Kinetics of the SARS-CoV-2 antibody response in immunocompetent convalescent patients: nationwide multicenter 15-month follow-up cohort study

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Abstract

The comprehension of a long-term humoral immune response against the SARS-CoV-2 virus can shed light on the treatment and vaccination of the disease, improve the control of the pandemic infection. We assessed the antibodies against SARS-CoV-2 nucleocapsid (N) protein in 1441 COVID-19 convalescent patients within 15 months longitudinal nationwide multicenter study from middle-developed country.

92.7 % of convalescent patients' serum contained antibodies against N protein and only 1.3% of patients had a delayed antibody response. In the majority of convalescent patients' the durability of antibodies lasted more than one year. The kinetics of neutralizing antibodies took a bell-shaped character – increased first 25-30 weeks, then started to decrease, but were still detectable for more than 15 months. Summing up, we found that anti-SARS-CoV-2 humoral response levels, in particular the level of peak antibodies, correlate with age, older patients developing more robust humoral response independently from sex, disease severity and BMI.

Highlights

SARS-CoV-2 infection induce rapid anti-SARS-CoV-2 antibodies in almost all infected patients (92.7%) with a durable more than 15 month's humoral response.

Anti-SARS-CoV-2 humoral response was positively correlated with the disease SARS-CoV-2 severity.

Anti-SARS-CoV-2 humoral response levels, in particular the level of peak antibodies, correlate with age, older patients developing more robust humoral response independently from sex, disease severity and BMI.

Introduction

At the end of 2019, patients with viral symptoms and pneumonia were found in Wuhan, China, leading to the discovery of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). More than 169 million cases and 3.5 million deaths were reported from SARS-CoV-2disease up to May 28, 2021.

Apprehending the immune responses and the features of antibody production after SARS-CoV-2 are key points in developing an effective treatment. Hence, the significance of improved understanding of immune response to SARS-CoV-2 virus is indisputable. There are confirmed facts that all arms of the immune responses to SARS-CoV-2, although many questions remain uncertain [1].

One of the central issues of the disease is the probability of reinfection and long-term immunity. It is still unclear whether or not getting infected with SARS-CoV-2 in humans nullifies any chances of reinfection and if so for how long. A limited number of documented and confirmed cases of re-infections are registered in immunocompetent individuals [2 3 4]. The resistance to re-infection may be less a function of the durability of the immune response, than the peculiarities of the individual response or the breadth of

immunity. During reinfection, high avidity IgG and elevated titers of neutralizing antibody were discovered. This indicates that the first infection's priming of immunity made for a more robust antibody response in the second infection [4].

As it is well known, during the common human coronaviruses neutralizing antibodies are induced and last for years, providing protection from reinfection or attenuated disease, even if individuals get re-infected [5]. Long-term follow-up studies of SARS-CoV1 showed the decline of antibody titers over 2 to 3 years, although in some patients neutralizing antibodies were detected 12 years after infection [6]. Thus, the decay in antibody production after SARS-CoV-2 infection cannot be extrapolated from early time points, demonstrating the need for longer-term follow-up studies [7]. Seroconversion and virus neutralization between 5 and 14 days after symptom onset have been well-documented, but scarce data are available about the durability of antibody production and immunity after a long period of SARS-CoV-2 infections. Contraindicating conclusions exist regarding the duration of immunity, with a rapid decay of protective antibodies within a 3-4 months [8 9 10 11] and in opposite persistence of antibodies more than 5-6 months.

Several factors have been evaluated in the relation to anti-SARS-CoV2 antibody response, such as disease severity [12 13 14], BMI [12 15 16], sex [12 13 14 17] and age [12 13 14 15 18 19 20], but factors associated with long term serological response are not fully evaluated. Therefore, in this study, we aimed to describe the seroprevalence and kinetics of SARS-CoV-2 N protein antibodies in convalescent immunocompetent patients and analyzed the factors associated with the seropositivity and the humoral response persistence.

