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FEATURES OF THE SPECIFIC HUMORAL IMMUNE RESPONSE IN PATIENTS RECOVERED FROM COVID-19

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COVID-19 is an acute respiratory viral infection caused by the novel coronavirus SARS-CoV-2. It is characterized by a wide range of clinical manifestations, from mild upper respiratory tract involvement to severe pneumonia and acute respiratory distress syndrome. This article presents the features of the humoral immune response formation after COVID-19, depending on age, sex, disease severity, presence of severe comorbidities, and frequency of infection.

The aim of our study is to analyze the characteristics of humoral immunity to SARS-CoV-2 in different age and sex groups, taking into account disease severity, recurrence of infection, and the presence of severe comorbidities.

Materials and methods. The object of the study was 121 patients after a confirmed coronavirus infection, verified by the detection of SARS-CoV-2 RNA via PCR and/or the presence of SARS-CoV-2 antigen using the immunochromatographic method (CITO TEST COVID-19 Ag, "Pharmasco"). The subject of the study was the assessment of the specific humoral immune response after COVID-19 by determining neutralizing IgG antibodies to the RBD region of the SARS-CoV-2 S1 subunit (SARS-CoV-2 S1-RBD IgG) in blood serum using the enzyme-linked immunosorbent assay (ELISA) kit "BD-COVID-19 IgG – Screen" (Best Diagnostics, Ukraine. Cat. No.: C-0101, Lot: 10/2).

Results. Severe COVID-19 is associated with a statistically significant effect, correlating with higher levels of SARS-CoV-2 S1-RBD IgG. A recurrent case of COVID-19 was characterized by higher SARS-CoV-2 S1-RBD IgG levels. Age is a significant factor influencing the level of SARS-CoV-2 S1-RBD IgG in the older patient group, with a median effect size of bage = -0,81 per year. Sex and severe comorbid conditions did not demonstrate a modifying effect on the level of SARS-CoV-2 S1-RBD IgG.

Keywords: COVID-19, specific humoral immune response, SARS-CoV-2 S1-RBD IgG, spike protein, viral infection.

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ОСОБЛИВОСТІ СПЕЦИФІЧНОЇ ГУМОРАЛЬНОЇ ІМУННОЇ ВІДПОВІДІ ОРГАНІЗМУ В ПАЦІЄНТІВ ІЗ ПЕРЕНЕСЕНИМ COVID-19
Вінницький національний медичний університет імені М. І. Пирогова, Вінниця, Україна

COVID-19 – гостра респіраторна вірусна інфекція, що спричинюється новим коронавірусом SARS-CoV-2 і характеризується широким спектром клінічних проявів. У статті проаналізовано особливості гуморальної відповіді після перенесеного COVID-19 залежно від віку, статі, тяжкості захворювання, наявності важкої супутньої патології та частоти захворювання. Встановлено, що важкий перебіг COVID-19 асоціюється зі статистично достовірним ефектом, який корелює з більш високим рівнем SARS-CoV-2 S1-RBD IgG. Повторний випадок COVID-19 характеризувався вищим рівнем SARS-CoV-2 S1-RBD IgG. Вік – суттєвий фактор впливу на рівень SARS-CoV-2 S1-RBD IgG у групі хворих старшої вікової категорії з медіанним рівнем ефекту – bage = −0,81 на рік. Стать та важка супутня патологія не проявили модифікуючого впливу на рівень SARS-CoV-2 S1-RBD IgG.

Ключові слова: COVID-19, специфічна гуморальна імунна відповідь, SARS-CoV-2 S1-RBD IgG, S-білок, вірусна інфекція.

Introduction

The acute respiratory viral infection caused by the novel coronavirus SARS-CoV-2 became the first pandemic of the current millennium and a major challenge for humanity. The disease has claimed more than 7.1 million lives [1] and is characterized by a wide spectrum of clinical manifestations, ranging from mild upper respiratory tract involvement to severe pneumonia and acute respiratory distress syndrome. Even mild forms of the infection were often accompanied by cardiovascular, neurological, and renal complications. Severe COVID-19 frequently led to multiorgan failure, sepsis, pulmonary thromboembolism, myocardial infarction, stroke, and other life-threatening conditions [2–3].

Simultaneously, various aspects of the disease began to be investigated. According to international studies, SARS-CoV-2 S1-RBD IgG antibodies start to appear in blood samples between days 7 and 14 after exposure to the virus [4]. However, the protective immune responses in COVID-19 remain insufficiently understood, and the complex interactions between different components of the humoral and T-cell responses require further clarification.

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The assessment of T-cell immunity as a screening method in individuals who have recovered from coronavirus disease is labor-intensive and costly [6].

