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ORIGINAL RESEARCH ARTICLE

Twelve-month anti-SARS-CoV-2 antibody kinetics in COVID-19 patients from Bejaia, Algeria

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Abstract

The COVID-19 pandemic has highlighted the importance of understanding long-term humoral immunity after SARS-CoV-2 infection. This study evaluated the kinetics and persistence of anti-SARS-CoV-2 immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies in hospitalized patients who recovered and identified factors associated with antibody responses. A total of 96 patients hospitalized with real-time polymerase chain reaction-confirmed COVID-19 between June and September 2020 were included. Sequential serum samples were collected up to 365 days after symptom onset. Anti-SARS-CoV-2 IgM and IgG antibodies targeting spike (S) and nucleocapsid (N) proteins were evaluated on days 28, 90, 180, and 365 using chemiluminescent immunoassay (MAGLUMI). Clinical, epidemiological, and radiological data were analyzed. All convalescent patients developed detectable IgG antibodies, and 92.7% were IgG seropositive. Antibody titers and seropositivity rates declined over time; however, IgG antibodies remained more stable and persisted throughout the 12-month follow-up, whereas IgM antibodies became undetectable in most cases. Nevertheless, 12.5% of patients still had detectable IgM antibodies one year after symptom onset, whereas IgG seropositivity remained above 70%. Higher IgG titers were significantly associated with age ≥ 50 years, severe COVID-19, and SARS-CoV-2 pneumonia. Patients vaccinated before the final follow-up demonstrated a strong booster response with significantly higher IgG levels than unvaccinated individuals. In conclusion, symptomatic COVID-19 induces a durable humoral immune response that persists for at least 12 months. Hybrid immunity resulting from natural infection combined with vaccination appears to provide the strongest protection against SARS-CoV-2.

Keywords: SARS-CoV-2; COVID-19; Antibody kinetics; Immunoglobulin M; Immunoglobulin G; Humoral immunity; Influencing factors

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1. Introduction

Emerging infectious diseases have always been a threat to public health worldwide. Since late December 2019, the world has been facing COVID-19, which is caused by SARS-CoV-2. Since then, this emerging, highly contagious disease has spread to 223 countries and territories, quickly becoming a global pandemic.[1] Since the start of the pandemic, the hypothesis of a decrease in humoral immunity in convalescent COVID-19 patients has raised concerns about the reliability of population-based seroprevalence studies, and more particularly about the long-term protection of antibodies against reinfection and, by extension, the sustainability of vaccine protection. Like most viral infections, COVID-19 results in the development of protective neutralizing antibodies in the vast majority of cases[2–5], and several reports have suggested a rapid decline in SARS-CoV-2 antibodies as early as three months after infection[6,7], while others have reported antibody persistence for up to eight months.[5,8,9]

Thus, establishing an immune response is essential in defense against SARS-CoV-2 infection, and to end the COVID-19 pandemic, it is essential to know how long immunity against SARS-CoV-2 will persist after infection. Therefore, data on the persistence and long-term effectiveness of the immune response are of vital importance for understanding the overall evolution of the pandemic and post-pandemic dynamics, especially in the era of emerging variants.[10–13] There are differences in individuals' immune responses to the virus, which open the door to scientific investigation into the factors that predict these responses, their magnitudes, and their durability. High antibody levels have been observed in patients with severe COVID-19, suggesting that disease severity may affect the immune response. Additionally, older patients tend to have a more positive immunoglobulin G (IgG) response and higher antibody levels than younger patients; therefore, the association between antibody titers and factors such as age, sex, comorbidities, and disease severity was explored in depth.

Furthermore, although several anti-COVID-19 vaccines currently show promising effectiveness in preventing SARS-CoV-2 infection and inducing antiviral antibodies[14–17], there remains no consensus regarding vaccination schedules for individuals with a history of SARS-CoV-2 infection.[18,19] Despite vaccination campaigns, a substantial percentage of the world's population remains unvaccinated, and their ability to resist infections relies only on naturally acquired immunity.[20] To address this challenge, longitudinal studies of natural infection can provide valuable information on the kinetics and durability of protective immune responses, improving vaccination strategy.

This study aims to achieve two objectives. The main objective is to describe the kinetics of anti-SARS-CoV-2 IgG and immunoglobulin M (IgM) antibodies over a period of 12 months in individuals convalescing from COVID-19, while the second objective is to evaluate the effect of epidemiological, clinical, and radiological variables on anti-SARS-CoV-2 antibody levels. Understanding antibody responses after natural SARS-CoV-2 infection can guide the COVID-19 vaccination schedule, particularly in resource-limited settings.

2. Materials and methods

This study is a prospective, descriptive, and longitudinal investigation conducted in the Infectious Diseases Department of Frantz Fanon Hospital, Béjaïa University Hospital, Algeria, from June 20, 2020, to September 30, 2021. The study population consisted of patients with confirmed COVID-19 who were hospitalized between June 20 and September 30, 2020, and subsequently recovered. Each patient was followed for 12 months, resulting in a total study duration of 15 months, with the last patient followed until September 30, 2021.

The study population included patients with COVID-19 confirmed using real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 who were hospitalized during the first wave of the pandemic and who recovered. Eligible participants were adults aged ≥ 16 years, as no pediatric unit is available at Frantz Fanon Hospital. Inclusion criteria were: confirmed SARS-CoV-2 infection by RT-PCR, positive serology after analysis, no prior history of SARS-CoV-2 exposure, and willingness to participate in the study.

Patients were excluded if they were managed on an outpatient basis, in accordance with Instruction No. 18 of June 21, 2020, on the updated therapeutic management of COVID-19 cases, which specified that only asymptomatic confirmed cases were followed as outpatients. Additional exclusion criteria were patients with probable COVID-19 (based on chest computed tomography [CT] but with negative or unavailable RT-PCR results) and patients who missed at least one follow-up visit, ensuring a matched sample with equal numbers of participants at each time point.

Diagnostic methods included RT-PCR targeting the open reading frame 1ab (*ORF1ab*) and the nucleocapsid (*N*) genes. To evaluate antibody kinetics, serial peripheral blood samples were collected from 96 convalescent individuals at days 28 (D28), 90 (D90), 180 (D180), and 365 (D365) after symptom onset. At each visit, 5 mL

of peripheral blood was collected, centrifuged at 3,000 rpm for 10 min, and stored at −80 °C under appropriate conditions until analysis.

