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【 ORIGINAL ARTICLE 】

Anti-SARS CoV-2 IgG in COVID-19 Patients with Hematological Diseases: A Single-center, Retrospective Study in Japan

Takayuki Fujii[1,2], Masao Hagihara[1], Keiko Mitamura[3], Shiori Nakashima[1], Shin Ohara[1], Tomoyuki Uchida[1], Morihiro Inoue[1], Moe Okuda[4], Atsuhiro Yasuhara[4], Jurika Murakami[4], Calvin Duong[4], Kiyoko Iwatsuki-Horimoto[4], Seiya Yamayoshi[4,5] and Yoshihiro Kawaoka[4,5]

Abstract:

Objective Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally. Although the relationship between anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies and COVID-19 severity has been reported, information is lacking regarding the seropositivity of patients with particular types of diseases, including hematological diseases.

Methods In this single-center, retrospective study, we compared SARS-CoV-2 IgG positivity between patients with hematological diseases and those with non-hematological diseases.

Results In total, 77 adult COVID-19 patients were enrolled. Of these, 30 had hematological disorders, and 47 had non-hematological disorders. The IgG antibody against the receptor-binding domain of the spike protein was detected less frequently in patients with hematological diseases (60.0%) than in those with non-hematological diseases (91.5%; p=0.029). Rituximab use was significantly associated with seronegativity (p=0.010).

Conclusion Patients with hematological diseases are less likely to develop anti-SARS-CoV-2 antibodies than those with non-hematological diseases, which may explain the poor outcomes of COVID-19 patients in this high-risk group.

Key words: COVID-19, SARS-CoV-2, SARS-CoV-2 IgG antibodies

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting illness, coronavirus disease (COVID-19), has spread rapidly across the world since the beginning of 2020. In Japan, the cumulative number of infected people is increasing, and as of the end of November 2021, more than 18,000 of those infected have died. In our institution, a large number of hospitalized patients had a nosocomial infection with SARS-CoV-2 in March 2020. In the hematology ward, the fatality rate was higher than that in the non-hematological departments (52.5% vs. 35.1%) (1). Similarly, previous reports have shown that patients with cancer, especially those with hematological malignancies, have a higher risk of mortality upon SARS-CoV-2 infection than those with non-cancer (2, 3).

Characterizing SARS-CoV-2 antibodies is fundamental for understanding COVID-19 epidemiology and reinfection potential, as well as for vaccinee development (2, 3). Some studies have reported that antibody testing is complementary to real-time-reverse-transcript polymerase chain reaction

[1]Department of Hematology, Eiju General Hospital, Japan, [2]Division of Hematology, Department of Medicine, Keio University School of Medicine, Japan, [3]Division of Infection Control, Eiju General Hospital, Japan, [4]Division of Virology, Institute of Medical Science, University of Tokyo, Japan and [5]The Research Center for Global Viral Diseases, Research Institute, National Center for Global Health and Medicine, Japan
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Correspondence to Dr. Takayuki Fujii, supercjump@gmail.com

(RT-PCR), which has a sensitivity limitation (false-negative rate: approximately 30%) (4, 5). Although several publications, including ours (6-12), have revealed an association between antibody titers and severity of infection, information on the seropositivity for specific types of disorders is still lacking. Some studies have shown that patients with hematological malignancies were less likely than those with non-hematological diseases to develop anti-SARS-CoV-2 antibodies, especially those receiving anti-CD-20 therapy, chimeric antigen receptor (CAR)-T-cell therapy, or stem cell transplants (13, 14).

Patients with hematological diseases, especially malignancies, have long-lasting immunodeficiency due to the nature of their disorders or anti-cancer treatments. The humoral immune response is assumed to be depressed or impaired, which might explain the poor outcomes in this population.

In the present study, we measured the anti-SARS-CoV-2 immunoglobulin G (IgG) antibody levels in our patients with nosocomial infections, with a focus on those with hematological diseases.

Materials and Methods

Study design

This was a retrospective, single-center, observational study. Among all hospitalized patients, there were 84 cases of nosocomial COVID-19 with SARS-CoV-2 confirmed by PCR, of whom 7 were excluded because they died within 14 days of contracting COVID-19. Among those who died, six and one patient had hematological and non-hematological diseases, respectively.

