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RESEARCH ARTICLE

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The kinetics and predictors of anti-SARS-CoV-2 antibodies up to 8 months after symptomatic COVID-19: A Czech cross-sectional study

Ladislav Štěpánek[1] | Magdaléna Janošíková[1] | Lubomír Štěpánek[2] | Marie Nakládalová[1] | Alena Boriková[1]

[1]Department of Occupational Medicine, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacký University Olomouc, Olomouc, Czech Republic

[2]Institute of Biophysics and Informatics, First Faculty of Medicine, Charles University, Prague, Czech Republic

Correspondence

Ladislav Štěpánek, Department of Occupational Medicine, University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacký University Olomouc, I. P. Pavlova 185/6, 779 00 Olomouc, Czech Republic.
Email: ladislav.stepanek@upol.cz

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Palacký University Olomouc; University Hospital Olomouc

Abstract

The presence of neutralizing SARS-CoV-2-specific antibodies indicates protection against (re)infection, however, the knowledge of their long-term kinetics is limited. This study analyzed the presence of COVID-19-induced antibodies in unvaccinated healthcare workers (HCWs) over the period of 1–8 months post symptom onset (SO) and explored the determinants of persisting immunoglobulin (Ig) seropositivity. Six hundred sixty-two HCWs were interviewed for anamnestic data and tested for IgG targeting the spike protein (S1 and S2) and IgM targeting the receptor-binding domain. A Cox regression model was used to explore potential predictors of seropositivity with respect to the time lapse between SO and serology testing. 82.9% and 44.7% of HCWs demonstrated IgG and IgM seropositivity, respectively, with a mean interval of 83 days between SARS-CoV-2 detection and serology testing. On average, HCWs reported seven symptoms in the acute phase lasting 20 days. IgG seropositivity rates among HCWs decreased gradually to 80%, 50%, and 35% at 3, 6, and 8 months after SO, while IgM seropositivity fell rapidly to 60%, 15%, and 0% over the same time intervals. The number of symptoms was the only predictor of persisting IgG seropositivity (odds ratio [OR] 1.096, 95% confidence interval [CI] 1.003–1.199, $p = 0.043$) and symptom duration a predictor of IgM seropositivity (OR 1.011, 95% CI 1.004–1.017, $p = 0.002$). Infection-induced anti-SARS-CoV-2 IgG rates drop to a third in seropositive participants over the course of 8 months. Symptom count and duration in the acute phase of COVID-19 are both relevant to the subsequent kinetics of antibody responses.

KEYWORDS

antibody, COVID-19, immunoglobulin, prediction, SARS-CoV-2, seropositivity

1 | INTRODUCTION

The pandemic of the coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread around the world violently with ongoing and prolonged high rates of new infections. Despite the fact that we have effective tools at our disposal to combat the disease, including vaccination, COVID-19 continuously presents a heavy burden on public health with enormous health resource strains.[1,2]

The SARS-CoV-2 infection induces an immune response activating the innate and adaptive immune system, which leads to viral clearance and spontaneous recovery in most cases. Virus-specific T

and B cells evolve and, consequently, plasma cells begin to produce virus-specific antibodies targeting the nucleocapsid (N) or the spike (S) protein of SARS-CoV-2. This usually happens a few days up to weeks after infection, depending on the immunoglobulin (Ig) subclass.[3]

The ability to defend a cell from an infectious particle by neutralizing the particle's biological effects, that is, the neutralizing capacity, is an essential characteristic of antibodies. Given their mechanism of action, neutralizing antibodies play a crucial role in the prevention of COVID-19 (re)infection. While antibodies targeting the N protein are unlikely to directly neutralize SARS-CoV-2, those targeting the S protein (specifically, the receptor-binding domain (RBD) of the S1 subunit) are considered to be the main neutralizers.[4–6] As the natural immune response to COVID-19 develops in the infected individual, IgM acts as the first antibody response and a powerful suppressor of SARS-CoV-2, while IgG appears later and remains present in the human body for months.[1,7]