Results

Patients' general characteristics

The study group included 1441 SARS-CoV-2 convalescent patients, out of which 74.1% were female (n=1004 patients) with mean age 47±15 years and BMI 27±5.2 kg/m^2. SARS-CoV-2 infection was asymptomatic in 104 cases (7.2%), mild in 846 cases (58.7%), moderate in 429 cases (29.8%) and severe in 62 cases (4.3%). The most common symptoms of SARS-CoV-2 infection were fever (n=1089; 80.4%), *fatigue* (n=924; 68.2%), headache (n=626; 46.2%), myalgia (n=531; 42.1%), cough (n=467; 34.5%), loss of taste (428; 31.6%) and olfactory impairment (n=537; 39.6%). The most common comorbidities were arterial hypertension (18.9%), autoimmune thyroiditis (6.3%) and diabetes mellitus (5.6%) without any cases of neoplasia or hematological disease or any immunosuppressive therapies. During the median follow-up of 44 weeks, only 1 (1.9%) convalescent patient developed a reinfection 12 months after of the first positive PCR testing and none received anti-SARS-CoV-2 vaccine (**Supplementary Fig. 1**).

Seroprevalence, seroconversion and kinetics

Anti-SARS-CoV-2 IgG antibodies measured over the time are represented in Figure 2. The serum of 92.7% (n=1336) of SARS-CoV-2 convalescent patients contained anti-SARS-CoV-2 IgG antibodies against nucleocapsid antigen (mean level 66.42±1.04). Notably, there was a substantial interindividual variation in antibodies levels varying importantly between patients. The anti-SARS-CoV-2 IgG antibodies levels in convalescent patients were significantly increased in comparison to pre-pandemic and pandemic healthy controls (**Supplementary Figure 2**). The median time to anti-SARS-CoV-2 IgG antibodies positivity was 16 weeks (ranges 3-61) and only 13 (1.3%) patients have a delayed antibody response (**Supplementary Figure 3**).

The levels of anti-SARS-CoV-2 antibodies gradually increased up to 5-6th months and the decline of the antibody level starts from 7th month, nevertheless, the mean level remains rather high up to 15th month (Figure 3). It is significant to mention that even in the group of convalescent patients who were tested after 52 weeks (up to 77 weeks), 95.3% of 211 samplings were still positives. Over the entire 18 week period of follow-up (5-54 weeks), only in 12 patients (1.7%) from 694 convalescent patients who were sampled at least 3 times, initially existing antibodies disappeared (**Supplementary Figure 4**).

Only 89 convalescent patients (6.2%), did not produce any anti-SARS-CoV-2 IgG antibodies during the consecutive measurements. Analyzing the factors associated with the absence of SARS-CoV-2 antibodies positivity among the time to antibodies testing, age, sex, disease severity and BMI, the younger age (43.4±15 years in seronegative vs 48.1±15 in seropositives; p=0.0028), the male sex (34% in seronegative vs 25% in seropositives; p=0.03), less severe disease (moderate and severe disease in 13% in seronegatives vs 65% in seropositives; p<0.0001) and the less BMI (25.5±4.5 vs 27.2±5.2 in seropositive; p=0.0076) were significantly associated with the probability to be seronegative for anti-SARS-CoV-2 IgG antibodies. In multivariate analysis only disease severity was significantly associated with the probability to develop SARS-CoV-2 antibodies with odds ratio 0.31 (0.17; 0.59) (p=0.004).

To describe the SARS-CoV-2 antibodies kinetics and correlate to disease severity, age, sex and BMI, we used a mixed statistical model previously described. The peak of antibodies response was estimated to 35UI (95% CI 29; 42), with decay rate at 1.11UI by week (95%CI 1.04; 1.17) (Figure 4A-C). Among factors associated with SARS-CoV-2 antibodies kinetics, peak of antibodies were significantly more important in females, moderate and severe SARS-CoV-2 disease and aged more than 60 years (Table 1), whereas the decay rates were not significantly different (Figures 4A-C). As the disease severity was significantly correlated with age (p<0.0001), we analyzed SARS-CoV-2 antibodies kinetics in patients groups considering the median age and the disease severity (age< 48 years with asymptomatic and mild Covid-19 infection and those ≥ 48 years and moderate to severe infection), demonstrating a significant correlation with only age (p=0.0089) and not disease severity when adjusted to age (p=0.22). Anti-SARS-CoV-2 antibody titers of samples during the first month after a positive PCR were considered according to 25th and 75th percentiles and thus classified in low responders (titers of IgG up to 25th percentiles; n=24), middle responders (titers of IgG 25-75 percentiles; n=53) (COI value 10-75) and high responders (n=24) (titer above 75th percentile; COI value above 76) (Figure 5). Interestingly, anti-SARS-CoV-2 antibody titers remained in the same levels in all these 3 groups during the subsequent monthly testings.

