

Combination of rRT-PCR and Clinical Features to Predict Coronavirus Disease 2019 for Nosocomial Infection Control

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Background: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), immediately became a pandemic. Therefore, nosocomial infection control is necessary to screen for patients with possible COVID-19.

Objective: This study aimed to investigate commonly measured clinical variables to predict COVID-19.

Methods: This cross-sectional study enrolled 1087 patients in the isolation ward of a university hospital. Conferences were organized to differentiate COVID-19 from non-COVID-19 cases, and multiple nucleic acid tests were mandatory when COVID-19 could not be excluded. Multivariate logistic regression models were employed to determine the clinical factors associated with COVID-19 at the time of hospitalization.

Results: Overall, 352 (32.4%) patients were diagnosed with COVID-19. The majority of the non-COVID-19 cases were predominantly caused by bacterial infections. Multivariate analysis indicated that COVID-19 was significantly associated with age, sex, body mass index, lactate dehydrogenase, C-reactive protein, and malignancy.

Conclusion: Some clinical factors are useful to predict patients with COVID-19 among those with symptoms similar to COVID-19. This study suggests that at least two real-time reverse-transcription polymerase chain reactions of SARS-CoV-2 are recommended to exclude COVID-19.

Keywords: severe acute respiratory syndrome coronavirus-2, coronavirus disease 2019, nosocomial infection control, nucleic acid test, obesity, cross sectional study, Japan

Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first emerged at the end of 2019. Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 subsequently became a pandemic and remains a burden to humans. Because COVID-19 has no characteristic symptoms,^{1,2} nucleic acid or antigen tests to detect the N gene or N protein of SARS-CoV-2 are necessary for the diagnosis; however, false-negative results are a critical medical problem.^{3,4} In November 2020, we experienced a large cluster of COVID-19 in our institute because a few patients with COVID-19 were missed. At that time, a single nucleic acid test was used to determine whether a patient had COVID-19. Thereafter, significant changes in nosocomial infection control of COVID-19 were established in our institute. More specifically, we organized conferences of respiratory physicians to differentiate COVID-19 from non-COVID-19 cases and decided to transfer patients without COVID-19 from the isolation ward to the general ward. In addition, multiple nucleic acid tests should be performed if COVID-19 could not be excluded based on physical and imaging findings even if a nucleic acid test was negative. This strategy may be effective in future pandemic events.

It is necessary to screen patients with possible COVID-19 for nosocomial infection control. Previous studies have mostly focused on mortality-related factors of COVID-19.^{5–9} However, only a few studies have analyzed the risk of COVID-19. Since November 2021, omicron variants have been reported worldwide, and there is growing concern about its infectivity, transmissibility, and antigenicity.^{10,11} Most notably, BA.5, an omicron variant that has been endemic in Japan since July 2022, has a predominance of increased infection and immune escape, compared with previous lineages.¹² Meanwhile, the previous lineages had a higher rate of severe illness and mortality than BA.5, making it crucial to prevent horizontal nosocomial transmission by strict isolation. In this study, we aimed to investigate the efficacy of clinical factors to predict patients with COVID-19 in the isolation ward before the emergence of the BA.5 lineage.

Subjects and Methods

Population and Data Collection

In this cross-sectional study, the clinical factors of COVID-19 at the time of hospitalization in routine practice at the Showa University Fujigaoka Hospital, from December 2020 to March 2022, were investigated. The line charts of COVID-19 diagnosis, the bars of the estimated variants of SARS-CoV-2, and the number of SARS-CoV-2 vaccinations during the same period in Japan are shown in Figures 1 and 2, respectively. The criteria for admission to the isolation ward were as follows: body temperature ≥ 37 degrees C, percutaneous oxygen saturation $< 96\%$, history of contact with patients diagnosed with COVID-19, or a ground-glass pattern on chest computed tomography images. All clinical data were collected from patients' medical records on the day of admission. The estimated glomerular filtration rate (eGFR) of each patient was calculated.¹³ Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73 m². The study protocol was approved by the Institutional Ethics Committee of Showa University (approved no. 22–131-B). The requirement to obtain informed consent from the patients was waived with the approval of the Ethics Committee due to the retrospective nature of this study. This study was conducted in accordance with the Declaration of Helsinki guidelines.