Neutralizing antibodies against SARS-CoV-2 provide the best current indication of being protected against reinfection (in previously infected subjects) or breakthrough infection (in vaccinated subjects). In other words, neutralizing antibodies are the most reliable markers indicating immunity to COVID-19 known to date.[6,8] The long-term characteristics of anti-SARS-CoV-2 antibodies, which include the persistence of antibodies and the duration of the immune protection, remain largely unclear, although some follow-up studies have revealed relatively stable IgG titers over several months following COVID-19 infection.[1,3,8] However, results vary depending on the sample size, population, comorbidities, treatment, and type of antibody detection assays. The immune characteristics of natural infection play a key and referenced role in estimating antibody effects after vaccination, and thus in creating vaccination strategies.[1]

The present study follows up on the pilot work of the same authors dealing with natural, infection-induced antibody responses after the acute phase of COVID-19.[9] The aim of the follow-up study was to analyze the kinetics of antibody responses in unvaccinated healthcare workers (HCWs) after COVID-19 in the period of 1–8 months post symptom onset (PSO) and to determine predictors of persistent IgG and IgM seropositivity.

2 | METHODS

2.1 | Study population

The study sample consisted of all HCWs (n = 662) from the Olomouc Region, Czech Republic, who requested to have their COVID-19 recognized as an occupational disease (OD) at the OD Center of the Department of Occupational Medicine, Olomouc University Hospital, between November 2020 and September 2021. These HCWs had their viral ribonucleic acid collected by a nasopharyngeal swab and detected using a reverse transcription-polymerase chain reaction (RT-PCR) test in the acute phase of the disease. The HCWs also brought a report about the course of their disease from their general practitioner (GP). They were examined at the OD Center according to a uniform protocol and submitted a blood sample for one-time serology testing. The examination took place at least 30 days and at the latest 8 months after their diagnostic RT-PCR test. All included cases were symptomatic and previously SARS-CoV-2 naïve. HCWs with SARS-CoV-2 reinfection and those who reported suspected COVID-19 symptoms after their recovery were excluded. Exclusion criteria also comprised vaccination against COVID-19 at the time of the examination and an insufficient medical report from the GP.

During the examination, the HCWs were asked about all symptoms of COVID-19 listed by the World Health Organization and the Centers for Disease Control and Prevention and their duration.[10,11] The presence of each particular symptom was determined by a yes/no question, and the total symptom duration was calculated by subtracting the symptom onset (SO) date from the symptom recovery date. Information provided by the participants was validated against the GP's report. In case of a discrepancy between the anamnestic data provided by the participant and the GP's report, the data were repeatedly verified (through other medical reports if available) and the data from the participant was finally taken into account. Disease severity was assessed according to the National Institutes of Health (NIH).[12]

Epidemiological data showed that in the period in which HCWs became infected with SARS-CoV-2, the wild-type variant of the virus was gradually replaced by the delta variant in the Czech Republic.[13] All participants signed an informed consent form regarding the anonymous use of their data. The study was approved by the Ethics Committee of the University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacký University Olomouc (reference no. 18/21).

2.2 | Laboratory analysis

The presence of antibodies was determined using SARS-CoV-2 chemiluminescence immunoassays by DiaSorin–Liaison SARS-CoV-2 S1/S2 IgG and Liaison SARS-CoV-2 IgM performed on the Liaison XL analyzer (DiaSorin S.p.A.). The automated IgG assay detects antibodies against the S1 and S2 subunits of the S protein, whereas the IgM assay detects antibodies targeting the RBD. For the diagnostic assays, DiaSorin guarantees clinical sensitivity and specificity above 95%, as well as excellent detection of neutralizing antibodies (94.4% positive agreement with the plaque reduction neutralization test).[14] Recent studies have proved that the performance of DiaSorin assays is comparable to other commercial immunoassays and opens the possibility of their application in epidemiological studies.[15–17] The level of IgG antibodies was considered negative at <15 AU/ml, positive at ≥15 AU/ml (i.e., seropositivity). For IgM antibodies, an index <1.1 represented seronegativity, an index ≥1.1 represented seropositivity.