2.1. Serological analysis and detection of anti-SARS-CoV-2 antibodies

Laboratory detection of anti-SARS-CoV-2 IgG and IgM antibodies was performed using the Snibe 2019-nCoV kit, a CE-IVD-marked quantitative assay, on the automated chemiluminescence analyzer (MAGLUMI 800, Shenzhen New Industries Biomedical Engineering Co, Ltd, China), a fully automated chemiluminescence immunoassay system. The assay uses both nucleocapsid and spike proteins as antigens to detect specific antibodies.

A total of 384 samples (four per patient) were analyzed. The assay is based on an indirect immunoassay principle, in which the emitted light signal, expressed in relative light units (RLUs), is proportional to the concentration of specific antibodies in the sample. RLU values are converted into arbitrary units (AU/mL) using a 10-point calibration curve. Results were interpreted according to the manufacturer's instructions, with values ≥ 1.00 AU/mL considered positive for both IgM and IgG.

The reported diagnostic sensitivity was 91.21% for IgG, 78.65% for IgM, and 95.60% for combined IgG/IgM, while diagnostic specificity was 97.33%, 97.50%, and 96.00%, respectively. No cross-reactivity was reported with antibodies against other bacterial or viral respiratory pathogens, including other coronaviruses.

To address the study objectives, the analysis was divided into two parts. The first part focused on describing the kinetics of anti-SARS-CoV-2 IgM and IgG antibodies. Seropositivity was defined as an IgM and/or IgG titer ≥ 1.00 AU/mL. The seropositivity rate was calculated as the proportion of convalescent individuals with detectable antibodies among the total study population. Antibody kinetics were assessed by analyzing changes in seropositivity rates and mean IgM and IgG titers at D28, D90, D180, and D365. The second part evaluated the influence of epidemiological, clinical, and radiological factors on antibody responses. These included age, sex, comorbidities, disease severity, and pulmonary involvement (pneumonia). Comparisons were performed between predefined groups: individuals aged < 50 years vs. ≥50 years, males vs. females, patients with vs. without comorbidities, mild vs. moderate vs. severe cases, and patients with vs. without pneumonia.

The study was conducted during the first wave of COVID-19. During follow-up, and prior to the final evaluation at D365 (i.e, between D180 and D365), a subgroup of convalescent individuals received SARS-CoV-2 vaccination following the introduction of vaccination campaigns on January 30, 2021. Although not initially planned, this aspect was included to assess its impact on antibody kinetics. Mean IgG titers at D180 and D365 were compared between vaccinated (n = 13) and unvaccinated (n = 83) participants.

2.2. Ethics approval and consent to participate

This study was approved by the Ethics Committee of the University of Bejaia, Algeria. The committee reviewed and authorized all aspects of the study protocol, including data collection, analysis, and the use of clinical information derived from human subjects. Informed consent was obtained from all patients who participated in this study. Consent was clear, voluntary, and provided in written form prior to inclusion in the study.

2.3. Statistical analysis

The IgG and IgM antibody concentrations (titers) at each time point were expressed as mean ± standard deviation, while seropositivity rates were presented as absolute frequencies and percentages. The normality of data distribution was assessed using the Kolmogorov–Smirnov test, which indicated a non-normal distribution; therefore, non-parametric tests were applied.

Changes in IgG and IgM antibody levels across different time points were analyzed using the Friedman test and the Wilcoxon signed-rank test for continuous variables, and the Cochran's Q test and the McNemar test for categorical variables. When overall differences were statistically significant in repeated or multiple group comparisons (Friedman or Kruskal–Wallis tests), post-hoc pairwise comparisons were performed using the Wilcoxon signed-rank test or Mann–Whitney U test, as appropriate. To control for type I error due to multiple comparisons, the Bonferroni correction was applied, and the adjusted significance level (α) was calculated by dividing 0.05 by the number of comparisons performed. All statistical tests were two-tailed. A p-value < 0.05 was considered statistically significant unless otherwise adjusted for multiple comparisons.

Results were stratified according to age (<50 years vs. ≥50 years), sex (male vs. female), presence of comorbidities (yes vs. no), disease severity (mild, moderate, severe), pulmonary involvement (presence vs. absence of pneumonia), and vaccination status (vaccinated vs. unvaccinated). Between-group comparisons were performed using the Mann–Whitney U test or Kruskal–Wallis test for continuous variables, and the χ^2 test or Cochran's Q test for categorical variables, as appropriate.

Changes in seropositivity rates over time were

illustrated using bar charts, while variations in mean IgG and IgM titers were presented as line graphs. The impact of vaccination on antibody levels was illustrated using boxplot graphs.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS 22.0, IBM, United States).

3. Results

3.1. Epidemiological, clinical, and radiological characteristics of patients with COVID-19

The study population consisted of 96 patients, including 61 men (63.5%) and 35 women (36.5%). The age of participants ranged from 26 to 83 years, with a median age of 51 years (Q1 = 45.00 years; Q3 = 60.75 years) and a mean age of 52.83 ± 12.07 years.

Most patients (68.75%) had at least one comorbidity, while 31.25% had none. The most frequent comorbidities were obesity (body mass index [BMI] ≥ 30 kg/m^2), hypertension, and diabetes. A large proportion of patients (80.2%; 95% confidence interval [CI]: 70.19–86.41%) had a BMI ≥ 25 kg/m^2, with a median BMI of 29.3.

All patients were symptomatic at admission, with the most common symptoms being fever, fatigue, and cough. Other symptoms included digestive disorders, sore throat, and dizziness. The mean duration of hospitalization was 7.35 ± 2.75 days (range: 2–16 days; 95% CI: 6.8–7.93).

According to clinical classification, patients were categorized as mild, moderate, or severe, with the majority presenting with moderate disease (74%). Chest CT scans were performed in all patients; findings were normal in eight patients (8.3%) and abnormal in 88 (91.7%), with predominantly moderate pulmonary involvement (55.2%).

During follow-up, 13 convalescent patients received SARS-CoV-2 vaccination between D180 and D365. Among them, nine received Sinovac, two received Sputnik, and two received AstraZeneca vaccines. Of these, 77% received two doses, while 23% received a single dose during the study period and completed vaccination afterward. The main characteristics of the study population are summarized in Table 1.

3.2. Kinetics of long-term anti-SARS-CoV-2 antibodies

Most participants developed a SARS-CoV-2-specific humoral immune response, with a progressive decline in both seropositivity rates and antibody titers over time (Figures 1–4).

