Ann Ig 2022 Jan-Feb; 34(1): 1-12. doi: 10.7416/ai.2021.2455. Epub 2021 June 11.

Antibody persistency and trend post-SARS-CoV-2 infection at eight months

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Key words: SARS-CoV-2, COVID-19, coronavirus, antibody trend, immunity
Parole chiave: SARS-CoV-2, COVOD-19, coronavirus, comportamento anticorpale, immunità

Abstract

Introduction. *A large amount of recent research has focused on the nature of immunity elicited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, particularly its robustness and the duration of protection it offers. As a vaccine's efficacy relies on its ability to induce a protective immune response, these questions remain particularly pertinent. An improved understanding of the immunity offered by the antibodies developed against SARS-CoV-2 in recovered patients is critical for the development of diagnostic tests and vaccines.*

Methods. *Our study aimed at the longitudinal analysis of antibody presence, persistence and its trend over eight months in a group of 30 COVID-19 recovered patients who tested positive by real-time quantitative PCR for SARS-CoV-2 in the period 1-30 March 2020. The subjects were divided into two groups based on disease severity: mild (n=17 subjects) and moderately-severe (n=13 subjects). The MAGLUMI 2019-nCoV lgM/lgG chemiluminescent analytical system (CLIA) assay was used to analyze these antibody titres.*

Results. *IgG antibody persistency was demonstrated in 76.7 % of the subjects (23 out of 30) at eight months post-infection. For the moderately-severe group, the titre trends for both IgM and IgG changed in a statistically significant way throughout the time period with IgM below and IgG above the set cut-off.*

Conclusions. *The results of this study highlight an important point in terms of the association between humoral immune response and disease severity. Patients who have experienced a relatively severe infection might develop a stronger immune response that could persist for a longer period.*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)

ISSN 1120-9135 https://www.annali-igiene.it

Introduction

The immunity offered by antibodies developed in recovered COVID-19 patients is a matter of ongoing debate and encompasses genuine concern for the future. Recent studies, as well as the media, have focused their attention on the role of vaccines offering immunity and persistence of humoral response ranging from six months (1) up to eight months (2, 3) post-infection. This study aimed at analyzing the antibody responses of 30 people, based in the Umbria region in Italy, who recovered from Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection over eight months through five sequential serological tests.

Methods

1. Study Design. A monocentric pilot longitudinal observational study was conducted on 114 subjects based in the Umbria region of Italy, who had tested positive by real-time quantitative polymerase chain reaction (RT-PCR) targeting E-gene, RdRP-gene, and N-gene for SARS-CoV-2 in the period between 1 and 30 March 2020. Blood samples were collected with the consent of patients and with the approval of the ethics committee of the Associazione Naso Sano (Ringgold Id: 567754, Document number ANS-2020/001). The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. All patients provided informed consent for the use of their data for research purposes. All identifying data were anonymized, according to the requirements set by the Italian Data Protection Code Legsl. Decree 196/2003). Written, informed consent was obtained from all subjects for voluntary participation. At the beginning of the study, 114 subjects, who had recovered from COVID-19, were invited to participate in serological testing to detect antibody levels. The demographic characteristics, blood groups, associated co-morbidities, clinical features, treatment undertaken, and dates pertaining to symptom onset and swab collections were recorded using a questionnaire. Out of these 114 subjects, only 30 subjects, who attended all follow-up visits were enrolled for the study. Sequential serum samples of these 30 subjects were collected at an accredited lab (Laboratory of Nuclear Lipid BioPathology, Centro Ricerche Analisi Biochimico Specialistiche, Perugia, Italy) over a period of eight months and the antibody titres were analyzed. The aim of this study was to investigate for presence, persistence, and trend of IgM and IgG developed against SARS-CoV-2 over time. As per the WHO guidelines, the subjects were divided into two groups, based on their disease severity: mild and moderately-severe (4).

