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Letter to the Editor

## Persistence of anti-SARS-CoV-2 IgM in convalescent COVID-19 patients

Dear Editor,

We read with interest the article by Cancella et al. on the performance of a immunoglobulin M (IgM)-immunoglobulin G (IgG) testing for the diagnosis of COVID-19 in the emergency department.[1] As discussed by the authors, current laboratory diagnosis of COVID-19 is based on reverse transcription polymerase chain reaction (RT-PCR), and serological testing for IgM and IgG production in response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] Despite the widespread use of RT-PCR as the standard diagnostic technique for COVID-19, the limitation of this technology is apparent. [2,3] Individuals who test positive by RT-PCR can be diagnosed with SARS-CoV-2 infection, yet infection in those who test negative cannot be ruled out.[3] IgM is usually the first antibody produced by the human immune system during a virus attack. Detection of IgM indicates that the patient is suffering an acute infection or has recently recovered from an infection. However, long-term SARS-CoV-2-specific IgM levels remain largely unknown. Here, we detected the longevity of anti-SARS-CoV-2 IgM among convalescent individuals who were discharged from hospital 1 year previously.

From March 16 to March 28, 2021, this cohort study was performed at Huanggang Central Hospital, Hubei, China. Participants had been previously hospitalized or isolated at an isolation point between January 24 and March 18, 2020.[4] Our inclusion criteria are consistent with our published article.[4] In Huanggang, Hubei Province, there were no new SARS-CoV-2 infections reported after all patients were discharged on 18 March 2020. During follow-up, all participants in our study underwent SARS-CoV-2 nucleic acid testing many times (at 1, 3, 6, and 12-months post-discharge); all tests were negative. Thus, SARS-CoV-2 reinfection did not occur in the individuals studied here.

Individuals were classified to four groups (severe, moderate, mild, and asymptomatic) according to their clinical features and chest imaging manifestations.[5] Chemiluminescence (AutoLumo A2000Plus; Autobio, Zhengzhou, China,) was used as described in our previous paper to detect the level of IgM antibodies against recombinant SARS-CoV-2 nucleoprotein (N) and spike (S) protein in serum.[4] An antibody level of $\geq$ 1 absorbance/cutoff (S/CO) was considered reactive (positive) and results of $<$ 1 S/CO were negative.[4] Ethical approval was provided by the Ethics Committee of Hunan Provincial People's Hospital. All participants provided verbal or written consent to the study.

Four hundred and seventy-three individuals with SARS-CoV-2 infection participated in this cohort study. The median age of the survivors was 52.5 years (SD, 13.9); 283 survivors (59.8%) were women. The degree of COVID-19 severity was categorized as severe (53/473, 11.2%), moderate (356/473, 75.3%), mild (21/473, 4.4%), or asymptomatic (43/473, 9.1%). Demographic details and clinical features of the patients are listed in Table 1.

