INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

2022 November; 29(1): 43-46
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

Antibody Responses to SARS-COV-2 of COVID-19 Patients Based on the Disease Severity

Fenty[1,2], I Made Adi Ananda Putra[1]

[1] Faculty of Pharmacy, Universitas Sanata Dharma, Yogyakarta, Indonesia. E-mail: fenty@usd.ac.id
[2] Clinical Pathology Laboratory, Bethesda Hospital, Yogyakarta, Indonesia

ABSTRACT

Any individual infected by COVID-19 can suffer various degrees of disease such as asymptomatic symptoms, mild, moderate or severe. Response to the antibody formation in the human body can be affected by the severity of COVID-19. Many researchers have stated that patients suffering a severe COVID-19 had a more significant antibody response, proven by higher antibody titers than those suffering mild or moderate severity. This research aimed to observe the different antibody responses in COVID-19 patients based on the severity of the disease. The research was a retrospective study with a cross-sectional design. The inclusion criteria were confirmed SARS-COV-2 patients determined by RT-PCR test results with age ≥18 years old and a complete medical record taken from electronic medical records and Laboratory Information System (LIS). This study involved 100 COVID-19 patients consisting of 51% non-severe and 49% severe COVID-19. Patients in the non-severe group had a relatively lower IgM and IgG antibody response than patients in the severe group. It could be primarily observed at the time of antibody measurement > 15th day of symptoms onset ($p < 0.05$).

Keywords: Antibody, SARS-COV-2, severity

INTRODUCTION

An infectious disease called Severe Acute Respiratory Syndrome Corona Virus Disease-2 (SARS-COV-2) was first found in the City of Wuhan, Province of Hubei, China, in December 2019. WHO declared a Public Health Emergency of International Concern (PHEIC) dated Jan 30, 2020, and COVID-19 has become a pandemic since Mar 11, 2020. [1-3]

Individuals infected with COVID-19 can suffer asymptomatic, mild, moderate, or severe symptoms. The current COVID-19 diagnosis still uses Nucleic Acid Amplification Test (NAAT) as the gold standard. If the NAAT test shows a negative result, the serologic test is needed to perform on any suspected individual.[4,5]

The serologic test can measure the response of antibodies to SARS-COV-2. This test is also significant for studying epidemiology, vaccine development, and evaluating passive antibody therapy toward patients. An accurate serologic test can improve any knowledge of virus distribution in specific communities, specifically among asymptomatic patients.[4,6,7]

Currently, one of the developed infectious COVID-19 therapies is plasma convalescence therapy.[8] However, some COVID-19 survivors can only be plasma convalescence donors, although 20% of COVID-19 patients having mild symptoms in Thailand did not have any IgG against SARS-COV-2 after two weeks of the onset symptoms.[9]

According to Long *et al.*, there is a significant difference in antibody levels to SARS-COV-2 between patients whose severe and non-severe symptoms.[10] Another research has argued that asymptomatic COVID-19 patients have a lower IgG than symptomatic patients in the acute phase.[11] Thus, the measurement of antibody formation in any individuals infected with SARS-COV-2 is necessarily performed to determine the immunity state. Based on the background above, the objective of this research was to determine the difference in antibody responses in COVID-19 patients based on the disease severity.

METHODS

The research was a retrospective study with a cross-sectional design. A sampling method in the analysis was performed by collecting data from COVID-19 patients based on the result of the RT-PCR test when treated in Bethesda Hospital, Yogyakarta from July 2020 to June 2021 and fulfilled the inclusion criteria. The inclusion criteria were SARS-COV-2

confirmed patients determined with RT-PCR test results with age ≥ 18 years old and a complete medical record taken from electronic medical records and Laboratory Information System (LIS).

