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LETTER TO THE EDITOR

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Persistently positive SARS-CoV-2-specific IgM during 1-year follow-up

Dear Editor,

Immunoglobulin M (IgM) antibodies typically appear in the early stage of infection and have a short maintenance time, so IgM is frequently used as a diagnostic criterion for acute or recent disease.[1] However, unconventional IgM-specific responses have been described in SARS-CoV-2 infection, raising doubts about the use of IgM as a biomarker for COVID-19 and the role of this antibody in immunity to SARS-CoV-2.[1,2]

We studied the antibody response after two doses of the CoronaVac and a booster shot of BNT162b2 (Pfizer-BioNtech) in a group of 46 volunteers for up to 1 year. Ethics permission was granted by the Ethics Committee of the Hospital Geral Dr. César Cals, through CAAE 39691420.7.0000.5049. We performed a longitudinal analysis of the humoral response (IgM for the viral spike (S) protein and IgG for the S and nucleocapsid (N) proteins) in samples collected before vaccination (F1), 28 days after the first CoronaVac dose (F2), 30 (F3) 90 (F4), 180 (F5), 230 (F6) days after the second CoronaVac dose and 30 (F7), 60 (F8), and 90 (F9) days after the BNT162b2 dose. The presence of antibodies IgM and IgG were measured by using Architect i2000 (Abbott®). The cut-off value was 50 AU/ml for IgG anti-S,1.4 index value (S/C) for IgG anti-N, and 1.0 index value for IgM anti-S. The volunteers also were monitored for SARS-CoV-2 infection by polymerase chain reaction (PCR) over time.

The dynamics of serum IgM of 46 participants in the different time points are shown in Figure 1. The serum IgM of most participants was sustained at low levels, increasing after the first and second dose of CoronaVac (P2 and P3), rapidly declining and increasing again after the boost dose with BNT162b2 (P7). Interestingly, four participants A, B, C, and D presented high IgM levels at baseline (P1), and their SARS-CoV-2-specific IgM remained positive for 1 year (P2–P9).

To investigate if these four participants with persistently positive IgM were infected by SARS-CoV-2, epidemiologic and clinical data were collected, and the presence of IgG anti-SARS-CoV-2 antibodies was evaluated (Figure 2).

The presence of IgG antibodies anti-N and anti-S at baseline in the participants B, C, and D with persistent IgM suggest previous exposure to the virus. This finding corroborates the typical COVID-19 symptoms and epidemiology reported by them.

Interestingly, participant A was negative to IgG anti-N and anti-S at baseline. She continued IgG-seronegative after the first dose of CoronaVac. The seroconversion occurred after the second dose of CoronaVac, just for S protein. Therefore, the anti-S IgG response in this participant seems to be elicited by the vaccine. Also, the participant did not develop anti-N antibodies, unlike other participants who expressed IgG anti-N at baseline and maintained the positivity for a long time. Since N protein is abundantly expressed during infection due to its functions associated with viral RNA packing and viral replication, it has been used to identify individuals who have had a recent or prior COVID-19.[3] Collectively, the ausence of IgG response before the vaccination and the absence of previous symptoms or epidemiology for COVID-19 indicate that IgM response in participant A may suggest to prior exposure to others coronavirus. Even though antibodies are pathogen-specific, there is a possibility of cross-reactivity in which antibodies against one pathogen can recognize another pathogen due to the presence of similar epitopes shared by different pathogens.[4] SARS-CoV-2 shares a highly homological sequence with SARS-CoV.[5] Also, evidence of antibody cross-reactivity between the SARS-CoV-2 and other human coronavirus has been reported.[6]

In general, the persistence of IgM is associated with reinfection or recurrence.[1] In this study, the volunteers were monitored by PCR for SARS-CoV-2 over time, discarding this possibility. The asymptomatic participants were tested monthly, and the symptomatic participants were tested within 5 days of symptoms onset. Therefore, the long-lived IgM response found here may indicate a suppression and/or dysregulation of the immune system that failed to eliminate the virus completely in a short time. The remaining virus continued to replicate but at low levels to the point of stimulating the immune system to produce antibodies but to the point of not being detected by PCR.