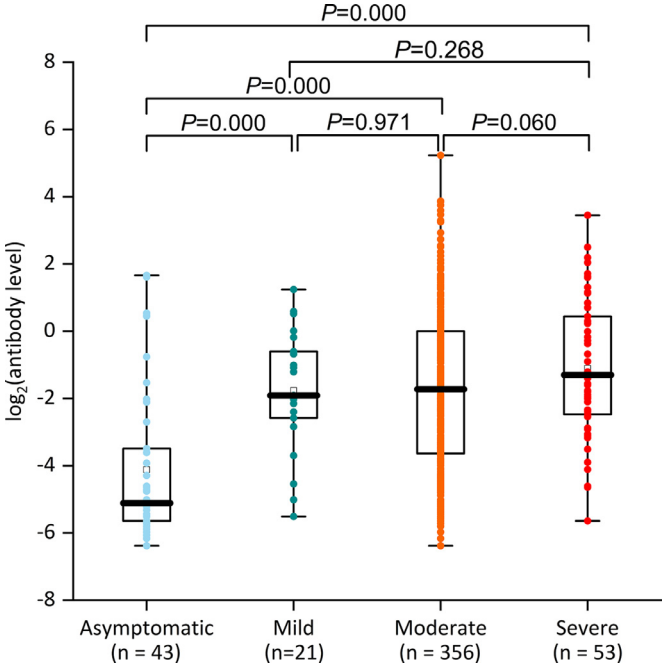


**Fig. 1.** IgM antibody responses against SARS-CoV-2 Comparison of SARS-COV-2-specific IgM titers between asymptomatic, mild, moderate, and severe patients. The boxplots show medians (middle line) and third and first quartiles (boxes), while the whiskers show 1.5 $\times$ the interquartile range (IQR) above and below the box. Numbers of patients ($n$) are shown underneath. The results were expressed as mean {log2 (Fluorescence intensity)} $\pm$ SD in different groups. Analysis of variance (ANOVA) were conducted to test difference in means among groups.

At 1 year after symptom onset, 30.2% (16/53) of the severe group had detectable anti-SARS-CoV-2 IgM, whereas 11.6% (5/43), 19.0% (4/21), and 24.7% (88/356) of asymptomatic, mild, and moderate groups, respectively, measured positive for anti-SARS-CoV-2 IgM (Table 1). The anti-SARS-CoV-2 IgM levels at 1 year post-SARS-CoV-2 infection in the severe, moderate, and mild groups were significantly higher ($P$ = 0.000) than that of the asymptomatic group (Fig. 1). Furthermore, anti-SARS-CoV-2 IgM levels gradually increased with increasing severity of COVID-19.

Similar to with SARS, Middle Eastern respiratory syndrome and many other virus infections, an increase in anti-SARS-CoV-2 IgM in the acute phase followed by an increase in anti-SARS-CoV-2 IgG at later phases has been observed over the course of SARS-CoV-2 infection.[6] IgM, and IgG can be detected in serum within 1–3 weeks of infection. However, IgM antibodies decay more rapidly than IgG. IgM-IgG testing is an effective approach for early diagno-

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**Table 1**
Characteristics of enrolled patients.

| Variable | All survivors ($n$ = 473) | Asymptomatic cases ($n$ = 43) | Mild cases ($n$ = 21) | Moderate cases ($n$ = 356) | Severe cases ($n$ = 53) | $P$ value* |
|---|---|---|---|---|---|---|
| Age, median(SD), y | 52.5 ± 13.9 | 44.9 ± 12.7 | 54.2 ± 12.9 | 52.5 ± 13.8 | 57.9 ± 13.9 | 0.000 |
| Sex | | | | | | |
| Male, no, (%) | 190 (40.2) | 13 (30.2) | 7 (33.3) | 146 (41.0) | 24 (45.3) | 0.414 |
| Female, no, (%) | 283 (59.8) | 30 (69.8) | 14 (66.7) | 210 (59.0) | 29 (54.7) | |
| Cigarette smoking | | | | | | |
| Never-smoker, no, (%) | 395 (83.5) | 40 (93.0) | 20 (95.2) | 292 (82.0) | 43 (81.1) | 0.348 |
| Current smoker, no, (%) | 53 (11.2) | 1 (2.3) | 1 (4.8) | 44 (12.4) | 7 (13.2) | |
| Former smoker, no, (%) | 25 (5.3) | 2 (4.7) | 0 | 20 (5.6) | 3 (5.7) | |
| Chronic medical illness | | | | | | |
| Hypertension, no, (%) | 96 (20.3) | 4 (9.3) | 4 (19.0) | 75 (21.1) | 13 (24.5) | 0.030 |
| Diabetes, no, (%) | 47 (9.9) | 1 (2.3) | 2 (9.5) | 37 (10.4) | 7 (13.2) | 0.039 |
| Cardiovascular diseases, no, (%) | 42 (8.9) | 0 | 2 (9.5) | 32 (9.0) | 8 (15.1) | 0.006 |
| Malignant tumour, no, (%) | 2 (0.4) | 0 | 0 | 2 (0.6) | 0 | 0.757 |
| Chronic pulmonary disease, no, (%) | 6 (1.3) | 0 | 0 | 5 (1.4) | 1 (1.9) | 0.257 |
| Liver disease, no, (%) | 3 (0.6) | 0 | 0 | 3 (0.8) | 0 | 0.674 |
| Chronic renal diseases, no, (%) | 2 (0.4) | 0 | 0 | 2 (0.6) | 0 | 0.757 |
| ICU admission, no, (%) | 23 (4.9) | 0 | 0 | 0 | 23 (43.4) | 0.000 |
| The hospitalization days of discharged patients | NA | NA | 8.8 ± 1.2 | 14.3 ± 4.2 | 23.9 ± 8.6 | 0.000 |
| One-year after discharge IgM levels, S/CO | | | | | | |
| <1, no, (%) | 360 (76.1) | 38 (88.4) | 17 (81.0) | 268 (75.3) | 37 (69.8) | 0.161 |
| ≥1, no, (%) | 113 (23.9) | 5 (11.6) | 4 (19.0) | 88 (24.7) | 16 (30.2) | |

