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ORIGINAL ARTICLE

Clinical risk factors for predicting anti-Sars-Cov-2 antibody immunoreactivity duration after mild COVID-19 infection

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Abstract

Introduction: coronavirus disease 2019 (COVID-19) is a complex multisystem disorder. It is not yet well known whether symptoms in the acute phase correlate with the duration of the immune response and the persistence of chronic symptoms.

Objective: this study aimed to assess and monitor the clinical symptoms of COVID-19 and correlate them with the production of neutralizing antibodies.

Methods: a cohort of 69 health workers at the University Hospital of the Federal University of Espírito Santo (HUCAM-UFES/EBSERH) diagnosed with SARS-CoV-2 infection confirmed via RT-PCR (Real-Time Reverse Transcription–Polymerase Chain Reaction) were evaluated from the onset of symptoms up to six months. SARS-CoV-2 IgG and IgM assays were used to detect the presence of IgG and IgM against the nucleocapsid protein of SARS-CoV-2 in serum samples. IgG and IgM antibody serology, pulmonary function via spirometry, and the clinical evolution of patients were performed at 15, 30, 45, 60, 90, and 180 days after the onset of COVID-19 symptoms.

Results: sixty-nine health workers (age, 40 ± 10 years; 74% women) were evaluated for six months. All subjects showed mild to moderate COVID-19. The mean number of symptoms was 5.1 (± 2.3). The most common initial symptoms were muscle pain (77%), headache (75%), anosmia (70%), ageusia (64%), runny nose (59%), fever (52%), and coughing (52%). After 30 days, the patients had anosmia (18%), asthenia (18%), adynamia (14%), muscle pain (7%), and ageusia (7%). Regarding lung function, 9.25% presented with an obstructive pattern, and all recovered after six months. Of all analyzed participants, 18/69 (26%) did not have any reactive IgG or IgM values in any of the assessments. The IgG serology curve showed a peak, whereas IgM had the highest mean value on the 15th day. There was a progressive decrease and levels similar to those at baseline after 90 days, and 15/53 (28%) remained with reactive IgG after six months. Sore throat and shortness of breath were found to be independent risk factors, and patients with these symptoms were 5.9 times more likely to have reactive IgG on the 180th day. Patients with diarrhea were four times more likely to have reactive IgM.

Conclusion: our findings showed that 26% of patients did not produce a humoral response post-mild COVID-19. Their antibody titers dropped significantly after 90 days, and only 28% maintained reactive IgG antibodies after six months. Sore throat and shortness of breath are predictors of a longer duration of the humoral immune response.

Keywords: COVID-19; SARS-CoV-2; antibodies; immunoreactivity; risk factors

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Authors summary

Why was this study done?
This research aims to understand the immunoreactivity in COVID-19 disease during a pandemic when still unknown facts about this subject. The SARS-CoV-2 virus has rapidly spread around the world, therefore demanding great efforts to understand its impacts on the human body, especially in relation to immunological defense mechanisms.

What did the researchers do and find?
In our cohort study, sixty-nine health workers were evaluated for six months during which IgG and IgM antibody serology, pulmonary function via spirometry, and the clinical evolution were performed All subjects showed mild to moderate COVID-19. 26% did not have any reactive IgG or IgM values in any of the assessments. There was a progressive decrease in antibodies titles and just 28% remained with reactive IgG by the end of the research. Sore throat and shortness of breath were found to be independent risk factors, and patients with these symptoms were 5.9 times more likely to have reactive IgG on the 180th day.

What do these findings mean?
These findings show that a great number of patients did not produce a humoral response post-mild COVID-19 and that antibody titers drop significantly passing the time. Sore throat and shortness of breath were predictors of a longer duration of the humoral immune response. Additionally, an improvement in spirometric parameters associated with the clinical resolution of symptoms indicates an overall improvement in patient health after the transitory inflammatory state, without long-term health implications.