RT-PCR was performed on nasopharyngeal swabs collected in 2 ml of universal transport media (UTM, COPAN Diagnostics Inc.). Viral RNA isolation was performed on 200 ml of the swab in UTM

using automatic nucleic acid magnetic beads extraction platform Zybio EXM 3000 and Nucleic acid extraction kit (Zybio). The final elution volume was 50 ml. RT-PCR was performed using two detection kits: the Novel Coronavirus (2019-nCoV) Real-Time Multiplex RT-PCR Kit (ZJ Bio-Tech Co., Ltd.) and the Allplex SARS-CoV-2 Assay (Seegene Inc.). Antibody detection and RT-PCR testing were performed in a certified microbiological laboratory of the university hospital in compliance with all standard procedures and manufacturer instructions of the used diagnostic kits and devices.

2.3 | Statistical analysis

Statistical analyses were conducted in the R software environment (R Foundation for Statistical Computing; http://www.r-project.org/). All numerical variables were characterized with descriptive statistics. The studied variables, especially antibody levels, showed a right-skewed distribution, as evidenced by the mean/median index $\gg 1$ (Table 1). We quantified the correlations of numerical variables with Spearman's correlation coefficient (r) and used regression analysis methods to explore the dependence of the serology status (seropositivity or seronegativity, inversely, as a disjunct event) on personal, anthropometric, and anamnestic data.

Taking into account the natural changes in antibody levels over time and the cross-sectional nature of the study with uneven intervals between the participants' SO and serology testing, we opted for a proportional hazards regression model (time-to-event analysis with right-censoring/Cox regression) to eliminate the effect of the intervals' irregularity. This means the model predicted the serology status bound to a specific interval from SO to serology testing (=the response variable consisted of two components). Other examined variables served as independent explanatory variables (predictors). The regression model was expanded upon by log-rank statistics and Kaplan–Meier curves to specify statistically significant predictors. The theoretical assumption of the model used is 100% seropositivity at the beginning of the interval between SO or PCR test, respectively, and serology testing, which is justified by the available knowledge of antibody development[3,18,19] and the minimum interval of 30 days required for inclusion in the study. The level of statistical significance was set at $p = 0.05$.

3 | RESULTS

3.1 | Studied characteristics and their correlation

The study population consisted of 662 HCWs aged 44 years on average, with a predominance of women ($n = 541$) over men ($n = 121$; Table 1). Both the mean and median concentrations of anti-SARS-CoV-2 IgG were above the seropositivity cutoff point. Specifically, 549 (82.9%) participants were IgG seropositive at the time of serology testing.

According to the median anti-SARS-CoV-2 IgM level, most of the HCWs were seronegative, but due to a right-skewed distribution of antibody values, the mean IgM value was above the immunoassay cutoff point. Two hundred ninety-six (44.7%) HCWs were IgM seropositive. The interval between SARS-CoV-2 detection and serology testing averaged 81 days, which was 2 days less than the average interval between SO and serology testing. In other words, the clinical manifestation of COVID-19 began about 2 days before an RT-PCR test could determine the infection. The interval between SO and serology testing was 1–3 months in 390 (58.9%) HCWs, 3–6 months in 192 (29%), and 6–8 months in 80 (12.1%) HCWs. The mean and median durations of COVID-19 acute phase symptoms were 19.8 and 14 days, respectively.

