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Persistence of SARS-CoV-2-specific antibodies in COVID-19 patients

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ABSTRACT

To better understand humoral immunity following SARS-CoV-2 infection, 114 hospitalised COVID-19 patients with antibody monitored over 8 weeks from symptom onset were retrospectively investigated. A total of 445 serum samples were assessed via chemiluminescence immunoassay. Positive rate of virus-specific IgM reached up to over 80% from the second week to the eighth week after symptom onset, then declined quickly to below 30% in the twelfth week. Concentrations of IgG remained high for at least 3 months before subsequently declining. As compared with the non-severe group, serum IgM level from week 3 to week 8 was significantly higher among the patients with severe clinical symptoms ($P = 0.012$) but not IgG ($P = 0.053$). Serum IgM level from week 3 to week 8 was correlated with positive virus RNA test ($r = 0.201$, $P = 0.044$), albumin level ($r = -0.295$, $P = 0.003$), lactic dehydrogenase (LDH) level ($r = 0.292$, $P = 0.003$), alkaline phosphatase (ALP) level ($r = 0.254$, $P = 0.010$), C-reactive protein (CRP) level ($r = 0.281$, $P = 0.004$) during the same course, while serum IgG level was correlated with age ($r = 0.207$, $P = 0.038$). This presented results provide insight into duration of SARS-CoV-2 antibodies and interaction between the virus and host systems.

1. Introduction

Coronavirus disease 2019 (COVID-19) has spread rapidly throughout the world since its discovery in December 2019 [1,2]. As of November 26, 2020, SARS-CoV-2 has affected a total of 60.3 million people, including 1.4 million deaths [3]. Most infected patients show mild symptoms, while some die of fatal pneumonia. Strategies for COVID-19 treatment and prevention are urgently needed, but limited up to now [4].

The SARS-CoV-2 belongs to the beta genus Coronavirus in the Corornaviridae family which has been confirmed to be highly infectious [5]. Antibodies are key components in the immune responses to viral infections [6,7]. Understanding potential postinfection immunity has important implications for serologic therapies, vaccines, and epidemiologic assessments. Similar with SARS-CoV-1 or MERS-CoV, patients infected by SARS-CoV-2 were reported to have antibody responses [8–10]. Zhou et al. showed the involvement of humoral immunity in COVID-19 patients [10]. Elevated levels of SARS-CoV-2-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) have been detected in the serum of COVID-19 patients with persistence up to 40 days from symptom onset [11,12]. Moreover, immunological studies indicated simultaneous or earlier IgG seroconversion than IgM in most patients [12–14]. Clinical characteristics evaluation in COVID-19 patients has been well studied, while less information is available about antibody persistence and correlated factors in COVID-19 survivors, which limits the serologically based diagnosis and of prognosis prediction.

Therefore, we investigated the levels of SARS-CoV-2-specific IgM and

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate aminotransferase; AUC, area under the ROC curve; BUN, Blood urea nitrogen; CHD, Coronary heart disease; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; hs-cTnI, High-sensitivity cardiac troponin I; IgM, Immunoglobulin M; IgG, Immunoglobulin G; IL6, Interleukin 6; IQR, interquartile range; LDH, Lactic dehydrogenase; PT, Prothrombin time; NT-proBNP, N-terminal pro brain natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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IgG in hospitalised COVID-19 patients with antibody monitored over 8 weeks between February 23, 2020, and April 26, 2020.