Thirty subjects were followed up for 8 months through five sequential serological tests. The median (1st quartile – 3rd quartile) age was 39.0 [30.0-59.0] years for the "mild" disease severity group (n=17) and 55.0 [38.0-57.0] years for the "moderately-severe" disease severity group (n=13). The M: F ratio was 0.7 in the mild group and 0.4 in the moderately-severe group.

2. Analytical systems used in our study. The MAGLUMI® 2019-nCoV lgM/lgG chemiluminescent analytical system (CLIA) assay was used to analyse the antibody titres in these subjects. (New Industries Biomedical Engineering Co., Ltd [Snibe], Shenzhen, China) (5). These immunoassays were granted Emergency Use Authorization by the US Food and Drug Administration. As per the Assay Specification, 2019-nCoV IgM (CLIA) + 2019-nCoV IgG (CLIA) sensitivity is 95.6 % and specificity is 96.0 %. Measurements and interpretation of results were made according to the manufacturer's instructions. The results were reported as measured chemiluminescence values divided

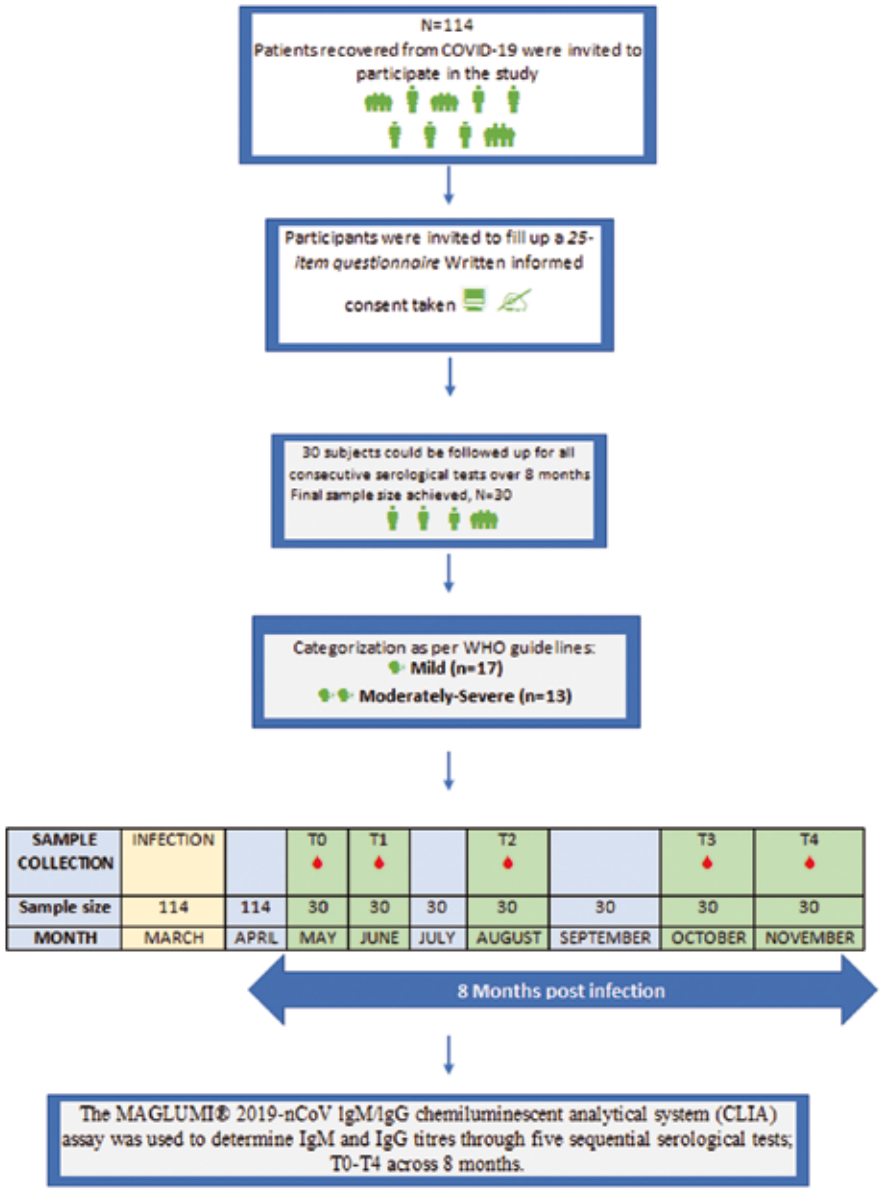

Figure 1 - A Block Diagram showing the Research Methodology Flowchart and the study timeline.