To date, numerous studies have been conducted in Ukraine and worldwide to investigate the specific humoral immune response to COVID-19; however, this issue remains highly relevant [7–11]. Recent scientific evidence indicates that measuring neutralizing IgG antibodies to the RBD region of the SARS-CoV-2 S1 protein in serum – as a marker of immune protection after prior infection or vaccination – is essential for assessing the characteristics of the humoral response in patients with COVID-19.

The aim of our study was to determine the features of post-infectious immunity to SARS-CoV-2 depending on age, sex, disease severity, frequency of reinfections, and comorbidities.

Materials and Methods

A total of 121 patients with coronavirus infection confirmed by detection of SARS-CoV-2 RNA via PCR and/or SARS-CoV-2 antigen using an immunochromatographic assay (CITO TEST COVID-19 Ag, "Farmasko") were included in our observation. All patients underwent inpatient treatment in the Infectious Diseases Department of the Municipal Non-Commercial Enterprise "Vinnytsia City Clinical Hospital No. 1" Vinnytsia. The study population was predominantly male – 70 individuals (58 %), while 51 were female (42 %). The mean age of the patients was 57 ± 1.73 years.

Age distribution was evaluated using the World Health Organization age classification (March 2025). The largest proportion of patients belonged to the elderly age group (60–74 years), comprising 44 individuals (36.36 %) with a mean age of 68.5 ± 0.61 years. The young adult group (18–44 years) included 32 patients (26.44 %) with a mean age of 31.37 ± 1.63 years. The middle-aged group (45–59 years) consisted of 25 patients (20.6 %), whose mean age was 50.76 ± 0.73 years. The smallest group was the older elderly population (75–89 years), represented by 20 patients (16.5 %) with a mean age of 81 ± 1.22 years.

Among the examined patients, 75 individuals (62 %) had a moderate course of the disease with lower respiratory tract involvement but without signs of respiratory failure and with oxygen saturation $SpO_2 \geq 94$ %. A severe course – defined as $SpO_2 < 94$ %, respiratory rate ≥ 30/min, $PaO_2/FiO_2 < 300$ mmHg, and/or rapidly progressive pulmonary infiltrates involving more than 50 % of lung tissue within 24 hours – was observed in 46 patients (38 %) [5]. Patients with mild COVID-19 were not included in the study, as only individuals requiring inpatient care were examined.

Severe comorbid conditions – including ischemic heart disease, stable exertional angina, diffuse and/or post-infarction cardiosclerosis, arterial hypertension ≥ stage II/grade 2, heart failure, type 1 and type 2 diabetes mellitus, chronic obstructive pulmonary disease, bronchial asthma, and alimentary-constitutional obesity ≥ class II – were diagnosed in 41 patients (34 %). The remaining 80 patients (66 %) had no significant comorbidities.

In our study, 101 patients (83.47 %) experienced COVID-19 for the first time, while 20 individuals (16.53 %) had a recurrent infection.

Exclusion criteria included: decompensated comorbidities at the time of enrollment, acute respiratory distress syndrome, septic shock, multiorgan failure, impaired consciousness, thrombotic complications, oncological or immunosuppressive diseases, pregnancy, and refusal to participate in the study.

The control group consisted of practically healthy individuals ($n = 45$), representative in terms of age and sex, who had neither been infected with COVID-19 nor vaccinated against it. All participants were informed about the study design and provided written informed consent to participate and to allow the processing of their personal data.

The specific humoral immune response was assessed by measuring neutralizing IgG antibodies to the RBD region of the SARS-CoV-2 S1 protein (SARS-CoV-2 S1-RBD IgG) in serum samples using an enzyme-linked immunosorbent assay (ELISA) kit "BD-COVID-19 IgG-Screen" (Best Diagnostik, Ukraine; Cat. No.: C-0101, Lot: 10/2). Measurements were performed over a 6-month period following the onset of clinical symptoms, with three assessments: the first within 7–10 days after symptom onset, the second at 3 months, and the third at 6 months. The units of measurement for the quantitative indicator of neutralizing antibodies to SARS-CoV-2 were BAU/ml.

Statistical analysis was performed using a first-order autoregressive model (AR1) with corresponding lagged linear regression coefficients for the factors listed above. The analytical module was written in the Stan programming language within the R environment (< rstan>) [12]. The module was executed in R with the < rstan> library loaded. IBM SPSS Statistics, version 12(20) (license No. 9593869), owned by the Department of Infectious Diseases of Vinnytsia National Pirogov Memorial Medical University, was used for the paired t-test. Microsoft Office Excel 2019 was also utilized for statistical processing.