Table 1
Factors associated with the kinetics of SARS-CoV-2 antibodies.

	SARS-CoV-2 antibodies peak (k, (log10 UI)) (95%CI)	P value	SARS-CoV-2 antibodies decay rate (a, (log10 IU)/week) (95% CI)	P value (a=0)
Sex male	1.40 (1.24; 1.56)	ref		ref
Sex female	1.60 (1.50;1.69)	0.042	0.051 (0.024;0.082)	0.21
Severity	1.45 (1.16;1.74)	ref	0.063 (-0.026;0.152)	ref
Asymptomatic	1.42 (1.32;1.53)	0.86	0.059 (-0.027;0.91)	0.93
Mild	1.78 (1.62;1.94)	0.053	0.015 (-0.035;0.64)	0.35
Moderate	1.81 (1.41;2.21)	0.16	0.035 (-0.086;0.156)	0.71
Severe				
Age	1.37 (1.20;1.55)	ref	0.074 (0.019;0.129)	ref
<35 years	1.50 (1.33;1.67)	0.30	0.074 (0.021;0.126)	0.99
35-47 years	1.70 (1.52;1.87)	0.0097	0.044 (0.008;0.0.96)	0.45
48-59 years	1.67 (1.50;1.84)	0.018	0.004 (0.048;0.055)	0.068
≥60 years				
Age<48 years and asymptomatic -mild disease	1.31 (1.12;1.50)	ref	0.066 (0.008;0.125)	ref
Age≥48 years and asymptomatic -mild disease	1.65 (1.39;1.91)	0.042	0.034 (-0.046;0.114)	0.52
Age≥48 years and moderate-severe disease	1.69 (1.56;1.83)	0.0015	0.022 (-0.019;0.0.63)	0.23

Discussion

In this large nationwide multicenter study from middle-developed European country, have been analyzed the long-term humoral response to SARS-CoV-2 infection and the factors associated with a durable response. Based on an extensive literature review, it is noticeable that this study is one of the most long-drawn and broad studies of the dynamic changes in anti-SARS-CoV-2 antibodies against N protein in convalescent SARS-CoV-2 patients. There is demanding importance to explain the robustness, the survival, and the functionality of anti-SARS-CoV-2 antibody response in different cases to discover the durability and protective features of antibodies in case of reinfection.

This serological 15-month cohort study prompts us to make several important conclusions about the humoral response after SARS-CoV-2 infection. First, SARS-CoV-2 infection induces a complete and rapid humoral response in almost all infected patients (92.7%), whereas only few patients developed a delayed humoral response (1.3%). Another study analyzing a shorter 180-day serological response to SARS-CoV-2 infection showed a relatively good humoral response, with much less seronegative patients and more proportion of delayed responses [21]. Only a small percentage of convalescent patients (1.7%) experienced a complete disappearance of antibodies during the 15 month follow-up, relatively similar to a previous study of 123 infected patients [19], however, followed-up only for 30 weeks. According to various authors, the persistence of antibodies depends on many factors, including the viral type [22], individual features, and environmental factors. This description serves to explain varying courses of the disease and the immune response in different individuals [23].

Second, analyzing the seropositive and seronegative SARS-CoV-2 convalescent patients, the severe form of the disease appeared as an independent factor to develop anti-SARS-CoV-2 humoral durable response. Several studies in other viral diseases, and also those including severe SARS-CoV-2 infected cases showed higher levels of anti-SARS-CoV-2 humoral response in more severe disease.