by the cut-off (absorbance/cut-off, S/CO): S/CO>1 was defined as positive and S/CO≤1 as negative (5). Time was treated as a factor and five different time points were defined: the first blood sample was collected in May, two months after infection (T0). Consecutive blood samples were collected at one month (T1), three months (T2), 5 months (T3), and 6 months (T4) after T0 in the months of June, August, October, and November, respectively. The methodology and timeline for the study are described in Figure 1.

3. Statistical analysis. The descriptive statistics for the main characteristics of the study group, including demographics, co-morbidities, laboratory data and treatment strategies were expressed as Median, [1st quartile – 3rd quartile] for continuous variables and as absolute frequency (column percentage) for the categorical variables (Table 1). The clinical features experienced during infection for both the severity groups were expressed as frequency (column percentage) (Table 2). Shapiro Wilks tested the normal distribution of the data. Chi-squared test was used to measure the association between disease severity and the categorical variables, while the Mann U Whitney test was used to assess the differences between groups for the continuous variables at each time point (Table 3). The Friedman test was applied to look for statistically significant differences over time between the two severity groups for IgM and IgG titres (Table 4). A bar plot was used to show the percentage of IgM and IgG positivity at

Table 1 - Descriptive statistics of the study sample (n=30) main characteristics expressed as Median, [q1-q3] quartile for continuous variables and absolute frequency and column percentage was reported for binary variables. The p-values result from Chi squared test and from Mann U Whitney test.

Variable	Mild	Moderate-Severe	p-value
	N=17	N=13	
Age [q1-q3] (years)	39.0 [30.0;59.0]	55.0 [38.0;57.0]	0.645
Sex			0.708
Male	7 (41.2%)	4 (30.8%)	
Female	10 (58.8%)	9 (69.2%)	
Blood Group			0.360
"O"	2 (11.8%)	4 (30.8%)	
Other	15 (88.2%)	9 (69.2%)	
Healthcare worker			0.599
Yes	8 (47.1%)	4 (30.8%)	
No	9 (52.9%)	9 (69.2%)	
Co-morbidities			
Diabetes			0.628
Yes	2 (11.8%)	3 (23.1%)	
No	15 (88.2%)	10 (76.9%)	
Hypertension			0.255
Yes	4 (23.5%)	6 (46.2%)	
No	13 (76.5%)	7 (53.8%)	
Cardiovascular disease			0.009
Yes	0 (0.00%)	5 (38.5%)	
No	17 (100%)	8 (61.5%)	
Asthma / seasonal allergies			0.355
Yes	4 (23.5%)	1 (7.69%)	
No	13 (76.5%)	12 (92.3%)	
Laboratory data			
Total Leucocytes (x 10^3/ul)	5.88 [5.19;6.69]	6.22 [5.72;6.88]	0.503
Total Lymphocytes (x 10^3/ul)	1.89 [1.66;2.34]	1.96 [1.72;2.68]	0.490
Eosinophil Count (%)	2.30 [1.50;3.10]	3.20 [2.40;3.40]	0.049
Total Platelets (x 10^3/ul)	229 [224;271]	247 [224;284]	0.558