The study was conducted in accordance with the principles of bioethics outlined in the Declaration of Helsinki ("Ethical Principles for Medical Research Involving Human Subjects") and the "Universal Declaration on Bioethics and Human Rights" (UNESCO) (Protocol No. 3 dated April 3, 2023).

Research results and their discussion

The study demonstrated that the level of SARS-CoV-2 S1-RBD IgG antibodies in patients' serum began to rise within 7–10 days from the onset of the disease and reached its peak values at three months (Fig. 1). At the first assessment, the serum level of SARS-CoV-2 S1-RBD IgG was 28.1 times higher than that of healthy individuals, and at the second assessment (after 3 months), this difference increased to 38.3-fold. During this period, the SARS-CoV-2 S1-RBD IgG level in patients' serum increased 1.35-fold compared with the initial measurement at disease onset.

Six months after infection, the serum level of SARS-CoV-2 S1-RBD IgG significantly decreased compared with the previous measurement ($p < 0.01$); however, it remained 35.4 times higher than in healthy individuals and 1.25 times higher than at the onset of the disease (7–10 days).

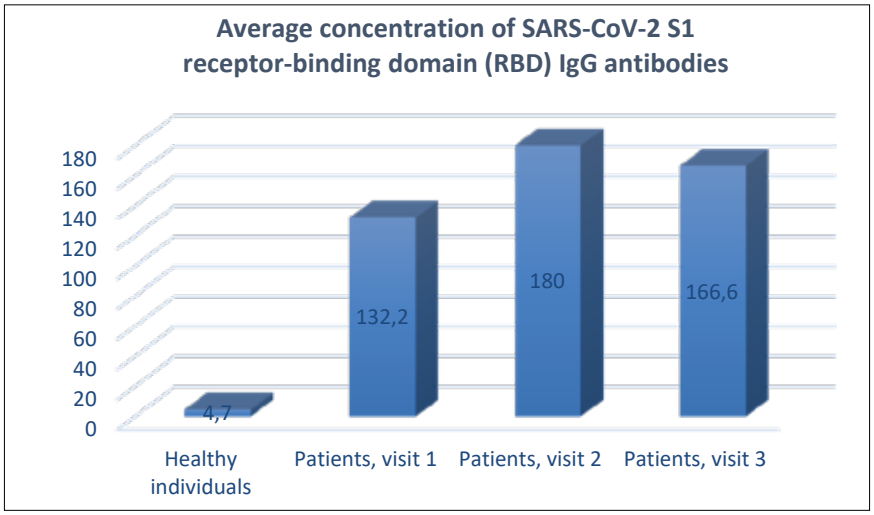


Fig. 1. Average concentration of SARS-CoV-2 S1 receptor-binding domain (RBD) IgG antibodies in healthy individuals and patients with coronavirus infection over a 6-month period

Analysis of the obtained results revealed a significant increase in the serum concentration of SARS-CoV-2 S1-RBD IgG across all age groups. On day 7 of the disease, SARS-CoV-2 S1-RBD IgG levels were already 22.1–29.2 times higher than in healthy individuals, reaching their peak during the second visit at 30.3–44.4 times higher. Six months after infection, a slight decrease of 0.8–0.96 times in these levels was observed across all age groups.

At the same time, the lowest serum levels of SARS-CoV-2 S1-RBD IgG were recorded in the older elderly patient group, being 1.3 times lower compared with all other patient groups at the peak of the disease. This pattern persisted throughout the entire observation period (Table 1, Fig. 2). Our findings are consistent with those of other researchers, who have shown that age and baseline health status influence the formation and duration of humoral immunity in coronavirus infection [13].

We did not observe a significant difference in the dynamics of serum SARS-CoV-2 S1-RBD IgG levels in patients based on sex. Similarly, other studies have found no association between the duration of elevated serum SARS-CoV-2 S1-RBD IgG levels and patient sex [14]. However, most studies have reported that females exhibit a stronger immune response to COVID-19 vaccination compared with males [15].

In patients with COVID-19 presenting a moderate course of the disease, serum levels of SARS-CoV-2 S1-RBD IgG were significantly higher compared with those in the severe disease group ($p \leq 0.01$) throughout the observation period, with the greatest difference – 1.2-fold – observed six months after recovery (Table 2, Fig. 3). Overall, the dynamics of SARS-CoV-2 S1-RBD IgG levels were similar between groups: in moderate cases, levels increased 1.36- and 1.29-fold, while in severe cases, increases of 1.32- and 1.2-fold were observed at the second and third visits, respectively.

