Advances in Infectious Diseases & Therapy *Research Article*

Clinical courses of COVID-19 cases with or without SARS-CoV-2 immunoglobulin antibodies identified during quarantine at international airports in Japan

Takeuchi S[1], Ishii K[1], Koshiba H[1], Hara K[1], Wakabayashi M[1], Matsumoto Y[1], Fujihara J[1], Ito T[1], Konuma S[1], Aoki T[1], Tsubota T[1], Hayashi T[2]

[1]*Department of Internal Medicine, JCHO Tokyo Kamata Medical Center, Tokyo, Japan.*

[2]*Infection control center, JCHO Tokyo Kamata Medical Center, Tokyo, Japan.*

ABSTRACT

Background: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has spread around the world and been classified as a global pandemic. This study aimed to determine the factors involved in the time to disappearance of SARS-CoV-2 from nasopharyngeal swabs in patients with COVID-19.

Methods: The study participants were 22 patients diagnosed with COVID-19 whose nasopharyngeal swabs tested positive for SARS-CoV-2 by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in quarantine before being admitted to our hospital. All patients underwent laboratory tests for anti-SARS-CoV-2 antibodies and chest X-ray on admission. Logistic regression analysis was conducted to investigate retrospectively the association between the number of days from nasopharyngeal to viral resolution and clinical factors.

Results: In the univariate analysis, no clinical or laboratory factors, including age, sex, highest body temperature, lowest peripheral oxygen saturation, presence of symptoms during hospitalization, laboratory results, and chest X-ray findings, were associated with negative RT-qPCR results at 5, 7, and 10 days from first detection of the virus. Although no statistically significant differences were found, the median times required until achieving two consecutive negative RT-qPCR results for SARS-CoV-2 from first detection of the virus were 5 and 10 days in cases without and with anti-SARS-CoV-2 immunoglobulin M (IgM) and/or immunoglobulin M (IgG) antibodies, respectively.

Conclusion: Although we only investigated the presence or absence of IgM and IgG antibodies to SARS-CoV-2 at the time of admission, our results suggest that humoral immunity may not be essential for the disappearance of SARS-CoV-2 in nasopharyngeal swabs.

KEYWORDS

Severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, polymerase chain reaction, antibody.

Corresponding Author Information

Koji Ishii, MD,
Director of JCHO Tokyo Kamata Medical Center, 2-19-2 Minamikamata, Otaku, Tokyo 144-0035, Japan, Phone: +81-3-3738-8221; Fax: +81-3-3733-7471.

Received: October 28, 2020; **Accepted:** November 12, 2020; **Published:** November 16, 2020

Citation: Takeuchi S, Ishii K, Koshiba H, Hara K, Wakabayashi M, et al. Clinical courses of COVID-19 cases with or without SARS-CoV-2 immunoglobulin antibodies identified during quarantine at international airports in Japan. Advances in Infec Diseases Therapy. 2020;1(1):1-5.

Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has spread around the world since it was identified in Wuhan, China, and been classified as a global pandemic [1]. Polymerase chain reaction (PCR) tests have begun to be conducted on passengers placed in quarantine after arriving at international airports in Japan, including returnees from SARS-CoV-2-affected countries, with those testing positives being placed in isolation at hotels or medical institutions, such as our hospital, until viral shedding has ceased [2,3]. However, time course data acquired by quantitative reverse transcription PCR (RT-qPCR) assays of asymptomatic or very mild COVID-19 cases remain limited [4,5].

Recently, antibody tests against SARS-CoV-2 have been developed by numerous companies [6,7]. However, an antibody test only shows that a person had the virus at some point in the past; it does not indicate whether the patient no longer has the virus or is still contagious. In the case of COVID-19, it still remains unclear to what extent immunity is conferred, and if so, for how long.

To determine the factors involved in the time to disappearance of SARS-CoV-2 from nasopharyngeal swabs in patients with COVID-19, we investigated the clinical courses, including the presence of antibodies against SARS-CoV-2, of 22 asymptomatic or very mild COVID-19 cases who had been placed in quarantine at Narita International and Haneda airports before being admitted to our hospital.