Method for the Diagnosis of COVID-19 and Determining Severity

COVID-19 was diagnosed based on nucleic acid tests to detect SARS-CoV-2 RNA using samples derived from the nasopharynx. Nasopharyngeal swabs were collected from patients with suspected COVID-19 and tested by real-time reverse-transcription polymerase chain reaction (rRT-PCR) performed using a SARS-CoV-2 Detection Kit Multi

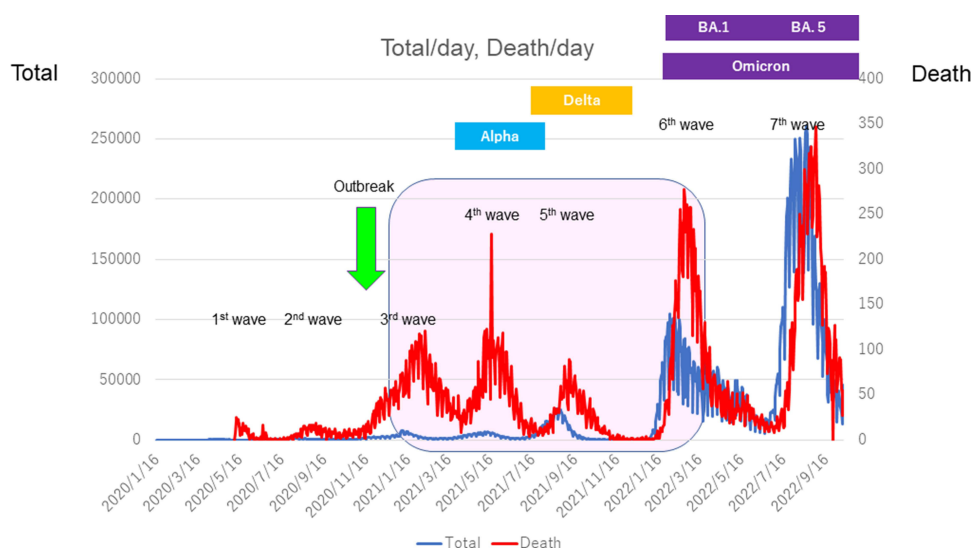


Figure 1 COVID-19 - Outbreaks and deaths in Japan. Line charts show the number of cases and deaths. Bars show the estimated variants of SARS-CoV-2. The arrow indicates an outbreak in our institute. Duration of this study in pink.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

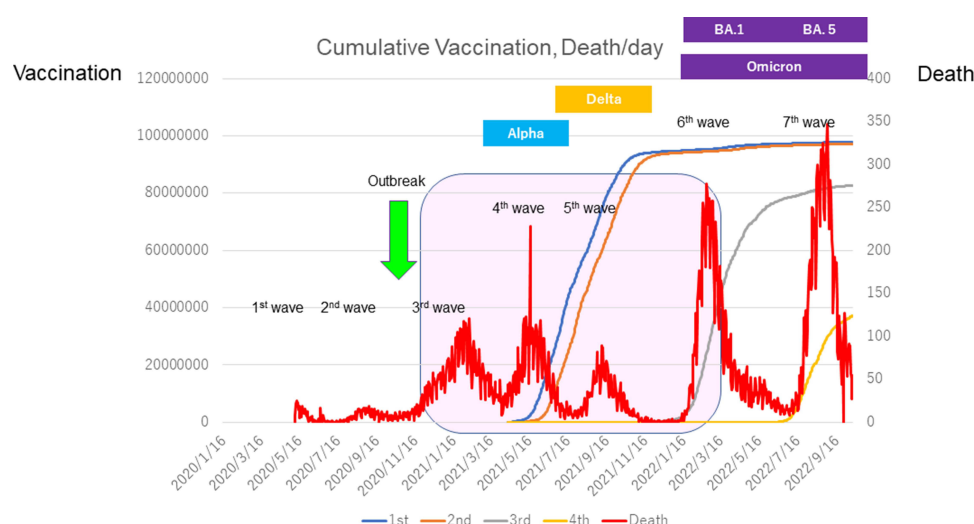


Figure 2 Status of SARS-CoV-2 vaccination in Japan. The line charts show the cumulative number of SARS-CoV-2 vaccinations from the first to the fourth, in addition to the number of deaths from COVID-19. Duration of this study in pink.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; COVID-19, coronavirus disease 2019.