Variable	Mild	Moderate-Severe	p-value
	N=17	N=13	
Age [q1-q3] (years)	39.0 [30.0;59.0]	55.0 [38.0;57.0]	0.645
Treatment strategies			
Admission			0.433
Yes	0 (0.00%)	1 (7.69%)	
No	17 (100%)	12 (92.3%)	
Antibiotics			0.165
Yes	5 (29.4%)	8 (61.5%)	
No	12 (70.6%)	5 (38.5%)	
Steroids			0.179
Yes	0 (0.00%)	2 (15.4%)	
No	17 (100%)	11 (84.6%)	
Oxygen			0.002
Yes	2 (11.8%)	9 (69.2%)	
No	15 (88.2%)	4 (30.8%)	
Viral Clearance [q1-q3] days	18 [17-21]	20 [18-28]	

each time point (Figure 2A). The positivity cut-off for CLIA was set at >1.00 and the median titre trends were plotted for IgM and IgG, for both severity groups (Figure 2B). Post-hoc analysis was performed with the Wilcoxon-signed ranks-test with Bonferroni-correction. All tests were two-sided, and a level of statistical significance was set at $p < 0.05$. All the statistical analyses were performed using R software environment for statistical computing and graphics version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Results

1. General characteristics of the study population

Thirty subjects were followed-up for 8 months through five sequential serological tests. The median (1st quartile – 3rd quartile) age was 39.0 [30.0-59.0] years for the mild group (n=17) and 55.0 [38.0-57.0] years for the moderately-severe (n=13) group. The M:F ratio was 0.7 in the mild group and 0.4 for the moderately-severe group. The majority of the patients were healthcare workers (12 patients, 40%) followed by general employees (7 patients, 23.3%), retired (5 patients, 16.66 %), businessman/woman (2 patients, 6.66 %), students (2 patients, 6.66 %), homemakers (2 patients, 6.66 %). The subjects with moderately-severe disease were older than those with mild disease (median age, 55 vs. 39 respectively) and were more frequently affected by hypertension (46.2 % vs. 23.5 % respectively), diabetes (23.1% vs 11.8% respectively) and cardiovascular disease (38.5% vs 0% respectively, p value= 0.009). At the time of infection, when compared with the mild group, the moderately-severe group also presented more frequently with fever (100% vs 88.2%, p value=0.4), shortness of breath (84.6% vs 11.8% p value <.001), fatigue (84.6% vs 35.3%, p value = 0.021), headache (61.5% vs 47.1%, p value=0.676), chest pain (38.5% vs 11.8%, p value= 0.190), muscle ache (84.6% vs 70.6%, p value=0.427) and diarrhea (53.8% vs 23.5%, p value=0.132). However, loss of smell was a more common finding in the mild group rather than the moderately-severe group (76.5% vs 69.2%, p value = 0.698).

Table 2 - Clinical features experienced during infection expressed as frequency (Column percentage) for both the severity groups; mild (n=17) and moderately-severe (n=13) of the study sample (n=30).

Clinical profile	Mild	Moderate-severe	P value
	N=17	N=13	
Fever			0.492
Yes	15 (88.2%)	13 (100%)	
No	2 (11.8%)	0 (0.00%)	
Rhinorrhea			0.705
Yes	5 (29.4%)	5 (38.5%)	
No	12 (70.6%)	8 (61.5%)	
Dry cough			0.930
Yes	11 (64.7%)	8 (61.5%)	
No	6 (35.3%)	5 (38.5%)	
Sore throat			0.809
Yes	5 (29.4%)	4 (30.8%)	
No	12 (70.6%)	9 (69.2%)	
Shortness of breath			<0.001
Yes	2 (11.8%)	11 (84.6%)	
No	15 (88.2%)	2 (15.4%)	
Fatigue			0.020
Yes	6 (35.3%)	11 (84.6%)	
No	11 (64.7%)	2 (15.4%)	
Headache			0.676
Yes	8 (47.1%)	8 (61.5%)	
No	9 (52.9%)	5 (38.5%)	
Skin eruption			0.290
Yes	1 (5.88%)	3 (23.1%)	
No	16 (94.1%)	10 (76.9%)	
Muscle ache			0.427
Yes	12 (70.6%)	11 (84.6%)	
No	5 (29.4%)	2 (15.4%)	
Diarrhea			0.132
Yes	4 (23.5%)	7 (53.8%)	
No	13 (76.5%)	6 (46.2%)	
Conjunctivitis			0.427
Yes	5 (29.4%)	2 (15.4%)	
No	12 (70.6%)	11 (84.6%)	
Loss of smell			0.698
Yes	13 (76.5%)	9 (69.2%)	
No	4 (23.5%)	4 (30.8%)	
Loss of taste			0.970
Yes	12 (70.6%)	10 (76.9%)	
No	5 (29.4%)	3 (23.1%)	
Chest pain			0.190
Yes	2 (11.8%)	5 (38.5%)	
No	15 (88.2%)	8 (61.5%)	