HCWs reported a mean of 7 symptoms present in the acute phase. The IgG seropositive reported a median of 7 symptoms, while the seronegative only 6. The interviewed symptoms were noted with the following frequency: 631 (95.3%) cases of fatigue, 540 (81.6%) headache, 526 (79.5%) muscle or body aches, 496 (74.9%) anosmia or ageusia, 470 (71%) fever or chills, 469 (70.8%) cough, 353 (53.3%) dyspnea, 335 (50.6%) congestion or runny nose, 245 (37%) chest pain or pressure, 202 (30.5%) diarrhea, 185 (27.9%) sore throat, 54 (8.2%) nausea or vomiting and 50 (7.6%) rash on skin. A mild course of the disease prevailed, being noted in 479 (72.4%) participants, followed by a moderate course in 168 (25.4%) participants, and a severe course in 15 (2.3%) participants. The correlations of numerical variables throughout the entire sample were weak; the strongest occurred between disease severity and symptom duration ($r = 0.4$,

TABLE 1 Studied characteristics of subjects

Characteristics		
N	662 (541 females, 121 males)	
	Mean (95% CI)	Median
Age (years)	44.09 (43.27; 44.91)	45
Weight (kg)	77.44 (76.14; 78.74)	74.5
Height (cm)	169.2 (168.36; 170.04)	169
BMI (kg/m^2)	27.56 (26.63; 28.48)	25.93
IgG level (AU/ml)	65.75 (60.8; 70.7)	46.65
IgM level (index)	3.08 (2.47; 3.68)	0.9
Symptom duration (days)	19.75 (18.26; 21.24)	14
Number of symptoms present (*N*)	6.9 (6.73; 7.07)	7
Interval between SARS-CoV-2 detection and serology testing (days)	81.24 (77.98; 84.49)	69
Interval between symptom onset and serology testing (days)	83.16 (79.82; 86.5)	71

Abbreviations: BMI, body mass index; CI, confidence interval; IgG, immunoglobulin G; IgM, immunoglobulin M; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

$p < 0.001$), and between disease severity and the number of acute phase symptoms ($r = 0.29$, $p = 0.002$). In all other cases, the correlation coefficient did not exceed 0.25 (Table 2).

3.2 | Persistence of Ig seropositivity

An inverse relationship was noted between the interval from SO to serology testing and both IgG and IgM seropositivity rates (Figure 1). The portion of participants with IgG levels above the cutoff point fell below 80% if serology testing was done more than 3 months PSO, below 60% if more than 6 months PSO, and below 35% at 8 months PSO. The decrease in the portion of IgM seropositive HCWs was even more radical. Less than 50% of them manifested IgM levels above the cutoff point 3 months PSO, and if serology testing was performed more than 6 months PSO, the proportion of IgM seropositive participants did not exceed 15%.

3.3 | Predictors of seropositivity

The only statistically significant predictor of IgG with respect to the time interval between COVID-19 SO and serology testing in the Cox regression was the number of symptoms present in the acute phase of the disease (Table 3). With each symptom recorded, the chance of detecting seropositivity increased 1.096 times ($p = 0.043$), and inversely, the chance of IgG seronegativity decreased 0.912 times.

Symptom numbers 3 through 6 showed the highest statistical significance in differentiating between seropositivity/seronegativity distribution analyzed by a log-rank test ($p < 0.01$). The particular distribution of IgG kinetics depending on the lower numbers of symptoms is captured by Kaplan–Meier curves (Figure 2). The curves show that early after infection, the number of symptoms in the acute phase played a significant role in how steeply IgG levels fell, whereas around half a year after infection, the effect of the symptom number on IgG weakened.

Only one variable, symptom duration, significantly predicted maintaining IgM levels above the cutoff point (Table 3). Each day of symptom duration increased the probability of IgM seropositivity 1.011 times ($p = 0.002$), and inversely, decreased the probability of seronegativity by 0.989 times. The log-rank test showed that the most significant difference in IgM seropositivity occurrence appeared when the sample was divided into subgroups with symptom duration shorter than 21 days and exceeding or equal to 21 days ($p < 0.001$; Figure 3).