(TOYOBO, Osaka, Japan) to amplify two regions (N1 and N2) in the N gene of SARS-CoV-2 RNA, according to the manufacturer's protocol. Cycle threshold (Ct) values were observed in a SARS-CoV-2 rRT-PCR-positive case ($Ct \leq 40$). Severity was defined as follows: (i) mild (percutaneous oxygen saturation (SpO_2) $\geq 96\%$), (ii) moderate I ($93\% < SpO_2 < 96\%$), (iii) moderate II ($SpO_2 \leq 93\%$), and (iv) severe (patients receiving intensive care during the acute COVID-19 period).¹⁴

Procedure to Release Patients with Suspected COVID-19 from the Isolation Ward

As shown in Figure 3, all patients meeting at least one of the criteria were admitted to the isolation ward. A SARS-CoV-2 rRT-PCR was performed for each patient. If the rRT-PCR test was negative, conferences to differentiate COVID-19 from non-COVID-19 cases were organized to decide on release of such patients from the isolation ward. The decision was established by two independent physicians in the Department of Respiratory Medicine, including at least one specialist, based on the clinical course and imaging studies. If COVID-19 was ruled out, patients were transferred to the general ward. Conversely, if COVID-19 could not be excluded, repeat rRT-PCR testing was required and conferences were reviewed to identify potential COVID-19 cases. When patients with COVID-19 diagnosed as rRT-PCR-positive were

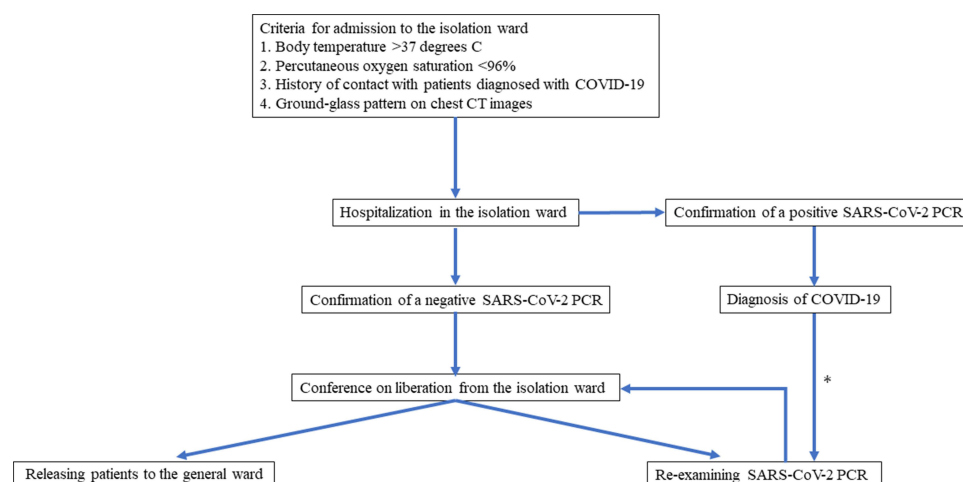


Figure 3 Study cohort recruitment flowchart.

Note: *In cases where the infectivity is estimated to be low.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; COVID-19, coronavirus disease 2019.

presumed to have decreased infectivity with time since illness onset, repeat SARS-CoV-2 rRT-PCRs were performed to compare the Ct values with those at the time of diagnosis, followed by conferences to decide whether such patients should be released.

Statistical Analysis

All data were expressed as mean \pm standard deviation for continuous variables or as percentages for categorical variables. Group mean values were compared using the Mann–Whitney rank-sum test. Pearson's chi-squared test or Fisher's exact test was used for the univariate analysis of the association between two categorical variables. The adjusted effects of multiple variables were evaluated using a logistic regression model, and the findings were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using JMP software version 16.0 (SAS Institute, Cary, NC).