Literature data also indicate that in some severely ill patients, the humoral response is lower, which may contribute to insufficient viral clearance and delayed recovery [16]. Other studies report that severe COVID-19 is associated with enhanced antibody production [17] and potentially a more prolonged humoral response [18]. Several studies have also highlighted the correlation between humoral response and disease severity. Hospitalized patients (with mild or severe symptoms) exhibited higher SARS-CoV-2 S1-RBD IgG titers compared with asymptomatic individuals or those with milder symptoms who did not require hospitalization [19]. This supports the hypothesis that the association of older age, male sex, obesity, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) with severe COVID-19 may be partially explained by a weakened immune response to SARS-CoV-2. Some researchers have expressed concern that humoral immunity against SARS-CoV-2 may be short-lived in individuals with mild disease, who constitute the majority of COVID-19 cases [20].

Table 1

Average concentration of SARS-CoV-2 S1 receptor-binding domain (RBD) IgG antibodies depending on age distribution in healthy individuals and patients with confirmed COVID-19

Age (years)	Healthy indivi-duals (n = 45), N (%)	Patients with confirmed COVID-19 (n = 121), N (%)	Healthy individuals	Patients with confirmed COVID-19		
				Visit 1	Visit 2	Visit 3
			SARS-CoV-2 S1-RBD IgG, BAU/ml			
18–44	12(26.6 %)	32(26.44 %)	4.5 ± 0.45	139.47 ± 15.74*	199.86 ± 10.79*	192.5 ± 10.57*
45–59	12(26.6 %)	25(20.6 %)	4.73 ± 0.4	135.97 ± 18.52*	195.18 ± 14.44*	183.53 ± 13.02*
60–74	16(35.5 %)	44(36.36 %)	4.25 ± 0.45	140.7 ± 14.05*	172.39 ± 10.37*	159.83 ± 9.96*
75–89	5(11.3 %)	20(16.5 %)	4.82 ± 0.43	103.87 ± 20.29*	146.12 ± 16.86*	118 ± 14.63*

Note. * $p \leq 0.01$, the difference is highly significant between healthy individuals and patients who recovered from COVID-19 across the three visits.

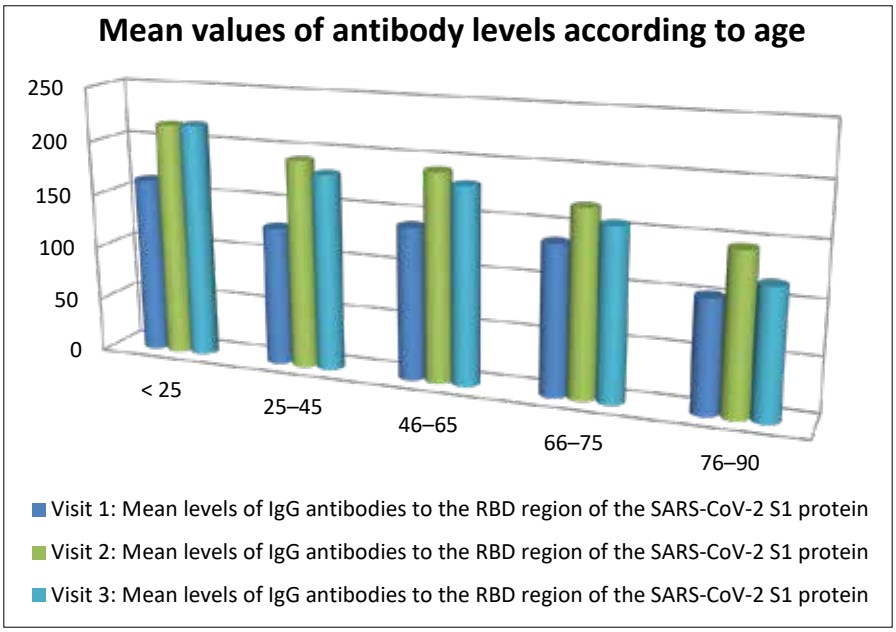


Fig. 2. Mean serum levels of SARS-CoV-2 S1-RBD IgG over a 6-month period after COVID-19, depending on age

Table 2

Mean levels of SARS-CoV-2 S1-RBD IgG depending on disease severity in patients with confirmed COVID-19 and healthy individuals

Parameter	Healthy indivi-dual (n = 45)	Patients with moderate severity of COVID-19 (n = 75(62 %))			Patients with severe COVID-19 (n = 46(38 %))		
		Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
SARS-CoV-2 S1-RBD IgG, BAU/ml	4.7 ± 0.88	137.89 ± 10.34*	188.3 ± 7.82*	177.95 ± 7.63*	125.63 ± 14*	166.5 ± 10.8*	148.5 ± 10.12*

Note. *$p \leq 0.01$ indicates a highly significant difference between the groups of healthy individuals and patients with a history of COVID-19 across three visits.