Third, initially different levels of induced SARS-CoV-2 antibodies remain stable at their levels during the 15-month follow-up. Based on the report of Nag et al. (2020) and Long et al. (2020) SARS-CoV-2 IgG antibodies degrade quickly over one to three months, possibly resulting in reinfections [10 11]. According to Dispinseri et al (2021), the titer of neutralizing antibodies dwindled rapidly after 5-8 weeks [24]. In contrast, our investigation showed the stability of anti-SARS-CoV-2 antibodies against nucleocapsid protein up to 25-30 weeks. Data similar to our results showing the increase of antibody levels were in another study analyzing 5 month humoral response (2021) [25]. Summarizing our data, we confirm that the level of anti-SARS-CoV-2 neutralizing antibodies takes bell-shaped character, continuously growing up to 5-6 months, remaining stable for a few months and slowly decreasing, but remaining to be detectable up to 60 weeks.

Collectively, our data demonstrates that regardless of the initial level of IgG, antibody production increases in the first stages. Depending on the point of departure in terms of anti-SARS-CoV-2 IgG level, the "future journey" of antibodies differs. Based on the anti-SARS-CoV-2 antibodies titer, we divided convalescent patients into 3 groups: low, middle and high responders. The findings affirm the hypothesis that the magnitude of antibody response in high responders remains higher throughout the whole period of antibody generation compared to low and middle responders, even we did not assess in this study their correlation with their functionality or avidity.

Another meaningful quest in the SARS-CoV-2 research is to discover correlations of the immune response with various individual factors such as age, sex or disease severity. In an Italian study, of healthcare professionals, a higher prevalence of positive IgG was found in females [26] .BMI did not influence the frequency of IgG-positivity in individuals, but it was directly proportional with the plasma concentration. In older patients (>60 year), the frequency of IgG positivity drops, but when assessing the difference of

IgG plasma levels across age ranges, an increased level of plasma IgG with older age is found [26] .Few studies found more important early increase of SARS-CoV-2 antibodies in men, but later in the disease the antibody levels were equal between sexes. In some studies, no association or even negative association between BMI and anti-SARS-CoV-2 antibodies was observed [27 28]. In contrary, we can affirm that the levels of SARS-CoV-2 humoral response, in particular the antibodies peak level, were significantly more important in older patients, regardless of their sex, disease severity and BMI.

The capability of reacting to infections decaying with age is a well-known fact. Besides the change of the functional types of T and B cells and the immune balance in the aging population, fewer cells able to identify and fight against new infections are produced with the age [29 30] .To form a completely new immune response to a novel infection is one of the weakened capacities of the elderly. The basis for this is the decline of naïve T cells which are required to start an entirely new immune response due to the shrinking of the thymus with age [31]. We hypothesized that the age-related changes to T cell immunosenescence can be the reason for the compensator increase of humoral immune response and antibody production in older individuals during the COVID-19. On the other hand, there are studies that shown the slower generation and lower virus neutralizing capacity of antibodies against attenuated yellow fever virus vaccine compared with the young population [30]. Therefore, we suggest that the high titer of antibodies in the elderly is compensation of the lower virus neutralizing capacity and low affinity of antibodies.

The condition that SARS-CoV-2 is a novel virus and older adults have not faced it ahead and makes vaccination more challenging. Nevertheless, the high level of stable humoral immune response in the elderly, which was confirmed by our study, gives a hope that immune memory can give a chance for effective vaccination. Future studies are needed to evaluate the neutralizing capacity of these antibodies in the older population.

Methods

Samples

In this prospective nationwide study, 1441 consecutive SARS-CoV-2 convalescent patients were recruited from all 10 regions of Armenia, and capital Yerevan city from August 2020 to June 2021. The inclusion criteria were (i) recent SARS-CoV-2 infection (compatible clinical features with positive RT– PCR result on nasopharyngeal swab samples), (ii) convalescent patients without any clinical symptoms equivocal of SARS-CoV-2 infection at the time of samples collection and (iii) absence of any induced or inherited immunodeficiency (HIV infection, neoplasia, hematological diseases, or immunosuppressive therapies).

Two groups of healthy donors were included in the study. The first, “pre-pandemic control group” consists of serum samples of 71 healthy donors before SARS-CoV-2 pandemic period (from 2017 up to February 2020), the second “SARS-CoV-2 pandemic group” consist of serum samples of 150 healthy donors throughout the SARS-CoV-2 pandemic period (started from March 2 of 2020).