Table 1. Epidemiological, clinical, and radiological data from participants in this study

Features	Results
Median age (IQR)	51 years (Q1 = 45.00 years; Q3 = 60.75 years)
Sex	
Men	61 (63.5%)
Women	35 (36.5%)
Comorbidities	
Without comorbidity	30 (31.25%)
With comorbidity	66 (68.75%)
Obesity (BMI ≥ 30 kg/m^2)	44 (45.8%)
Hypertension	35 (36.5%)
Diabetes	24 (25%)
Heart disease	9 (9.4%)
Chronic kidney failure	4 (4.2%)
Chronic respiratory pathology	2 (2.1%)
Immunosuppression	2 (2.1%)
BMI	
<25 kg/m^2	19 (19.8%)
25–29.9 kg/m^2	33 (34.4%)
≥30 kg/m^2	44 (45.8%)
Average length of hospitalization	7.35 days ± 2.75 (95% CI: 6.80 to 7.93)
Clinical signs	
Fatigue	92 (95.8%)
Fever	69 (71.9%)
Cough	63 (65.6%)
Dyspnea	39 (40.6%)
Desaturation	24 (25.0%)
Chest pain	33 (34.4%)
Anosmia	60 (62.5%)
Ageusia	59 (61.4%)
Sore throat	37 (38.5%)
Dizziness	38 (39.6%)
Clinical severity	
Mild COVID	7 (7.3%)
Moderate COVID	71 (74%)
Severe COVID	18 (18.7%)
Chest scan	
With SARS-CoV-2 pneumonia	88 (91.7%)
Without SARS-CoV-2 pneumonia	8 (8.3%)

(*Cont'd...*)

Table 1. (*Continued*)

Features	Results
All study recruits (convalescents)	96 (100%)
Seropositive participants	96 (100%)
Convalescents vaccinated between D180 and D365	13
Sinovac	9 (69.2%)
AstraZeneca	2 (15.4%)
Sputnik V	2 (15.4%)
Doses of vaccine received before D365	
1 dose before follow-up on D365	3 (23%)
2 doses before follow-up on D365	10 (77%)

Abbreviations: BMI: Body mass index; CI: Confidence interval; IQR: Interquartile range.

At D28, IgM and IgG antibodies were detected in 87.5% (84/96) and 97.9% (94/96) of convalescents, respectively. Mean antibody levels were 11.93 ± 11.46 AU/mL for IgM and 25.09 ± 13.97 AU/mL for IgG. At D365, seropositivity rates declined to 12.5% for IgM and 71.9% for IgG, with corresponding mean titers of 0.67 ± 2.13 AU/mL and 6.42 ± 9.56 AU/mL.

A significant decrease in both IgM and IgG seropositivity rates and antibody levels was observed over time (all $p < 0.001$). However, IgG remained detectable in a substantially higher proportion of individuals than IgM did throughout follow-up. IgM levels declined rapidly: seropositivity decreased from 87.5% at D28 to 37.5% at D90, and further declined to 12.5% at D365. Mean IgM titers decreased sharply from 11.93 ± 11.46 AU/mL at D28 to 3.59 ± 6.67 AU/mL at D90, and continued to decline at D180 (1.21 ± 3.47 AU/mL) and D365 (0.67 ± 2.13 AU/mL) (Figures 1 and 2). In contrast, IgG seropositivity remained relatively stable between D28 (97.9%) and D90 (~99%), followed by a slight decrease at D180 (94.8%) and a more pronounced decline at D365 (71.9%). Mean IgG titers also decreased progressively over time: 25.09 ± 13.97 AU/mL at D28, 16.96 ± 12.57 AU/mL at D90, 9.66 ± 9.67 AU/mL at D180, and 6.42 ± 9.56 AU/mL at D365 (Figures 3 and 4).

Overall, these findings demonstrate a sustained but declining humoral immune response, with detectable antibodies persisting for at least 12 months after symptom onset.

3.3. Influence of epidemiological, clinical, and radiological characteristics on antibody titers

3.3.1. Influence of epidemiological characteristics

The impact of epidemiological factors, namely age and sex, on IgM and IgG antibody titers was evaluated. For age, participants were divided into two groups (<50 years and ≥50 years). No significant differences in mean IgM levels were observed between the two age groups at any time point ($p > 0.05$), including D28 and D90 ($p = 0.282$ and $p = 0.517$, respectively), where slight differences were noted but were not statistically significant (Figure 5). In contrast, individuals aged ≥ 50 years exhibited significantly higher mean IgG titers compared to those aged < 50 years at all follow-up time points ($p < 0.05$) (Figure 6). These results indicate a positive association between age and IgG antibody levels.

Regarding sex, mean IgM titers were slightly higher in men than in women at D28 and D90, while values were similar at D180 and D365; however, these differences were not statistically significant ($p > 0.05$) (Figure 7). Similarly, mean IgG titers were higher in women than in men at all time points, but without statistically significant differences ($p > 0.05$) (Figure 8). Overall, no significant association was observed between antibody titers (IgM or IgG) and sex.

3.3.2. Influence of clinical characteristics

The impact of clinical characteristics, including comorbidities and disease severity, on antibody responses was evaluated. Regarding comorbidities, patients were classified as having or not having pre-existing conditions. At D28, participants with comorbidities had slightly higher mean IgM titers compared to those without comorbidities (12.69 ± 11.39 vs. 10.25 ± 11.63, respectively; $p = 0.208$). However, IgM levels were comparable between the two groups at other follow-up time points ($p > 0.05$) (Figure 9). Similarly, mean IgG titers were higher in patients with comorbidities than in those without; however, these differences were not statistically significant at any time point ($p > 0.05$) (Figure 10). Overall, no significant association was observed between antibody titers (IgM or IgG) and the presence of comorbidities.

In contrast, disease severity was significantly associated with antibody responses. Mean IgG titers were consistently higher in patients with severe COVID-19 compared to those with moderate or mild forms at all follow-up time points (D28 to D365), with statistically significant differences ($p = 0.000$, $p = 0.001$, $p = 0.002$, and $p = 0.003$, respectively) (Figure 11). For IgM, mean titers were also higher in the severe group compared to mild and moderate groups; however, statistically significant differences were

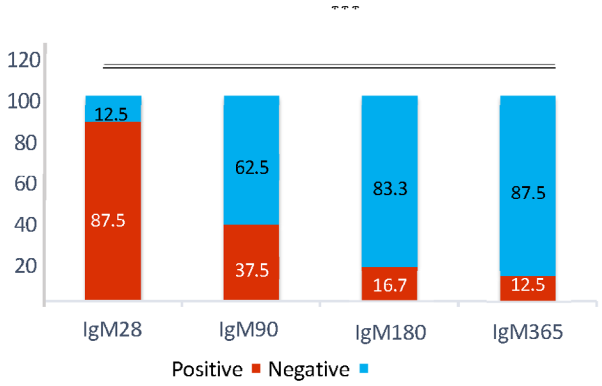

Figure 1. Anti-SARS-CoV-2 IgM seropositivity rate, Bejaia University Hospital, Algeria, 2020–2021
Note: ***$p < 0.001$.
Abbreviation: IgM: Immunoglobulin M.

