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SARS-CoV-2 neutralizing antibody levels are correlated with severity of COVID-19 pneumonia

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ABSTRACT

The emerging coronavirus disease 2019 (COVID-19) has become a serious global public health threat. With more and more recovered patients, it is urgently needed for evaluation of the neutralizing antibody (NAb) in these patients. In this study, we collected blood samples from 49 patients recently recovered from COVID-19. Serum NAbs were measured using a novel surrogate virus neutralization test (sVNT). Factors associated with NAb titers were analyzed using Ordinary Least Squares regression model. The median age of the study participants was 37 years (IQR, 30.0–54.5) and 55.1 % (27/49) of which were male. The median time to blood collection (for NAb analysis) from illness onset, viral clearance and discharge were 43.0 days (IQR, 36.0–50.0), 27.0 days (IQR, 20.5–37) and 17.0 days (IQR, 15.0–33.0), respectively. Patients had a median NAb titer of 1: 40 (IQR, 1:15–1:120). NAbs were not detected in two asymptomatic children who quickly cleared the virus. NAb titers were higher in patients with older age (p = 0.020), symptomatic infection (p = 0.044), more profound lung involvement (p < 0.001), abnormal C-reactive protein level (p < 0.01) and elevated lactate dehydrogenase (p = 0.019). Multivariable analysis revealed that severity of pneumonia and having comorbidity positively correlated with NAb titers in recovered patients (p < 0.01). Our study suggests that some COVID-19 patients may not have detectable NAb after recovery. SARS-CoV-2 NAb titers are positively correlated with severity of COVID-19 pneumonia.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is a major global crisis for human being, which has spread worldwide with such devastating speed and has caused a huge death toll and economic loss [1]. The causative pathogen, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to the subgenus Sarbecovirus of the genus Betacoronavirus and shares 79.6 % sequence identity to SARS-CoV [2]. Unlike SARS-CoV which generally causes severe lung injury, SARS-CoV-2 infection has wider disease spectrum ranging from asymptomatic infection to life-threatening respiratory failure [3,4]. The asymptomatically infected COVID-19 patients pose great public concern as they could also transmit SARS-CoV-2 and are difficult to be recognized without extensive testing [3,5,6]. Serologic surveillance of COVID-19 is attracting great interest because it not only helps to identify the affected cases but may also provide important information of herd immunity, SARS-CoV-2 infection has wider disease spectrum ranging from asymptomatic infection to life-threatening respiratory failure [3,4]. The asymptomatically infected COVID-19 patients pose great public concern as they could also transmit SARS-CoV-2 and are difficult to be recognized without extensive testing [3,5,6]. Serologic surveillance of COVID-19 is attracting great interest because it not only helps to identify the affected cases but may also provide important information of herd immunity.
immunity. During SARS-CoV infection, viral specific IgG peaks at month 4 after disease onset and decreases markedly after 16 months [7]. Although antibody responses are generally regarded as protective, detrimental effects, known as antibody-dependent enhancement (ADE), may also occur in the course of SARS-CoV infection [8–10]. It is unclear whether ADE play a role in the pathogenesis of COVID-19. A recent study showed that critically ill patients with COVID-19 had higher total SARS-CoV-2 antibody titers compared with patients with less severe diseases [11]. However, whether higher neutralizing antibody (NAb) titers are associated with more profound lung damage has yet to be elucidated.

In this study, we analyzed the SARS-CoV-2 NAb titers in patients recently recovered from COVID-19 using a novel SARS-CoV-2 surrogate virus neutralization test (sVNT) [12]. Also, we retrospectively measured and semi-quantified the lung injury of patients based on their chest computed tomography (CT) at admission through a previously described grading system [13]. We found the NAb levels among recovered patients varied. Remarkably, the NABs were not detected in two recovered COVID-19 children. Taken together, NAb levels in recovered COVID-19 patients were positively correlated with the severity of lung injury. Our study suggested that recovered patients of COVID-19 may incur reinfection, and ADE could possibly contribute to progression of COVID-19 pneumonia.