Results

Patient Characteristics and COVID-19 Diagnosis

During this period, 1237 patients were admitted to the isolation ward. Of these patients, 38 with fever during hospitalization, 49 with re-admission cases, and 63 from cluster outbreaks were excluded. Eventually, 1087 patients were statistically analyzed. Patient characteristics are shown in Table 1. Of the patients, 669 (61.5%) were male and 418 (38.5%) were female,

Table 1 Association of Each Variable with COVID-19

No. (%)	All Patients	Patients with COVID-19	Others	P-value
	1087	352	735	
Age (years)				
Mean \pm SD	71.4 \pm 18.1	62.3 \pm 19	75.7 \pm 15.9	<0.0001*
Sex				
Male	669	208 (19.1)	461 (42.4)	0.2496
Female	418	144 (13.2)	274 (25.2)	
BMI				
Mean \pm SD	21.7 \pm 4.4	23.7 \pm 4.6	20.7 \pm 3.9	<0.0001*
Albumin (g/dL)				
Mean \pm SD	3.4 \pm 0.7	3.5 \pm 0.6	3.3 \pm 0.7	<0.0001*
LDH (U/L)				
Mean \pm SD	302 \pm 244.4	358.9 \pm 283.5	274.7 \pm 218.2	<0.0001*
C-reactive protein (mg/dL)				
Mean \pm SD	8.3 \pm 8.1	7.6 \pm 6.8	8.7 \pm 8.7	0.892
Receiving oral corticosteroids ^a				
Yes	30	0 (0)	30 (2.8)	0.0001*
No	1057	352 (32.4)	705 (64.8)	
Diabetes mellitus				
Yes	249	76 (7)	173 (15.9)	0.4749
No	838	276 (25.4)	562 (51.7)	
Malignancy				
Yes	283	31 (2.9)	252 (23.2)	<0.0001*
No	804	321 (29.5)	483 (44.4)	
CKD				
Yes	443	110 (10.1)	333 (30.6)	<0.0001*
No	644	242 (22.3)	402 (37)	
Autoimmune disease				
Yes	53	9 (0.8)	44 (4)	0.014*
No	1034	343 (31.6)	691 (63.6)	

Notes: * $P < 0.05$ was considered statistically significant. ^aMore than 10 mg of prednisolone per day.

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; LDH, lactate dehydrogenase; CKD, chronic kidney disease.

with ages ranging from 5 to 101 years. The mean values of age, body mass index (BMI), serum albumin, lactate dehydrogenase (LDH), and C-reactive protein (CRP) were 71.4 ± 18.1 years, 21.7 ± 4.4 , 3.4 ± 0.7 g/dL, 302.4 ± 244.4 U/L, and 8.3 ± 8.1 mg/dL, respectively. Overall, 30 (2.8%) patients were receiving corticosteroids (at least 10 mg/day of prednisolone) for various indications, and 249 (22.9%) had diabetes mellitus. Moreover, 283 (26%) patients had various malignancies ([Supplementary Table 1](#)), including 93 diagnosed within 1 year and 48 receiving chemotherapy within 3 months. In addition, 443 (40.8%) patients had CKD and 53 (4.9%) had autoimmune diseases ([Supplementary Table 2](#)). Of the 1087 patients, 352 (32.4%) were diagnosed with COVID-19 based on rRT-PCR, which included 67 patients with mild, 55 with moderate I, 200 with moderate II, and 30 with severe diseases at the time of admission.

Cases of Suspected COVID-19

[Table 2](#) indicates the details of the suspected COVID-19 cases. The majority of cases were bacterial infections, including respiratory, intra-abdominal, and urinary tract infections, which accounted for approximately 69.4% (510 of 735) of all suspected COVID-19 cases. Among non-infectious diseases, interstitial pneumonia, ground-glass opacities of unknown etiology, and cardiogenic pulmonary edema were frequently observed.

Statistical Analysis of COVID-19 and Clinical Features

In the univariate analyses, COVID-19 was found to be significantly associated with age, BMI, serum albumin, LDH, oral corticosteroid use, malignancy, CKD, and autoimmune disease. However, no significant association was found between COVID-19 and sex, CRP, and diabetes mellitus.