Patient sera were collected immediately after the patients developed COVID-19, between March 25 and May 14, 2020, and an enzyme-linked immunosorbent assay (ELISA) was performed to detect the anti-SARS-CoV-2 spike in the receptor-binding domain (RBD) IgG, as previously reported (8). Samples were collected every two to five days. The optical density (OD) value of the phosphate-buffered saline (PBS) well was subtracted from the OD value of the RBD wells to correct for background. A subtracted OD value ≥0.75, at a 40-fold serum dilution, was considered positive. In the previous report (8), the cut-off was set at 0.1 because the experiment required samples containing antibodies detectable on ELISA. However, in this study, a subtracted OD value ≥0.75 at a 40-fold serum dilution was considered positive.

In this study, patients who survived for more than 14 days after the onset (defined as the beginning of symptoms or the date of a positive real-time RT-PCR result) were enrolled, as at least 14 days are required to develop IgG antibodies (6). Their clinical information was retrospectively reviewed from their electronic medical records and documented anonymously.

The study was approved by the Research Ethics Review Committee of the Institute of Eiju General Hospital.

Statistical analyses

All statistical analyses were performed using Easy R (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander, designed to add statistical functions frequently used in biostatistics (15). Proportions were compared using Fisher's exact test. Multivariate regression analyses were performed using logistic regression analyses. p values <0.05 were considered statistically significant.

Results

A total of 77 patients were enrolled: The median age was 75 (interquartile range, 70.0-82.0) years old, and 50 (64.9%) of the patients were men. Thirty had hematological diseases, and 47 had non-hematological diseases. Of the 30 with hematological diseases, 12 had myeloid neoplasms including 7, 4, and 1 with acute myeloid leukemia, myelodysplastic syndrome (MDS), and myeloproliferative neoplasm, respectively. One patient had acute lymphoblastic leukemia, nine had malignant non-Hodgkin's lymphomas [six diffuse large B-cell lymphomas (DLBCL), one primary DLBCL of the central nervous system lymphoma, one follicular T-cell lymphoma, and one angioimmunoblastic T-cell lymphoma], five had plasma cell neoplasms [all multiple myeloma (MM)], and three had non-malignant diseases [two with immune thrombocytopenic purpura and one with pure red cell aplasia (PRCA)]. Of the 47 patients with non-hematological diseases, 11, 5, 5, 3, 2, 2, 6, 3, 2, 3, and 5, respectively, had cardiovascular diseases, gastrointestinal diseases, cerebral apoplexies, chronic kidney disease, diabetes mellitus, neurological diseases, pneumonia, urinary tract infection, cellulitis, fractures, and no underlying disease. The patients' characteristics are reported in Table 1.

Table 2 compares the patients' characteristics between those with hematological and non-hematological diseases. A lack of any marked differences in the age and sex was confirmed. There were significant differences in the lymphocyte count at the disease onset, latest treatments, and seropositivity. The death rate was significantly higher in those with hematological disease than in those with non-hematological diseases, and ultimately, 22 of the 77 patients (28.6%) died, with all deaths due to COVID-19.

Table 3 shows the relationship between seropositivity and clinical features. We identified severity of COVID-19, type of diseases, and latest treatments as potential key confounders for seroconversion and performed a multivariable logistic regression analysis. The lymphocyte count at the disease onset was entered into the multivariable logistic regression model because it was statistically significant ($p< 0.05$) in the univariate analysis. Asymptomatic patients tended not to be seropositive without statistical significance ($p=0.066$). SARS-CoV-2 IgG was more frequently detected

Table 1. Patient's Characteristics.