Materials and Methods

Participants

The study participants were 22 patients diagnosed with COVID-19 whose nasopharyngeal swab samples tested positive for SARS-CoV-2 by RT-qPCR in quarantine before being admitted to our hospital between March 30 and May 12, 2020 (shown in Table 1). All cases underwent laboratory tests and chest X-ray on admission. Any remaining serum samples collected were stored at –40 °C. In accordance with Japanese law, people with SARS-CoV-2 infection can be released from quarantine after two consecutive negative RT-qPCR tests, so all patients were tested several times a week at the government quarantine facility. The characteristics of the 22 cases (15 males, 7 females; median age, 39 years; age range, 20–65 years) are shown in Table 1. Among the cases, 19 were Japanese, and one each was American, Filipino, and Brazilian. Before entering Japan, 8 persons were asymptomatic, while 14 had fever, cough, malaise, taste disorder, olfactory disorder, or digestive disorder. Pneumonia was found in four cases on chest X-ray at admission. In addition, those who had symptoms abroad had mostly disappeared by the time they entered Japan.

Assay

We detected immunoglobulin (IgM) and immunoglobulin G (IgG) antibodies against SARS-CoV-2 in serum samples taken

Characteristics		N=22
Median age, years (range, IQR)		39 (20-65 , 28.5-44.5)
Sex	Male	15
	Female	17
Duration of hospitalization, days (range, IQR)		9 (4-65, 6-13.25)
Antibody	IgG-positive	11 (50.0%)
	IgM-positive	9 (40.9%)
Vital signs	Median highest body temperature, °C (range, IQR)	36.9 (36.1-37.1, 7-37.0)
	Median lowest peripheral oxygen saturation, % (range, IQR)	98 (93-99, 98-98)
Symptoms	Fever	9 (40.9%)
	Malaise	4 (18.2%)
	Cough	5 (22.7%)
	Gastrointestinal symptoms	2 (9.1%)
	Taste disorder	2 (9.1%)
	Olfactory disorder	5 (22.7%)
	Pneumonia	4 (18.2%)
	Asymptomatic	8 (36.3%)
Laboratory findings	Median white blood cell count, × 10 7 L (range, IQR)	5,760 (2,860-9,750, 4,555-7,790)
	Median lymphocyte count, × 10 7 L (range, IQR)	1,739 (1,010-3,599, 1,422-2,166)
	Median C-reactive protein, mg/dL (range, IQR)	0.11 (0.02-0.59, 0.04-0.22)
	Median AST, U/L (range, IQR)	19 (11-49, 14.3-27.5)
	Median ALT, U/ L (range, IQR)	22 (9-65, 13.2-44.8)
	Median lactate dehydrogenase, U/L (range, IQR)	166 (120-262, 151-197)
	Median, γ–GTP, IU/ L (range, IQR)	22 (10-212,16-34.5)
	Median creatinine, mg/dL (range, IQR)	0.76 (0.46-1.06, 0.62-0.91)
	Median blood sugar, mg/dL (range, IQR)	89.5 (77-410, 85.5-97.8)
IQR: Interquartile range		

Table 1.Patient characteristics

Table 2 X-ray findins and laboratory data andon admission, and symptoms, maximal body tenparature, and minimal saturation during hospitalization