Multivariate analyses were employed to control for the potential confounding effects of these variables. Because of significant bias in the distribution chart, thresholds were established for age, LDH, and CRP ([Supplementary Figure 1](#)). [Table 3](#) presents the logistic regression models of factors associated with COVID-19. The frequency of COVID-19

Table 2 Cases of Suspected COVID-19

	No. (%)
Lower respiratory tract infection	358 (48.7)
Intra-abdominal infection	68 (9.2)
Interstitial lung disease	57 (7.7)
Urinary tract infection	52 (7.1)
Ground-glass opacity	28 (3.8)
Cardiac pulmonary edema	22 (3)
Pneumothorax	15 (2)
Upper respiratory tract infection	13 (1.8)
Carcinomatous peritonitis	10 (1.4)
Drug-induced pneumonia	10 (1.4)
Hemoptysis	10 (1.4)
Paraneoplastic fever	10 (1.4)
Malignant pleural effusion	9 (1.2)
Anemia	8 (1.1)
Cutaneous infection	7 (0.9)
Osteomyelitis	5 (0.7)
Asthma attack	5 (0.7)
Fever of undetermined origin	5 (0.7)
Febrile neutropenia	4 (0.5)
Acute pancreatitis	3 (0.4)
Pulmonary thromboembolism	3 (0.4)
Others*	29 (4.5)
Total	735 (100)

Note: *Including two cases of meningitis and one case of uterine infection.

Table 3 Logistic Regression Models of COVID-19

	Category	OR	95% CI	P-value
Age≥65 (Years)	Yes/no	0.2659	0.1843–0.3837	<0.0001*
Sex	Female/male	1.6902	1.2205–2.3406	0.0016*
BMI		1.1148	1.0699–1.1615	<0.0001*
Albumin (g/dL)		1.1173	0.8569–1.4569	0.4126
LDH≥300 (U/L)	Yes/no	3.4544	2.4916–4.7894	<0.0001*
C-reactive protein≥10 (mg/dL)	Yes/no	0.5261	0.3645–0.7594	0.0006*
Receiving oral corticosteroids ^a	Yes/no	0	-	0.9961
Diabetes mellitus	Yes/no	1.0619	0.7233–1.5589	0.7593
Malignancy	Yes/no	0.2302	0.1479–0.3582	<0.0001*
CKD	Yes/no	1.0433	0.7435–1.4639	0.8065
Autoimmune disease	Yes/no	0.4737	0.2010–1.1164	0.0876

Notes: * $P < 0.05$ was considered statistically significant. ^aMore than 10 mg of prednisolone per day.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; LDH, lactate dehydrogenase; SD, standard deviation.

increased significantly with BMI (OR, 1.1148; 95% CI, 1.0699–1.1615). COVID-19 was independently associated with age ≥ 65 (OR, 0.2659; 95% CI, 0.1843–0.3837), female sex (OR, 1.6902; 95% CI, 1.2205–2.3406), LDH ≥ 300 (OR, 3.4544; 95% CI, 2.4916–4.7894), CRP ≥ 10 (OR, 0.5261; 95% CI, 0.3645–0.7594), and malignancy (OR, 0.2302; 95% CI, 0.1479–0.3582). Serum albumin, corticosteroid use, diabetes mellitus, CKD, and autoimmune diseases were not significantly associated with COVID-19.

Outcome of Patients in the Isolation Ward

The details of the outcomes in the isolation ward are shown in Table 4. Significant differences were found between the COVID-19 group and the non-COVID-19 group in terms of transfer to the general ward or intensive care unit (ICU), leaving the hospital, transferring to another hospital, but not in terms of death. The frequency of SARS-CoV-2 rRT-PCR was significantly lower in the COVID-19 group than in the non-COVID-19 group, while the COVID-19 group spent significantly more time in the isolation ward than the non-COVID-19 group. Approximately two rRT-PCR assays were required to exclude COVID-19. Table 5 indicates the details of the deaths. The majority of deaths in the COVID-19 group were attributed to pneumonia caused by COVID-19. The top three causes of death in the non-COVID-19 group were bacterial pneumonia, interstitial pneumonia, and malignancy.