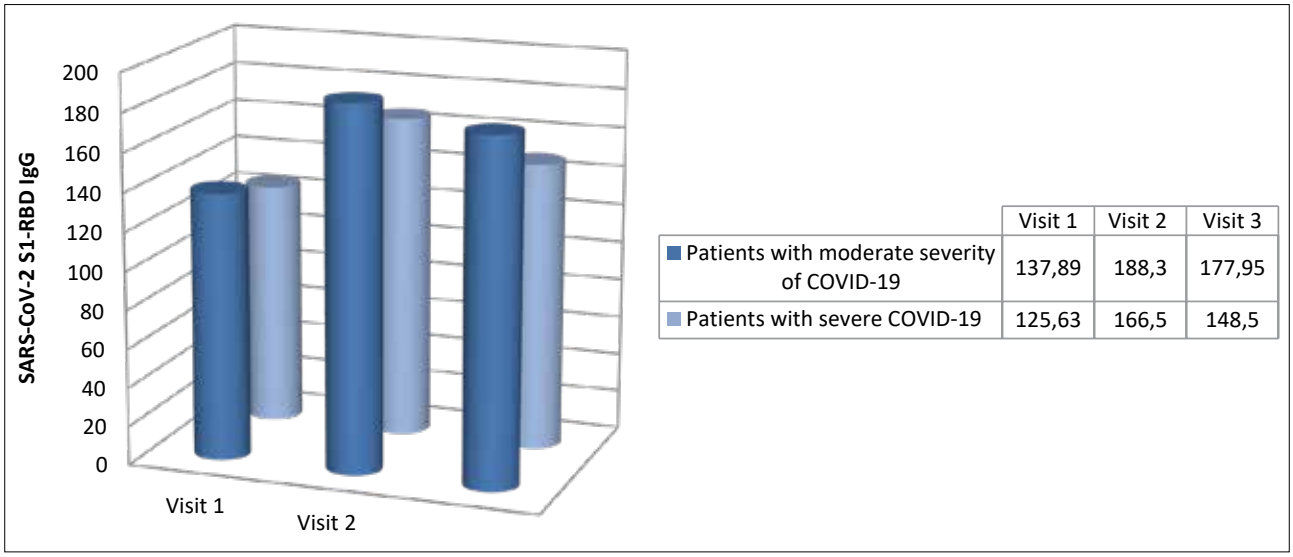


Fig. 3. Mean levels of SARS-CoV-2 S1-RBD IgG according to disease severity in COVID-19

Regardless of the presence or absence of comorbidities in patients with coronavirus infection, we observed a distinct dynamic in serum SARS-CoV-2 S1-RBD IgG levels. In the group of patients with comorbid conditions, antibody levels increased 1.3-fold at three months and 1.2-fold at six months compared with baseline values measured on days 7–10 of illness (Table 3, Fig. 4). A similar pattern was seen in patients without comorbidities, whose serum SARS-CoV-2 S1-RBD IgG levels increased 1.4-fold and 1.3-fold, respectively. We found significantly higher SARS-CoV-2 S1-RBD IgG levels in patients without comorbidities compared with those who had comorbid conditions at all observation points ($p \leq 0.01$).

In patients who contracted COVID-19 for the first time, a steady increase in serum SARS-CoV-2 S1-RBD IgG levels was recorded at 3 and 6 months of follow-up – 1.3-fold compared to the levels on days 7–10 of the disease (Table 4, Fig. 5). At the same time, in the reinfection group, this difference was 1.4-fold after three months, whereas after six months a slight decrease to 1.2-fold was observed. Serum SARS-CoV-2 S1-RBD IgG levels in patients who experienced reinfection were significantly higher compared to those infected for the first time three months after disease onset ($p \leq 0.01$); at other follow-up visits this difference persisted as a trend.

Posterior distributions of the effects of age, sex, disease severity, presence of severe comorbidities, and reinfection status on antibody levels

The analysis of the posterior distribution of the effect of disease severity on SARS-CoV-2 S1-RBD IgG levels demonstrated a higher value (bCOVID = 11.15) in patients with severe COVID-19. This effect is statistically significant, as the 2.5 % percentile of the posterior distribution takes a negative value. Considering the large magnitude (–9.95), we cannot assert the reliability of this effect based on our study (Fig. 6). The result obtained from the posterior distribution contrasts with the findings from the direct assessment of the effect of disease severity on antibody levels (Table 2, Fig. 3), which may be explained by the incorporation of additional criteria (new patient information) into the prior assumptions.