The severity of disease in this study was classified into the non-severe and severe groups. The non-severe group consisted of mild and moderate symptoms of COVID-19, while the severe group consisted of severe and critical COVID-19 symptoms. In addition, the severity of COVID-19 in this study was based on a diagnosis by a medical doctor and blood oxygen saturation ≤ 93. Data of antibody SARS-COV-2 determined by Chemiluminescence immunoassay analyzer (CLIA) (Mindray, China) and a complete medical record comprising diagnostic criteria with the severity were used. The result was reported reactive if the cut-off index/COI ≥ 1 for IgM and ≥ 10 U/mL for IgG.[12] The data were then statistically analyzed using SPSS version 22, independent T-test, and p-value <0.05 was considered as significant. All antibody SAR-COV-2 from 100 patients were statistically analyzed using an independent T-test based on severity (non-severe vs. severe), and then each specific group with a time of the measurement of antibody ≤ 7th day, 7th -14th day and > 15th day of symptoms onset (non-severe vs. severe). Approval of ethical eligibility was obtained from the Health Research Ethics Committee of Bethesda Hospital, Yogyakarta, with No. 99/ KEPK-RSB/ VII/20.

RESULTS AND DISCUSSIONS

A total of 100 COVID-19 patients with age ≥ 18 years old were involved as respondents in this study, consisting of 51% non-severe and 49% severe COVID-19. Table 1 shows that most respondents were female (58%), and their age range was between 50 and 64 (39%). Mortality during hospitalization was reported in 22% of patients with severe COVID-19. The characteristic of respondents in our study was almost similar to another research in Makassar, which also found that most of the research subjects were female (52.4%) with age ranging from 30 to 49 years (50.8%).[13]

The research demonstrated a different response of antibodies characterized by IgM and IgG levels from both COVID-19 patient groups. The IgM and IgG levels in the non-severe group were relatively lower than the severe group, with p<0.05 (Table 2). This result was in line with previous studies.[9-11] The explanation related to this finding has yet to be elucidated; however, the currently believed hypothesis stated that this might be due to a robust inflammation response in the severe state, including B lymphocytes producing antibodies.[9] In addition, another research indicated that titer antibody IgG in the non-severe can delay the formation or has low to moderate level.[14]

Table 1. Characteristic of 100 COVID-19 patients based on the severity of disease

Characteristic	Severity of Disease		Total (%)
	Non-severe n:51	Severe n:49	
Age (years)			
18-49	23	10	33
50-64	14	25	39
≥ 65	14	14	28
Gender			
Male (%)	23	19	42
Female (%)	28	30	58
Mortality	0	22	22

Table 2. IgM and IgG antibody responses to SARS-COV-2 based on the severity of the disease

Antibody SARS-COV-2	Non-severe (n:51)	Severe (n:49)	p
IgM	1.39 (0.09-16.64)	4.45 (0.07-18.59)	0.001
IgG	13.7 (0.00-355.64)	124.92 (0.18-295.92)	0.000

Median (minimum-maximum

An antibody formed as a response to SARS COV-2 infection was also determined by the time of antibody measurement since the symptom onset in the symptomatic patient. Long *et al.* argued that the median of seroconversion occurrence on IgM and IgG formation was 13 days after symptom onset.[10] However; Liu *et al.* stated that IgG and IgM antibodies were not formed on the 0-3rd day since the symptom onset, but IgM and IgG were formed since the 4th day and the 7th day, respectively.[15]

This study found that reactive IgM and IgG were not formed in 18 COVID-19 patients of the non-severe group and 6 COVID-19 patients whose antibodies were measured more than 15 days from the symptom onset. Similarly, seroconversion was not found in 5 COVID-19 patients of the severe group. Three of those 5 COVID-19 patients were tested in the first week, and 2 COVID-19 patients were tested within the 8th-14th day since the first symptom. Another study found that 20% of patients with mild symptoms showed no detectable IgG antibodies more than two weeks after symptoms onset.[9]

This research found no detectable antibody caused by the earlier measurement after the onset of symptoms, such as the first week. Therefore, it was suggested that the body did not initiate the strong response that no reactive antibody to SARS COV-2 was produced.

Table 3. IgM and IG antibody responses to SARS COV-2 based on the severity of disease and measurement of antibody ≤ 7th day of symptoms onset

SARS-COV-2 Antibody	Non-severe (n:20)	Severe (n:15)	p
IgM	0.82 (0.09-8.75)	3.83 (0.07-7.45)	0.117
IgG	2.49 (0.17-163.34)	39.685 (0.18-295.29)	0.067

Median (minimum-maximum)

Table 4. IgM and IgG antibody responses to SARS COV-2 based on the severity of disease and measurement of antibody 7th -14th day of symptoms onset