Table 3 - IgM and IgG titres for mild (n=17) and moderately-severe (n=13) groups evaluated at each time point, T0-T4 where the first blood sample was collected two months after infection in the month of May 2020 (T0) and then, one month (T1), three months (T2), five months (T3), six months (T4) after T0.
The p-values result from Mann U Whitney test.

Variable	Mild	Moderately-severe	P-value
	n=17	N=13	
IgM.T0	0.50 [0.46;0.52]	0.64 [0.64;1.07]	<0.001
IgM.T1	0.61 [0.52;0.64]	0.70 [0.66;1.44]	0.006
IgM.T2	0.36 [0.18;0.53]	0.66 [0.24;0.84]	0.194
IgM.T3	0.23 [0.17;0.33]	0.59 [0.31;0.82]	0.030
IgM.T4	0.21 [0.18;0.35]	0.54 [0.25;0.81]	0.057
IgG.T0	1.84 [0.68;3.54]	2.37 [1.14;20.7]	0.621
IgG.T1	1.81 [0.56;2.90]	1.48 [0.83;20.6]	0.832
IgG.T2	1.70 [0.88;5.02]	4.10 [2.38;16.1]	0.269
IgG.T3	3.05 [0.50;3.80]	2.25 [1.04;10.2]	0.724
IgG.T4	3.13 [1.05;3.66]	1.89 [0.83;8.53]	0.724

Table 4 - IgM and IgG titres for mild (n=17) and moderately-severe (n=13) groups evaluated at each time point, T0-T4 where the first blood sample was collected two months after infection in the month of May 2020 (T0) and then, one month (T1), three months (T2), five months (T3), six months (T4) after T0.
The p-value results from Friedman test. PWC= pairwise multiple comparisons.

Variable	T0	T1	T2	T3	T4	p-value	PWC
Mild							
IgM	0.50 [0.46;0.52]	0.61 [0.52;0.64]	0.36 [0.18;0.53]	0.23 [0.17;0.33]	0.21 [0.18;0.35]	<0.001	T0≠T2 T0≠T3 T0≠T4 T1≠T2 T1≠T3 T1≠T4
IgG	1.84 [0.68;3.54]	1.81 [0.56;2.90]	1.70 [0.88;5.02]	3.05 [0.50;3.80]	3.13 [1.05;3.66]	0.205	
Moderately-severe							
IgM	0.64 [0.64;1.07]	0.70 [0.66;1.44]	0.66 [0.24;0.84]	0.59 [0.31;0.82]	0.54 [0.25;0.81]	<0.001	T0≠T2 T0≠T3 T0≠T4 T1≠T3 T1≠T4 T3≠T4
IgG	2.3 [1.14;20.7]	1.48 [0.83;20.6]	4.10 [2.38;16.1]	2.25 [1.04;10.2]	1.89 [0.83;8.53]	0.013	T0≠T4 T2≠T3 T2≠T4 T3≠T4