Number of COVID-19 cases	n=77
Age (median)	75.1 (IQR 70.0, 82.0)
Gender	
Male	n=50 (64.9%)
Female	n=27 (35.1%)
Type of diseases	
Hematology	n=30 (39.0%)
Acute myeloid leukemia	n=7 (9.1%)
Myelodysplastic syndrome	n=4 (5.2%)
Myeloproliferative neoplasm	n=1 (1.3%)
Acute lymphoblastic leukemia	n=1 (1.3%)
Diffuse large B-cell lymphoma (DLBCL)	n=6 (1.3%)
Primary DLBCL of the central nervous system lymphoma	n=1 (7.8%)
Follicular T-cell lymphoma	n=1 (1.3%)
Angioimmunoblastic T-cell lymphoma	n=1 (1.3%)
Multiple myeloma	n=5 (6.5%)
Immune thrombocytopenic purpura	n=2 (2.6%)
Pure red cell aplasia	n=1 (1.3%)
Non-hematology	n=47 (61.0%)
Cardiovascular disease	n=11 (14.3%)
Gastrointestinal disease	n=5 (6.5%)
Cerebral apoplexy	n=5 (6.5%)
Chronic kidney disease	n=3 (3.9%)
Diabetes mellitus	n=2 (2.6%)
Neurological disease	n=2 (2.6%)
Pneumonia	n=6 (7.8%)
Urinary tract infection	n=3 (3.9%)
Cellulitis	n=2 (2.6%)
Fracture	n=3 (3.9%)
No underlying disease	n=5 (6.5%)
Latest treatments	
Treatment with corticosteroid	n=14 (18.2%)
Treatment with rituximab	n=6 (7.8%)
Any chemotherapy	n=21 (27.3%)

in patients with hematological diseases than in those with non-hematological diseases (p=0.029). Patients who received rituximab-containing treatments had a significantly lower likelihood of seroconversion than those who did not receive such treatments (p=0.010). The interval between last rituximab exposure and developing COVID-19 was 1, 2, 7, 15, 16, and 22 days in one patient each, and of these six patients, only the patient who developed COVID-19 22 days after receiving rituximab developed anti-SARS-CoV-2 antibodies.

Discussion

IgG or IgM are elicited in most COVID-19 patients within 1 to 2 weeks after the infection against the spike (S) or nucleocapsid (N) proteins of SARS-CoV-2, contributing to viral clearance (16-18). The S protein is a surface glycoprotein that binds to the cellular viral receptor, angiotensin-converting enzyme-2 (ACE-2), on the host cells via its RBD. The anti-RBD IgG antibody generally correlates well with neutralizing antibodies, the development of which appears to increase the survival chance by blocking viral entry into host cells or protecting against re-infection (19). Recently, our group reported that anti-RBD IgG antibodies peak at higher titers in patients suffering from a severe infection than in those with mild or moderate infections (8). Other studies have also shown that the antibody titers in critically ill COVID-19 patients are significantly higher than those in non-critically ill patients and are independent factors for disease severity classification (7, 9, 10, 12).

The survival of cancer patients presenting with COVID-19 has been reported to be dismal, with an approximately 30% mortality rate (20, 21). However, limited information about the antibody responses against SARS-CoV-2 in these vulnerable populations has been reported. Marra et al. found that the rate of seroconversion was not inferior in cancer patients compared with healthcare workers (22); however, this observation should be interpreted with caution, as most (80-90%) of the participants in that study had mild COVID-19. In contrast, two other reports have demonstrated that cancer patients have significantly lower detection rates of IgG anti-

Table 2. Comparison of Patients' Characteristics between Hematological Diseases and Non-hematological Diseases.

	Type of diseases		p value (univariate)
	Hematology (n=30)	Non-hematology (n=47)	
Age	73.0 (IQR 70.25, 80.75)	77.0 (IQR 69.50, 83.0)	0.798
Gender			0.476
Male	18 (60.0%)	32 (68.1%)	
Female	12 (40.0%)	25 (31.9%)	
Lymphocyte count at disease onset			0.021
>1,000/μL	21 (70.0%)	27 (57.4%)	
<1,000/μL	9 (30.0%)	20 (42.6%)	
Latest treatments			
Treatment with corticosteroid	11 (36.7%)	3 (6.4%)	0.002
Treatment with rituximab	6 (20.0%)	0 (0.0%)	0.003
Any chemotherapy	21 (70.0%)	0 (0.0%)	<0.001
SARS-CoV-2 IgG			0.001
Positive	18 (60.0%)	43 (91.5%)	
Negative	12 (40.0%)	4 (8.5%)	
Outcome			
Death	13 (43.3%)	9 (19.1%)	0.037
Survival	17 (56.7%)	38 (80.9%)	

Table 3. The Relationship between Seropositivity and Clinical Features.