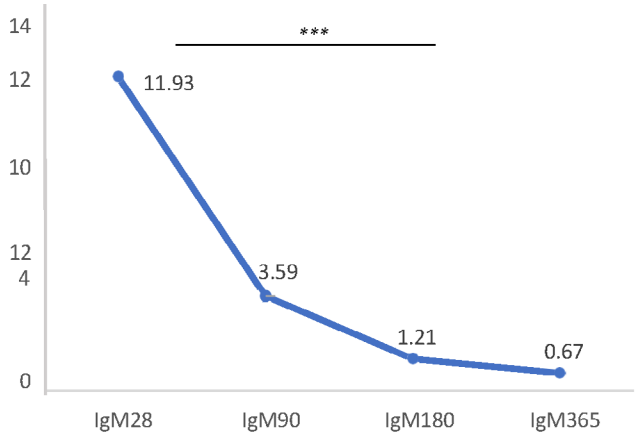

Figure 2. Dynamics of average anti-SARS-CoV-2 IgM titers over 12 months, Bejaia University Hospital, Algeria, 2020–2021
Note: ***$p < 0.001$.
Abbreviation: IgM: Immunoglobulin M.

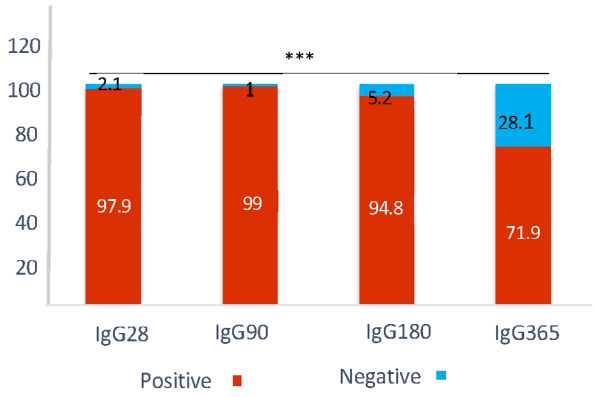

Figure 3. Anti-SARS-CoV-2 IgG seropositivity rate, Bejaia University Hospital, Algeria, 2020–2021
Note: ***$p < 0.001$.
Abbreviation: IgG: Immunoglobulin G.

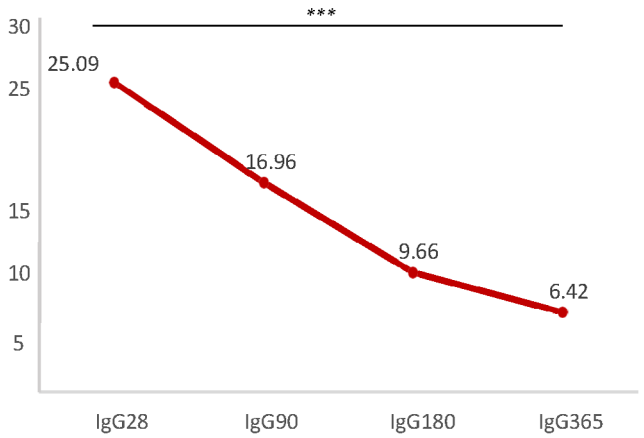

Figure 4. Dynamics of average anti-SARS-CoV-2 IgG titers over 12 months, Bejaia University Hospital, Algeria, 2020–2021
Note: ***$p < 0.001$.
Abbreviation: IgG: Immunoglobulin G.

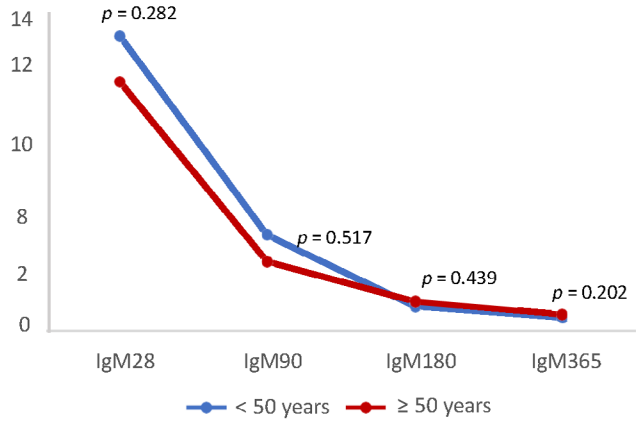

Figure 5. Dynamics of average anti-SARS-CoV-2 IgM titers according to age (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgM: Immunoglobulin M.

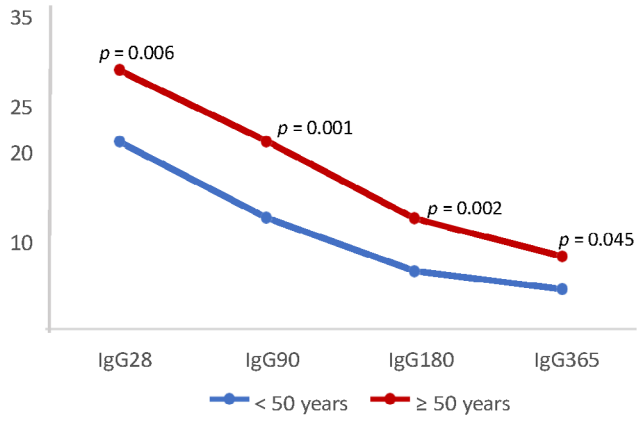

Figure 6. Dynamics of average anti-SARS-CoV-2 IgG titers according to age (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgG: Immunoglobulin G.

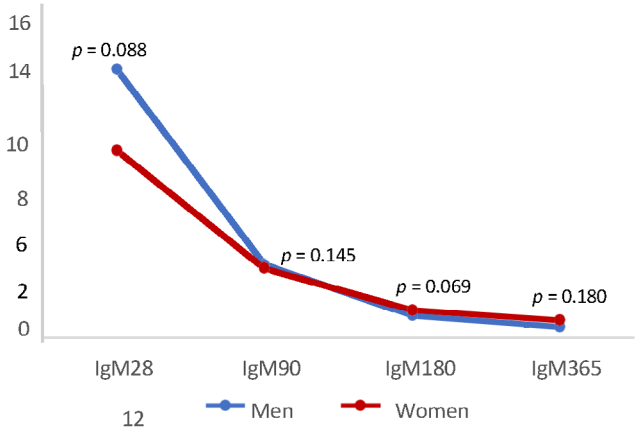

Figure 7. Dynamics of average anti-SARS-CoV-2 IgM titers according to gender (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgM: Immunoglobulin M.