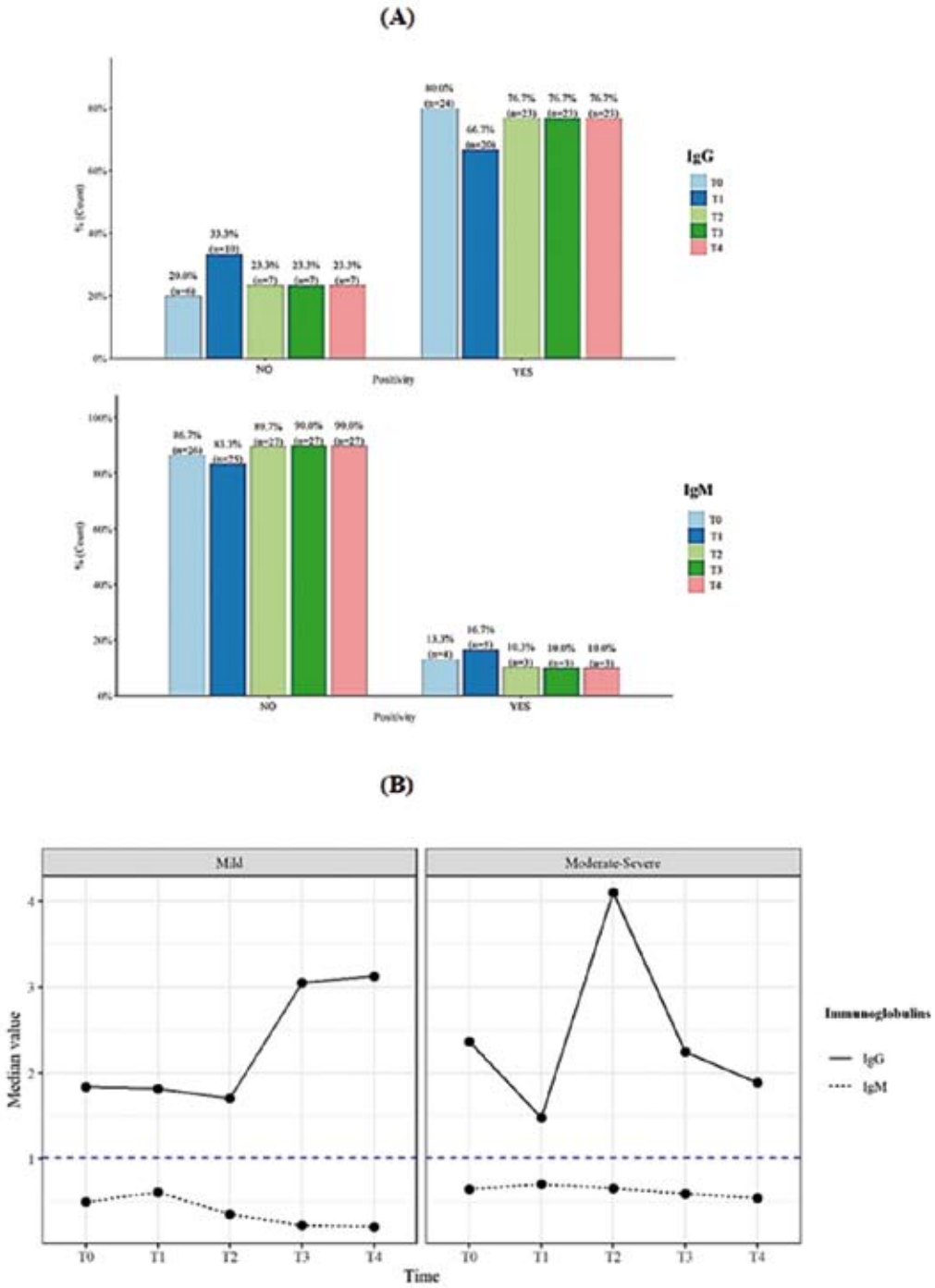

Figure 2 - Bar plot showing IgM and IgG positivity for all subjects of the study group (N=30) (CLIA cut-off >1.00) in (A) and the Median trends for IgM and IgG within the two disease severity groups: mild and moderately-severe. The dashed horizontal line shows the threshold (CLIA positivity Cut-off: >1) for the sample in (B). Time discretization is the following: basal values were collected in May 2020 (T0) and then, one month (T1), three months (T2), five months (T3), six months (T4) after T0

2. Serologic status and viral clearance during hospitalization

The median time taken for viral clearance, calculated by the number of days between the first positive PCR test and the first negative PCR test was 18 [17-21] days for the mild group and 20 [18-28] days for the moderate-severe group (Table 2).