Highlights
• A cohort of 69 health workers at the HUCAM-UFES/EBSERH diagnosed with SARS-CoV-2 infection confirmed via RT-PCR were evaluated from the onset of symptoms up to six months.
• 26% of patients did not produce a humoral response post-mild COVID-19.
• Sore throat and shortness of breath are predictors of a longer duration of the humoral immune response, and patients with these symptoms were 5.9 times more likely to have reactive IgG on the 180th day.
• Patients with diarrhea were four times more likely to have reactive IgM.
• Their antibody titers dropped significantly after 90 days, and only 28% maintained reactive IgG antibodies after six months.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by severe acute respiratory coronavirus 2 (SARS-CoV-2). It is capable of causing a complex multisystem disorder in patients[1] and is induced by inflammatory processes[2,3]. Studies have shown that the uncontrolled release of pro-inflammatory cytokines triggered by exacerbated immunological responses is directly related to the aggressiveness of the disease[2-4]. However, the humoral immunological response pattern and antibody kinetics in patients and their implications on immunological memory have not been fully elucidated. Although complications caused by COVID-19 have led to more than 6,5 million of deaths worldwide according to WHO dashboard, and over 657 million of confirmed cases. The majority of infected people tend to have a mild-to-moderate presentation, where approximately 40% are mild and 40% moderate[3]. These patients do not need hospitalization or intensive care[5].

Moreover, recent studies have investigated whether persistent symptoms indicate sequelae that could be related to lung function or other systemic alterations[6]. Examples of this include long-COVID, considered as having persistent symptoms for weeks or months; post-COVID-19 conditions, known as any recurrent, new, or persistent health problem presented after more than four weeks post-COVID-19 disease[7]; and the implication of these conditions upon vaccination, are new concerns related to COVID-19 worldwide. We believe that observations of mild symptomatic presentations help gain knowledge of the natural outcome of the disease[8], providing short-term clinical applicability and contributing to the long-term understanding of the treatment and prevention of more severe scenarios.

COVID-19 is a complex multisystem disorder. It is not yet well known whether symptoms in the acute phase correlate with the duration of the immune response and the persistence of chronic symptoms. Therefore, this study aimed to assess and monitor the clinical symptoms of a cohort of health workers for six months and correlate them with the production of neutralizing antibodies.

METHODS

Study Design

This longitudinal study was conducted at the Federal University of Espírito Santo (UFES) in Vitória/ES and was approved by the Ethics Committee of the Cassiano Antônio de Moraes University Hospital (HUCAM/UFES) under protocol no. 4,058,734. All participants signed a consent form before enrollment. This study aimed to perform a 6-month longitudinal follow-up (from April 28 to August 26, 2020) in a cohort of health workers between 18 and 70 years of age with a confirmed diagnosis of COVID-19 via RT-PCR for SARS-CoV-2 to evaluate the duration of their humoral immune response by detecting their serum levels of IgM and IgG antibodies. In addition, we studied whether clinical symptoms were risk factors for humoral immune response duration. All patients underwent pulmonary function tests and clinical evaluation over the study period.

Clinical criteria for COVID-19 were defined as (1) at least two of the following signs and symptoms: fever, chills, sore throat, headache, cough, or runny nose; (2) flu syndrome plus dyspnea, chest pain, or O2 saturation less than 93% in room air or bluish color of the lips or face; or (3) anosmia or sudden ageusia without reports of other previous symptoms. The severity of the disease was categorized according to the patient's clinical presentation, as follows: 1) mild, with only flu-like symptoms, or 2) severe, when presenting with pneumonia or severe acute respiratory syndrome (SARS). All cases were confirmed using RT-PCR.

After recruitment, the participants were evaluated on days 15, 30, 45, 60, 90, and 180 (D15, D30, D45, D60, D90, and D180, respectively) after the onset of symptoms. Symptoms were monitored during follow-up. A serological test was performed at each evaluation to assess antibody kinetics over time. On the 15th day, a standardized clinical questionnaire was administered to define the demographic profile of the participants. On the 30th day, anthropometric measurements, bioimpedance, blood pressure measurement, electrocardiogram (EKG), pulse wave speed test (PWV), and spirometry were performed. On the 60th day, no other examinations were performed besides blood collection for further antibody serum analysis. On the 90th and 180th days, the serology tests stated above were repeated, and an EKG and spirometry test were performed on patients who presented alterations in their previous exam.

