-2 IgG-positive and IgG-negative patients

Characteristic	N (%) of patients ^a			P value
	All Patients (n=111)	Antibody-positive (n=78)	Antibody-negative (n=27)	
Age group				
<30	36 (32.4)	22 (28.2)	9 (33.3)	0.63
30 - 39	21 (18.9)	15 (19.2)	6 (22.2)	
40 - 49	12 (10.8)	8 (10.3)	4 (14.8)	
50 - 59	16 (14.4)	12 (15.4)	3 (11.1)	
60 - 69	18 (16.2)	15 (19.2)	3 (11.1)	
70 - 79	7 (6.3)	6 (7.7)	1 (3.7)	
≥ 80	1 (0.9)	0 (0.0)	1 (3.7)	
Sex				
Male	76 (68.5)	57 (73.1)	18 (66.7)	0.53
Female	35 (31.5)	21 (26.9)	9 (33.3)	
Underlying medical conditions				
Any	41 (36.9)	28 (35.9)	11 (40.7)	0.65
Smoking	17 (15.3)	12 (15.4)	4 (14.8)	1.0
Diabetes mellitus	7 (6.3)	6 (7.7)	1 (3.7)	0.67
Hypertension	14 (12.6)	9 (11.5)	5 (18.5)	0.35
Congestive heart failure	1 (0.9)	1 (1.3)	0 (0.0)	1.0
Ischemic heart disease	6 (5.4)	4 (5.1)	2 (7.4)	0.65
Lung disease	5 (4.5)	2 (2.6)	2 (7.4)	0.27
Chronic kidney disease	2 (1.8)	2 (2.6)	0 (0.0)	1.0
Immunosuppression	3 (2.7)	3 (3.8)	0 (0.0)	0.57
Symptoms				
Any	93 (83.8)	68 (87.2)	20 (74.1)	0.13
Fever ^b	54 (48.6)	45 (57.7)	7 (25.9)	0.004
Chills ^b	37 (33.3)	31 (39.7)	5 (18.5)	0.045
Cough	69 (62.2)	51 (65.4)	14 (51.9)	0.21
Dyspnea	45 (40.5)	37 (47.4)	7 (25.9)	0.051
Sore throat ^b	37 (33.3)	21 (26.9)	14 (51.9)	0.018
Headache	36 (32.4)	25 (32.1)	8 (29.6)	0.81
Myalgia	47 (42.3)	35 (44.9)	10 (37.0)	0.48
Abdominal pain	18 (16.2)	13 (16.7)	3 (11.1)	0.76
Nausea and vomiting	23 (20.7)	18 (23.1)	3 (11.1)	0.18
Diarrhea	35 (31.5)	26 (33.3)	6 (22.2)	0.28
Loss of smell or taste	39 (35.1)	28 (35.9)	6 (22.2)	0.19
Treatment				
Oxygen support	15 (13.5)	14 (17.9)	1 (3.7)	0.11
Experimental SARS-CoV-2 directed therapy	18 (16.2)	17 (21.8)	1 (3.7)	0.037

^a 6 out of 111 patients examined had intermediate serology

^b Independent correlates as revealed by multivariate analysis

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The most common presenting symptoms noted in the entire cohort were cough (62.2%), fever (48.6%) and dyspnea (40.5%) (Table 1). IgG-positive patients had significantly higher rates (compared to IgG negative patients) of fever (57.7% vs. 25.9%, $p<0.0001$), chills (39.7% vs. 18.5%, $p=0.04$) and dyspnea (47.4% vs. 25.9%, $p=0.047$) at presentation. Fourteen of the 15 patients who required oxygen support were positive for SARS-CoV-2 IgG, although the difference between the IgG-positive and IgG negative patients did not reach statistical significance (17.9% vs. 3.7%, $p=0.11$). A significantly higher proportion of IgG positive patients had received SARS-CoV-2 experimental therapies (i.e., hydroxychloroquine, azithromycin, lopinavir/ritonavir) compared to IgG negative patients (21.8% vs 3.7%, $p=0.029$).