Table 4 Outcome of Patients in the Isolation Ward

	All Patients	Patients with COVID-19	Others	P-value
	No.	No. (%)	No. (%)	
Moving to the general ward	642	17 (4.8)	625 (85)	<0.0001*
Direct discharge from the isolation ward	299	246 (69.9)	53 (7.2)	<0.0001*
Transferred to another hospital	76	64 (17.9)	13 (1.8)	<0.0001*
Death	64	21 (6)	43 (5.9)	1
Moving to the ICU	6	5 (1.4)	1 (0.1)	0.0253*
Total	1087	352 (100)	735 (100)	
Frequency of SARS-CoV-2 PCR	1.9 \pm 1.1	1.6 \pm 1.6	2.0 \pm 0.8	<0.0001*
Duration of hospitalization in the isolation ward (days)	6.4 \pm 6.5	11.5 \pm 7.8	3.9 \pm 3.8	<0.0001*

Note: * $P < 0.05$ was considered statistically significant.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Table 5 Details of the Death

Patients with COVID-19		Others	
	No. (%)		No. (%)
COVID-19 ^a	17 (81)	Bacterial pneumonia	16 (37.2)
Bacterial pneumonia	2 (9.5)	Interstitial pneumonia	9 (20.9)
Malignancy	1 (4.8)	Malignancy	8 (18.6)
Myocardial infarction	1 (4.8)	Pneumothorax	2 (4.7)
		Empyema	2 (4.7)
		<i>Pneumocystis jiroveci</i> pneumonia	1 (2.3)
		Alveolar hemorrhage	1 (2.3)
		Cerebral infarction	1 (2.3)
		Encephalopathy	1 (2.3)
		Cholangitis	1 (2.3)
		Cardiac failure	1 (2.3)
Total	21 (100)	Total	43 (100)

Note: ^aPneumonia caused by COVID-19.

Abbreviation: COVID-19, coronavirus disease 2019.

Discussion

In this study, the correlation between COVID-19 and commonly measured clinical variables was analyzed in patients who met at least one of the criteria shown in Figure 3. Notably, clinical factors were found to be predictive of patients with COVID-19 among those with symptoms similar to COVID-19. Of the 1087 patients, 352 (32.4%) were diagnosed with COVID-19. Multivariate analysis indicated that the likelihood of COVID-19 at the time of hospitalization was significantly associated with age, sex, BMI, LDH, CRP, and malignancy. Malnutrition, corticosteroid use, diabetes mellitus, CKD, and autoimmune diseases were not more frequent in the COVID-19 group than in the non-COVID-19 group.

This study indicated that COVID-19 was more common in patients aged < 65 years and that females were more likely to be infected with COVID-19 than males. Previous reports on the relationship between COVID-19 infection and age or sex are inconsistent.^{15–17} This may be related to race, ethnicity, age distribution of the population, lifestyle, or health care system. This study excluded the occurrence of clusters including nursing homes and was limited to community-acquired infections. In the case of community-acquired infections, individuals who engaged in physical activities could encounter SARS-CoV-2 more frequently than those with sedentary lifestyle. Indeed, several studies have indicated that COVID-19 relatively rarely occurs in older people.^{18,19} In this study, although the absolute number of COVID-19 was lower in females than in males, females were more likely to suffer from COVID-19 than males after adjustment for relevant confounders. Male sex has been reported to be an important independent predictor of SARS-CoV-2 infection,¹⁷ whereas the male dominance for the risk of COVID-19 may not be as great as previously estimated. Additionally, this study period coincided exactly with the completion of the second SARS-CoV-2 vaccination drive. In Japan, the rate of SARS-CoV-2 vaccine evasion was higher among females than among males,²⁰ whereas the rates of first and second vaccination were higher among males than among females.²¹ Therefore, the sex difference in this study may have been influenced by SARS-CoV-2 vaccination.

Obesity has been reported to be associated with severe COVID-19.^{7,8} In overweight and obese individuals, detrimental adipocytokine production, including tumor necrosis factor- α , monocyte chemotactic protein-1, and interleukin-6 (IL-6), is derived from the enlarged adipocytes.²² This cytokine production in adipose tissue has been reported to be associated with BMI.²³ Indeed, the anti-IL-6 antibody tocilizumab was found to be beneficial in patients with COVID-19 and mild obesity.²⁴ However, whether obesity is a risk factor for susceptibility to SARS-CoV-2 is uncertain. Obesity is characterized by a chronic state of low inflammation. In a mouse model, a high-fat diet leads to an increase in Toll-like receptor 7 (TLR7) expression, followed by an increase in inflammatory cytokines.²⁵ TLR7 is an innate immune receptor that recognizes single-stranded RNA viruses, including SARS-CoV-2, and plays a key role in antimicrobial host defense. Chronic activation of TLR7 induced by obesity would lead to the development of TLR tolerance²⁶ and may fail

to prevent SARS-CoV-2 infection. Indeed, several studies have indicated that obesity is associated with an increased risk of a positive SARS-CoV-2 test.^{18,27}