2. Materials and methods

2.1. Study design and participants

A total of 114 hospitalised COVID-19 patients with detectable levels of serum IgM and IgG against SARS-CoV-2 examined between February 23, 2020, and March 26, 2020 in Tongji Hospital were retrospectively investigated. In brief, the patients described here were all hospitalised patients in Tongji Hospital ("The specific hospital for the treatment of COVID-19 patients in Wuhan" designated by Chinese government) with (1) examined levels of serum IgM and IgG against SARS-CoV-2 (2–8 serum specimens per patient), both of which were positive for at least once by chemiluminescence assay, (2) chest radiographic evidence of pneumonia, (3) a positive throat swab nucleic acid test by real-time RT-PCR, and (4) discharged from Tongji hospital with antibody monitored over 8 weeks since symptom onset. We defined the severity of disease based on the Seventh Revised Trial Version of the COVID-19 Diagnosis and Treatment Guidance (2020) of China, including any following criteria: respiratory rate $\geq$ 30 breaths/min, oxygen saturation $\leq$ 93% at a rest state, the ratio of arterial partial pressure of oxygen (PaO2) and oxygen concentration (FiO2) $\leq$ 300 mmHg, or patients with $>$ 50% lesions progression within 24 to 48 h in lung imaging. Information collection was accomplished through our hospital's electronic medical record system. Clinical, laboratory parameters and clinical severity were obtained with standardised forms for all subjects involved. Laboratory examinations except immunoglobulins were obtained on admission. Two researchers independently reviewed the data. The initial test laboratory parameters from the third week to the eighth week were selected when the antibody levels were at the plateau level. This study was reviewed and approved by the Medical Ethical Committee of Tongji Hospital of Huazhong University of Science and Technology (IRB ID: TJ-IRB20200343), and all relevant personnel exempt from informed consent due to the particularity of the disease outbreak.

2.2. Antibody measurement

Serum IgM and IgG antibodies against SARS-CoV-2 were detected by a chemiluminescence immunoassay (YHLO-CLIA-IgG, YHLO-CLIA-IgM kits) and an iFlash 3000 CLIA System supplied by Yhlo Biotech Co. LTD (Shenzhen, China) as described previously [15,16]. A threshold of 10 AU/ml was used for both IgM and IgG as recommended by the manufacturer. The recombinant antigens contain nucleoprotein and spike protein of SARS-CoV-2.

2.3. Analysers used to measure laboratory parameters

The blood cell count was analysed using the XN-9000 Sysmex haematology analyser (Sysmex, Kobe, Japan) according to the manufacturer's instructions. Coagulation functions were detected using STA-R coagulation analyzers analyser (Diagnostica Stago, Saint-Denis, France). Biochemical items were measured with ROCHE COBAS 8000 (Mannheim, Germany).

2.4. Statistical analysis

The statistical software SPSS 23.0 was used in this study. Categorical variables are described as frequencies and percentages, and continuous variables are described using the median values with interquartile ranges (IQRs). When the data were normally distributed, continuous variables were analysed by t tests and by Mann-Whitney tests otherwise. Categorical variable proportions were compared using the $\chi 2$ test with Yates' correction. Receiver operating characteristic (ROC) curves were used to evaluate IgM and IgG as potential predictors for clinical severity. Correlation analysis was evaluated by the Pearson test. All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

3. Results

Among the 114 subjects included, 36 patients were severe, while 78 patients were non-severe during the clinical course. As summarized in Table 1, the patients with severe clinical symptoms were significantly older, with lower lymphocyte count, higher levels of inflammatory biomarkers, such as C-reactive protein (CRP), Interleukin 6 (IL6), and higher organ damage indices (LDH, NT-proBNP, D-dimer), which was similar with previous studies [17,18].

The levels of virus-specific IgM and IgG increased during the first 3 weeks after onset of symptoms (Fig. 1A, B). Positive rate of IgM peaked up to 92.0% in the third week, stayed at a high level until the eighth week, then declined quickly to below 30% in the twelfth week. Concentrations of IgG were elevated to the plateau level in the second week, remained high in the thirteenth week, and subsequently declined in the fourth month. The highest IgG levels in three patients whose IgG turned negative within 4 months were all<50 AU/ml, not much higher than the detection threshold.

Serum IgM level from week 3 to week 8 was higher among patients with severe COVID-19 (IgM 75.3 AU/ml [40.4–235.1]) than in the non-severe patients (IgM 40.0 AU/ml [20.4–86.8], $P = 0.012$) (Fig. 2A). High IgG levels were more common among patients with severe clinical symptoms during the same period, although this difference was not significant ($P = 0.053$). Meanwhile, the area under the ROC curve (AUC) for IgM antibody was 0.661 (95% confidence interval: 0.548–0.774, $P = 0.012$), while the AUC for IgG antibody was 0.624 (95% confidence interval: 0.499–0.748, $P = 0.053$). Furthermore, we found that IgM level from week 3 to week 8 was positively correlated with positive virus RNA ($r = 0.201$, $P = 0.044$) (Fig. 2B). No association was found between prolonged detection of viral RNA (≥36 days after onset of symptoms) and severity of illness ($p = 0.232$). Interestingly, one patient had detectable viral RNA for up to 98 days and positive IgM for 87 days after symptom onset (Fig. 2C). Serum IgM level from week 3 to week 8 was positively correlated with CRP level ($r = 0.281$, $P = 0.004$), LDH level ($r = 0.292$, $P = 0.003$), alkaline phosphatase (ALP) level ($r = 0.254$, $P = 0.010$), and negatively with albumin level ($r = -0.295$, $P = 0.003$) (Fig. 2B). Similarly, the concentrations of SARS-CoV-1 specific IgG were higher in older adults than in younger adults ($r = 0.207$, $P = 0.038$) [14,19].

