Original Article

DOI: 10.5582/ddt.2022.01111

Age distribution and disease severity of COVID-19 patients continued to change in a time-dependent manner from May 2021 to April 2022 in the regional core hospital in Japan

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SUMMARY The present retrospective study aimed to examine the real-world data regarding time-dependent changes in the age distribution of patients with coronavirus disease 2019 (COVID-19) as well as the severity and infectivity in a regional core hospital in Japan. Patients with COVID-19 who visited the fever outpatient branch in Takagi Hospital during phase I (May 1 to December 31, 2021), and during phase II (January 1 to April 30, 2022) were evaluated. The age distribution of outpatients and the characteristics of inpatients aged > 75 years were compared between phases I and II. The age distribution of outpatients shifted from the older generation in phase I to the younger generation in phase II ($p < 0.01$). Disease severity might be reduced in a time-dependent manner with a decrease in the hospitalization rate (phase I: 145/368 (39.4%); phase II: 104/1496 (7.0%); $p < 0.01$) and mortality rate (phase I: 10/368 (2.7%); phase II: 7/1496 (0.5%); $p < 0.01$). The number of patients increased in phase II (374.0/month) compared to that in phase I (36.8/month). Regarding the older inpatients, the disease severity of COVID-19 and hospitalization days were reduced in phase II compared to those in phase I ($p < 0.01$, each). In conclusion, the present study suggests a change in the age distribution of patients with COVID-19, a decrease in toxicity, and an increase in infectivity of severe acute respiratory syndrome coronavirus 2 in a time-dependent manner.

Keywords SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, mortality, infectivity

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was detected in China in 2019 (*1*). The infection was limited in the regional area in the primary stage (*2,3*), but since then has been progressing rapidly and widely worldwide (*4,5*). Disease severity and the high infectivity of COVID-19 have serious consequences (*6,7*). With the rapid progress in COVID-19 infection, vaccinations and medications for COVID-19 have been developed and adapted widely (*8-10*). However, the pandemic and explosive infection of COVID-19 was not controlled until August 2022.

With repeated epidemics, SARS-CoV-2 has evolved from alpha and delta variants to the omicron variant. These mutations have induced several changes in the pathology of COVID-19 and policies for the treatment and prevention of the disease (*10-13*). Epidemiological data from the world, as well as Japan, suggest that the initial stage of COVID-19 mainly affected the middle and older generations, and rarely the young generations, including children (*14,15*). This trend has shifted over time, with COVID-19 being more prevalent among younger generations and children (*16*). Recent epidemiological reports suggested that COVID-19 may be becoming a milder illness in a time-dependent manner in recent times, while infectivity may be increasing (*17*).

The present study aimed to examine real-world clinical data regarding time-dependent changes in the age distribution of patients with COVID-19 and the severity and infectivity of the disease in Kouhou-kai Takagi Hospital, which is the regional core hospital in Japan and treats patients at the mild and moderate stages of COVID-19, as well as non-severe patients. The data were compared with those from phase I (May 1, 2021, to December 31, 2021), and phase II (January 1, 2022, to April 30, 2022).

2. Methods

The present retrospective study included patients with COVID-19 who visited the fever outpatient branch of Kouhou-kai Takagi Hospital between May 1, 2021, and April 30, 2022. The patients were divided into two groups: phase I (May 1, 2021, to December 31, 2021) and phase II (January 1, 2022, to April 30, 2022). Takagi Hospital is the regional core hospital in Okawa city and the surrounding cities (population of approximately 150,000); most patients with COVID-19 visit Takagi Hospital, including those with mild and moderate disease severity. COVID-19 diagnosis in all patients was confirmed by SARS-CoV-2 polymerase chain reaction (PCR); loop-mediated isothermal amplification (LAMP) and quantitative antigen tests were also included (*18,19*). Ribonucleic acid (RNA) extraction was done using the Loopamp Viral RNA Extraction Kit (Eiken Chemical, Tokyo, Japan). The collected nasopharyngeal sample was stirred several times using a Loopamp Viral RNA Extraction Reagent. The LAMP assay was performed using 10 μL of the sample or solution alone (negative control) with Primer Mix 2019-nCoV (15 μL). The reaction was allowed to proceed for 2 min with an RNA amplification reagent in a Loopamp Realtime Turbidimeter (Eiken Chemical). The threshold time was recorded for detecting SARS-CoV-2 virus RNA (*18*).