In conclusion, this study described the persistence of IgM to SARS-CoV-2 for up to 1 year and a possible case of cross-reactivity with other human coronaviruses. The use of IgM antibodies to identify the stage of the infection needs to be evaluated with caution and the role that cross-reactivity may play against SARS-CoV-2 needs to be further investigated. Also, the persistent IgM can be indicative of the presence of the virus for a long time in the host. So, patients with long-lived IgM for SARS-CoV-2 must be closely monitored given the possibility of organ damage.

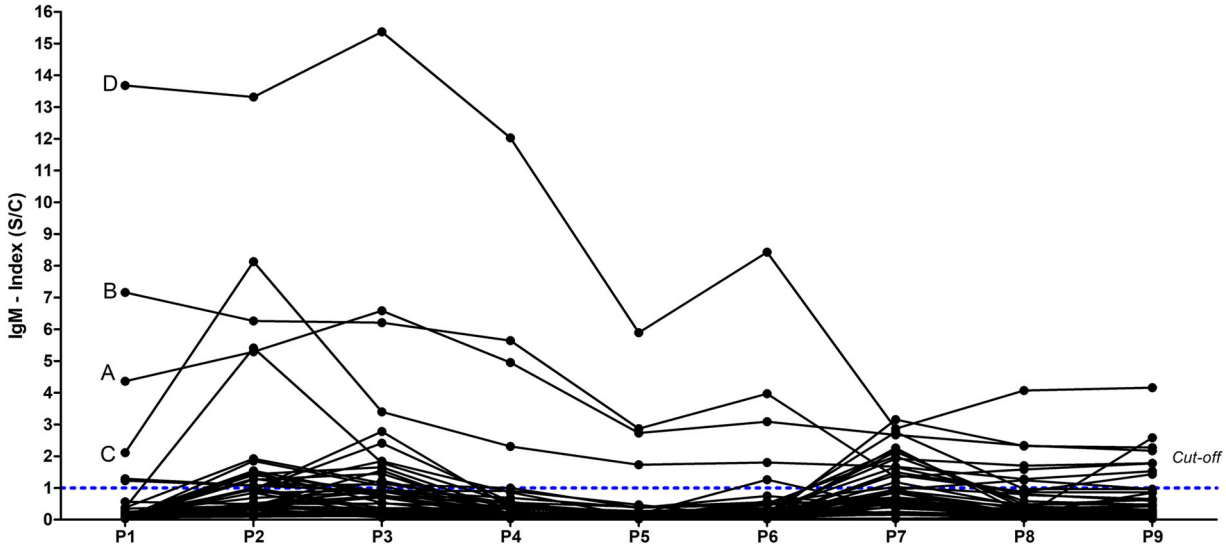

FIGURE 1 Dynamics of SARS-CoV-2-specific immunoglobulin M (IgM) using individual data of 1-year follow-up. The antibody levels before the vaccine (P1); 28 days after the first dose of vaccine (P2); 30 (P3), 90 (P4), 180 (P5), 230 (P6) days after the second dose of CoronaVac and 30 (P7), 60 (P8), and 90 (P9) days after the boost dose with BNT162b2 (Pfizer) of the 46 volunteers followed by 1 year. A, B, C, and D are the volunteers with persistent IgM. The horizontal dotted line indicates the cut-off value of the assay.