3. Serologic status at 8 months post-infection

At eight months post-infection, not a single case of reinfection was reported and the antibody titres for the 30 subjects were followed-up. The percentage of IgM and IgG positive subjects were analyzed over time and results were expressed as bar plots (CLIA positivity limit set at > 1.00). IgM was not detected in 27 out of 30 (90.7%) participants. IgG antibody persistency was demonstrated in 23 out of 30 participants (76.7%) at T4, eight months post-infection, expressed as bar plots (Figure 2A). The median titre trends were plotted for IgM and IgG, for both severity groups across 8 months (Figure 2B). For the mild group, the IgM titre median trend stayed below the set cut-off throughout the time and changed in a statistically significant way. The IgG titre trend dipped at T2 only to return to an almost linear trend at T3, but did not change in a statistically significant way. For the moderately-severe group, the titre trends for both IgM and IgG changed in a statistically significant way throughout 8 months, with IgM below and IgG above the set cut-off. The IgG titre trend in this group dipped at T1 and peaked at T2.

Discussion

Since there are no long-term studies yet regarding the longevity of immunity offered by vaccination, a clear understanding of post-SARS-CoV-2 humoral response is necessary to predict the success of a worldwide vaccination strategy. Out of the four structural proteins of the SARS-CoV-2 beta coronavirus, namely: Spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein, the S protein is responsible for eliciting potent neutralizing antibody responses. The antibodies directed against the receptor-binding domain (RBD) of the S1-subunit has neutralizing capacity and, therefore, could "prevent infection" (6, 7).

Several studies have demonstrated the presence, as well as the persistence, of antibodies up to 8 months post-infection (8, 9). Moreover, an interesting study by Zhang et al. not only demonstrated persistence of antibody response, but also hinted towards a significant reduction in the antibody titres over time (10). Similar findings from other studies have raised questions across the scientific community regarding the longevity of humoral immune response post-infection (11-13).

Although a similar decrease in antibody titres was observed in our study, we would hypothesize it to be a "contraction of the immune response" with "development and persistence of B cell memory" rather than "waning of immunity", as was described by Hartley et al. (9).

Another important point that needs to be highlighted is the association between humoral immune response and disease severity. Patients who might have experienced a relatively severe infection may develop immunity that could persist for a longer duration. This observation was in accordance with a study by Choe et al., demonstrating an association between prolonged viral shedding period (severe disease) and long-term antibody positivity (2).

In this study, the IgM titre trend for the mild group stayed below the set cut-off throughout the time, but changed in a statistically significant way. The IgG titre trend dipped at T2 only to return to an almost linear trend at T3 but did not change in a

statistically significant way. Similar findings were observed in previous studies (14, 15). For the moderately-severe group, the titre trend for both IgM and IgG changed in a statistically significant way throughout the time, with IgM below and IgG above the set cut-off. The IgG titre trend in this group dipped at T1 and peaked at T2. This dip experienced for both mild and moderately-severe groups for IgG might be due to contraction of the immune response and may not indicate waning of immunity (16).

A systematic review and meta-analysis conducted by Bastos et. al demonstrated that the pooled sensitivity with CLIA was 97.8% as compared to 84.3% with ELISA (17). CLIA immunoassay has been used for determining antibody titres in this study, which is more sensitive when compared to ELISA.

The strengths of our study include a diverse sample quality involving multiple family clusters of different age groups from the same region, the adoption of CLIA as a method of analyzing the antibody titres and a relatively long-term follow up of 8 months post-infection.

The limitations of our study included its small sample size of 30 patients and the antibody titre analysis, which might not reflect the overall immunity, as some studies have proven that both, lymphoid and myeloid immunity, have a role to play in offering protection against secondary infections (3). While humoral immunity comprises the action of antibodies developed against the infection, cell-mediated immunity involves the action of T cells.