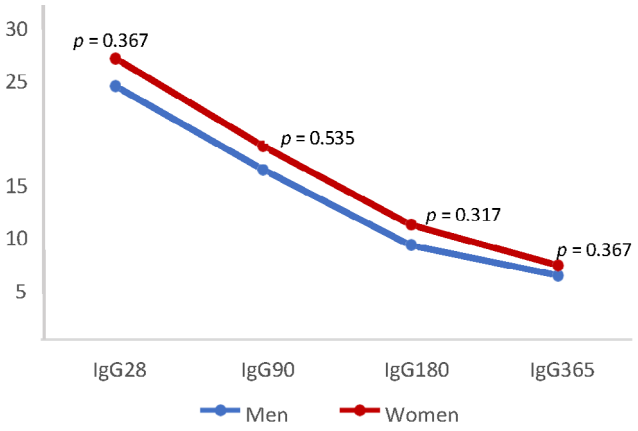

Figure 8. Dynamics of average anti-SARS-CoV-2 IgG titers according to gender (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgG: Immunoglobulin G.

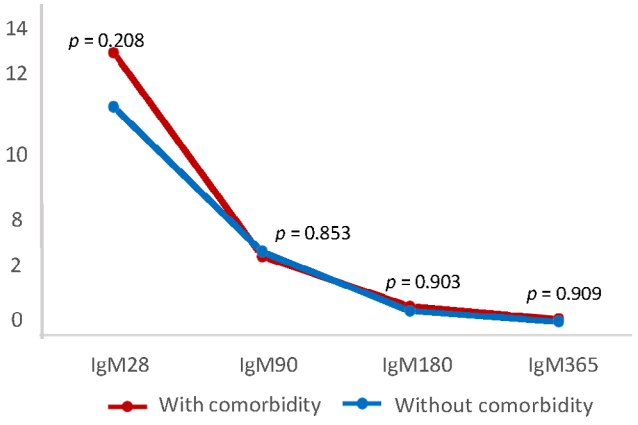

Figure 9. Dynamics of average anti-SARS-CoV-2 IgM titers with or without comorbidities (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgM: Immunoglobulin M.

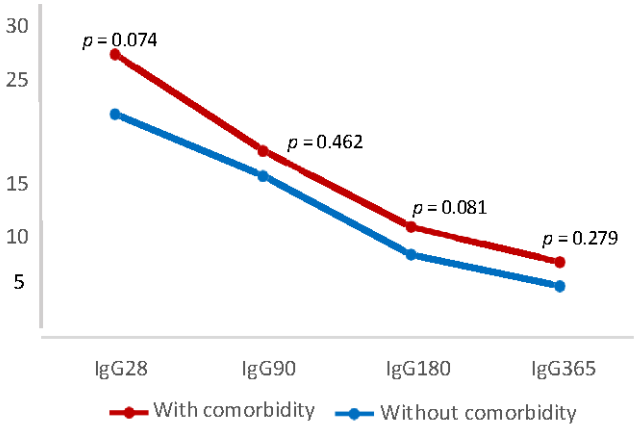

Figure 10. Dynamics of average anti-SARS-CoV-2 IgG titers depending on the existence or absence of comorbidities (Bejaia University Hospital, Algeria, 2020)
Abbreviation: IgG: Immunoglobulin G.

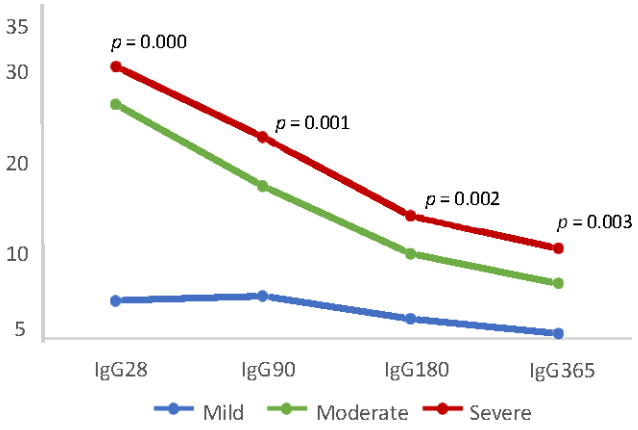

Figure 11. Dynamics of average anti-SARS-CoV-2 IgG titers by disease severity (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgG: Immunoglobulin G.

observed only at D28 and D90 ($p = 0.000$ and $p = 0.040$, respectively) (Figure 12). Overall, these findings indicate that anti-SARS-CoV-2 antibody responses are positively associated with COVID-19 severity.

3.3.3. Influence of radiological characteristics

The influence of radiological findings, specifically pulmonary involvement, on antibody responses was also assessed. Mean IgM and IgG titers were consistently higher in convalescent patients with pneumonia compared to those without pneumonia at all follow-up time points. These differences were statistically significant for IgG throughout the follow-up period ($p < 0.05$), whereas for IgM, significance was observed only at D28 and D90 ($p < 0.05$) (Figures 13 and 14). In summary, higher IgG antibody titers were significantly associated with SARS-CoV-2 pneumonia.

3.3.4. Influence of anti-SARS-CoV-2 vaccination on antibody titers

A subgroup of 13 convalescent participants received SARS-CoV-2 vaccination between D180 and D365. Among them, three individuals received a single dose of the Sinovac vaccine 14 to 28 days before the D365 sampling (mean interval: 24.88 days), with the second dose scheduled after the end of follow-up. The remaining 10 participants received two vaccine doses: AstraZeneca ($n = 2$), Sputnik ($n = 2$), or Sinovac ($n = 6$), administered 5–60 days before the D365 sampling (mean interval: 46.08 days).

To evaluate the impact of vaccination on antibody kinetics, IgG titers were compared between D180 and

D365 in vaccinated and unvaccinated convalescent groups (Figure 15). In the vaccinated group ($n = 13$), a clear increase in anti-SARS-CoV-2 IgG titers was observed following vaccination. Mean IgG levels increased from 13.09 ± 9.93 AU/mL at D180 (pre-vaccination) to 19.22 ± 15.08 AU/mL at D365 (post-vaccination), with a statistically significant difference ($p = 0.000$). These findings indicate a strong boosting effect of vaccination on humoral immunity in previously infected individuals.