4. Discussion

The dynamics of SARS-CoV-2 specific IgM and IgG have important implications for the diagnosis and treatment of COVID-19. As previously shown, seroconversion of IgG was simultaneous with or earlier than of IgM in most cases; the duration of the rate of positivity that exceeded 80% was 7 weeks for IgM, and at least 3 months for IgG. Similarly, the IgG levels remained high until 120 days after the onset of symptoms [20,21]. Therefore, IgG is more suitable for epidemiologic assessments, although negative results will be more presented since the fourth month. SARS-CoV-2 is a coronavirus with a higher transmissibility and weaker pathogenicity than severe acute respiratory syndrome coronavirus (SARS-CoV-1) [7,22]. Following infection, SARS-CoV-1-specific IgM peaked in the third week and dropped to the cut-off value after 60 days [8,23]. Concentrations of SARS-CoV-1-specific IgG remained high for 4 to 5 months before declining slowly during the next 2 years [23]. Consistent with our study, SARS-CoV-2-specific antibody loss was quicker than that reported for SARS-CoV-1 [21]. A relatively weaker pathogenicity in SARS-CoV-2 explains the relatively shorter duration of the immune response and suggests a strategy for screening for SARS-CoV-2 [7,18]. A study reported that 4 rhesus macaques infected with SARS-CoV-2 did not become reinfected when rechallenged 28 days after the first inoculation, indicating the protective role of postinfection

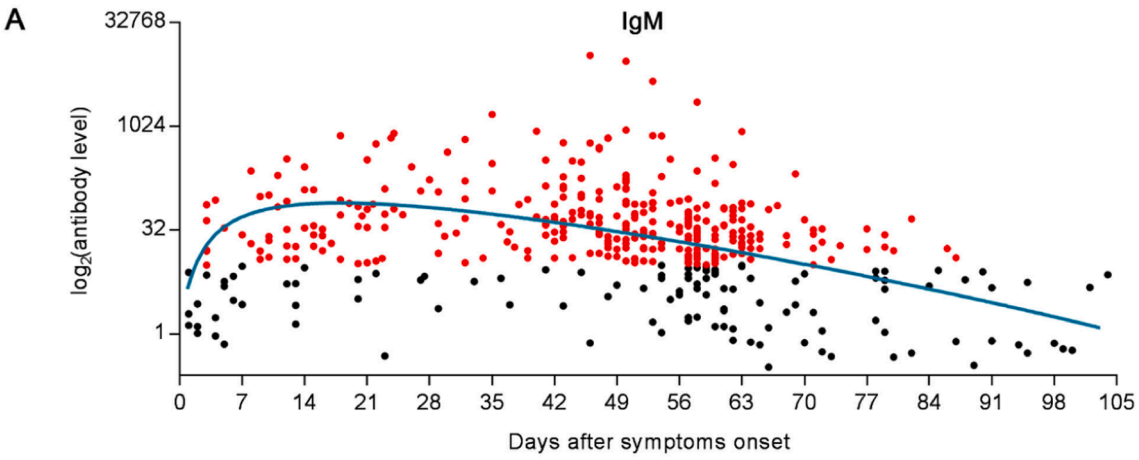
Table 1
Demographic, clinical and laboratory findings of COVID-19 patients.