4 | DISCUSSION

The obtained results demonstrate a gradual decrease in infection-induced antibody responses to COVID-19 during the months following its acute phase. Only about a third of the participants were IgG seropositive after 8 months. Both IgG and IgM levels wane

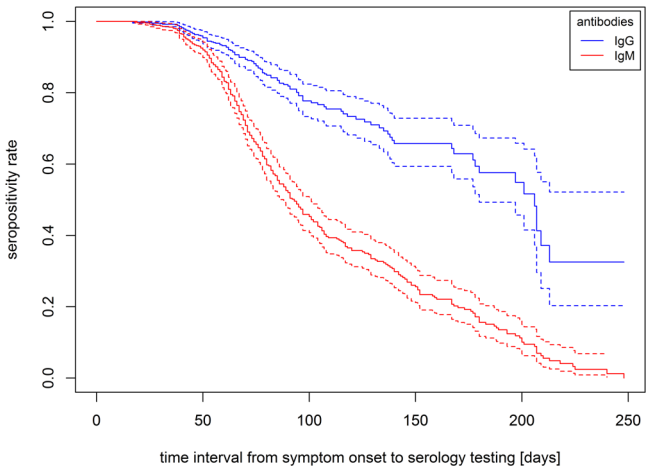

FIGURE 1 Decrease in immunoglobulin (Ig) seropositivity with respect to the interval from symptom onset to serology testing with 95% confidence bands.

TABLE 2 Matrix of correlation coefficients between examined variables.

	Age	BMI	IgG level	IgM level	Number of symptoms present	Disease severity	Symptom duration
BMI	0.12						
IgG level	0.09	0.05					
IgM level	0.09	0.02	0.25*				
Number of symptoms present	0.09	0.06	0.12	0.03			
Disease severity	0.19	0.07	0.23*	0.13	0.29*		
Symptom duration	0.24*	0.02	0.16	0.13	0.24*	0.4*	
Interval between symptom onset and serology testing	0.07	0.05	0.16	−0.12	0.04	0.1	0.12

Abbreviations: BMI, body mass index; IgG, immunoglobulin G; IgM, immunoglobulin M.

*$p < 0.05$.

TABLE 3 Proportional hazards (Cox) regression expressing the chance of seronegativity (or seropositivity as an inverse value) with respect to the interval between symptom onset and serology testing.

Explanatory variable/predictor	OR	95% CI	Std. error	*z* value	*p* value
Immunoglobulin G					
Age	0.983	0.966–1.001	0.009	−1.870	0.061
Sex = female	0.908	0.550–1.497	0.255	−0.380	0.704
BMI	0.984	0.957–1.012	0.014	−1.142	0.254
Number of symptoms present	0.912	0.834–0.997	0.045	−2.026	0.043
Disease severity	0.737	0.354–1.437	0.319	−0.956	0.301
Symptom duration	0.989	0.977–1.002	0.028	−1.623	0.105
Immunoglobulin M					
Age	0.991	0.981–1.001	0.005	−1.735	0.083
Sex = female	0.903	0.682–1.197	0.143	−0.709	0.478
BMI	0.996	0.987–1.005	0.005	−0.869	0.385
Number of symptoms present	0.989	0.939–1.042	0.023	−0.485	0.673
Disease severity	0.839	0.650–1.049	0.103	−1.699	0.501
Symptom duration	0.989	0.983–0.996	0.003	−3.109	0.002

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

following a similar pattern—however, IgM wanes faster. Many questions regarding the robustness and longevity of antibody responses to SARS-CoV-2 remain unanswered.[20] Longitudinal studies have observed relatively stable levels of IgG to the S protein after 3,[21,22] 6[23,24] and 6–8 months[25,26] PSO of COVID-19. However, others found that IgG levels above diagnostic cutoffs lasted only around 3 months PSO.[27] The results of such studies are influenced by a number of possible factors, as mentioned above in the Introduction. Studies assessing anti-SARS-CoV-2 antibody kinetics have found that IgM peaked between Weeks 3 and 4 PSO and waned thereafter.[5] A Spanish longitudinal study stated that the neutralizing capacity of anti-SARS-CoV-2 IgG was maintained for up to 7.7 months PSO.[5] In our study, 80% of the participants 3 months PSO and 60% of the participants 6 months PSO, respectively, maintained IgG seropositivity. For IgM, the portions of seropositive subjects were 50% and 15% at the same time points. In the case of serology testing 8 months PSO, IgG seropositivity occurred only in one third of the participants, and IgM no longer achieved concentrations above the cutoff point (Figure 1).