SARS-CoV-2 convalescent patients were examined for anti-SARS-CoV-2 antibodies after 3-4 weeks of positive PCR testing, and then monthly up to 19 months (Figure 1A-C). During the study inclusion period, 4266 serum samples of 1441 convalescent patients were collected at different times after SARS-CoV-2 infection (Figure 1B-C). The number of SARS-CoV-2 convalescent patients for the 4th, 5th, 6th and 7th months overpassed the threshold of the national population study for Armenia (>384). Healthy pre-pandemic control and SARS-CoV-2 pandemic donors were sampled only once.

Patient's general characteristics, SARS-CoV-2 infection features, comorbidities and treatments were recorded at the time of first sample testing.

Serological assay

Serum samples of each patient were analyzed for Anti-SARS-CoV-2 with commercially available "**Elecsys**" assay from *Roche Diagnostics* for *in vitro* detection of high-affinity IgG antibodies against full-length nucleocapsid (N) antigen of SARS-CoV-2. Based on producer instructions, results were automatically determined in the form of a cutoff index (COI), with COI quantitative values and COI <1 were considered as negative, and ≥1 as positive result.

Ethics

This study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of Yerevan State Medical University (N 8-2/20; 02.07.2020). Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the IBM_22.0.0 SPSS statistical package (IBM, Armonk, NY) and SAS v9.4 (SAS Institute, Cary, NC). Continuous variables with normal distribution were presented as means, standard deviation (SD), whereas categorical variables as numbers and percentages. The persistence of anti-SARS-Cov-2 levels over time was estimated using non-linear mixed effects models that estimate the peak and the rate of antibodies decay [32]. Individual antibody data measured during the 15-month study period were modeled using a power law model, given by: f (t) = k − a log (c + t) (1) where *f (t)* is the log antibody titer at time of post infection (starting from t0= 4 weeks), *k* is the peak log level, *a* is the decay rate, and *c* is an arbitrary small constant (set to 1). The models were fitted by a mixed effects method, where *k* and *a* are random effects, allowed to be patient specific and are assumed to be drawn from *a* bivariate normal distribution. This allowed a prediction of the antibody dynamics to be made for each person. Predicted results over time are reported as GMTs. Parametric bootstrap was used to estimate confidence intervals. A logistic regression model was used to derive multivariable-adjusted odds-ratio estimates of factors associated with a negative serology. All p values were from 2-tailed tests, and results were deemed statistically significant with $P<0.05$.

Declarations

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Ethics declarations

Competing interests

AM is investigator of CELGENE, ROCHE, CHUGAI founded trials with APHP and Hopital 15-20 promotion; AM received several fees for congress travels and experts' use from LFB, SANOFI, SHIRE, and CELGENE.

KY is principal investigator of ROCHE IIS named "COQOS".