In the presence of severe comorbid pathology, the SARS-CoV-2 S1-RBD IgG antibody levels did not differ significantly, with a median effect value of bcomorb = 7.52 (Fig. 6). As shown in the figure, most effect values are concentrated near zero.

In our study, age was found to be a significant factor in the older age category. A notable effect on SARS-CoV-2 S1-RBD IgG levels was observed in this age group, with a median effect of b_age = –0.81 and a 95 % credible interval

Table 3

Mean SARS-CoV-2 S1-RBD IgG levels depending on the presence of severe comorbidities in patients with confirmed COVID-19 and in healthy individuals

Comorbidities	Healthy individual (n = 45), N (%)	Patients with confirmed COVID-19 (n = 121), N (%)	Healthy individuals	Patients with confirmed COVID-19		
				Visit 1	Visit 2	Visit 3
			SARS-CoV-2 S1-RBD IgG, BAU/ml			
Presence of comorbi-dities	18(40 %)	41(34 %)	4.25 ± 0.36	130 ± 13.74*	170.2 ± 11.5*	155.62 ± 10.7*
Without comorbi-dities	27(60 %)	80(66 %)	4.68 ± 0.29	134.7 ± 10.45*	185 ± 7.68*	172.3 ± 7.58*

Note. $p \leq 0.01$ – the difference is highly significant between healthy individuals and patients who recovered from COVID-19 across all three visits.

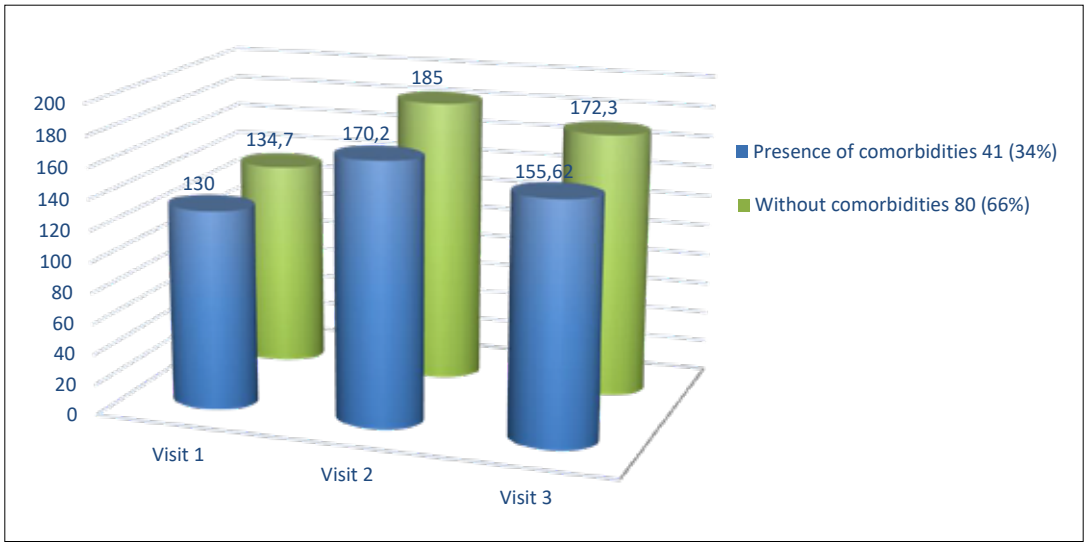


Fig. 4. Mean levels of SARS-CoV-2 S1-RBD IgG depending on the presence of severe comorbidities in COVID-19 patients

Table 4

Mean SARS-CoV-2 S1-RBD IgG levels depending on the frequency of COVID-19 infection in patients with confirmed COVID-19 and in healthy individuals

Disease frequency	Patients with COVID-19 (n = 121), N (%)	Healthy individuals (n = 45)	Patients with confirmed COVID-19		
			Visit 1	Visit 2	Visit 3
		SARS-CoV-2 S1-RBD IgG, BAU/ml			
Patients with a first episode	101(83.47 %)	4.7 ± 0.88	131.6 ± 9*	176.9 ± 7.2*	165.6 ± 6.89*
Patients with a second episode	20(16.53 %)	4.7 ± 0.88	141 ± 20.8*	195.6 ± 13*	171.6 ± 14.46*

Note. $p \leq 0.01$ – the difference is highly significant between healthy individuals and patients who had recovered from COVID-19 across all three visits.