2. Patients and methods

2.1. Patients

This study enrolled 49 patients who recently recovered from COVID-19, and were scheduled for their first follow-up visits in outpatients of the second hospital of Nanjing, China, from March 5, 2020 to March 16, 2020. The diagnosis of COVID-19 in those patients was based on positive nucleic acid test for SARS-CoV-2 from throat swab sample during their previous hospitalization. During inpatient days, SARS-CoV-2 viral loads from throat swab specimens were evaluated every other day using nucleic acid test for SARS-CoV-2 from throat swab sample during their quantitative reverse transcription polymerase chain reaction (qRT-PCR). The serum/HRP-RBD mix (100 μl) was added to each well and incubated at 37°C for 30 min. Unbound HRP-RBD were removed by four washes, followed by addition of chromogenic substrate TMB and incubation at 25°C for 15 min. Colorimetric reaction was stopped by addition of stop solution. The absorbance reading at 450 nm was measured using microplate reader (BioTek Synergy H1). Inhibition (%) = (1 - Sample OD450 value/Negative Control OD450 value) × 100. The reciprocal of the maximal dilution with 50% inhibition was counted as the titer of neutralizing antibody in tested serum sample.

2.4. Statistical analysis

Continuous variables were expressed as the medians and inter-quartile ranges (IQR). Categorical variables were summarized as the counts and percentages in each category. Comparison between groups was done using the Mann-Whitney U test, and Chi-Square test or Fisher’s exact test for categorical variables as appropriate. The Bonferroni correction was used to analyze the trend of median NAB titers with age or pulmonary radiological abnormalities. Correlation was measured using Spearman’s rank correlation coefficient. For the multivariable analyses, we developed Ordinary Least Squares (OLS) regression model to identify the clinical variables associated with the NAB titers after controlling for age and gender. Since the antibody NAb titer was a skewed distribution, we standardized it and used its Z score (mean = 0 and Std = 1) as the dependent variable. In our regression model, comorbidity, corticosteroid treatment, and intravenous immunoglobulin usage were dichotomized into “Yes vs. No”, and C-reactive protein (CRP) was dichotomized into “>10 mg/l vs. ≤ 10 mg/l.”. CT score, lymphocyte count, and days from virus clearance used their original values. The statistical analysis was done by SPSS version 22.0 (IBM). A P value <0.05 is considered statistically significant. Distributions of NAB titers among different patient groups were plotted by graphpad prism version 6.

3. Results

3.1. Clinical characteristics of the patients

Of the 49 patients, 2 had severe illness and 8 had asymptomatic infection. The median age was 37 years (IQR, 30.0–54.5). 55.1% (27/49) were male, 8.2% (4/49) were daily smokers, and 22.4% (11/49) had underlying comorbidities, including hypertension (12.2%, 6/49), and diabetes (2.0%, 1/49). The median time to blood collection (for NAB analysis) from illness onset, viral clearance and discharge were 27.0 days (IQR, 20.5–37) and 17.0 days (IQR, 15.0–33.0), respectively (Table 1).

At the time of admission, 26.5% (13/49) of the patients had leukopenia and 12.2% (6/49) of the patients had lymphopenia. Elevated lactate dehydrogenase (LDH), CRP and D-dimer levels were found in 30.6% (15/49), 42.9% (21/49) and 14.3% (7/49) of the patients, respectively. The median CT score of the patients was 4 (IQR, 1.5–6) (Table 1). During hospitalization, the vast majority of the patients received antiviral treatment with protease inhibitors (lopinavir/ritonavir or darunavir/cobicistat). Corticosteroids were administered in a quarter of the patients (Table 1). At the time of follow-up, the patients did not show obvious symptoms. Almost all patients had normal blood white cell count, lymphocyte count and CRP level. Elevated LDH and D-dimer levels were found in 10.2% (5/49) and 20.4% (10/49) of the patients (Table 1).

Serum NAs against receptor binding domain (RBD) of SARS-COV-2 were measured by a sVNT with the commercial kit provided by GenScript (Catalog number, L00847) as described recently with modification [12]. Samples were tested in duplicate. Briefly, 200 ng/well hACE2 was coated in the carbonate-bicarbonate coating buffer. The serum samples were pre-inactivated at 56°C for 30 min, diluted with 2-fold serial gradients, and incubated with equal volume of horseradish peroxidase-conjugated RBD (HRP-RBD) at 37°C for 30 min. Then, the serum/HRP-RBD mix (100 μl) was added to each well and incubated at 37°C for 15 min. Unbound HRP-RBD were removed by four washes, followed by addition of chromogenic substrate TMB and incubation at 25°C for 15 min. Colorimetric reaction was stopped by addition of stop solution. The absorbance reading at 450 nm was measured using microplate reader (BioTek Synergy H1). Inhibition (%) = (1 - Sample OD450 value/Negative Control OD450 value) × 100. The reciprocal of the maximal dilution with 50% inhibition was counted as the titer of neutralizing antibody in tested serum sample.
There was no statistical difference with regard to sex, smoking history, underlying comorbidities, and blood parameters at the time of admission between patients with relatively higher NAb titers (≥1:80) and patients with lower NAb titers (<1:80). To explore the possible factors associated with NAb titers, variables were compared between patients with relatively higher NAb titers (≥1:80) and patients with lower NAb titers (<1:80). There was no statistical difference with regard to sex, smoking history, underlying comorbidities, and blood parameters at the time of admission between patients with relatively higher NAb titers (≥1:80) and patients with lower NAb titers (<1:80).