Regarding pulmonary function analysis, we only included patients who underwent spirometry tests 30 days after the initial COVID-19 symptoms. Patients with a history of lung disease were excluded, and patients with altered spirometry results were reevaluated. The data were evaluated through descriptive and comparative analyses of the examination measurements.

Confirmation of SARS-CoV-2 infection via RT-PCR using clinical specimens

SARS-CoV-2 presence was confirmed using the following RT-PCR kits: SARS-CoV-2 Fluorescent PCR (MACCURA, China; target genes: E, ORF, and N); OneStep/COVID-19 (Instituto de Biologia Molecular do Paraná – IBMP, Brazil; target genes: ORF and N); TaqPath™ COVID 19 CE IVD RT PCR Kit (Thermo Fisher Scientific, USA; target genes: S, ORF, and N); and 2019-nCoV RUO Kit (IDT - Integrated DNA Technologies, USA; target genes: N1 and N2). None of the manufacturers listed above was involved in assessing and interpreting the study results. The respective reaction mixtures were prepared according to the manufacturer's instructions. Thermal cycling for either reverse transcription or amplification was performed using the QuantStudio 5 and QuantStudio Real-Time PCR systems (Thermo Fisher Scientific). The cutoff threshold (Ct value) for each sample was recorded, and samples with Ct values < 36 were considered positive.

SARS-CoV-2-specific IgM and IgG immunoreactivity assessment

The presence of specific IgM and IgG antibodies against the nucleocapsid protein of SARS-CoV-2 was evaluated using a chemiluminescent microparticle immunoassay (CMIA; SARS-CoV-2 IgM assay; Abbott Laboratories, IL, USA), using an ARCHITECT i1000SR immunoassay analyzer. Results > 1.4 for IgG or >1.0 for IgM were considered positive.

Statistical analysis

IBM SPSS Statistics version 24 and STATA version 14.0 were used for statistical analyses. Categorical data were presented as the number of individuals and their respective percentages, while continuous variables were reported as the mean, median, and standard deviation. The assessment of the normal probability distribution was verified using the Kolmogorov–Smirnov test. Friedman's non-parametric test was used to compare the median values of the IgG and IgM levels. The Wilcoxon or Student's t-tests for paired samples were used to compare the medians or means of the parametric tests. The alpha level of significance used in all analyses was 5%.

RESULTS

A total of 73 individuals were initially included, but four were excluded because of a new SARS-CoV-2 infection, with 69 patients included in the final analysis. All the patients showed mild-to-moderate symptoms. The mean age of the patient cohort was 40 (±10) years and was predominantly female (74%; N=54). Of the 69 patients, 55 (78.77 %) had a medical history of comorbidities: 9 (12.3%) had hypertension, 2 (2.7%) had type 2 diabetes, 25 (36.23%) had pre-obesity, and 19 (27.54%) had obesity. It was found that 21.74% of the patients were taking at least one medication for chronic disease, 17.7% were smokers, 49 (71.01%) consumed alcoholic beverages, and 30 (43.48%) engaged in physical exercise. More details regarding the demographic data of the patients are shown in Table 1. The mean number of symptoms the patients experienced in the acute phase was 5.1 (±2.3). The most common symptoms in this phase were muscle pain, headache, anosmia, and ageusia. On the 30th day, the main symptoms were fatigue expressed as asthenia (18%), adynamia (14%), anosmia (18%), ageusia (7%), and muscle pain (7%).