Nasopharyngeal viral RNA was still detected in 23.8% of the patients at the time of serum sampling. While the detection rate of viral RNA appeared to be somewhat lower among IgG-positive patients (20.5%) compared with IgG negative patients (33.3%), this difference did not reach statistical significance ($p=0.18$).

Comparing additional laboratory parameters, we found that median ferritin levels were higher in the IgG positive group (129.2 vs. 78.9 mg/dL, $p=0.039$), whereas white blood cell and platelet counts, and CRP levels did not differ between the two groups.

A multivariate analysis identified the presence of fever (OR 5.13; 95% CI 1.53 – 17.45; $p=0.008$), chills (OR 6.82; 95% CI 1.60 – 29.08; $p=0.009$), and the time-from-diagnosis (OR 1.18; 95% CI 1.06 – 1.32; $p=0.004$) as independent predictors of the presence of SARS-CoV-2 IgG within the first month from diagnosis.

Semi-quantitative analysis of IgG levels

A wide (> 1 log) IgG level range was identified in IgG positive patients. Dividing the IgG positive patients into subgroups with high- and low-antibody levels (with a cutoff set at a ratio of 5.0; see Patients and Methods), we found that patients with high IgG levels were significantly older [51.0 ± 13.6 vs. 37.4 ± 18.7 years, $p<0.001$]. Notably, both ferritin and CRP levels were higher in the high-IgG group with the latter showing a statistically significant difference (median ferritin levels 165.1 vs. 98.1 mg/dL, $p=0.14$; median CRP levels 0.36 vs. 0.07 mg/dL, $p=0.001$). There were no significant differences between the two subgroups with regard to the time post diagnosis, demographic and clinical parameters, and the presence of viral RNA in concurrent nasopharyngeal swab samples.

Discussion

There is a need to better define the patterns and clinical correlates of antibody response to SARS-CoV-2. By now, several case series and studies of antibody response have been reported in COVID-19 patients,

focusing primarily on the performance of the different antibody detection assays examined (10-13), and on the analysis of the kinetics of specific antibody response against the viral S and N proteins (10).

Here we determined the temporal pattern of SARS-CoV-2 anti-S1 IgG detection in 111 COVID-19 patients who had presented with mild disease, and further identified clinical and laboratory features associated with early antibody response - during the first month from the diagnosis.

While a considerable variability in the timing of antibody response was found between individual patients in this cohort, general antibody detection rates steadily increased from 47.1% to 93.8% between the first and the fourth week, with the highest serological shift (60.9% to 84.4%) noticed between the second and third week from diagnosis. This observed temporal pattern is overall in agreement with previous reports (14-17), although the use of diverse antibody detection assays (i.e, in-house and commercial ELISA assays, lateral flow immunoassays, pseudotyped-lentiviral-vector-based neutralization assay) along with the relation of antibody detection to the time of symptoms onset (versus the time of diagnosis), and the inclusion of patients with varying disease severity, make it difficult to directly compare the findings in the different studies.

Importantly, we found that in patients with mild COVID-19, the presence of detectable antibodies within a month from diagnosis correlated with more symptomatic disease at presentation. In particular, antibody-positive patients manifested higher rates of fever, chills, and dyspnea (the latter of borderline significance) (Table 1), with a higher rate of experimental SARS-CoV-2-directed therapies (probably reflecting the more profound presentation). Additional symptoms, including myalgia, cough, gastrointestinal symptoms, and loss of taste (with the exception of sore throat), as well as the requirement for oxygen support, were also more common, albeit not reaching statistical significance, in the antibody-positive group. In fact, apart from the time-from-diagnosis, the presence of fever and chills independently correlated with the development of SARS-CoV-2 IgG, as revealed by multivariate analysis. The association of more profound inflammatory-related symptoms with early antibody response could reflect the effect of a higher viral load and/or a more marked innate immune activation on antibody formation. The latter mechanistic notion is supported The recent finding that asymptomatic patients with SARS-CoV-2 infection have reduced inflammatory response and antibody levels relative to symptomatic patients despite longer duration of viral shedding (18). By analogy, early activation of innate immunity is known to translate into higher antibody responses following both infections and vaccinations (19). The correlation between the immune activation state and the extent of antibody response is further suggested by our findings that IgG positive patients had higher ferritin levels ($p=0.039$), and that higher antibody levels further correlated with higher CRP levels ($p=0.001$).