Autopsy findings indicate that SARS-CoV-2 is detected in type II alveolar epithelial cells, and alveolar inflammation induced by viral infection is considered the major cause of COVID-19-related lung disease.²⁸ Diffuse alveolar damage is characteristic of severe cases as well as acute respiratory distress syndrome or acute exacerbation of interstitial pneumonia.²⁹ Thus, LDH should be elevated in COVID-19 due to lung parenchymal damage. CRP is an acute-phase inflammatory protein that plays a role in biological defense mechanisms. CRP binds to phosphorylcholine in the cytoplasmic membrane of bacteria and activates the complement pathway of innate immunity.³⁰ Bacterial infection is a potent stimulus for marked CRP elevation, whereas the level of CRP is not very high in viral infection.^{31,32} In the present study, approximately 70% of the cases with suspected COVID-19 had bacterial infections. Therefore, the cut-off value of 10 mg/dL could differentiate between bacterial infection and COVID-19.

Patients with any malignancy had a significantly increased risk of COVID-19.²⁷ Especially, within the first year after diagnosis of malignancy, the risk of contracting COVID-19 should be even higher.³³ However, in this study, patients with malignancy had lower ORs for COVID-19, and the rates of COVID-19 in patients with malignancy diagnosed within 1 year were comparable to those of other patients with malignancy (data not shown). One of the possible reasons is that patients with malignancy performed normal activities of daily living while being more cautious about developing infections than other patients. Reducing activities of daily living, such as staying at home, may reduce the risk of contracting COVID-19, and this finding is consistent with the low likelihood of COVID-19 in elderly patients in this study. Regarding antineoplastic therapy, patients receiving antineoplastic agents that can decrease the expression of angiotensin-converting enzyme 2 (ACE2) expression, including tyrosine kinase inhibitors or antimetabolites, may have a lower rate of contracting COVID-19 than patients receiving other antineoplastic agents³⁴ because SARS-CoV-2 infects human cells by attaching its spike glycoproteins to ACE2.

As shown in Table 4, significant differences in outcomes were found between the COVID-19 and the non-COVID-19 groups, except for mortality. These data suggest that mortality in the elderly is not extremely increased by COVID-19. Patients with COVID-19 were basically discharged to home. In addition, they were encouraged to be transferred to another hospital as much as possible in accordance with administrative policy, even if the discharge criteria were not satisfied.³⁵ Thus, few patients with COVID-19 were transferred to the general ward. Compared with the non-COVID-19 group, more patients in the COVID-19 group, who were initially considered to have a mild or moderate disease, subsequently developed severe disease and were transferred to the ICU; even patients with mild COVID-19 should be carefully monitored during the course of the disease. In this study, no new outbreaks have occurred since the new strategy was implemented, and at least two rRT-PCRs of SARS-CoV-2 were recommended to rule out COVID-19. Together, multiple SARS-CoV-2 rRT-PCRs are needed for nosocomial infection control.

This study had several limitations. First, the study was conducted in a single facility, which might have reduced the generalizability of the findings. However, the nosocomial infection control measures are unique to our institute and cannot be easily copied by other facilities. Second, COVID-19 cases in this study were mostly mild or moderate; therefore, the presented nosocomial infection control measures may not be applicable to facilities with more severe cases. Third, as mentioned repeatedly, this study was conducted before the emergence of the omicron variant BA.5 and may not be applicable to the current situation.

Conclusion

This study demonstrates the prediction of patients with COVID-19 using clinical findings in routine practice. Although not perfect, the data from the current study suggest that rRT-PCR of SARS-CoV-2 should be performed at least twice to exclude COVID-19. Multiple rRT-PCR of SARS-CoV-2 may be useful to prevent nosocomial infection. Clinical analysis following the emergence of omicron variant BA.5 is warranted.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

We declare that we have no conflict of interest in connection with this paper, and we received no payment or services from a third party in relation to this study.

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