No.	Sex	Age	On admission												During hospitalization						
			IgM	IgG	Pneumonia	WBC	Ly(%)	Ly(/ μ l)	CRP	AST	ALT	LDH	Cr	BS	Malaise	Cough	Digestive	Taste	Olfactory	BT(max)	SpO2(%)
1	F	45	−	−		9660	15.3	1477.98	0.06	13	15	132	0.61	85						36.8	98
2	F	44	−	−		7190	26.8	1926.92	0.02	14	10	142	0.57	87						36.9	99
3	M	21	−	−		4690	41.8	1960.42	0.16	18	29	136	0.74	84						36.2	99
4	M	20	−	−		7000	40.7	2849.00	0.03	31	55	175	0.78	81			+			36.7	98
5	M	37	−	−		9750	21.5	2096.25	0.05	14	9	130	0.8	111	+					35.9	98
6	M	47	−	−		5220	34.7	1811.34	0.05	23	21	160	0.98	87		+				37.1	98
7	F	62	−	−		6410	40.7	2608.87	<0.02	14	13	157	0.5	94						37.0	97
8	M	40	−	−		8290	33.1	2743.99	0.59	28	50	230	1.06	85						36.6	93
9	M	24	−	−		5940	23.4	1389.96	0.02	20	41	164	0.96	97					+	36.0	99
10	M	27	−	−		3130	45.7	1430.41	0.22	22	23	120	0.87	77				+	+	35.7	97
11	F	20	−	−	+	4180	29.4	1228.92	0.02	15	10	157	0.54	90		+				36.6	98
12	M	42	+	+		4510	38.4	1731.84	0.46	28	27	234	0.92	98	+					36.5	98
13	M	65	+	+		9700	37.1	3598.70	0.15	26	31	192	0.85	91						35.7	98
14	M	56	+	+		5470	25.2	1378.44	0.2	28	48	205	0.85	410						36.6	98
15	M	39	+	+	+	5760	28.8	1658.88	0.3	15	11	163	0.64	90	+	+				36.8	98
16	F	34	+	−		5470	27.8	1520.66	0.15	14	15	199	0.64	100	+					36.7	97
17	M	30	+	+		7990	27.4	2189.26	0.02	18	14	149	0.6	101						36.4	98
18	M	46	+	+		4330	32.8	1420.24	0.27	24	46	171	0.94	79						37.0	98
19	M	39	+	+		2860	35.3	1009.58	0.56	17	13	189	0.74	89		+				37.0	98
20	F	37	+	+		5760	30.2	1739.52	0.11	11	16	167	0.46	88					+	36.6	98
21	M	39	+	+	+	9240	36.3	3354.12	0.1	48	65	262	1.02	89		+	+		+	36.0	98
22	F	20	+	−	+	4170	41.7	1738.89	0.05	49	54	211	0.62	153				+	+	36.6	99