The results of a serology examination of IgG after a long time has passed since COVID-19 infection greatly depend on which specific parts of SARS-CoV-2 the antibodies are detected against. Many studies consistently observe that IgG to the N protein, found inside the virus or infected cells, decays faster than IgG to the S protein, and as such is a marker of a more recent infection. It is, however, less sensitive for assessing population seroprevalence.[5] Titers of IgG targeting the RBD appear to be very robust over time, as shown by a longitudinal study from Switzerland with a progressive increase in titers at 1, 3, and 6 months PSO.[28] An Austrian study found that even after 12 months, antibodies against the RBD persisted in all cases with increasing concentrations.[29] Our study involved the detection of IgG directed nonspecifically against various epitopes of the S1 and S2 subunits of the S protein.

The kinetics of SARS-CoV-2-specific antibodies are multifactorial, with a number of identified factors influencing Ig persistence. Moreover, data on particular factors is still limited or even conflicting.[30] Available studies most often report a positive association of disease severity with both antibody levels[24,25,31] and seropositivity persistence[24] in the months following the acute phase. In other words, the more severe the course of COVID-19 is, the later seroreversion occurs. However, comparisons between studies in this regard are complicated by the inconsistent definitions of disease severity.[12,32] Our data did not suggest disease severity to be a statistically significant determinant of seropositivity persistence. The only statistically significant predictor of IgG seropositivity was the number of symptoms present in the acute phase and symptom duration in the case of IgM, respectively. In particular, differences in low numbers of symptoms had the strongest impact on the kinetics of IgG antibodies. Symptom duration of at least 21 days led to the maintenance of IgM seropositivity. Significant, albeit weak, correlations were found between disease severity and the two predictors identified in the regression analysis. However, these correlation linear relationships did not translate into a statistically significant link between disease severity and seropositivity in the regression model. In this light and for the following serology status, the definition of disease severity developed by the NIH may be slightly suboptimal, as it does not reflect the number of COVID-19 symptoms or symptom duration.[12]

Some studies have, in agreement with ours, associated antibody responses to SARS-CoV-2 with the number of symptoms in the acute phase. An Italian 10-month longitudinal study using multivariate linear regression analysis showed that older age, the number of symptoms in the acute phase, and disease severity were all independent predictors of long-term immunity for both IgG and IgM.[33] An Estonian cross-sectional study showed a higher number of symptoms of the acute phase of COVID-19 (median 6) in participants with persisting IgG seropositivity several months after COVID-19, compared to seronegative participants (median 5).[34] In our study, the numbers of recorded symptoms in the same subgroups were one unit higher (medians 7 and 6). Finally, a cross-sectional study from the United States among participants who examined 2–3 months PSO proved decreasing seronegativity rates inversely to an increasing number of symptoms reported in the acute phase.[35] Most symptoms are organ-specific, so a higher number of symptoms usually means a higher number of affected body systems, which can be reflected in subsequent IgG antibody responses, as in the case of documented lung involvement.[36]