Table 1: Demographic characteristics of the health worker cohort evaluated in this study (n= 69)

Variables	Frequency (n)	Percentage (%)
Contact with patients		
Sometimes	11	15.94
No	10	14.49
Yes	48	69.57
Worksite at the hospital		
Administrative function	5	10.61
Outpatient care (outpatient, social care, etc.)	13	16.67
Care for Inpatients	24	28.79
Support service (laboratory, pathology, nutrition, pharmacy)	6	19.70
Other locations	8	4.55

Continuation - Table 1: Demographic characteristics of the health worker cohort evaluated in this study (n= 69)

Variables	Frequency (n)	Percentage (%)
Professional role in the hospital		
Administrative services	7	3.03
Nurse	11	13.64
Nursing technician or assistant	19	10.61
Physician	13	16.67
Pharmacist/laboratory, biomedical or radiology technician	3	28.79
Nutrition	2	19.70
Cleaning, transportation, maintenance	2	4.55
Other functions not listed above	9	3.03
Home office		
No	50	72.46
Semi-presential	6	8.70
Yes	13	18.84
Risk factors		
Diabetes	2	2.90
Respiratory diseases (asthma, COPD*, etc.)	3	4.35
Systemic Arterial Hypertension	12	17.40
Obesity	10	14.50
Others	16	23.20
Smoker		
No	51	82.26
Yes	2	3.23
Past in any time	9	14.52
Frequency of alcohol use		
Rarely	37	53.62
4 or more times a week	1	1.45
23 times a week	11	15.94
Physical activity		
No	39	56.52
Yes	30	43.48

Variables	Minimum - Maximum	Median	Mean (±SD)
Age (years)	22 - 62	38	40.0 (± 10)
Number of symptoms acute phase	1 - 11	5	5.1 (± 2.3)

*COPD, chronic obstructive pulmonary disease. Source: author.

The lung function of 54 patients was evaluated using spirometry (15 did not undergo the pulmonary function test due to previous diagnostic of respiratory disease). Most of these patients were women (43/54; 79.6%), with a mean age of 39.7 (±10.1) years. Of these patients, five (9.25%) showed a mild obstructive pattern with an FEV1/FVC lower than the reference value and FEV1 > 60%. None of the patients showed a restrictive pattern. Three patients had prolonged respiratory symptoms and were medicated with beclomethasone (400 µg, 12/12h) or salbutamol (100 µg, rescue medication). On the second pulmonary evaluation (after 180 days), all patients were asymptomatic and had normal lung function according to spirometry parameters (FEV1 and FEV1/FVC). All medications were already discontinued after this phase.

The Kolmogorov-Smirnov test showed a non-normal distribution at all observation periods for IgG and IgM, so the non-parametric technique was applied for these data. There was a significant difference in the medians of IgG and IgM levels in all the assessments ($p < 0.001$).

The IgG serology curve had a peak median value on the 30th day (3.25). In contrast, the IgM serology curve had the highest median value on the 15th day (3.37), then a continuous decrease in subsequent assessments. The IgG and IgM antibody kinetic evaluations are shown in Figures 1 and 2, respectively.