4. Discussion

Regarding the kinetics of long-term anti-SARS-CoV-2 IgM and IgG antibodies, this study evaluated seropositivity rates and mean titers of IgM and IgG at different time points (D28, D90, D180, and D365) over a 12-month period following symptom onset. The aim was to assess the persistence of the humoral immune response after natural SARS-CoV-2 infection and to identify long-term antibody trends.

During the follow-up period, a decrease in seropositivity rates for both IgM and IgG was observed from D28 to D365 (all $p = 0.000$), while IgG titers remained higher than IgM titers, consistent with several studies.[21–23] In other words, IgM and IgG seropositivity decreased with disease progression in our participants. This progressive decline in anti-SARS-CoV-2 antibodies over time has also been reported in several published studies (Table 2).[21–23,24–27]

Table 2. International studies that have shown the regression of anti-SARS-CoV-2 antibodies over time

Country (ref.)	Year	Number of patients	Follow-up duration
Strasbourg[21]	2020–2021	393	13 months
Czech[22]	2020–2021	662	8 months
Belgium[23]	2020–2021	116	12 months
Italy[24]	2020–2021	32	14 months
China[25]	2020	284	7 months
United Kingdom[26]	2020–2021	20	11 months
Thailand[27]	2020–2021	531	12 months
Algeria	2020–2021	96	12 months

Furthermore, serological follow-up up to 365 days after symptom onset shows that anti-SARS-CoV-2 IgM and IgG antibodies can persist over time, up to 12 months, in agreement with other studies[21,27–36]. Nevertheless, continuous monitoring highlights

important differences in IgM and IgG antibody dynamics and confirms the long-term durability of IgG responses induced by SARS-CoV-2 infection.[25]

The antibody response to SARS-CoV-2 infection may be comparable to that observed in SARS-CoV or other viral infections.[36] IgM titers declined more rapidly than IgG titers; IgM was transient and became undetectable in more than half of the convalescents after approximately three months (D90), with only 37.5% remaining positive. Therefore, as with other viral infections[37], anti-SARS-CoV-2 IgM may serve as a marker of acute infection. Isho *et al.*[2] also reported that IgM persists for a short duration in serum and saliva, and several other studies have also demonstrated a rapid decline in IgM levels.[38–42]

However, a notable finding was the persistence of IgM in a small proportion of convalescents (12.5%) throughout the 12-month follow-up. Similar results have been reported in another study, where, after 12 months of follow-up in 538 convalescents, only 69 remained IgM-positive (12.8%).[42] This is consistent with other studies, although the rate observed in our study was higher than that reported in some investigations.[42,43] This persistence may be explained by the continued presence of viral antigens in certain body compartments, which act as reservoirs and stimulate the immune system, as suggested in previous studies.[44] Further specific studies are required to better understand this phenomenon.

In contrast to IgM, IgG titers remained elevated over time. By comparing antibody levels at different time points, we found that IgG seropositivity plateaued between D28 and D90. This study confirmed that IgG levels remained stable for approximately three months, consistent with previous reports[33,45–51], before declining thereafter. Isho *et al.*[2] also reported that IgG levels remain relatively stable up to 105 days after symptom onset. Additionally, 71.9% of IgG remained detectable for up to 12 months, consistent with some studies, lower than in others, and higher than reported in several studies where rates exceeded 70% (Table 3).[31,42–45,51,52]

The persistence of IgG antibodies over time has been widely reported, particularly in studies with follow-up periods of 6–8 months.[39,53–55] Some studies have shown that humoral immunity may persist for more than 12 months after symptom onset, despite a gradual decline in antibody levels.[28,31,55–56] Xiang *et al.*[57] also found that most patients recovering from COVID-19 developed detectable IgG antibodies one year after symptom onset. Other studies have reported IgG persistence up to 18 and 20.5 months in recovered patients.

In comparison, studies on SARS-CoV by Feng *et al.*[58], which shares approximately 79.6% genomic sequence identity with SARS-CoV-2 and uses the same receptor,

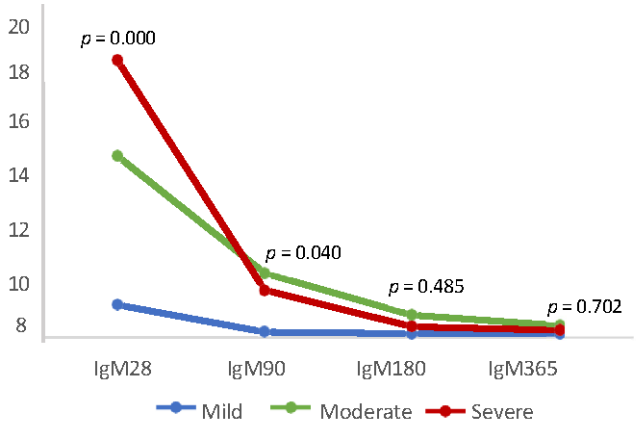

Figure 12. Dynamics of average anti-SARS-CoV-2 IgM titers according to the severity of the disease (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgM: Immunoglobulin M.

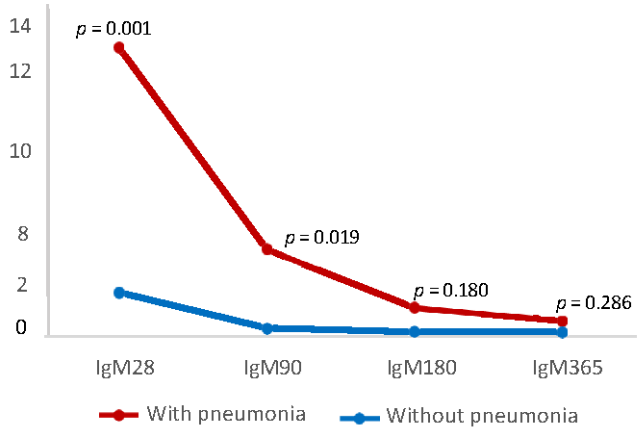

Figure 13. Dynamics of average anti-SARS-CoV-2 IgM titers depending on the existence or absence of pneumonia (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgM: Immunoglobulin M.