SARS-COV-2 Antibody	Non-severe (n:18)	Severe (n:21)	p
IgM	2.05 (0.11-14.94)	5.835 (0.11-18.59)	0.382
IgG	88.1 (0.00-355.64)	103.975 (0.24-294.01)	0.889

Median (minimum-maximum)

Table 5. IgM and IgG antibody responses to SARS COV-2 based on the severity of disease and measurement of antibody >15th day of symptoms onset

SARS-COV-2 Antibody	Non-severe (n:13)	Severe (n:13)	p
IgM	0.21 (0.09-16.64)	7.00 (0.46-13.49)	0.010
IgG	1.07 (0.00-205.27)	198.19 (7.13-293.62)	0.001

Median (minimum-maximum)

Based on Tables 3, 4, and 5, there were different responses in both the non-severe and severe groups based on the measurement result of the SARS-COV-2 antibody using the CLIA method. The antibody levels in the non-severe group were relatively lower than the severe group; however, a significant difference was only found in respondents with antibody measurements≥ 15 days (Figures 1 and 2).

This study also showed that some patients in the non-severe group had a robust IgM antibody response from the measurement of antibody ≤ 7th day, 7th -14th day, and > 15th day of symptoms onset (Figure 1). Two patients in the nonsevere group had strong IgG antibody response from the measurement of antibody ≤ 7th day and 7th -14th day of symptoms onset (outliers in Figure 2). Similarly, Liu *et al.* pointed out that a robust antibody formation might be found in some patients with mild cases starting on the 9th day from the symptom onset. Their study also showed that some patients with mild disease tended to develop faster peak IgM antibody responses compared with those with severe disease.[15]

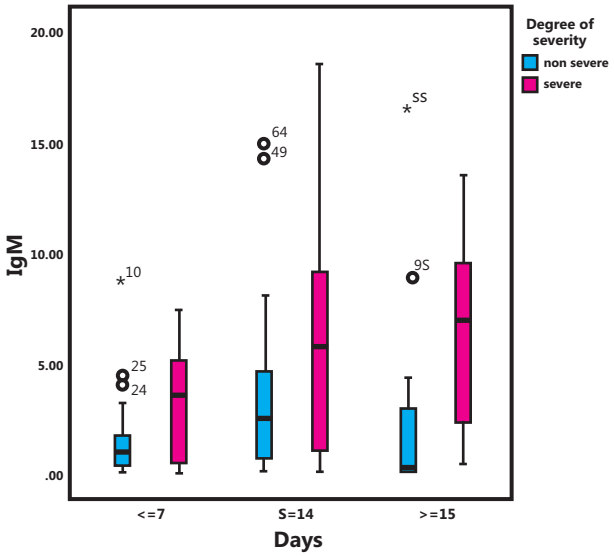

Figure 1. Profile of IgM response to SARS-COV-2 based on the severity of disease and time of measurement after symptom onset

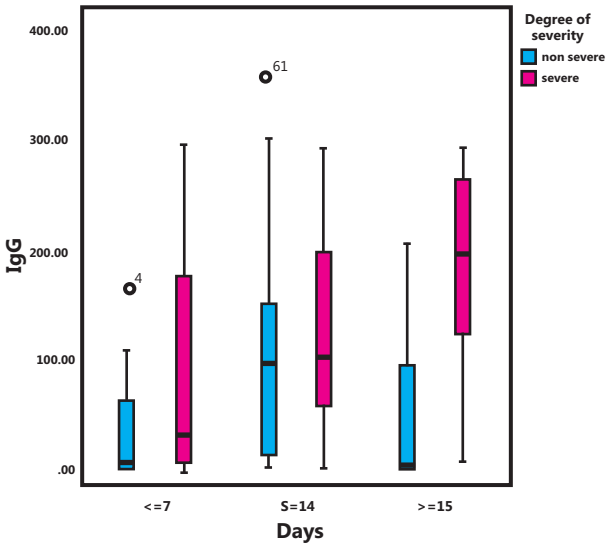

Figure 2. Profile of IgG response to SARS-COV-2 based on the severity of disease and time of measurement after symptom onset

The description related to the findings of this research was probably due to the different times of antibody testing between one subject with others since this study merely used secondary data. The formation of antibody concentration towards SARS-COV-2 was highly dependent on the time of measurement between the symptom onset and patients' serum collection.[16] Moreover, the different response of the antibody formation towards SARS-COV-2 in any individual was related to immunity status and affected by age and comorbidity.[15] The use of semi-quantitative measurement of SARS-COV-2 antibody using the CLIA method remains the limitation of this study.