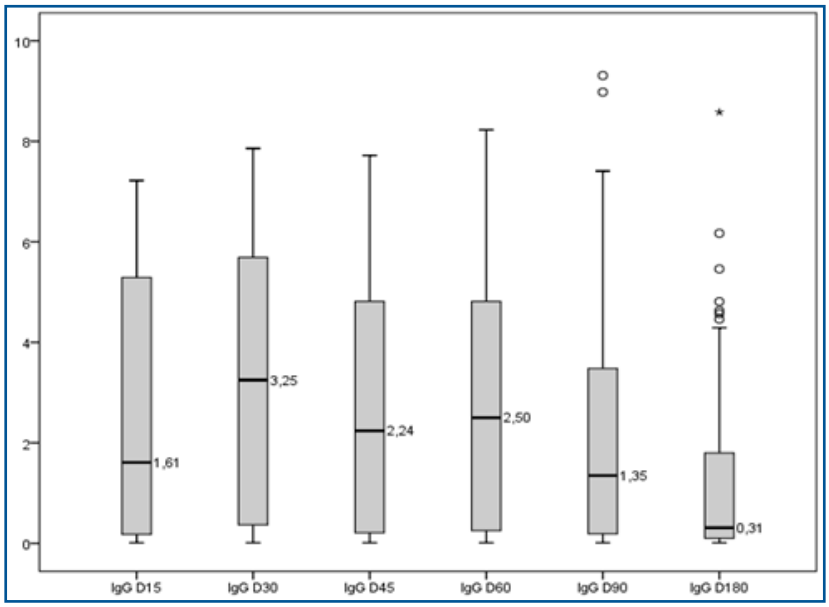

Figure 1: Anti-SARS-CoV-2 nucleocapsid IgG kinetics at each time point. The presence of specific IgM and IgG antibodies against the nucleocapsid protein of SARS-CoV-2 was evaluated using a chemiluminescent microparticle immunoassay (CMIA). Results > 1.4 are considered positive

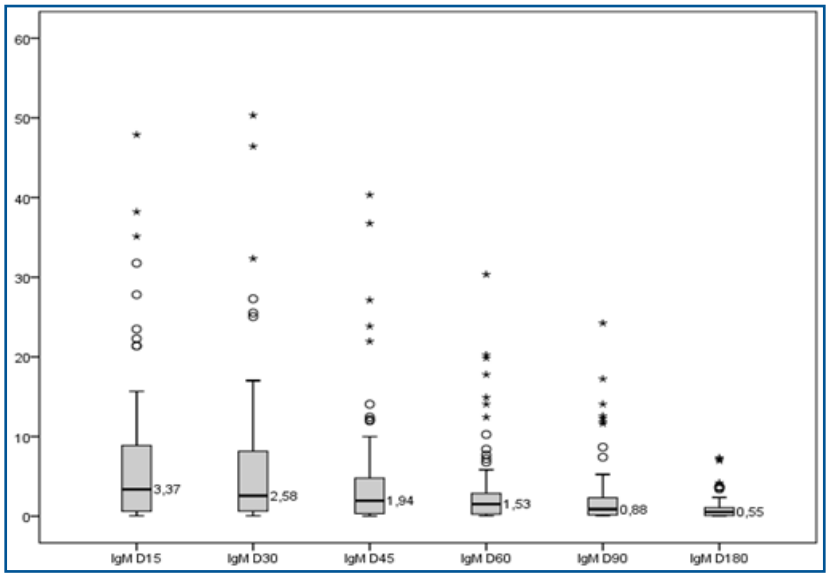

Figure 2: Anti-SARS-CoV-2 nucleocapsid IgM kinetics at each time point. The presence of specific IgM and IgG antibodies against the nucleocapsid protein of SARS-CoV-2 was evaluated using a chemiluminescent microparticle immunoassay (CMIA), Abbott's SARS-CoV-2 antibodies assay (Abbott Laboratories, IL, USA) by ARCHITECT i1000SR immunoassay analyzer. Results > 1.0 are considered positive

*D15, D30, D45, D60, D90, and D180 indicate 15, 30, 45, 60, 90, and 180 days after the onset of the first symptoms, respectively.

Of all the participants analyzed, 26% did not have any reactive values for IgG or IgM in any assessment. Of the 53 patients at the 180-day evaluation, 72% were non-reactive, and 28% and 26% had reactive IgG and IgM, respectively. There was a significant association between sore throat and shortness of breath and reactive IgG levels. Patients presenting with sore throat and shortness of breath were 5.4 and 5.9 times more likely to have a reactive IgG on day 180, respectively, than patients without this symptom. (table 2).