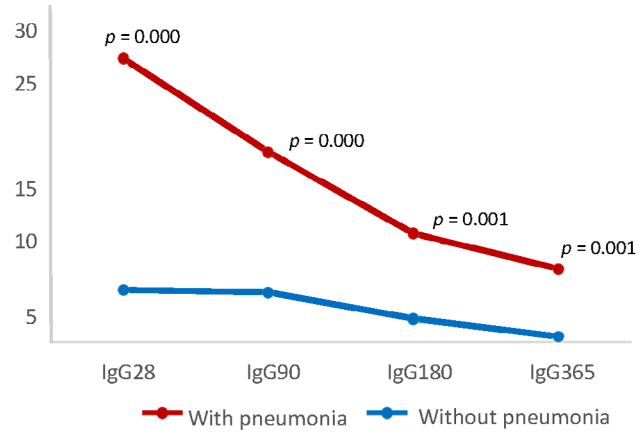

Figure 14. Dynamics of average anti-SARS-CoV-2 IgG titers in patients with or without pneumonia (Bejaia University Hospital, Algeria, 2020–2021)
Abbreviation: IgG: immunoglobulin G.

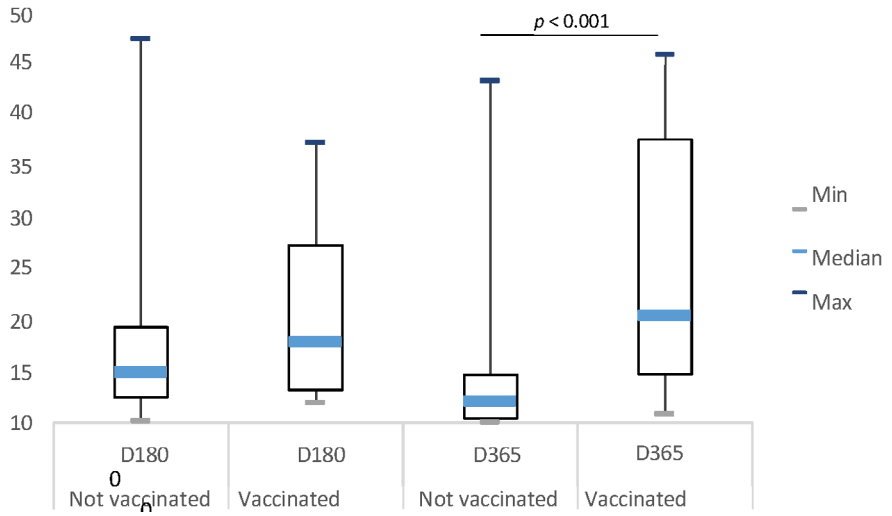

Figure 15. Comparison of the dynamics of immunoglobulin G antibody titers between two vaccinated and unvaccinated groups of convalescents at two follow-up times (D180 and D365 after infection)

have shown that more than 70% of patients retained detectable IgG titers up to 1, 2, and 3 years. Furthermore, prolonged IgG persistence beyond two years in SARS-CoV-recovered patients has also been reported[59,60], highlighting the importance of long-term monitoring of antibody responses.

Table 3. Seropositivity rate of IgM and IgG anti-SARS-CoV-2 and their persistence at 12 months after symptoms in different international studies

Studies (ref.)	Attendees	IgM positivity rate at 12 months	IgG positivity rate at 12 months
Li *et al.*[31]	869	–	70%
Zeng *et al.*[42]	538	12.8% (69/538)	82.9% (446/538)
Lu *et al.*[43]	74	26%	95%
Zhang *et al.*[44]	101	26%	95%
Xiao *et al.*[45]	51	35.3%	88.2%
Zhan *et al.*[51]	121	4%	62%
Zhou *et al.*[52]			
Algeria	96	12.5%	71.9%

Abbreviations: IgG: Immunoglobulin G; IgM: Immunoglobulin M.

As for seropositivity, both IgM and IgG titers decreased over time following a similar pattern, with a significant downward trend observed from D28 to D180 (both $p < 0.001$). However, IgM declined more rapidly than IgG. Several studies have reported a rapid decline in antibody titers among recovered COVID-19 patients.[46,61–64]

For IgG, a significant decrease in mean titers was observed at D90 (16.96 ± 12.57 AU/mL vs 25.09 ± 13.97 AU/mL at D28; $p = 0.000$), followed by a continued decline up to 12 months. These findings are consistent with previous studies showing that IgG titers decline significantly within 2–3 months after infection[65], and that antibody levels continue to decrease over time.[45,66] Previous reports have indicated that antibody responses peak between 2 and 5 weeks after infection and then decline.[62,65,67]

Regarding IgM, a marked decrease was observed after three months (D90), with a mean level of 3.59 ± 6.67 AU/mL, compared to 11.93 ± 11.46 AU/mL at D28 ($p = 0.000$), and consistently lower than IgG. These differences may be explained by increased antibody affinity and avidity over time, which compensates for the decline in antibody concentration, or by changes in the recognized epitopes.[68]

In summary, most individuals develop a measurable humoral immune response against SARS-CoV-2. Although antibody levels decline over time, they remain detectable for up to 12 months after infection, highlighting the persistence of immune memory and the importance of long-term monitoring.

4.1. Influence of epidemiological, clinical, and radiological characteristics on the development of the long-term anti-SARS-CoV-2 antibody titer

The relationship between age and antibody titers following natural SARS-CoV-2 infection is complex. In the systematic review by Long *et al.*[69], evidence regarding the correlation between age and antibody response remains conflicting or

inconclusive.

Several studies have reported that antibody titers gradually increase with age during adulthood, reaching a peak between 60 and 80 years.[70] A study including COVID-19 patients aged 16 to over 65 years showed that antibody titers were associated with age, with higher titers observed in older individuals.[69] In a Tel Aviv University study (in press) involving 26,000 participants, Noam Shomron's group also reported age-related differences in antibody levels[71], with titers beginning to increase at age 51.

In our study, we evaluated the effect of age on anti-SARS-CoV-2 antibody titers and found that IgG titers were significantly higher in individuals aged ≥ 50 years than in those aged < 50 years at all stages of infection ($p < 0.05$). These findings are consistent with several studies reporting higher antibody titers in older individuals.[46,62,72,73] This increase may be explained by higher viral loads and a more pronounced inflammatory response in elderly individuals, leading to stronger antibody production. However, several studies have reported no clear association between IgG titers and age.[74–76]

The influence of sex on immune responses to SARS-CoV-2 remains unclear. Evidence regarding the association between sex and antibody response is also conflicting.[77] Sex-based differences in immune responses may be explained by hormonal factors, transcriptional regulation, and incomplete inactivation of immune-related genes on the second X chromosome in females.[78,79]

In our study, no significant association was observed between SARS-CoV-2-specific antibody titers and sex. This finding is consistent with previous studies reporting no gender differences in antibody responses among COVID-19 patients.[46,49,57,80,81] Similar weak or inconsistent associations between sex and antibody titers have also been reported elsewhere.[75,76,82]

In contrast, other studies have reported sex-related differences in antibody responses to SARS-CoV-2.[83,84] Some authors found higher antibody titers in men than in women, although antibody levels in men tend to decline more rapidly after infection.[85,86] Conversely, a small study involving 42 convalescent individuals (only four of whom were women) reported higher IgG responses in women during the early phase of infection.[87] Several studies suggest that women may develop stronger immune responses to viral infections, possibly due to sex hormones, genetic factors (X chromosome), or environmental influences.[88]

However, such sex-related differences were not observed in all studies after SARS-CoV-2 infection.[87–90] Although no significant sex-based differences were detected in our study, the sample size does not allow definitive conclusions regarding this association.