While we did not identify a correlation between age and early development of antibodies per se, an older age was found to be associated with higher antibody levels, in agreement with the higher levels of neutralizing antibody titers reported in elderly and middle-age patients compared to young adult patients from China (15). Future studies should explore the underlying mechanism of the age-related enhancement of antibody response to the SARS-CoV-2, and whether it could be related to an augmented

innate immune response or to the recently reported presence of pre-existing immunity to the virus in older individuals (20).

To our knowledge, this is the first study describing the inflammation-related clinical correlates of early antibody response in patients with mild COVID-19. Our study has several limitations. First, we used a single S1-protein specific ELISA assay, which does not reflect the full array of anti SARS-CoV-2 antibody formation and the functional neutralizing activity (6). Additionally, we did not address the individual kinetics of antibody response, as patients were tested at a single time point within one month from the time of diagnosis (which also differs to a variable extent from the time of disease onset), rather than longitudinally. The inclusion of patients residing in isolation-hotels may have created a bias towards those with continued viral detection. While we showed that neither the presence nor the levels of antibodies correlated with clearance of viral RNA, this finding should be interpreted with caution with regard to its implication for immune protection, in the absence of antibody neutralization or sample infectivity data. Finally, we were unable to define disease severity according to accepted definitions (such as the national early warning score 2) due to a lack of information regarding patients' clinical presentation. However, the low rate of oxygen support required and COVID-19 directed therapy and the lack of ICU admissions, support the result as representing the serology patterns of mild COVID-19 cases. Despite these limitations, patients with mild disease constitute the majority of COVID-19 patients, hence focusing on a large cohort of these patients, the use of an ELISA assay which has been shown to be comparable with other major commercially-available assays (<https://www.fda.gov/medical-devices/emergency-situations-medical-devices/eua-authorized-serology-test-performance>; (21, 22)), along with the recently demonstrated lower antibody response in asymptomatic patients (18), support the generalizability of our findings.

Conclusions

Our findings, demonstrating the patient-to-patient variability and the general temporal pattern of SARS-CoV-2 IgG detection show that in patients with mild COVID 19, fever and chills along with basic inflammation-related markers, positively correlate with enhanced IgG response during the early period post diagnosis. Older age and higher CRP levels are associated with enhanced antibodies response among IgG positive patients. These findings, along with future analysis of additional innate immune activation markers, long-term follow-up, and functional antibody studies, could contribute to better prediction and understating of the immune response against SARS-CoV-2, and inform therapeutic donor plasma selection.

List Of Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 19; ARDS, acute respiratory distress syndrome; RT, reverse transcriptase; PCR, polymerase chain reaction; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay;

Declarations

Ethics Approval and Consent to Participate: The study was approved by the institutional Helsinki committee. Patient included after providing informed consent.

Consent for Publication: Not applicable

Data Availability: The datasets generated and/or analysed during the current study are not publicly available, due to patient discretion, but are available from the corresponding author on reasonable request.

Competing Interests: The authors have no conflict of interest to declare regarding this manuscript.

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Authors' Contribution: All authors participated in conducting the presented study. The manuscript was prepared by AK, AK, DW and YI and was revised and edited by all the other authors.

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Figures

Figure 1

Temporal pattern of SARS-CoV-2 IgG detection. Time from diagnosis is presented by weeks.