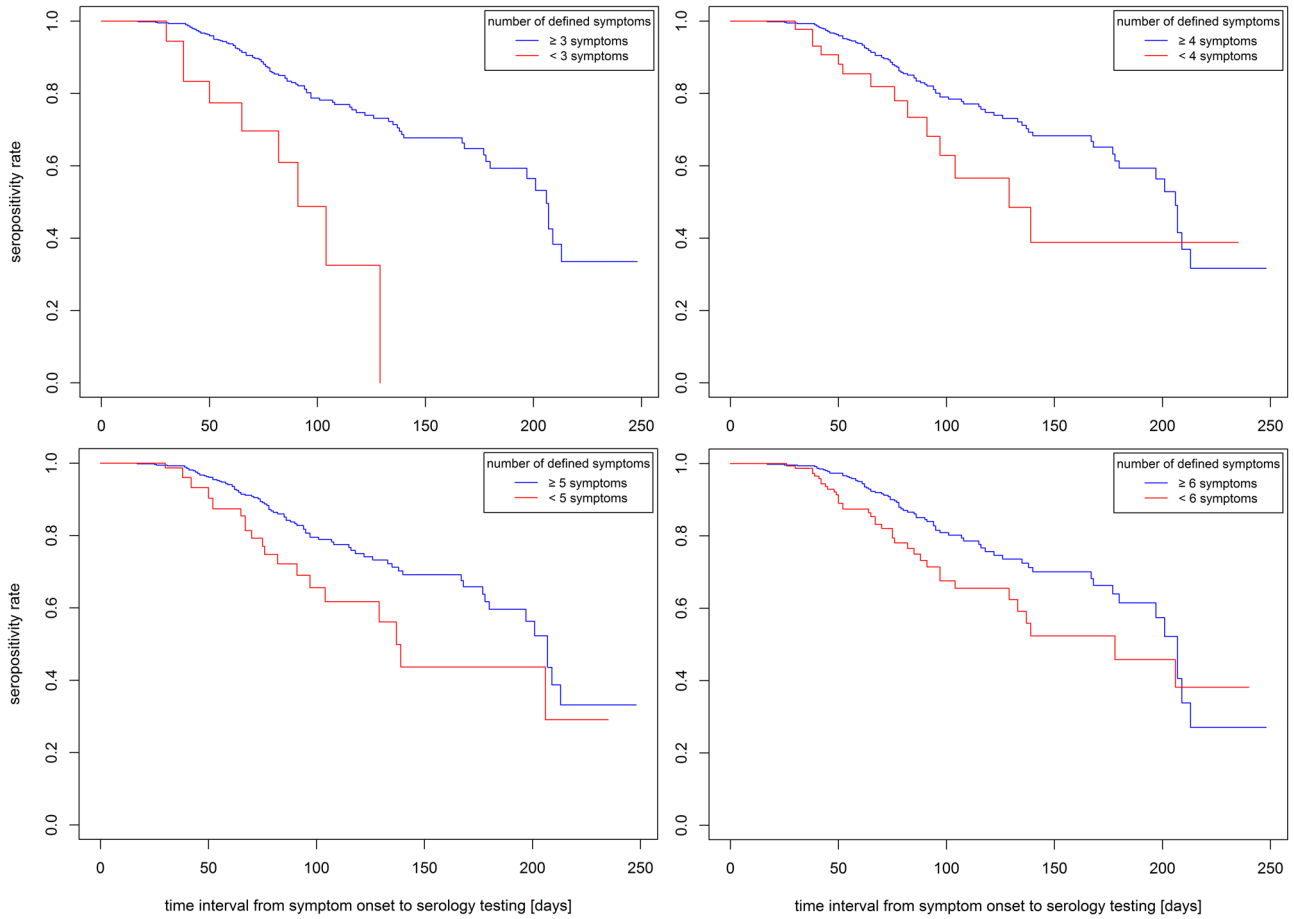

FIGURE 2 Distribution of immunoglobulin G seropositivity according to the most statistically significant numbers of symptoms based on the log-rank test.