Systematic reviews and meta-analyses have demonstrated that comorbidities such as hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cancer are strongly associated with COVID-19 severity and prognosis.[91–95] However, few studies have investigated the impact of comorbidities on immune responses to SARS-CoV-2.[96–99]

Huang *et al.*[100] reported that diabetes was associated with higher IgG titers, suggesting that individuals with more severe disease due to comorbidities may develop stronger antibody responses.[5] Similar findings were reported by Gudbjartsson *et al.*[41], Huang *et al.*[100], and Terpos *et al.*[101], In contrast, our study found no significant difference in antibody responses between participants with and without comorbidities, consistent with another study.[49] However, an American study reported that certain comorbidities were associated with higher IgG titers.[97]

Numerous studies have reported a positive association between disease severity and antibody titers.[101–103] Severe COVID-19 is often associated with a cytokine storm characterized by elevated pro-inflammatory cytokines.[104,105] Humoral and cellular immune responses have been shown to correlate positively with disease severity.[106,107] Higher antibody titers in severe patients may be related to higher viral loads[108,109], excessive T-cell activation[110–112], and an exaggerated immune response. This uncontrolled immune activation may contribute to disease pathogenesis through systemic inflammation ("cytokine storm") and organ damage.[82]

In our study, severe patients exhibited higher antibody titers than moderate or mild cases, while mild cases showed the lowest titers, consistent with previous studies.[61,107,112–117] Several studies have reported lower and delayed IgG seroconversion in asymptomatic individuals compared to symptomatic patients.[118] Other studies also reported higher antibody titers in severe cases, which aligns with our findings.[5,119–121] In contrast, several studies have reported lower IgG titers in severe cases, possibly due to prolonged viral exposure or impaired immune responses[101], with similar findings in other studies.[39,122–124]

Regarding pulmonary involvement, convalescent patients with pneumonia tended to develop higher antibody responses than those without pneumonia. Mean IgG titers were significantly higher in the pneumonia group ($p < 0.05$). These findings are consistent with previous studies showing higher and more persistent IgG levels in patients with pneumonia.[27,80,125,126]

A subset of participants ($n = 13$) received SARS-CoV-2

vaccination after infection (starting January 30, 2021) and were included to assess the impact of vaccination on antibody titers. IgG levels were analyzed at D180 and D365, and vaccinated participants showed significantly higher mean IgG titers than unvaccinated participants. This increase is expected, as vaccination boosts the immune response induced by prior infection. Previous studies have shown that vaccination in previously infected individuals induces higher antibody titers compared to unvaccinated individuals, although these titers may decline over time.[127–129]

Overall, our results show that IgG titers gradually declined over time up to D365 after infection, while vaccination induced a significant increase in IgG levels. These findings are consistent with previous studies.[33,130–133] These results support the recommendation of vaccination for individuals with prior SARS-CoV-2 infection. Individuals with hybrid immunity exhibit stronger antibody responses than those with infection alone. This is particularly important in the context of emerging variants.[133,134] However, data regarding the optimal timing and number of vaccine doses in previously infected individuals remain limited.[135]

Our findings also suggest that immune responses vary according to disease severity, which may inform vaccination strategies. For example, individuals with mild infection may benefit from earlier vaccination, as they tend to have lower long-term antibody levels compared to those with severe disease.[10] Additionally, antibody titers decline rapidly within the first three months after infection. These observations may be useful for determining optimal vaccination schedules. The decline in IgG titers observed around the third month suggests that a booster dose may be necessary annually.

5. Conclusion

This study showed that most recovered COVID-19 individuals develop a humoral immune response and produce robust SARS-CoV-2-specific IgM and IgG antibodies. Anti-SARS-CoV-2 antibody titers declined over time but persisted for at least 12 months, with IgG seropositivity remaining above 70%. These findings provide insight into the presence and persistence of SARS-CoV-2-specific antibodies.

The IgG antibodies persisted in the vast majority of recovered patients, regardless of disease severity, age, sex, or comorbidities, for up to 12 months after symptom onset. A positive association was observed between IgG antibody titers and age, disease severity, and the presence of SARS-CoV-2 pneumonia. Furthermore, individuals aged ≥ 50 years, those with severe disease, and those who developed pneumonia were more likely to exhibit stronger antibody responses than individuals aged < 50 years, those with mild or moderate disease, or those without pneumonia. Similarly, vaccination was associated with higher IgG levels. The mean IgG titer was significantly higher in the vaccinated group than in the unvaccinated group. This increase is expected, as vaccination enhances the immune response induced by prior infection. In contrast, antibody levels were not significantly influenced by sex or the presence of comorbidities.

Overall, the results indicate a sustained and prolonged immune response in patients who recovered from COVID-19. Vaccination remains highly relevant for this population. Although antibody levels gradually declined over time, they remained detectable, suggesting ongoing immune protection. These findings may help guide the planning of booster vaccination strategies, including for individuals with prior SARS-CoV-2 infection. In conclusion, based on our findings and the large body of published studies, further efforts are needed to develop standardized approaches for evaluating individual immune protection against SARS-CoV-2 that account for clinical characteristics and patient-specific factors.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Sabrine Boufarou
Formal analysis: Sabrine Boufarou, Nassima Achour
Investigation: All authors
Methodology: Sabrine Boufarou
Writing–original draft: Sabrine Boufarou
Writing–review & editing: Sabrine Boufarou, Nassima Achour

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the University of Bejaia, Algeria. The committee reviewed and authorized all aspects of the study protocol, including data

collection, analysis, and the use of clinical information derived from human subjects. Informed consent was obtained from all patients who participated in this study. Consent was clear, voluntary, and provided in written form prior to inclusion in the study.

Consent for publication

Verbal consent for publication was obtained from all patients involved in this study. All identifying information has been carefully anonymized to ensure patient confidentiality.

Availability of data

Data are available upon reasonable request from the corresponding author.

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