Disease severity was evaluated according to the severity classification and management of the Japan Ministry of Health Labour and Welfare COVID-19 clinical practice guide (*20*): mild, no dyspnea + no pneumonia + ≥ 96% of oxygen saturation; moderate I, dyspnea + pneumonia + 93% to 96% of oxygen saturation; moderate II, dyspnea + pneumonia + ≤ 93% of oxygen saturation; and severe, patients who required medical therapy in the intensive care unit and/or with a ventilator. Patients classified as severe did not visit Takagi Hospital, but a higher-functioning hospital. The age distribution of patients who visited the outpatient branch and those who were admitted to Takagi Hospital was examined. The hospitalization criteria were: disease severity levels of moderate I or II; and those with mild severity > 75 years, severe comorbidity, and impossibility of eating with illness. The characteristics of the hospitalized patients (> 75 years old) were evaluated, including blood tests, age, sex, height, body weight, mortality, comorbidity, performance status, disease severity, therapeutic medicines, and duration of hospitalization. The therapeutic medicines for COVID-19 infection treatment used in Takagi Hospital during the examined period were remdesivir, dexamethasone, favipiravir, tocilizumab, and neutralizing antibodies. The general condition of the patients was evaluated by the Eastern Cooperative Oncology Group Performance Status at admission (*21*) as follows: status 0: fully active, able to carry on all pre-disease performance without restriction; status 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature like light housework and office work; status 2: ambulatory and capable of all self-care but unable to carry out any work activities up, and approximately more than 50% of waking hours; status 3: capable of only limited self-care, and confined to bed or chair for more than 50% of waking hours; status 4: wholly disabled and unable to carry out any self-care, and confined to bed or chair.

The Kouhou-kai Ethical Committee approved this study (#430, May 2021). The data between phases I and II were compared using the Chi-squared or Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables. JMP Pro 16 was used for all the analyses. Statistical significance was defined as $p < 0.05$.

3. Results

Table 1 shows the age distribution of the patients with COVID-19 who visited the fever outpatient branch in Takagi Hospital in phase I and phase II. The number of patients increased ten times in phase II (phase I: 36.8/month; phase II: 374.0/month). In phase I, the

Table 1. Age distribution of the patients with COVID-19 detected by the PCR who visited the fever outpatient branch in the Takagi hospital during phase I (May 1, 2021 to December 31, 2021) and phase II (January 1, 2022 to April 30, 2022)

Age (years old)	Phase I (*n*)	Phase II (*n*) **
0-9	16 (4.3%)	183 (12.2%)
10-19	29 (7.9%)	256 (17.1%)
20-29	45 (12.2%)	276 (18.4%)
30-39	36 (9.8%)	197 (13.2%)
40-49	41 (11.1%)	172 (11.5%)
50-59	77 (20.9%)	122 (8.2%)
60-69	22 (6.0%)	90 (6.0%)
70-79	32 (8.7%)	88 (5.9%)
80-89	54 (14.7%)	79 (5.3%)
90 ≤	16 (4.3%)	33 (2.2%)
Total	368	1496

** $p < 0.01$: age distribution was different between phases I and II. PCR: SARS-CoV-2 polymerase chain reaction. n, number of patients.

prominent age group infected with COVID-19 were the middle-aged and older generations, and the number of children affected was limited. In contrast, the phase II included the middle-aged and younger generations, including children, and the change observed in the age distribution was significant ($p < 0.01$).

The number of inpatients hospitalized during phases I and II is shown in Table 2. Patients in Phase I ranged in age from the elderly to the young. In phase II ($p < 0.01$), inpatients were mostly from the middle and older generations. Mortality in patients was limited to older generations (> 75 years old) in both phases at Takagi Hospital. The hospitalization ratio (inpatient/outpatient) decreased markedly in phase II ($p < 0.01$) when compared with that in phase I.

Table 2. Age distribution of the COVID-19 patients who hospitalized the Takagi hospital during phase I (May 1, 2021 to December 31, 2021) and phase II (January 1, 2022 to April 30, 2022)

Age (years old)	Phase I (*n*)	Phase II (*n*) **
0-19	17 (0: 0%)	1 (0)
20-49	47 (0: 0%)	12 (0)
50-74	32 (0: 0%)	30 (0)
75 ≤	49 (10: 20.4%)	61 (7: 11.5%)
Hospitalization rate (inpatients/outpatients)	145/368 (39.4%)	104/1496 (7.0%) **

** $p < 0.01$: administration ratio to the hospital among the outpatients was decreased in phase II. n, number of patients.