Conclusion

As per the Health Authorities, the Umbria region in Italy is currently experiencing a surge in daily cases due to multiple variants; the United Kingdom (B.1.1.7), Brazil (P.2 and P.1), and South Africa (three variants of the B.1.351 lineage) (18). There have been studies indicating that vaccines are successful only in partial cross-neutralization of the novel variants. Therefore, booster doses or reformulation of the existing vaccines shall be required to include diverse spike sequences to tackle these variants (19, 20).

Since there have been zero cases of re-infection in our study group, we can hypothesize that the protection offered by the antibodies developed against the initial wild-type SARS-CoV-2 in our study subjects may still have a role in providing protection against these recent variants. In such a scenario, where the availability of vaccines could be scarce, individuals with a prior history of natural infection need not be prioritized for vaccination. Knowledge of the duration of humoral immunity to SARS-CoV-2 is essential for the prediction of immunity offered and interpretation of seroepidemiologic data.

Acknowledgments: The Association Naso Sano is grateful to all the members of the Association Naso Sano TASK FORCE and the international members for their valuable input. We thank the health personnel who allowed the constant monitoring and related sampling in the EUROMEDICA and CRABION diagnostic centers. The study was also made possible by the collaboration of the Rotary Club Fortebraccio Montone.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests: The authors declare that there is no conflict of interests.

Ethics statement: Human samples were collected with the consent of patients and with the approval of the Ethics Committee of the Associazione Naso Sano (RINGGOLD ID: 567754) (ANS-2020/001). The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. All patients provided informed consent for the use of their data for research purposes. In any case, data were previously anonymized, according to the requirements set by the Italian Data Protection Code (Legisl. Decree 196/2003).

Data availability statement*:* The datasets generated during and/or analyzed during the current study are available from the corresponding author on motivated request.

Riassunto

Durata e comportamento degli anticorpi otto mesi dopo l'infezione da SARS-CoV-2

Introduzione. Gran parte della ricerca più recente si è focalizzata sulla natura dell'immunità provocata, nei pazienti di COVID-19, dall'infezione da Coronavirus SARS-CoV-2, ed in particolare sulla sua consistenza e sulla durata della protezione che induce. Dato poi che l'efficacia di qualunque vaccino dipende dalla sua capacità di provocare una risposta immunitaria protettiva, il tema appare di una pertinenza evidente. Una comprensione più approfondita dell'immunità offerta dagli anticorpi che si sviluppano nei confronti del SARS-CoV-2 nei soggetti che guariscono è quindi fondamentale per lo sviluppo di test diagnostici e di vaccini.

Metodi. Il nostro studio si è proposto di condurre un'analisi longitudinale della presenza degli anticorpi, della loro persistenza e del loro comportamento tendenziale negli otto mesi dopo la guarigione, in un gruppo di 30 soggetti guariti e divenuti positivi per gli anticorpi specifici, misurati con il test PCR quantitativo in tempo reale per il SARS-CoV-2 nel periodo 1-30 Marzo 2020. Questi soggetti sono stati suddivisi in due gruppi in base alla gravità della malattia: gravità lieve (17 soggetti) e moderatamente elevata (13 soggetti). Per misurare i loro livelli anticorpali è stato usato il CLIA (sistema analitico a chemiluminescenza MAGLUMI 2019-nCov IgM/IgG).

Risultati. La persistenza degli anticorpi IgG è stata documentata in 23/30 dei soggetti (76,7%) a 8 mesi dall'infezione; nei soggetti moderatamente gravi il comportamento tendenziale dei titoli sia degli IgM che degli IgG è cambiato significativamente durante quel periodo di 8 mesi, con gli IgM al di sotto e gli IgG al di sopra del cut off.

Conclusioni. I risultati di questo studio sottolineano un aspetto importante per quanto riguarda l'associazione tra la risposta immune umorale e la gravità della malattia: i soggetti che hanno sofferto una forma relativamente più grave della malattia sono quelli che hanno sviluppato una più forte risposta immune, persistente per un periodo piu lungo.

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