### 3.2. NAb levels in different patient groups

To determine the NAb titers, we utilized the sVNT kit, which targeted the RBD of SARS-CoV-2. Among the 49 recovered patients, the median NAb titer was 1: 40 (IQR: 1:15-1:120). 24.5 % (12/49) of the patients had NAb titers less than 1:20. To explore the possible factors associated with NAb titers, variables were compared between patients with relatively higher NAb titers (≥1:80) and patients with lower NAb titers (<1:80). There was no statistical difference with regard to sex, smoking history, underlying comorbidities, and blood parameters at the time of admission (white blood cell count, lymphocyte count and v-dimer) (Table 1). Treatment during hospitalization (antiviral treatment, corticosteroid administration, and intravenous use of immunoglobulin) between these two groups had no significant difference. In addition, lymphocyte subgroups were similar between the two groups (Table 1).
L) or elevated LDH (>245 IU/L) level at the time of admission had significantly higher NAb titers during recovery ($p = 0.004$ and $p = 0.019$, respectively, Fig. 1D and E). Patients with lymphocytopenia (lymphocyte count $< 0.8 \times 10^9$ cells/L) had similar NAb titers as compared with those without lymphocytopenia ($p = 0.478$, Fig. 1F).

There was a statistically significant trend of higher median NAb titers with higher levels of pulmonary abnormalities, as reflected by larger CT scores ($p < 0.001$, Fig. 1G). NAb titers were not significantly different between patients with or without corticosteroid treatment (or intravenous immunoglobulin) ($p = 0.478$, Fig. 1F).

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### 3.3. Multivariable analysis of the factors associated with NAb titers

It's worthy mentioning that patients with higher NAB titers had significant higher levels of pulmonary abnormalities ($p < 0.001$, Fig. 1G). To further analyze their correlation, we first used Spearman's rank correlation coefficient to measure the strength of correlation between NAB levels and pulmonary injury. As shown in Fig. 2, there was a positive correlation between NAB titers and chest CT score ($r = 0.518$, $p < 0.001$). For multivariable analysis, we used the OLS model (multiple

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**Fig. 1. Distribution of neutralizing antibody titers in different patient groups.**

NAb, neutralizing antibody; CT, computed tomography; CRP, C-reactive protein; LDH, lactate dehydrogenase.
3.4. Characteristics of two patients with no detectable NAb

For our interest, among the 49 patients, two pediatric patients had no detectable NAb. They were 5 and 6 years old. Consistently, their total antibodies as well as the anti-RBD antibody titers were also relatively low, ranged from 1:20 to 1:40 (Fig. 3). Both children had asymptomatic infections, and were identified by screening of the close contacts by local Centers for Disease Control and Prevention. Before being transferred to the second hospital of Nanjing for quarantine, nucleic acid tests for SARS-CoV-2 from throat swab samples were positive. However, the tests became negative after admission. Routine blood laboratory parameters of the patients, including complete blood count, liver and renal function, creatine kinase, lactate dehydrogenase, myocardial enzymes, coagulation profile, interleukin-6, procalcitonin, C-reactive protein and erythrocyte sedimentation rate, were all within the normal range. The chest CT scans were also normal.

Table 2

| OLS regression model for neutralizing antibody titer Z score. | Unstandardized coefficient | Standardized coefficient | p-value |
|------------------|-------------------------|-------------------------|---------|
| Intercept        | −0.29                   | 0.00                    | 0.59    |
| Age              | 0.01                    | 0.17                    | 0.24    |
| Male (vs. Female)| −0.29                  | −0.15                   | 0.22    |
| CT score         | 0.10                    | 0.36                    | 0.02    |
| Comorbidity (vs. No) | 0.67              | 0.28                    | 0.02    |
| Corticosteroid treatment (vs. No) | −0.83         | −0.36                   | 0.01    |
| Intravenous Immunoglobulin (vs. No) | 0.23             | 0.12                    | 0.41    |
| CRP > 10 mg/l (vs. CRP ≤ 10) | 0.33              | 0.16                    | 0.28    |
| Lymphocyte count | −0.03                   | −0.14                   | 0.25    |
| Days from virus clearance | −0.02       | −0.16                   | 0.18    |

R² = 0.52.