The patient characteristics of the older inpatients (≥ 75 years) with COVID-19 are shown in Table 3. The number of patients and mortality rate were not different between phases I and II. The mortality rate calculated with the outpatients decreased in phase II ($p < 0.01$), whereas the mortality rate calculated with the inpatients did not differ between phases I and II. Disease severity was high ($p < 0.01$), and hospitalization days were prolonged ($p < 0.01$) in phase I. The therapeutic approach changed between the two phases. Remdesivir was more frequently administered to patients in phase II ($p < 0.01$), and neutralizing antibodies were more available in phase II. The prescription rate of dexamethasone decreased in phase II, and tocilizumab was rarely prescribed in this phase (*p*

Table 3. Patient-characteristics of aged COVID-19 patients more than 75 years olde who hospitalized the Takagi hospital during phase I (May 1, 2021 to December 31, 2021) and phase II (January 1, 2022 to April 30, 2022)

Items	Phase I	Phase II	*p* value
Total number of aged patients (n)	49	61	
Mortality (n)	10	7	
Mortality rate			
Mortality/aged inpatients	10/49 (20.4%)	7/61 (11.5%)	0.2
Mortality/total inpatients	10/145 (6.9%)	7/104 (6.7%)	1
Mortality/total outpatients	10/368 (2.7%)	7/1496 (0.5%)	< 0.01
Mortality caused by COVID-19	3	1	0.33
Age (years old)	85 ± 6.2	86 ± 6.1	0.84
Genders (males/females)	17/32	27/34	0.30
Height (cm)	153.0 ± 9.4	152.0 ± 10.2	0.50
Body weight (kg)	46.2 ± 12.0	45.4 ± 11.3	0.88
Serum total protein (g/dl)	6.6 ± 0.7	6.5 ± 0.8	0.81
Serum albumin (g/dl)	3.2 ± 0.6	3.2 ± 0.6	0.85
Hemoglobin (g/dl)	12.2 ± 1.3	11.7 ± 1.9	0.08
White blood cells (/µl)	4390 ± 3292	5250 ± 3056	0.29
CRP (mg/dl)	3.9 ± 5.6	1.3 ± 4.8	0.07
Creatinine (mg/dl)	0.69 ± 0.43	0.84 ± 0.20	0.03
Disease severity (mild/moderate I/ moderate II/severe) at hospitalization	2/15/32/0	24/23/14/0	< 0.01
Performance status (0/1/2/3/4)	7/3/6/15/16	0/5/17/23/16	0.35
Hospitalized duration (days)	20.0 ± 10.7	12.0 ± 6.3	< 0.01
Comorbidities (n)			
Cardiovascular diseases	25	35	0.77
Cerebrovascular diseases	17	19	0.72
Renal diseases	1	8	0.08
Respiratory diseases	11	10	0.49
Gastrointestinal diseases	0	2	0.51
Diabetes mellitus	11	10	0.49
Dementia	25	22	0.15
Others	19	35	0.17
Therapeutic medicines for COVD-19 (n)			
Remdesivir	19	45	< 0.01
Dexamethasone	43	16	< 0.01
Favipiravir	2	0	0.20
Tocilizumab	41	3	< 0.01
Neutralizing antibodies	1	5	0.22

Data are mean ± SD. n, number of patients.

< 0.01, each). The other factors did not differ between the two phases. Table 4 shows the causes of death in the inpatients. Most patients were > 85 years, and three patients in phase I and one in phase II died directly due to COVID-19. Three of four patients who died directly due to COVID-19 had renal dysfunction with a high creatinine value. Other patients in phase I died from bacterial pneumonia, including aspiration pneumonia, and those in phase II died because of bacterial pneumonia and comorbidities, including hepatocellular and gastrointestinal bleeding. In phase II, five of seven patients who died did not receive COVID-19 vaccination, whereas the vaccination information was unavailable for the patients who died in phase I.

4. Discussion

The present study demonstrated that *i*) the age distribution of the patients suffering from COVID-19 moved from the older to the younger generation, including children, concomitant with the variants of SARS-CoV-2; *ii*) the disease severity of the COVID-19 infection might be reduced in a time-dependent manner, which was demonstrated by the decrease in the hospitalization and mortality rates; *iii*) the increase in the number of the patients in present times suggested that infectivity of COVID-19 might be enhanced, whereas the virus toxicity might be attenuated.