	SARS-CoV-2 IgG antibody		OR (multivariate)	p value (multivariate)
	Positive	Negative		
Severity of COVID-19			4.890	0.066
Asymptomatic (n=11)	7 (63.6%)	4 (36.4%)		
Symptomatic (n=66)	54 (81.8%)	12 (18.2%)		
Type of diseases			0.121	0.029
Hematology (n=30)	18 (60.0%)	12 (40.0%)		
Non-hematology (n=47)	43 (91.5%)	4 (8.5%)		
Latest treatments				
Treatment with corticosteroid (n=14)	10 (71.4%)	4 (28.6%)	3.730	0.303
Treatment with rituximab (n=6)	1 (16.7%)	5 (83.3%)	0.021	0.010
Any chemotherapy (n=21)	12 (57.1%)	9 (42.9%)	3.090	0.245

bodies than those with non-cancer (23, 24).

Patients with hematological diseases have an immunodeficiency because of the disorder itself as well as because of their anti-cancer or immunosuppressive treatments. Therefore, the immune response to COVID-19 is delayed in these patients, who have been shown to be vulnerable to COVID-19 (25). Indeed, the fatality rate is somewhat worse for hematological malignancies than for solid tumors (26). Several serious COVID-19 cases among patients with hematological cancers have affected humoral responses to SARS-CoV-2. Among chronic lymphocytic leukemia (CLL) cases with a COVID-19 diagnosis, 14 out of 21 (67%) tested positive for antibodies against the N protein of SARS-CoV-2. Anti-CLL-directed chemotherapy and COVID-19 disease severity appear to affect the development of antibodies (3). In a study of MM cases, almost all (22/23; 96%) of the patients developed anti-SARS-CoV-2 IgG, although the targets of these antibodies were not clarified (11). In several other cases, anti-SARS-CoV-2 antibodies often failed to develop, and these patients died or were resuscitated by COVID-19 convalescent plasma infusion (27, 28). In the present study, patients with symptomatic COVID-19 tended to be seropositive for anti-SARS-CoV-2 IgG antibodies. Furthermore, our findings suggested that it is more difficult for patients with hematological diseases to develop antibodies than patients with other disorders. This poorer potential to induce immune responses may be due to the properties of the hematological disorders and to anti-cancer therapies, which were provided to most of the patients with hematological diseases. It is important to know whether or not antibodies can develop and whether or not they persist when chemotherapy is resumed after COVID-19. A majority (82%) of COVID-19 cases with hematological malignancies under chemotherapies developed SARS-CoV-2 IgG antibodies in a previous report (13), which is contrary to the present study findings. These discrepant results may have be due to differences in the pa-

tients' background characteristics, such as the prevalence of community-acquired or nosocomial infections, disease status, or performance status.

Patients receiving rituximab treatment are poor responders to various types of vaccinations, including vaccines against influenza viruses, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (29, 30). Rituximab has also been reported to provoke other serious viral conditions, such as hepatitis B reactivation and progressive multifocal leukoencephalopathy, caused by the John Cunningham virus (31). Anti-CD20 monoclonal antibodies deplete normal B lymphocytes and thereby impair humoral immunity. Several reports have revealed the persistence of COVID-19 pneumonia or failure to develop anti-SARS-CoV-2 antibodies during rituximab therapy (32-34). In our study, rituximab-combined treatment interfered with antibody production, as only one of six patients turned out to be seropositive. Similar delayed antihumoral responses due to rituximab therapy have resulted in prolonged incubation periods (35) of up to 21 days.

Several limitations associated with the present study warrant mention. First, it was a retrospective, single-center study and the sample size was too small to provide definitive evidence. Second, the patients with hematological diseases had a variety of conditions and disease states, so these data may not reflect the antibody response in certain individual types of hematological disorders.

Conclusion

This is the retrospective study to analyze the antibody production using an assay and detect anti-RBD IgG in relation to the clinical features or outcomes of COVID-19 among hospitalized patients with hematological diseases. Patients with hematological diseases are less likely to develop antibodies than those with non-hematological diseases, which might be one of the reasons for the poor COVID-19 outcomes in this high-risk group. Given that antibody titers likely decline over three to four months, even after the administration of recently introduced anti-SARS-CoV-2 vaccines (36), serial monitoring of antibody titers post-vaccination or infection is essential. Further efforts should focus on identifying efficient ways to maintain sufficient titer levels to control infection.

This study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Patients gave their written informed consent. This study was approved by the Research Ethics Review Committee of the Institute of Eiju General Hospital.

The authors state that they have no Conflict of Interest (COI).

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