There is no competing interest for the remaining authors

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Figures

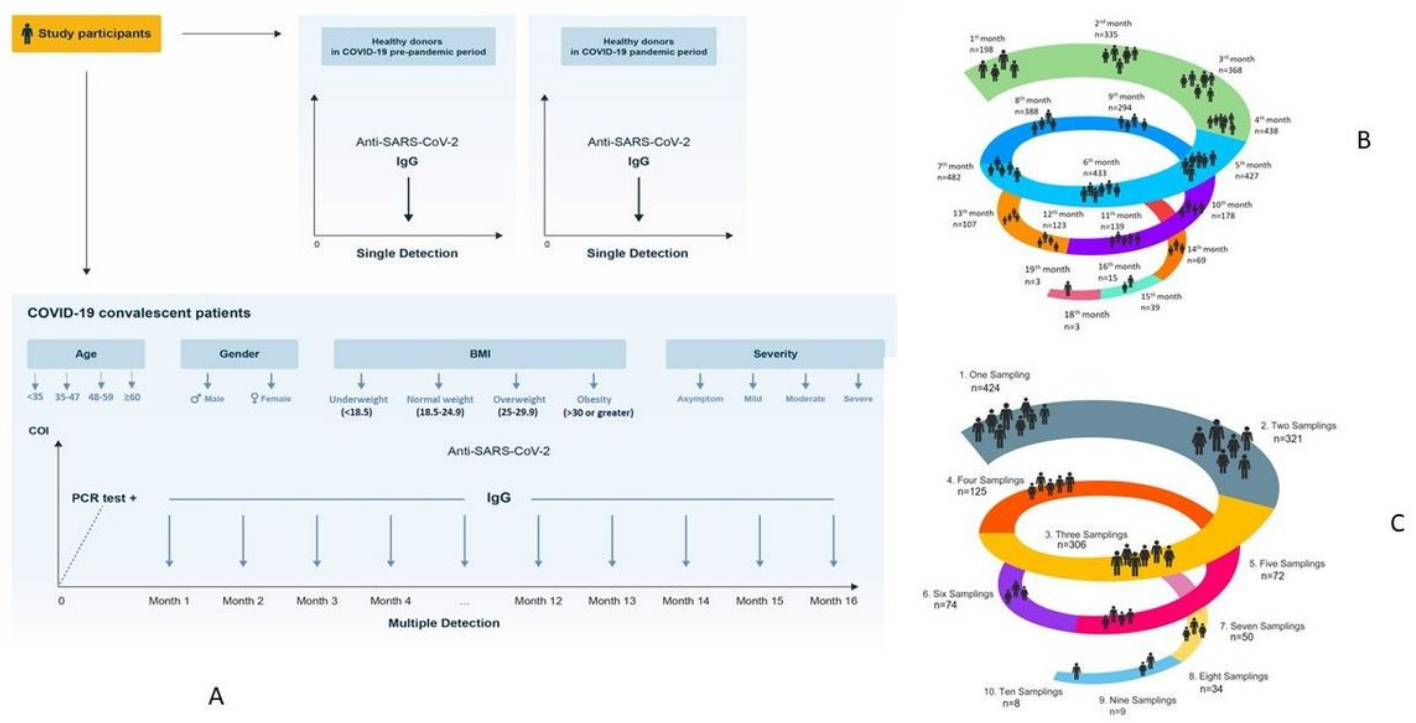

Figure 1

Figure 1

Design of the prospective study A. SARS-CoV-2 convalescent patients were involved in the study after maximum of a month of positive PCR testing, and then sampled monthly up to 19 months (subsequent detailed analysis of antibodies titer was performed for 15 months follow-up). Two groups of healthy donors were also included in the study: “pre-pandemic control group” - healthy donors before SARS-CoV-2 pandemic period (from 2017 up to February 2020), and “SARS-CoV-2 pandemic group” -healthy donors throughout the SARS-CoV-2 pandemic period (started from March 2 of 2020). B. Number of patients’ inclusion per months C. The distribution of patients with different number of samplings for anti-SARS-Cov2 antibodies

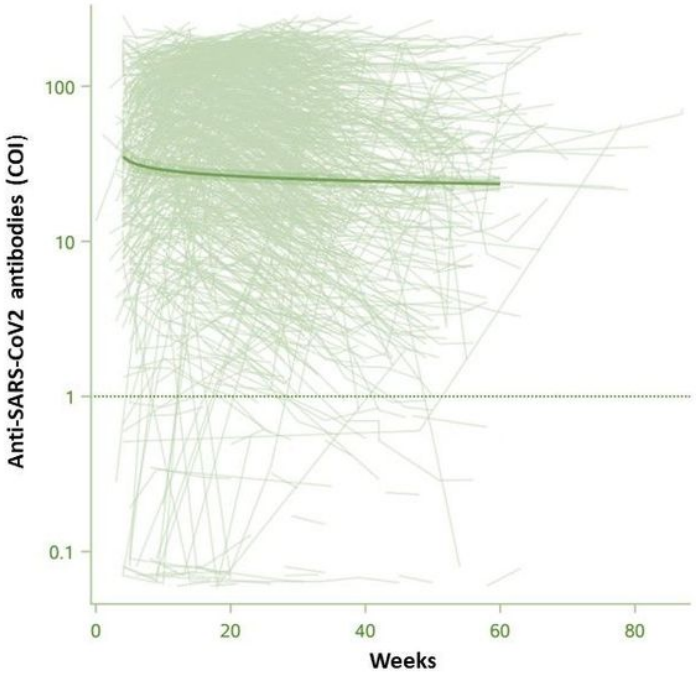

Figure 2

Figure 2

Serum anti-SARS-CoV-2 IgG titers of convalescent patients (n=1441) at the different times of sampling (expressed in logarithmic expression). IgG against SARS-CoV-2 N protein were measured by “Elecsys”