Several epidemiological reports worldwide and in Japan have demonstrated that age distribution has changed in a time-dependent manner (*14,15*). At the start of the COVID-19 pandemic, most patients with COVID-19 were adults, and the infection concomitant with the COVID-19 variant progression spread to the younger generation and children (*16*). The infection trend in the epidemiological reports showed that SARS-CoV-2 variants were alpha and delta in phase I (May 1, 2021, to December 31, 2021) and omicron in phase II (2022 January 1, 2022, to April 30, 2022) (*10-13*).

The present study demonstrated that the hospitalization (39.4% in phase I, 7.0% in phase II) and mortality (2.7% in phase I, 0.5% in phase II) rates were decreased in the present times, which suggested that the viral toxicity was diminished in a time-dependent manner. In addition, the ratio of direct deaths caused by COVID-19 tended to decrease in phase II, where most patients died due to severe comorbidities. This observation is equivalent to that reported in several official releases of epidemiological data and clinical reports (*4,15,17,20,22-26*).

The present data of the time-dependent increase in the number of patients per month (phase I: 36.8/month, phase II: 374.0/month) suggested increased infectivity of COVID-19, although the toxicity of the virus was reduced, and this tendency was demonstrated in the official epidemiological data worldwide (*4,20*). An accurate diagnosis of COVID-19 tended to not be performed, and accuracy in recording the number of cases has not been demonstrated in most countries because of the marked increase in the number of patients and the dramatic decrease in mortality directly caused by COVID-19.

The limitations of the present study were as follows: the data were examined in a single regional institute in Japan, the number of patients was limited, and the patients with severe illness due to COVID-19 were excluded and hospitalized in an advanced medical institution because the patients with mild/moderate

Table 4. Characteristics of the fetal patients during phase I (May 1, 2021 to December 31, 2021) and phase II (2022 January 1, 2022 to April 30, 2022)

Age	Gender	PS	Disease severity	Hospital stay	Cause of death	Vaccination	Cr
Phase I							
85	female	4	moderate I	43 days	aspiration pneumonia	N.A.	0.68
96	female	4	moderate II	52 days	aspiration pneumonia	N.A.	0.69
86	male	4	moderate II	29 days	aspiration pneumonia	N.A.	0.76
88	male	4	moderate II	17 days	bacterial pneumonia	N.A.	0.93
98	female	4	moderate I	23 days	aspiration pneumonia	N.A.	0.37
92	male	4	moderate II	33 days	aspiration pneumonia	+	0.74
85	female	4	moderate II	17 days	bacterial pneumonia	+	0.38
92	female	3	moderate II	9 days	COVID-19	N.A.	2.31
90	male	3	moderate II	10 days	COVID-19	N.A.	1.45
87	female	4	moderate II	13 days	COVID-19	N.A.	0.65
Phase II							
87	male	4	moderate I	12 days	hepatocellular carcinoma	-	0.84
86	male	4	moderate I	10 days	hepatocellular carcinoma	-	1.50
75	male	3	moderate II	31 days	bacterial sepsis	+	0.84
99	female	3	mild	8 days	gastrointestinal bleeding	-	1.52
91	female	3	mild	4 days	bacterial sepsis	-	0.52
93	female	4	mild	17 days	bacterial pneumonia	-	0.72
92	female	4	moderate II	2 days	COVID-19	+	2.87

PS: performance status. Cr: creatinine. N.A.: the patient data of vaccination of COVID-19 was not available. +: vaccination received. -: vaccination not received.

COVID-19 visited the fever outpatient branch of Takagi Hospital. The effect of vaccination was not indicated in the present study, as information on vaccination in phase I was unavailable. However, five of seven patients who died did not receive vaccination in phase II. At last, although we checked the variants of SARS-CoV-2 in several patients in Phase I and II, we could not fully define that patients in Phase I were mainly infected with alpha and delta variants while patients in Phase II were mainly infected with omicron variant.

5. Conclusion

The present retrospective study in a regional core hospital in Japan demonstrated a change in the age distribution of patients with COVID-19, a decrease in toxicity, and an increase in infectivity in a time-dependent manner.

Acknowledgements

We appreciate all the medical staff at Takagi Hospital for the medical treatment and care of patients with COVID-19.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received December 2, 2022; Revised February 10, 2022; Accepted February 24, 2023.

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Released online in J-STAGE as advance publication February 26, 2023.