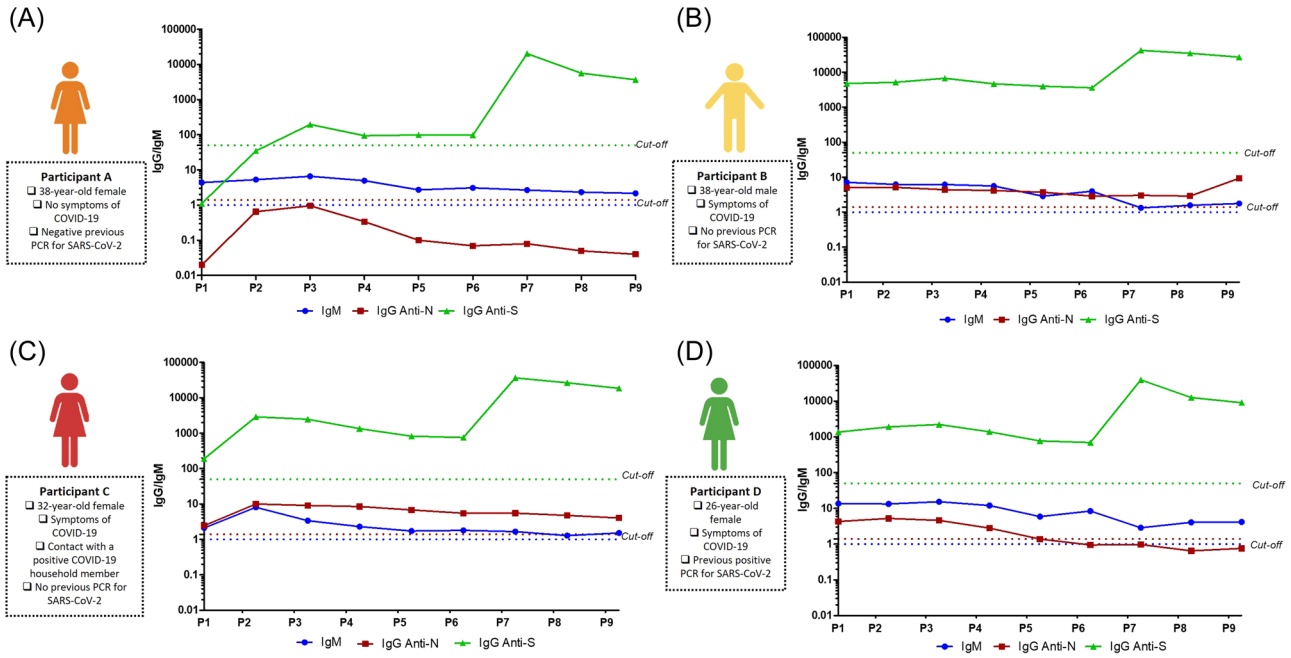

FIGURE 2 The antibody responses in the volunteers (A-D) with persistent immunoglobulin M (IgM). The IgM anti-spike (in blue), IgG anti-spike (IgG anti-S; in green), and IgG antinucleocapsid (IgG anti-N; in red) antibody levels before the vaccine (P1); 28 days after the first dose of vaccine (P2); 30 (P3) 90 (P4), 180 (P5), 230 (P6) days after the second dose of CoronaVac and 30 (P7), 60 (P8), and 90 (P9) days after the boost dose with BNT162b2 (Pfizer-BioteNch). The horizontal dotted line indicates the cut-off values of the assays. Epidemiological and clinical data were informed to the left of the graph.

AUTHOR CONTRIBUTIONS

Marcela H. G. Fonseca conceived the work, contributed to the design of the study, and the writing of the manuscript. Maria F. S. Silva, Ana C. M. D. Pinto, Amanda C. L. de Melo, and Fátima de C. E. de Oliveira were responsible for the recruitment, follow-up, data collection, laboratory analysis, and data processing work. Maria F. S. Silva and Fátima de C. E. de Oliveira made the graphs and figures. Fernanda M. de C. Araújo and Luiz O. M. de Andrade

supervised the Project. All authors approved the final manuscript version.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy or ethical restrictions. The data that support the findings of this study are available from the corresponding author.

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