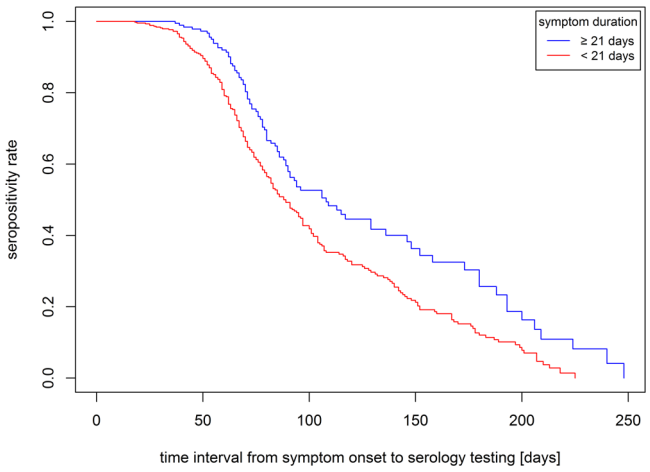

FIGURE 3 Distribution of immunoglobulin M seropositivity according to the most statistically significant symptom duration of 21 days based on the log-rank test.

Viral shedding lasts considerably longer in symptomatic patients compared to asymptomatic patients.[37] IgM plays a major role in the capacity of plasma to neutralize SARS-CoV-2.[7] The proportion of IgM seropositive individuals increases with each week of symptom duration in the acute phase of COVID-19, as shown by an Italian cross-sectional study.[38] These facts may explain the significant positive association between symptom duration and persisting IgM seropositivity noted in our sample of COVID-19 convalescents, as a longer acute phase may have required a greater need for SARS-CoV-2 neutralization.

In a pilot version of our study conducted among 152 HCWs, symptom duration appeared to be the only statistically significant predictor of IgG.[9] However, the pilot sample was different from the one used in the present study, especially as the mean interval between SO and serology testing was shorter by 25 days. Mean antibody levels and seropositivity rates differed too. Predictors of IgM, which was now symptom duration, were not determined in the pilot sample.[7]

The ability to predict the level of antibody protection in COVID-19 convalescents is important for planning epidemiological measures (infection prevention and control) as well as the development of vaccination strategies.[39] With the constant emergence of new SARS-CoV-2 variants carrying the risk of vaccination failure, knowing the kinetics and determinants of infection-induced adaptive immunity are important, and it is also crucial with respect to a possible outbreak of a completely new coronavirus pandemic.[2,40] Anamnestic data seems to have the potential to predict the

development of adaptive immunity after COVID-19 and should not be underestimated, seeing how easy it is to acquire them from patients. The cross-sectional nature of the study could be considered a limitation, but its effect was eliminated by including the interval between SO and serology testing in the response variable. Possible bias caused by using only a single immunoassay was minimized by working only with information about seropositivity, not particular Ig levels, throughout the entire study. Recall bias concerning anamnestic data was minimized by verifying against the GP's report. Only symptomatic HCWs were enrolled because asymptomatic COVID-19 cannot be recognized as an OD, which is a study limitation.

5 | CONCLUSIONS

This study demonstrates the relevance of COVID-19 symptom count and duration in the acute phase of the disease to the subsequent kinetics of antibody responses. The probability of maintaining IgG seropositivity over the following months increases 1.096 times with each symptom present in the acute phase. Each day of symptom duration increases the probability of IgM seropositivity 1.011 times. Familiarity with the kinetics of antibody responses to SARS-CoV-2 is critical for effective disease surveillance and vaccination strategies. Over the months following the acute phase of COVID-19, there is a gradual seroreversion of anti-spike Ig. IgG levels above the cutoff point were found in 80% of the participants and IgM levels in 50% of the participants 3 months PSO, and 60% and 15% of the participants 6 months PSO, respectively. In a serology test done 8 months after the acute phase, IgG seropositivity occurs in only a third of the subjects and IgM no longer reaches concentrations above the cutoff point.

AUTHOR CONTRIBUTIONS

Ladislav Stepanek: Conceptualization; methodology; Writing–original draft. Magdalena Janosikova: Formal analysis; data curation. Lubomir Stepanek: Methodology; formal analysis. Marie Nakladalova: Conceptualization; supervision. Alena Borikova: Data curation.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (Ladislav Stepanek) upon reasonable request.

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