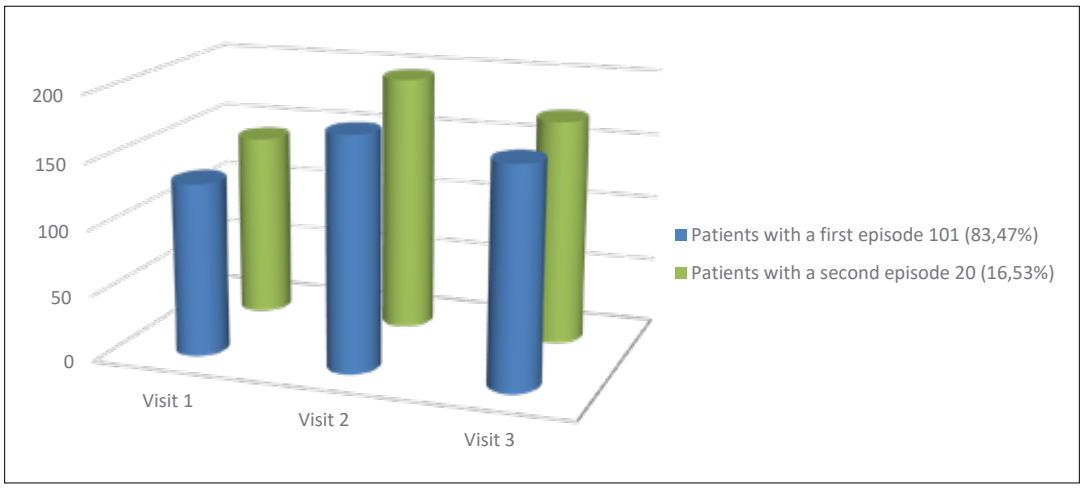


Fig. 5. Mean levels of SARS-CoV-2 S1-RBD IgG according to disease frequency in COVID-19 patients

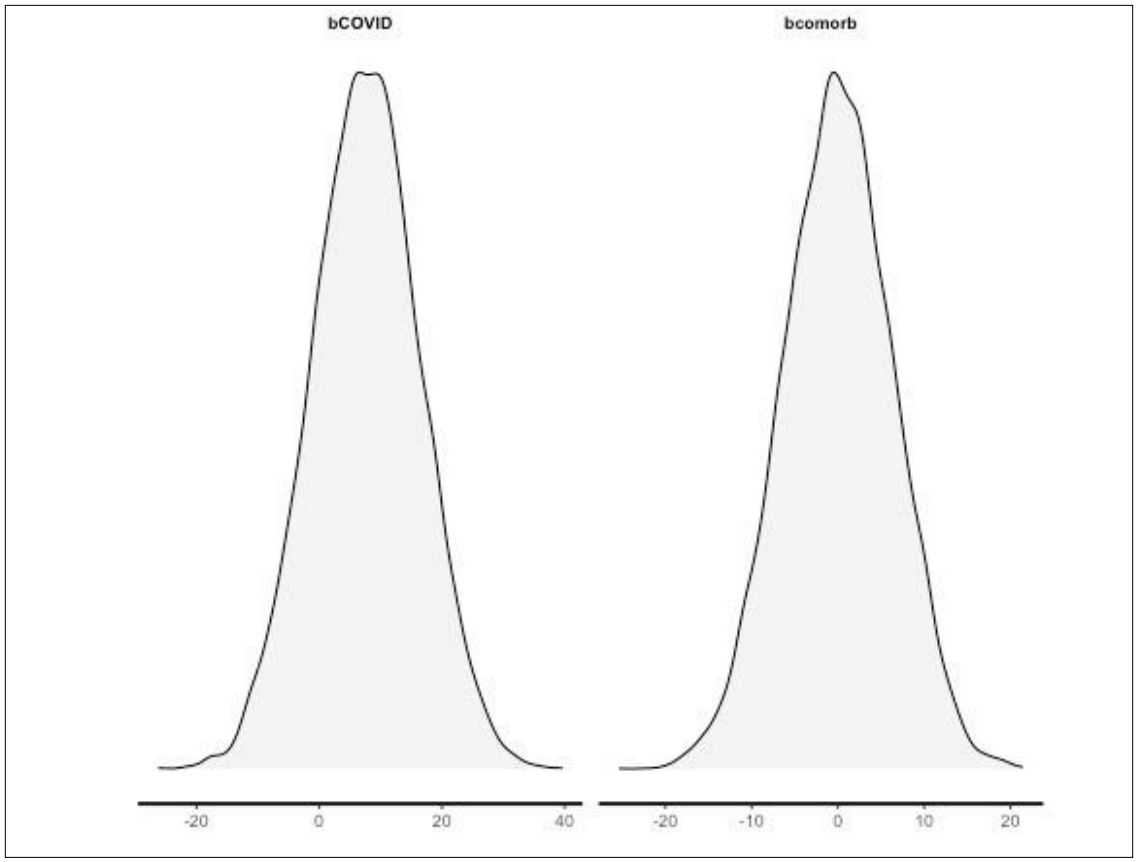


Fig. 6. Posterior distributions of the effects of COVID-19 severity (b_COVID) and the presence of severe comorbid pathology (b_comorb) on antibody dynamics

that excludes zero. Each additional year of age in the older patient group was associated with a decrease of 0.81 BAU/ml in antibody levels (Fig. 7).