Table 2: Association between sore throat and shortness of breath with reactive anti-SARS-CoV-2 nucleocapsid IgG levels at 180 days

Dependent variable - IgG (reactive)		P-value*	OR	95% confidence interval for	
				Lower limit	Upperlimit
Shortness of breath	Yes	0.038	5.962	1.102	32.255
Sore throat	Yes	0.023	5.383	1.257	23.047

*Multiple logistic regression with backward variable selection method; 1 - Reference category; significant if p < 0.05

DISCUSSION

In this study, a cohort of health workers with mild COVID-19 was evaluated to determine the antibody kinetics and clinical risk factors for the duration of the humoral immune response during the disease. The most common symptoms in the acute phase were muscle pain, headache, anosmia, and ageusia. After 30 days, the main symptoms were fatigue, muscle pain, anosmia, and ageusia. Similarly, according to a follow-up in patients with non-critical COVID-19[9], anosmia was the most frequent complaint at 30 and 60 days after initial symptom onset, and 50% had asthenia after 30 days. Persistent asthenia/fatigue was also reported after 60 days in more than half of the patients in an Italian cohort[10], although the patients were not classified based on disease severity. Additionally, in a six-month follow-up in Wuhan, China[11], fatigue or muscle weakness (63%) and difficulty sleeping (26%) were among the most frequent complaints in patients with mild and moderate COVID-19 evaluate at approximately 186 days after the initial onset of symptoms.

The results of this study suggest that persistent symptoms such as fatigue or asthenia could be among the most harmful symptoms since they can make it difficult for patients to return to normal activities, such as work and physical exercise, directly impacting their quality of life. On the other hand, anosmia has been discussed more as a potential stress factor[12] than a physical disablement. Even before the COVID-19 pandemic, a correlation between changes in mood triggered by a loss of smell has been shown[13]. However, further research is required to elucidate the physiological and psychological repercussions of this condition.

The majority of healthcare workers in this study showed seroconversion to IgG; however, 26% did not show a humoral response at any time. Previous studies reported detectable IgG levels of 95%[14] and 92.6%[15] in healthcare workers and mild-to-moderate cases, respectively. Milder symptoms and the use of different methods could explain the lower seroconversion rates observed in this study.

Moreover, consistent with other studies on seroconversion[16], IgG and IgM serum levels had peaked at different periods. Our results showed that IgG values varied more between patients, resulting in more dispersed data than IgM values. Studies have argued that in terms of the timing and quantity of antibody production, this is a common phenomenon associated with individual factors such as comorbidities, and age[17]. Our results showed that IgG measurements peaked at 30 days after symptom onset and started to decrease at day 90, while IgM measurements began decreasing from day 30, continuing until days 90 and 180. Similarly, this pattern was also observed in an antibody kinetics report in patients with mild-to-moderate COVID-19, in which a slight decrease in antibody titers occurred around 90 days[18]. This corroborates the hypothesis that a stronger immunological response at the initial stage of infection leads to a milder disease presentation due to better control of disease development[19]. Thus, considering the correlation between symptom severity and IgG and IgM levels, it is also possible to associate these expected patterns with the syndromic presentations seen in patients in clinical settings.

In particular, we observed that sore throat and shortness of breath were independent risk factors for a longer duration of IgG antibody reactivity, while a prospective cohort in a Brazilian population showed similar correlations with a higher frequency of patients with cough (15). Taken together, these results suggest that respiratory symptoms are more strongly associated with the humoral immune response in COVID-19.

In addition, the assessment of lung function through spirometry revealed mild obstructive patterns in five patients during the first 30 days after the onset of symptoms, showing improvements after six months of follow-up, with no patients presenting with a restrictive pattern after the onset of symptoms post-mild COVID-19. These results were consistent with a study of 47 patients with mild COVID-19 infection, in which none of the patients presented with pulmonary impairments four months after the onset of initial symptoms as measured via spirometry[20]. This indicates that there may be no persistent pulmonary impairment in patients with mild-to-moderate infections. However, a 4-month follow-up study showed that the diffusion capacity of pulmonary function is commonly altered in COVID-19, which could be correlated with prolonged fatigue in patients[20]. Although we were not able to evaluate this factor in this study, other reports have suggested that impairments in diffusion capacity, and consequently a reduction in the ability to perform gas exchange, are correlated to immune response-mediated damage to the microcirculatory system of the lung[21]. Therefore, lung function impairment due to mild cases of COVID-19 cannot be excluded. Nevertheless, the three patients in our sample who had persistent respiratory symptoms that required medication showed spirometric improvement in FEV1 and FEV1/FVC values, indicating better airflow. Moreover, on day 180, all patients with lung function impairment at the first assessment showed an improvement in their second spirometry tests.