CONCLUSIONS AND SUGGESTIONS

The IgM and IgG response in the non-severe group was lower than in the severe group in this study. It was mainly found in antibody testing carried out 14 days after the symptom onset of COVID-19. Therefore, further research investigating the antibody of SARS-COV-2, particularly antibody neutralizing S1-receptor binding protein, was necessarily required.

REFERENCES

1. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel Coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol, 2020; 92(6): 568-76.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus–infected pneumonia in Wuhan, China. JAMA, 2020; 323(11): 1061.
3. Kemenkes RI. Pedoman pencegahan dan pengendalian Coronavirus Disease (COVID-19). Revisi ke-5, Kementrian Kesehatan RI, 2020; 16-7.
4. World Health Organization. Diagnostic testing for SARS-CoV-2: Interim guidance, Sept 11 2020. Geneva, World Health Organization, 2020. (WHO/2019-nCoV/laboratory/2020.6). Available from: https://apps.who.int/iris/handle/10665/334254 (accessed Nov 24, 2021).
5. Kolifarhood G, Aghaali M, Mozafar SH, Taherpour N, Rahimi S, *et al.* Epidemiological and clinical aspects of COVID-19; A narrative review. Arch Acad Emerg Med [Internet]. 2020. Available from: https://journals.sbmu.ac.ir/aaem/index.php/AAEM/article/view/620 (accessed Nov 24, 2021).
6. Suhandynata R, Hoffman M, Kelner M, McLawhon R, Reed S, Fitzgerald R. Longitudinal monitoring of SARS-CoV-2 IgM and IgG seropositivity to detect COVID-19. The Journal of Applied Laboratory Medicine, 2020; 5(5): 908-920.
7. Post N, Eddy D, Huntley C, van Schalkwyk MCI, Shrotri M, *et al.* Antibody response to SARS-CoV-2 infection in humans: A systematic review. PLos One, 2020; 15(12): e0244126.
8. Nuccetelli M, Pieri M, Grelli S, Ciotti M, Miano R, *et al.* SARS-CoV-2 infection serology: A useful tool to overcome lockdown?. Cell Death Discovery, 2020; 6: 1.
9. Kowitdamrong E, Puthanakit T, Jantarabenjakul W, Prompetchara E, Suchartlikitwong P, *et al.* Antibody responses to SARS-CoV-2 in patients with differing severities of Coronavirus disease 2019. PLos One, 2020; 15(10): e0240502.
10. Long Q, Liu B, Deng H, Wu G, Deng K, Chen Y, *et al.* Antibody responses to SARS-CoV-2 in patients with COVID-19. Nature Medicine, 2020; 26(6): 845-848.
11. Yongchen Z, Shen H, Wang X, Shi X, Li Y, Yan J, *et al.* Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients. Emerg Microbes Infect. 2020; 9(1): 833–6.
12. Mindray leaflets. SARS-COV-2 IgG & IgM (CLIA). Accessed Nov 24, 2021.
13. Selanno Y, Widyaningsih Y, Esa T, Arif M. Analysis of neutrophil-lymphocyte ratio and absolute lymphocyte count as predictors of severity of COVID-19 patients. Indonesian Journal of Clinical Pathology and Medical Laboratory. 2021; 27(2): 184 – 9.
14. Hu W, Howell J, Ozturk T, Benameur K, Bassit L, *et al.* Antibody profiles according to mild or severe SARS-CoV-2 infection, Atlanta, Georgia, USA, 2020. Emerging Infectious Diseases, 2020; 26(12): 2974-2978.
15. Liu X, Wang J, Xu X, Liao G, Chen Y, Hu CH. Patterns of IgG and IgM antibody response in COVID-19 patients. Emerg Microbes Infect. 2020; 9(1): 1269-1274.
16. Markewitz R, Torge A, Wandinger K, Pauli D, Franke A, *et al.* Clinical correlates of anti-SARS-CoV-2 antibody profiles in Spanish COVID-19 patients from a high incidence region. Scientific Reports, 2021; 11: 1.