Fig. 3. Antibody analysis in two patients with negative neutralizing antibody test results. RBD, receptor binding domain; N, nucleocapsid protein.

4. Discussion

According to the Johns Hopkins case-tracking dashboard, as of July 3, 2020, there are over 10 million confirmed cases of COVID-19, leading to more than 520 thousand deaths. In the meantime, more than 5.7 million people have officially recovered. One important question is whether recovered patients have protective immunity against re-infection. To answer this question, accurate measurement of NAb in recovered COVID-19 patients will be a necessary first step. However, NAb detection currently relies on virus neutralization test (VNT) or pseudovirus-based virus neutralization test (pVNT), which requires handling live viruses in high biosafety level containment laboratory and also needs well trained staff to perform the tedious and time consuming procedure [15–17]. Even in the most developed nations or regions, those could not be easily available. In the present study, a novel sVNT, which was demonstrated to correlate well with VNT [12], was used to evaluate the NAb in patients recently recovered from COVID-19. NAbs were not detected in two asymptomatic children who quickly cleared the virus. Although the exact reason for undetectable NAb was not known, the finding highlights the needs to further investigate the possibility of re-infection for those recovered COVID-19 patients with no detectable NAbs.

A recent study in Shanghai evaluated the SARS-CoV-2 NAb titers using pVNT, which found that NAb titers were higher in patients with older age, higher CRP levels and lower lymphocyte counts [17]. Of note, those parameters are associated with disease severity of COVID-19 [18–20]. Nevertheless, a direct evaluation of the relationship of NAb titers with severity of COVID-19 pneumonia has not yet been reported. In the present study, we used a previously described semi-quantitative method to grade the severity of COVID-19 pneumonia [13]. CT score was assigned to each chest CT. A score of 0 represented normal chest CT
and a score of 25 generally represented the most severe lung damage. As shown in Table 1 and Fig. 1, patients with higher NAb titers indeed had poorer baseline chest CT scores (more profound pneumonia). In multivariate analyses, after adjustment for age, sex, comorbidity, corticosteroid treatment, CRP level, lymphocyte count and time of NAB analysis, baseline chest CT scores still strongly correlated with NAb titers in patients recovered from COVID-19 (Table 2, p = 0.02). The finding suggested that pneumonia progression related to antibody level can occur during COVID-19. However, whether this is a reflection of ADE needs much more research for COVID-19 pathogenesis.

ADE has been described in many virus infections, including dengue virus, Zika virus, Ebola virus, and coronavirus [21]. In the context of Middle Eastern respiratory syndrome coronavirus (MERS-CoV) infection, binding of specific neutralizing antibodies to the virus could facilitate the entry of virus into immune cells through Fc receptors [22]. Importantly, lung epithelial cells could also express functional neonatal Fc receptor [23]. An immunological therapy with intravenous immunoglobulin to block Fc receptors has been advised as a potentially therapeutic strategy for patients with COVID-19 [24]. In our study, corticosteroid treatment was found to negatively impact the generation of NAB (Table 2, p = 0.01). If ADE is indeed a major problem in the pathogenesis of COVID-19, it is possible that corticosteroid could be used to mitigate the progression of COVID-19 pneumonia. Recently, studies did suggest that COVID-19 patients with moderate-to-severe illness could benefit from corticosteroid-treatment [25,26].

It should be noted that “correlation” does not imply “causation”. The finding that NAB titers were positively correlated with baseline pulmonary abnormalities did not prove that NAB and the associated ADE caused lung damage. However, our study, to some extent, raised the concern regarding the antibody-based treatment for COVID-19 patients of novel coronavirus disease 2019, Clin. Infect. Dis. (2020). [20] W. Liu, A. Fontanet, P.-H. Zhang, L. Zhan, Z.-T. Xin, L. Baril, F. Tang, H.Lv, W.-C. Cao, Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome, J. Infect. Dis. 193 (6) (2006) 792–795.

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Appendix A. Supplementary data
Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.biopha.2020.110629.

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