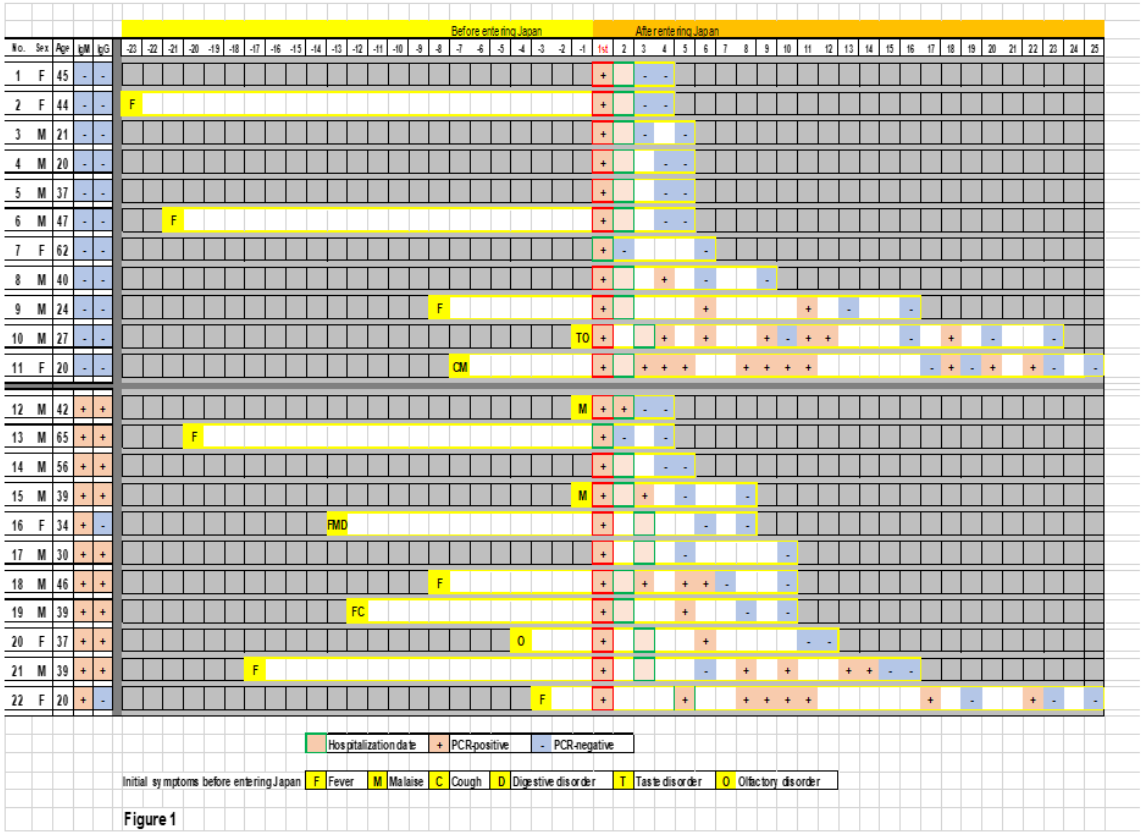

Figure 1

Figure 1: Profile of participants who had symptoms before entering Japan, status of antibodies against SARS-CoV-2, and the sequences of the RT-qPCR results.

and stored on admission to our hospital using a rapid lateral flow immunoassay (Innovita® Biological Technology Co., Ltd., Tangshan, China). This immunoassay can provide results in 10 minutes using a finger-pricked blood sample.

We conducted logistic regression analysis to investigate retrospectively the association between the number of days from nasopharyngeal to viral resolution and clinical factors, including age, sex, highest body temperature, lowest peripheral oxygen saturation (SpO_2), presence of symptoms, laboratory results, and imaging findings. In addition, we divided the COVID-19 cases into two groups based on the presence or absence of serum IgM and/or IgG antibodies against SARS-CoV-2, and then compared the time to disappearance of SARS-CoV-2 RNA in nasopharyngeal swabs.

Statistical analysis

The results are presented as medians and 25th to 75th percentiles. The chi-squared test was used to compare characteristics between the two groups. A p value < 0.05 was considered to indicate statistical significance.

Results

The sequences of the RT-qPCR results for all cases are shown in Figure 1. Viral clearance was observed in all 22 cases. In the univariate analysis, no clinical or laboratory factors, including age, sex, highest body temperature, lowest SpO_2, presence of symptoms after entering our hospital, laboratory results, or chest X-ray findings, were associated with negative RT-qPCR results at 5, 7, or 10 days from first detection of the virus (Table 2). All 22 asymptomatic or mild COVID-19 cases were healthy and had no difficulties in normal social life.

Among all 22 cases, two tested positive for only anti-SARS-CoV-2 IgM type and nine for anti-SARS-CoV-2 IgM type and IgG type antibodies. The remaining 11 cases tested negative for both anti-SARS-CoV-2 IgM and IgG antibodies.

Although no statistically significant differences were observed, the median times required until achieving two consecutive negative RT-qPCR results for SARS-CoV-2 from first detection of the virus were 5 (range, 4–25) and 10 (range, 4–25) days in cases without and with anti-SARS-CoV-2 IgM and/or IgG antibodies, respectively.

Discussion

In the univariate analysis, no clinical data were associated with negative SARS-CoV-2 RNA tests from first detection of the virus. Antibody tests showed that 11 cases had anti-SARS-CoV-2 IgM and/or IgG antibodies; the remaining 11 cases did not have anti-SARS-CoV-2 IgM and/or IgG antibodies at admission to our hospital.

Six of the 11 cases with anti-SARS-CoV-2 IgM and/or IgG antibodies and a history of high fever within 3-20 days before entering Japan. On the other hand, three of the 11 cases without anti-SARS-CoV-2 IgM and/or IgG antibodies had history of high fever 8–23 days before entering Japan. Some cases were found to have antibodies, whereas others were not, even if they had a recent history of high fever. No significant differences were observed between a history of high fever before entering Japan and the presence or absence of anti-SARS-CoV-2 IgM and/or IgG antibodies at the time of admission to our hospital.

Studies on past severe cases of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) showed that virus-specific antibodies were detectable in 80–100% of patients at 2 weeks after symptom onset [8-12]. Recently, it was reported that 100% of patients tested positive for antiviral IgG within 19 days after symptom onset [13]. In that report, IgG and IgM seroconversion occurred simultaneously or sequentially. In that study, both anti-SARS-CoV-2 IgG and IgM titers plateaued within 6 days after seroconversion. It has also been reported that the seroconversion rate at 15 days after SARS-CoV-2 infection was significantly lower in patients with cancer than in health care workers (30% vs. 71%, respectively) [14].