CONCLUSION

In conclusion, our findings showed that 26% of patients did not produce a humoral response post-mild COVID-19 and that antibody titers dropped significantly after 90 days, with only 28% maintaining reactive IgG antibodies after six months. Sore throat and shortness of breath were predictors of a longer duration of the humoral immune response. Additionally, an improvement in spirometric parameters associated with the clinical resolution of symptoms indicates an overall improvement in patient health after the transitory inflammatory state, without long-term health implications.

Author Contributions

All authors contributed to the manuscript.

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Conflicts of Interest

The authors report no conflict of interest.

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Resumo

Introdução: a doença causada pelo coronavírus (COVID-19) é complexa e multissistêmica. Ainda não se sabe se os sintomas da fase aguda estão correlacionados com a duração da resposta imune e com a persistência dos sintomas crônicos.

Objetivo: o presente estudo visa acessar e monitorar os sintomas clínicos do COVID-19, correlacionando-os com a produção de anticorpos neutralizantes.

Método: uma coorte de 69 profissionais da saúde da Universidade Federal do Espírito Santo (HUCAM-UFES/EBSERH) diagnosticados com infecção por SARS-CoV-2 confirmada via RT-PCR (Real-Time Reverse Transcription-Polymerase Chain Reaction) foram avaliados do início dos sintomas até seis meses depois. Exames laboratoriais de IgG e IgM foram utilizados para detectar a presença de IgG e IgM contra a proteína do nucleocapsídeo do vírus SARS-CoV-2 nas amostras de plasma sanguíneo. Sorologia de anticorpos IgG e IgM, função pulmonar via espirometria e avaliação clínica dos pacientes foram realizadas nos dias 15, 30, 45, 60, 90 e 180 após o início dos sintomas da doença.

Resultados: sessenta e nove profissionais da saúde (idade, 40 ± 10 anos; 74% mulheres) foram avaliados por seis meses. Todos apresentaram a forma leve a moderada do COVID-19. O número médio de sintomas foi 5.1 (± 2.3). O sintoma inicial mais comum foi dor muscular (77%), cefaleia (75%), anosmia (70%), ageusia (64%), coriza (59%), febre (52%), e tosse (52%). Após 30 dias, os pacientes mantiveram anosmia (18%), astenia (18%), adinamia (14%), dor muscular (7%), e ageusia (7%). Em relação à função pulmonar, 9.25% apresentaram padrão obstrutivo e todos recuperaram ao final dos seis meses. Dentre todos os participantes analisados, 18/69 (26%) não obtiveram nenhum valor de IgG e IgM considerados reagentes nos exames realizados. A curva sorológica de IgG mostrou um pico enquanto a de IgM apresentou seu maior valor médio no 15º dia. Houve um declínio progressivo e níveis similares aos basais aos 90. 15/53 (28%) permaneceram com IgG reagente após seis meses. Dor de garganta e dispneia foram considerados fatores de risco independentes, e os pacientes com esses sintomas tiveram 5,9 vezes mais chances de apresentar IgG reativa no 180º dia. Pacientes com diarreia tiveram quatro vezes mais chances de apresentar IgM reagente.

Conclusão: nossos achados mostraram que 26% dos pacientes não produziram uma resposta humoral pós-COVID-19 leve. Seus títulos de anticorpos caíram significativamente após 90 dias e apenas 28% mantiveram anticorpos IgG reativos após seis meses. Dor de garganta e dispneia foram preditores de maior duração da resposta imune humoral.

Palavras-chave: COVID-19; SARS-CoV-2; anticorpos; imunorreatividade; fatores de risco.