Indicators	Total ($N = 114$)	Non-severe ($N = 78$)	Severe ($N = 36$)	p value
Characteristics				
Age, years	61.5(51.0–68.0)	60·0(45.0–66.0)	64.0(52.0–72.0)	**0.038***
Sex				0.673
Male	46(40%)	33(42%)	13(36%)	
Female	68(60%)	45(58%)	23(64%)	
Comorbidities				
Hypertension	47(41%)	25(32%)	22(61%)	**0.006***
Diabetes	12(11%)	8(10%)	4(11%)	1.000
CHD	7(6%)	2(3%)	5(14%)	0.055
COPD	9(8%)	5(6%)	4(11%)	0.623
CKD	1(1%)	0	1(3%)	0.316
Malignancy	5(4%)	3(4%)	2(6%)	1.000
Surgery	22(19%)	16(21%)	6(17%)	0.819
Allergy	10(9%)	7(9%)	3(8%)	1.000
Others	7(6%)	4(5%)	3(8%)	0.279
Initial symptoms				
Fever	69(61%)	46(59%)	23(64%)	0.770
Cough	73(64%)	49(63%)	24(67%)	0.851
Dyspnea	45(39%)	24(31%)	21 (58%)	**0.010***
Diarrhoea	7(6%)	5(6%)	2(6%)	1.000
Sore throat	14(12%)	9(12%)	5(14%)	0.961
Laboratory examinations				
Leucocytes count, ×10^9/L	6.1(4.8–7.5)	6.1(5.0–7.4)	6.0(4.3–8.1)	0.968
Neutrophils count, ×10^9/L	3.8(2.8–4.9)	3.7(3.0–4.8)	3.9(2.4–6.0)	0.779
Lymphocytes count, ×10^9/L	1.4(1.0–1.9)	1.5(1.1–1.9)	1.3(0.9–1.6)	**0.006***
Monocytes count, /μL	540.0(415.0–690.0)	545.0(415.0–690.0)	535.0(390.0–697.5)	0.491
Eosinophils count, /μL	80.0(20.0–142.5)	100.0(27.5–172.5)	50.0(0.0–117.5)	0.073
Hemoglobin, g/L	123.0(114.0–137.0)	126.0(117.8–139.3)	120.0(105.5–128.0)	**0.004***
Platelets count, ×10^9/L	231.0(189.5–304.0)	233.0(191.0–296.0)	226.0(166.0–317.5)	0.803
ALT, U/L	21.0(12.0–31.5)	21.0(12.0–33.0)	19.5(12.3–29.8)	0.296
AST, U/L	22.0(16.0–29.0)	22.0(16.0–28.0)	23.5(17.3–33.8)	0.459
LDH, U/L	214.0(176.3–263.0)	205.5(170.0–248.3)	236.5(205.3–367.5)	**0.001***
ALP, U/L	69.0(55.0–85.3)	69.0(55.0–85.0)	69.0(53.3–89.0)	0.816
Albumin, g/L	39.8(33.4–42.7)	41.1(36.9–43.3)	34.3(29.4–39.8)	**<0.001***
Globulin, g/L	30.3(27.1–33.7)	29.1(26.4–33.3)	32.4(29.5–35.9)	**0.002***
Albumin / Globulin	1.3(1.0–1.6)	1.4(1.2–1.7)	1.0(0.9–1.3)	**<0.001***
BUN, mmol/L	4.3(3.4–5.5)	4.3(3.5–5.0)	4.6(3.0–6.3)	0.335
Creatinine, μmol/L	66.5(58.8–80.0)	65.5(59.8–77.5)	69.5(56.3–88.8)	0.136
NT-proBNP ($N = 101$), pg/mL	83.0(32.5–241.0)	54.0(24.5–113.8)	261.0(99.0–796.0)	**<0.001***
hs-cTnI ($N = 71$), pg/mL	5.6(3.4–15.8)	5.0(2.9–10.1)	6.9(4.5–21.4)	0.050
ESR ($N = 51$), mm/hour	28.0(10.0–56.0)	18.0(8.0–45.0)	44.5(16.8–70.8)	0.064
CRP ($N = 113$), mg/L	5.1(1.2–33.8)	3.0(1.0–15.7)	17.5(2.5–60.8)	**0.003***
IL6 ($N = 111$), pg/mL	3.2(1.7–10.1)	2.6(0.0–6.5)	6.5(2.7–17.6)	**0.001***
Ferritin ($N = 55$), ng/mL	393.8(212.5–833.6)	310.8(188.0–631.7)	603.9(273.9–885.4)	0.056
Procalcitonin ($N = 88$), pg/mL	60.0(50.0–100.0)	60.0(50.0–70.0)	90.0(40.0–205.0)	0.057
D-dimer ($N = 111$), μg/mL	0.6(0.3–1.4)	0.4(0.2–0.8)	1.3(0.6–2.4)	**<0.001***
PT ($N = 110$), s	13.6(13.0–14.0)	13.5(12.9–14.0)	13.7(13.1–14.1)	0.052