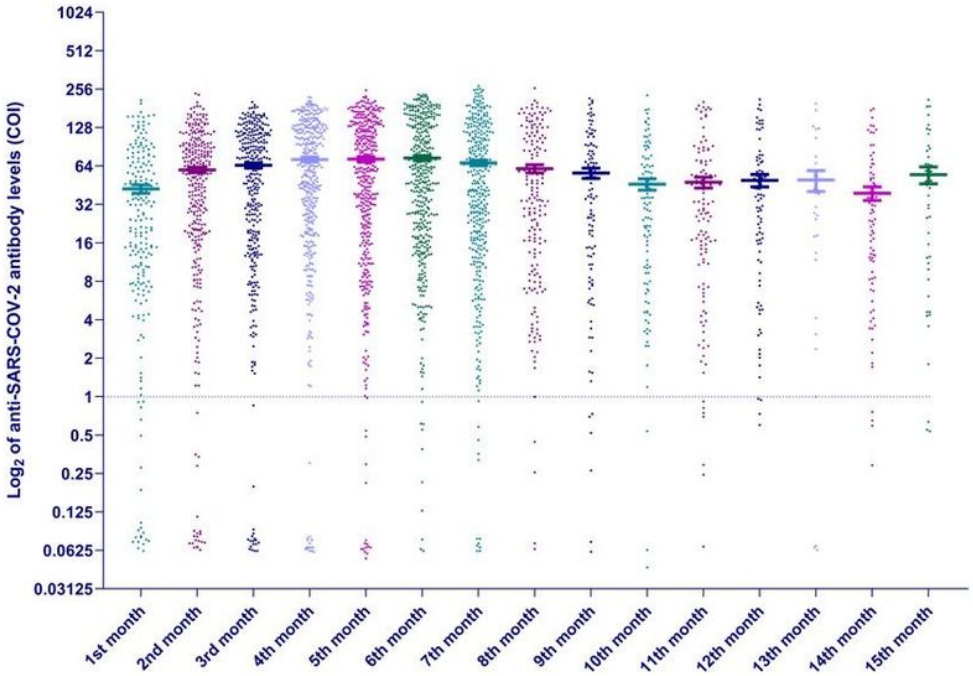

Figure 3

Figure 3

Anti-SARS-CoV-2 antibodies titers after the positive PCR testing every month (medians with ranges in logarithmic expression)