In this study, no significant differences were seen in the time until a negative SARS-CoV-2 RT-qPCR result between cases with anti-SARS-CoV-2 IgM and/or IgG antibodies, or those who were antibody-free, whose antibody titers may have been below the sensitivity of the measurement. Six cases without anti-SARS-CoV-2 IgM and/or IgG antibodies obtained two consecutive negative RT-qPCR test results for SARS-CoV-2 RNA within 5 days, while three of the 11 cases with anti-SARS-CoV-2 IgM and/or IgG antibodies obtained two consecutive negative results within 5 days; however, no statistically significant difference (chi-squared test) was found between the two groups. People in the two groups had a good post-hospitalization course without severe symptoms. There was no difference in hospital course between the 2 groups. These results suggest that humoral immunity may not be essential for the disappearance of SARS-CoV-2 in nasopharyngeal swabs in those patients, although at the time of admission, we only examined the presence or absence of IgM and/or IgG type antibodies against SARS-CoV-2.

Therefore, it may be possible that nonspecific (innate) immunity and specific cell-mediated immunity are involved in the disappearance of SARS-CoV-2 from the nasopharynx, but not in humoral immunity. It would be helpful to examine the courses of patients who tested negative for anti-SARS-CoV-2 antibodies at the time of admission to our hospital, but these cases are scattered throughout Japan and do not attend our hospital, so their cases remain unclear. We look forward to the results of future epidemiological studies involving large-scale antibody retention rates.

Acknowledgements

The authors would like to thank Dr. Shintaro Hasuike (Shinjuku-Ekimae Clinic), because the antibody kit was kindly donated by him.

References

1. Bedford J, Enria D, Giesecke J, et al. WHO Strategic and Technical Advisory Group for Infectious Hazards. COVID-19: towards controlling of a pandemic. Lancet. 2020;395:1015-1018.
2. Kakimoto K, Kamiya H, Yamagishi T, Matsui T, Suzuki M, Wakita T. Initial investigation of transmission of COVID-19 among crew members during quarantine of a cruise ship - Yokohama, Japan, February 2020. MMWR Morb Mortal Wkly Rep. 2020;69:312–313.
3. Zhang S, Diao M, Yu W, Pei L, Lin Z, Chen D. Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: a data-driven analysis. Int J Infect Dis. 2020;93:201–204.
4. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020;63:706–711.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–1062.
6. DeMarco C. 7 things to know about COVID-19 antibody testing. MD Anderson Cancer Center. Available at: https://www.mdanderson.org/publications/cancerwise/7-things-to-know-about-coronavirus-COVID19-antibody-testing.h00-159381156.html. Published April 22, 2020.
7. Veesler D. Antibody neutralizes SARS and COVID-19 coronaviruses. Medical press. May 18, 2020.
8. Corman VM, Albarrak AM, Omrani AS, et al. Viral shedding and antibody response in 37 patients with Middle East respiratory syndrome coronavirus infection. Clin Infect Dis. 2016;62:477–483.
9. Li G, Chen X, Xu A. Profile of specific antibodies to the SAES-associated coronavirus. N Engl J Med. 2003;349:508–509.
10. Hsueh PR, Huang LM, Chen PJ, Kao CL, Yang PC. Chronological evolution of IgM, IgA, IgG and neutralization antibodies after infection with SARS-associated coronavirus. Clin Microbiol Infect. 2004;10:1062–1066.
11. Park WB, et al. Kinetics of serologic response to MERS coronavirus infection in humans, South Korea. Emerg Infect Dis. 2015;21:2186–2189.
12. Drosten C, et al. Transmission of MERS-coronavirus in household contacts. N Engl J Med. 2014;371:828–835.
13. Long Q, Liu B, Deng H, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. 2020. https://doi.org/10.1038/s41591-020-0897-1
14. Slater H. Detection rate of SARS-CoV-2 antibodies after COVID-19 in patients with cancer. Available at: https://www.cancernetwork.com/news/detection-rate-sars-cov2-antibodies-after-covid-19-patients-cancer. Published May 15, 2020.