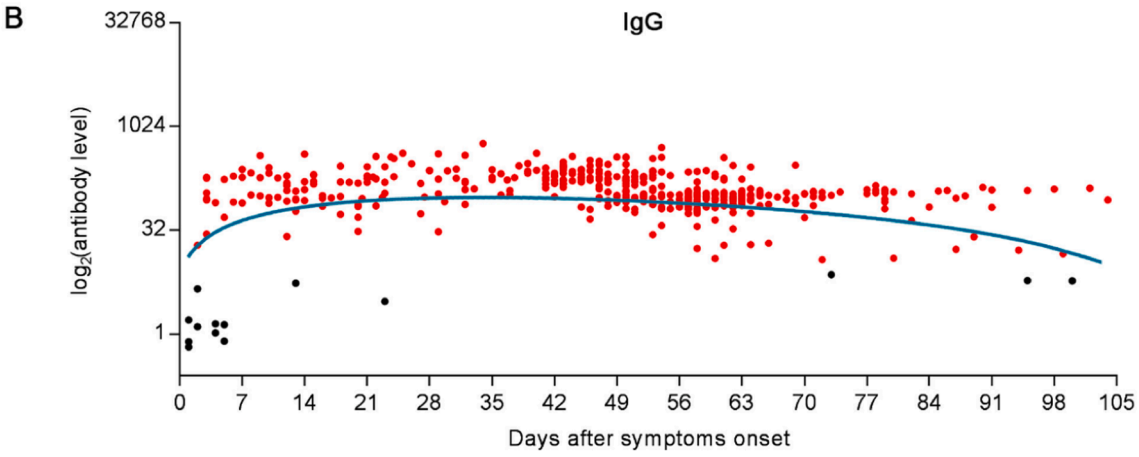
Abbreviation: COVID-19, Coronavirus disease 2019; CHD, Coronary heart disease; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; ALT, Alanine transaminase; AST, Aspartate aminotransferase; LDH, Lactic dehydrogenase; ALP, Alkaline phosphatase; BUN, Blood urea nitrogen; NT-proBNP, N-terminal pro brain natriuretic peptide; hs-cTnI, High-sensitivity cardiac troponin I; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; IL6, Interleukin 6; PT, Prothrombin time. Continuous variables were described as median (Interquartile range). p values were calculated by Mann-Whitney U non-parameter test for skewed distributed data. Categorical variables were expressed as number (%). p values were calculated by chi-squared test with Yates' correction for 2 × 2 contingency data. *$p < 0.05$.

immunity [24]. Some COVID-19 patients might be at risk of reinfection > 3 months after their initial exposure due to the relatively short-lived SARS-CoV-2-specific antibodies. The results still call for caution regarding antibody-based "immunity passports" and vaccine durability [21].

Postinfection immunity provides insight into interaction between the virus and host systems. The serum IgM level from week 3 to week 8 was higher among patients with severe COVID-19 but not IgG. Meanwhile, as shown by the ROC curve analysis, the IgM antibody was a predominant predictive factor for the clinical severity of patients with COVID-19 pneumonia (AUC = 0.661, P = 0.012). Similarly, another team found that a higher SARS-CoV-2 specific antibody titre was associated with more severe clinical disease [25]. Furthermore, IgM levels from week 3 to week 8 were positively correlated with positivity for viral RNA, indicating that positive duration of IgM was associated with viral load in COVID-19 patients. As reported, detectable viral RNA in the blood is a strong indicator for a poor outcome [26]. But even if the virus persisted in the throat, IgM might turn negative in some cases. A relatively weaker pathogenicity explains the early disappearance of IgM in some cases or stages and provides a strategy for patient screening in the future. No association was found between prolonged detection of viral RNA and severity of illness. Similar to previous reports, the concentrations of IgG against SARS-CoV-2 were higher in older adults, consistent with poor prognosis in elderly patients. Although SARS-CoV-2 specific antibody response is associated with the clinical outcome in COVID-19 patients, its role in virus elimination is not clear. A neutralizing antibody can bind to the surface spike protein of coronaviruses and mediate viral entry into IgG Fc receptor-expressing cells, indicating the complex roles of antibodies in viral elimination [27]. Serum IgM levels were positively correlated with CRP levels, LDH levels, ALP levels, and negatively with albumin levels, indicating that IgM might be involved in the uncontrolled inflammatory responses and subsequent organ damage in severe



Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14+
N of samples	24	26	25	21	21	30	44	73	109	26	14	14	10	8
Positive IgM	8	21	23	17	18	27	40	64	82	15	10	4	2	0
Positive rate (%)	33.3	80.8	92.0	81.0	85.7	90.0	90.9	87.7	75.2	57.7	71.4	28.6	20.0	0



Weeks	1	2	3	4	5	6	7	8	9	10	11	12	13	14+
N of samples	24	26	25	21	21	30	44	73	109	26	14	14	10	8
Positive IgG	15	25	25	20	21	30	44	73	109	26	13	14	10	6
Positive rate (%)	62.5	96.2	100	95.2	100	100	100	100	100	100	92.9	100	100	75.0

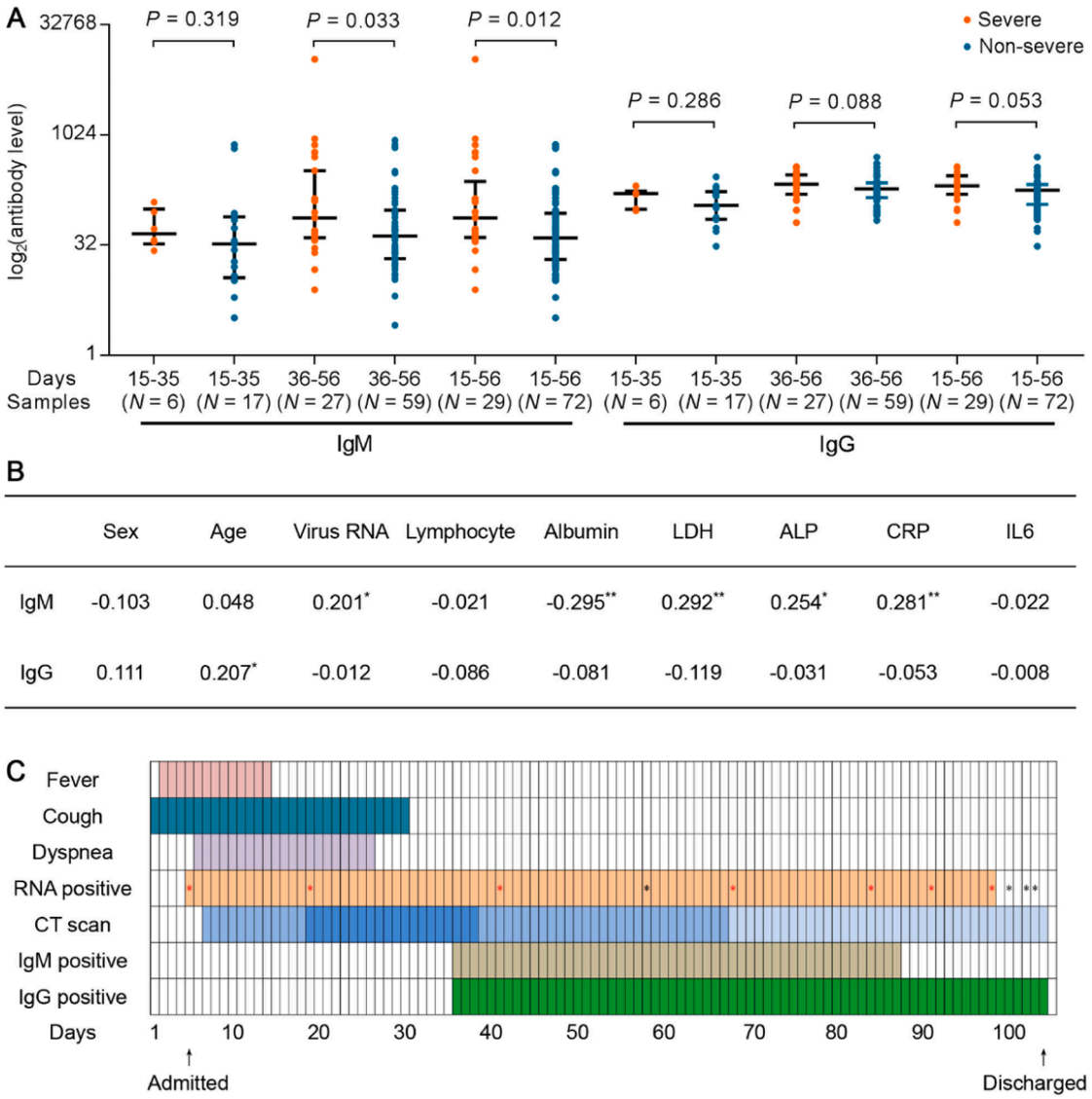
Fig. 1. Serum antibody responses against SARS-CoV-2. (A) Graph of positive rates of serum SARS-Cov-2-specific IgM versus days after symptom onset in 445 serum samples from 114 patients. (B) Dynamics of serum SARS-Cov-2-specific IgG versus days after symptom onset in 445 serum samples from 114 patients. Abbreviation: *N*, Number. The red colour means positive result while black colour means negative result. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cases. Further studies are needed to ascertain the role of antibodies in responses to SARS-CoV-2 infections.