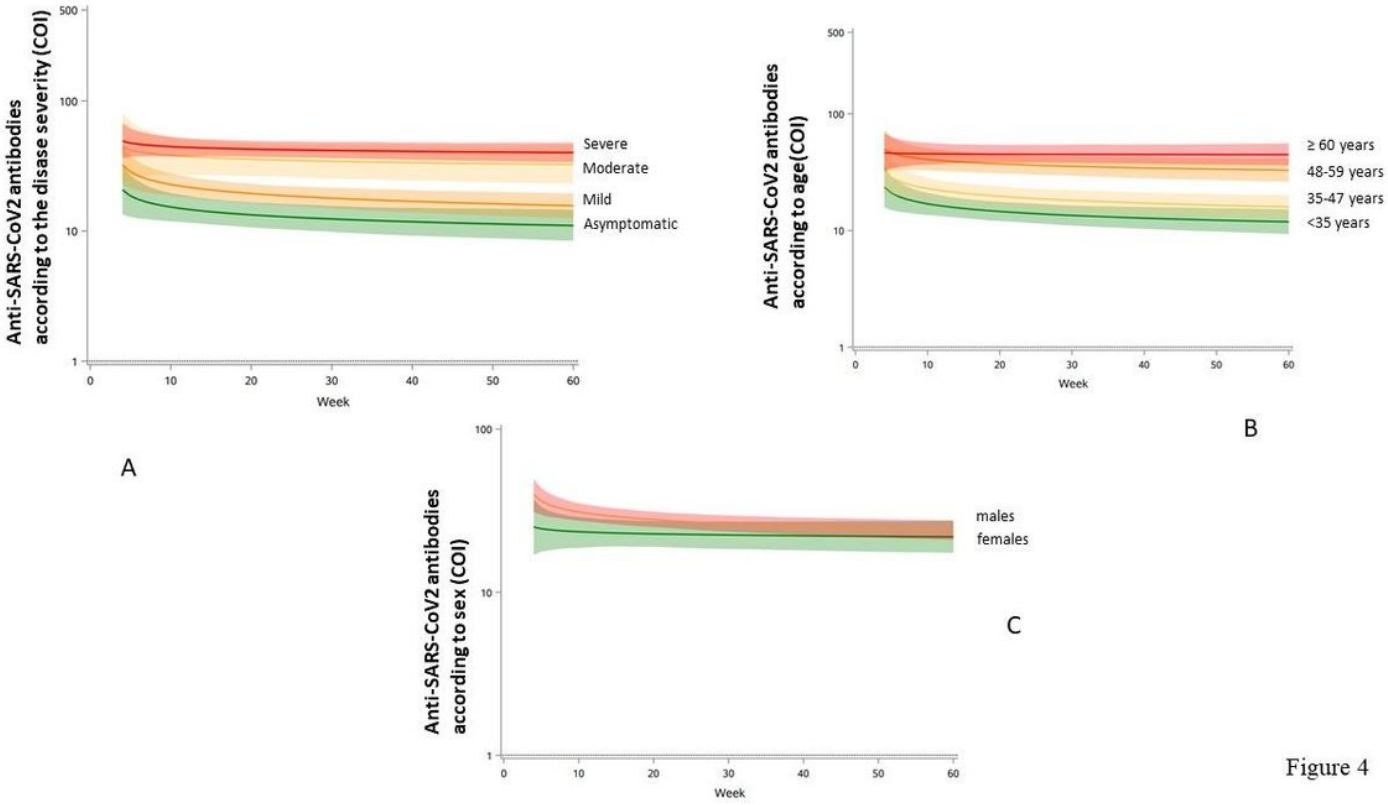

Figure 4

Anti-SARS-CoV-2 antibodies kinetics according to the disease severity, age and sex. A. The kinetics of anti-SARS-CoV-2 antibodies in asymptomatic, mild, moderate, and severe patients' groups. B. The kinetics of anti-SARS-CoV-2 antibodies according to age within<35; 35-47, 48-59, ≥60 groups. C. The kinetics of anti-SARS-CoV-2 antibodies in males (green) and females (pink).

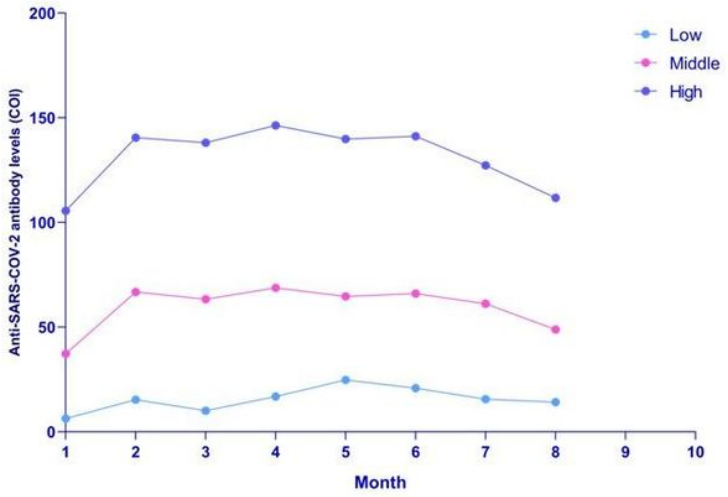

Figure 5

Figure 5

Anti-SARS-CoV-2 antibodies in low, middle and high responders

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplfigure1kinetics.jpg
- Supplfigure2kinetics.jpg
- Supplfigure3kinetics.jpg
- Supplfigure4kinetics.jpg
- SupplementaryFigureLegends.docx