Sex did not modify antibody levels, as the posterior distribution is nearly symmetric around zero (see effect b_sex) (Fig. 7).

The analysis of the posterior distribution of the effect of reinfection shows that a repeated COVID-19 episode was characterized by higher SARS-CoV-2 S1-RBD IgG levels. However, the reliability of this effect is limited by the fact that the 2.5 % percentile of the posterior distribution for the effect, b_episode, equals –2.80 (Fig. 7).

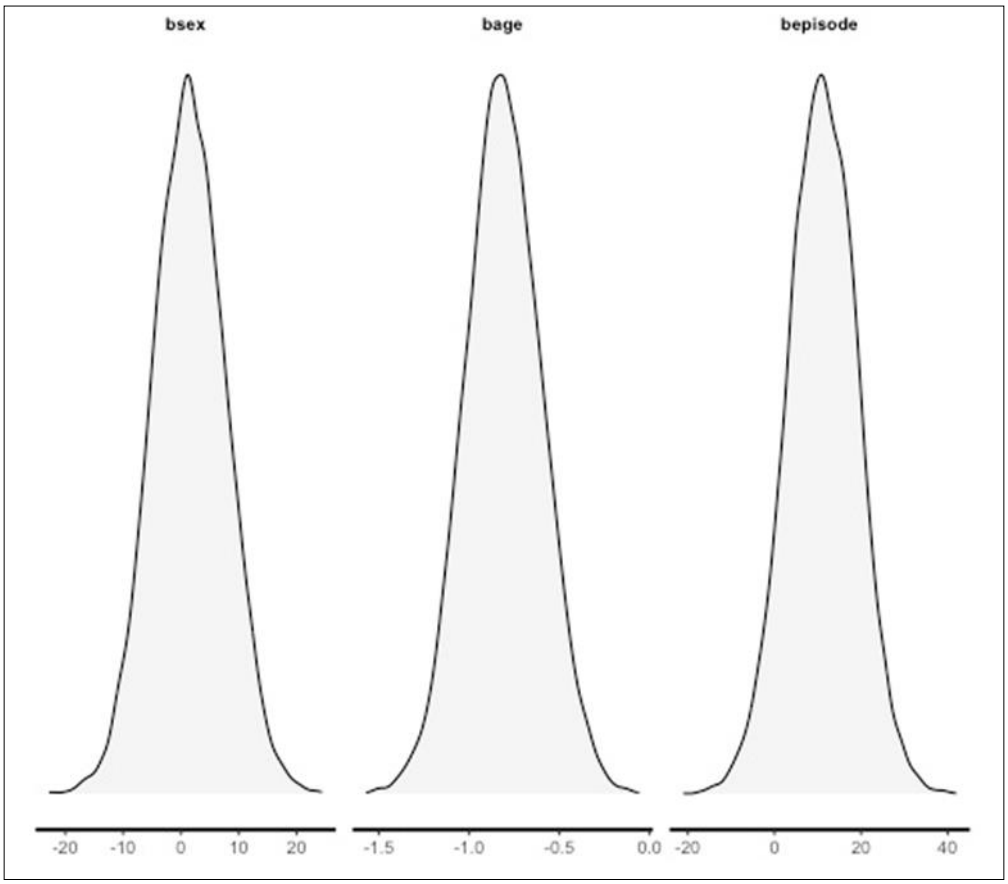


Fig. 7. Posterior distributions of the effects of sex (bsex), age (bage), and reinfection (bepisode) of COVID-19 on antibody dynamics

Conclusions

Based on the results of this study, the following conclusions can be drawn:

1. Serum levels of SARS-CoV-2 S1-RBD IgG in COVID-19 patients peaked at three months after disease onset and were 1.35-fold higher compared with levels measured on days 7–10 of illness.

2. Severe COVID-19 was associated with a statistically significant effect correlating with higher SARS-CoV-2 S1-RBD IgG levels. Age was a significant factor affecting SARS-CoV-2 S1-RBD IgG levels in older patients, with a median effect of bage = –0.81 per year.

3. Reinfection with COVID-19 was characterized by higher SARS-CoV-2 S1-RBD IgG levels.

4. Sex and the presence of severe comorbidities did not demonstrate a modifying effect on SARS-CoV-2 S1-RBD IgG levels.

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