Data are mean (SD), or $n$ (%), unless otherwise specified.
*Difference among all types. Differences of measurement data among asymptomatic cases, mild cases, moderate cases, and severe cases were compared with analysis of variance (ANOVA) and LSD for post-hoc tests. Chi-square test was used for categorical variables.

sis of COVID-19.[1] IgM-IgG testing also can identify individuals with resolving or past virus infection, thus helping us to better understand the epidemiology of COVID-19. A systematic review has indicated that anti-SARS-CoV-2 IgM peaked in the 2–5 weeks after the onset of symptoms, then declined over time to below the detection limit.[7] In two cohort studies, anti-SARS-CoV-2 IgM was undetectable in virtually all cases approximately 6 weeks after symptom onset.[8,9]

Notably, we found that 113 (23.9%) convalescent individuals who recovered from SARS-CoV-2 infection 1 year previously had positive SARS-CoV-2-specific IgM results, and 16 (30.2%) severe cases remained demonstrably positive for SARS-CoV-2-specific IgM. In our previous publication, we found that anti-SARS-CoV-2 IgG levels depend on COVID-19 severity.[4] In this cohort study, we also found that the anti-SARS-CoV-2 IgM titers of symptomatic patients were significantly higher than those of asymptomatic patients, and that individuals with severe COVID-19 had the highest SARS-CoV-2-specific IgM titers. One possible mechanism is that uncontrolled replication of SARS-CoV-2 and/or excessive inflammation caused by severe COVID-19, may lead to overproduction of antibodies.[4,10]

Currently the numbers of individuals previously infected with SARS-CoV-2 and vaccinated individuals are increasing. Thus, when interpreting IgM/IgG test results, it is necessary to consider virus infection and/or vaccination histories. Additionally, a negative IgM/IgG test does not exclude previous infections, because some individuals with SARS-CoV-2 infection might not produce measurable antibodies. Finally, potential false negative or false positive results should be considered when interpreting IgM/IgG test results.

Our study has two limitations that should be acknowledged. First, our IgM test results were determined only 1 year after discharge and therefore do not capture dynamic changes in IgM levels from initial infection. Second, we used chemiluminescence as the detection method, and the results of techniques such as enzyme-linked immunoassay and colloidal gold may be different.

In conclusion, our study showed the long-term presence of anti-SARS-CoV-2 IgM in 23.9% of survivors for up to 1 year after symptom onset. IgM testing does not replace RT-PCR and should not be recommended to determine the presence of acute SARS-CoV-2 infection. IgM testing is also not appropriate for determining the need to quarantine. These results are important for health and anti-epidemic agencies to formulate quarantine measures for the disease. The mechanism underlying the long persistence of anti-SARS-CoV-2 IgM in some individuals remains largely unclear and needs further long-term research.

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## Declaration of Competing Interest

No conflicts of interests declared by an author.

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