This study has some limitations. First, it is a single-centre retrospective study with a limited number of serum samples over a relatively long time span, so the exact duration of post-infection immunity is unknown. Second, the majority of patients admitted to our hospital were critically ill or had a long duration of positivity on nucleic acid test, which means that population bias exists. Third, we did not detect antibodies by virus-neutralization tests, therefore the neutralizing activities of these antibodies are unknown. In addition, quantitative viral load monitoring were not available.

5. Conclusions

In this retrospective study, we analysed the dynamics of of SARS-CoV-2-specific IgM and IgG antibodies among 114 hospitalised patients with 445 serum samples assessed. Seroconversion of IgG was more suitable for epidemiologic assessments, though false-negatives will be more and more generated since the fourth month. Positive duration of IgM was shorter and correlated with the clinical severity, positive virus



B

	Sex	Age	Virus RNA	Lymphocyte	Albumin	LDH	ALP	CRP	IL6
IgM	-0.103	0.048	0.201*	-0.021	-0.295**	0.292**	0.254*	0.281**	-0.022
IgG	0.111	0.207*	-0.012	-0.086	-0.081	-0.119	-0.031	-0.053	-0.008

Fig. 2. Association between the antibody levels and clinical characteristics. (A) Comparison of the levels of SARS-Cov-2-specific antibodies between severe and non-severe patients at different times after symptom onset. Medians and interquartile range (IQR) were shown.(B) The association between the antibody levels at the plateau and clinical characteristics. Pearson correlation coefficients (r) are depicted. *P < 0 05, **P < 0 01.(C) Clinical course of a COVID-19 patients (female, 60 years) with long-lasting RNA positive. The red asterisks means positive viral RNA while black asterisks means negative result. Deepened colour indicates the viral pneumonia worsens in the line of CT deterioration. Abbreviation: Virus RNA, positive virus RNA test; LDH, Lactic dehydrogenase; ALP, Alkaline phosphatase; CRP, C-reactive protein; IL6, Interleukin 6. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

RNA test, CRP levels, albumin levels, LDH levels, and ALP levels, providing insight into interaction between the virus and host systems.

6. Author contributors

HL and CY made substantial contributions to the study design. JL and YW were in charge of the manuscript draft. YW took responsibility for obtaining ethical approval. CY and HL took responsibility for data acquisition. JL made main contributions to data analysis and interpretation. JL and HL participated in the diagnosis and treatment of health professionals. PL and GS made substantial revisions to the manuscript. PL, Grant Recipient.

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Declaration Competing Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Lifespan institutional research committee and with the 1964 Helsinki declaration and

its later amendments or comparable ethical standards.

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