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High mortality and morbidity among vaccinated residents infected with the SARS-CoV-2 Omicron variant during an outbreak in a nursing home in Kyoto City, Japan

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Highlights

- A COVID-19 outbreak occurred in a nursing home that did not provide medical care
- Most of the residents with severe hypoxemia could not be transferred to a hospital
- Despite vaccination, high mortality and morbidity were observed among the residents
- All genomes from residents and staff belonged to the Omicron variant BA.1
- Avoiding management of severe COVID-19 cases in nursing homes is needed

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Abstract

Background. Outbreaks of coronavirus disease 2019 (COVID-19) in long-term care facilities are difficult to control and are associated with mortality, although vaccination have contributed to improvements. This study reports clinical impacts of a COVID-19 outbreak in a nursing home for elderly individuals in Kyoto City, Japan.

Methods. We performed epidemiologic and molecular investigations of the outbreak and characterized outcomes of the nursing home residents.

Results. During the outbreak period, a total of 31 residents (39.2%) and 26 staff members (49.1%) were infected with COVID-19. All residents and staff received two doses of a vaccine approximately 7 months prior. Only four residents were admitted to hospitals, and 10 residents with severe hypoxemia could not be transferred to a hospital due to a shortage of beds for

COVID-19 patients. Within 90 days of the onset of the outbreak, 8 residents with COVID-19 (25.8%) and 3 uninfected residents (6.2%) died. A total of 48.4% of residents with COVID-19 and 8.3% of uninfected residents developed one or more comorbidities. Viral genome analysis showed that the outbreak was caused by the Omicron BA.1.1.2 variant.

Conclusions. Despite vaccination, high mortality and morbidity were observed in the COVID-19 outbreak due to the Omicron variant. Limiting medical care for residents with COVID-19 in facilities that experience ongoing outbreaks may be needed to reduce the risk of mortality among nursing home residents.

Keywords: COVID-19, SARS-CoV-2, nursing home, outbreak, viral genome

Background

Long-term care facilities (LTCFs) for elderly individuals are prone to COVID-19 outbreaks with rapid and widespread dissemination, and residents in these facilities are at high risk of mortality due to their age and frailty (1, 2). As of May 2020, 20–35% of LTCFs in the USA had outbreaks (3), and residents of LTCFs accounted for 14-33% of total deaths in European countries (1). In Kyoto City, outbreaks with >5 COVID-19 cases occurred in 21% of the 379 LTCFs for elderly individuals during April 2021-March 2022. Although vaccination is effective for lowering the risk of infection and mortality, specific severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOCs) with higher transmissibility, severity, and mortality than non-VOCs have spread worldwide. The Omicron BA.1 variant was estimated to have a threefold higher reproduction number than existing variants (4) and succeeded in spreading worldwide, including in Japan (5). Despite lessons from several waves of COVID-19 cases and the enforcement of medical care systems for COVID-19 patients, Japanese hospitals in certain regions were overwhelmed due to a record high number of cases during the sixth wave (December 2021–March 2022) when BA.1 was prevalent (6).

Kyoto City public health officials and Kyoto University Hospital collaborated to establish citywide COVID-19 infection control programs targeting facilities for elderly or disabled people, including nursing homes (7). The programs consisted of mass polymerase chain reaction (PCR) testing for weekly screening and active screening when a single case was identified, implementation of strategies to prevent transmission within a facility, and vaccination. Residents and staff in LTCFs were designated as vaccine priority groups (7); two doses of a vaccine have been given since April 2021 and a booster shot was provided starting in December 2021.

In this study, we investigated the characteristics and outcomes of residents and staff involved in a COVID-19 outbreak caused by Omicron at a nursing home in Kyoto City, Japan, who underwent public epidemiological investigations and infection control interventions by Kyoto City and Kyoto University Hospital under a severe shortage of hospital beds.

Material and Methods

Setting

Facility A is a special nursing home for elderly individuals that provides long-term care for up to 80 frail, cognitively impaired individuals who do not need high-level medical care. The building has 80 beds divided into four units (A, B, C, and D) for long-term care residents and 10 beds for short-term care residents. The facility employs 44 care workers, 6 nurses, and 3 nutritionists who have direct contact with residents. Nurses are available only during the daytime. To prevent COVID-19 outbreaks, the facility prohibited visits, and all staff were tested by reverse transcription polymerase chain reaction (RT-PCR) once a week. Quarantine for newly admitted asymptomatic residents was not performed.

Definition of cases

A COVID-19 case during the outbreak was defined as a resident or staff member in the long-term care units who was positive for SARS-CoV-2 antigen or RT-PCR testing during the outbreak period between the earliest onset date (designated as day 0) and 14 days after the last onset date among the test-positive cases (day 41).

Epidemiological investigation and characteristics of residents

The Health and Welfare Bureau of Kyoto City, the department responsible for public health and LTCFs, performed case investigations and contact tracing for all laboratory-confirmed COVID-19 cases following national guidelines for active epidemiological investigations (8). In response to the identification of multiple COVID-19 cases in Facility A, public health nurses and infection control specialists from Kyoto University advised the facility on how to control the spread. In addition to the information collected during the above epidemiological investigations, we retrospectively collected the following clinical characteristics of residents in the long-term care units: the Clinical Frailty Scale score, the Charlson Comorbidity Index score, vaccination status, treatment, hospitalization, and outcomes. Outcomes included mortality between days 0 and 90 of the outbreak and changes in activities of daily living (ADLs), development of decubitus, progression of dementia, and decreased oral intake during the outbreak period.

Economic impact

We calculated the decrease in profits due to facility closure by multiplying the resident-days of absent residents in the long-term and short-term care units with average usage fees per day according to the classified care levels defined by the Japanese long-term care insurance system. Additional labor costs and costs for equipment purchases (e.g., personal protective equipment, PPE) and infectious waste disposal needed for the care of COVID-19 residents were also calculated.

Molecular diagnosis and analysis

For the detection of COVID-19 cases, nasal swab or saliva samples were tested using the RT-PCR assay (Japanese National Institute of Infectious Disease N2 with EAV) (9) at the reference laboratory (Kyoto University). All positive samples were subjected to viral genome analysis using the COVIDSeq Test (RUO version; Illumina, San Diego, CA) with the ARTIC V4.1 primer set and the NextSeq1000 platform (Illumina). The data were processed using DRAGEN COVID Lineage App version 3.5.8 (Illumina), and consensus sequences were generated using the SARS-CoV-2 reference genome (NC_045512). Genomes sequenced with a

>90% breadth of coverage of the reference genome underwent lineage assignment using Pangolin version 4.0.6 (10). Phylogenetic analysis was performed using IQ-TREE multicore version 2.1.2 COVID-edition. The SARS-CoV-2 sequences obtained in this study are available in the GISAID database. The accession numbers are shown in Supplementary Dataset1.

Statistical analysis

Categorical variables were compared by Fisher's exact test. Continuous variables were compared by the Mann–Whitney U test. Cox proportional hazards regression models were used to determine the association of COVID-19 with mortality. A P value < 0.05 was considered statistically significant. We conducted the statistical analyses using R version 4.1.3 (R Foundation for Statistical Computing, https://www.r-project.org).

Ethics approval

The Ethics Committee of Kyoto University Graduate School and the Faculty of Medicine approved this study (R2379) and waived the need to obtain informed consent from each patient.

Results

Description of the outbreak and control measures

In February 2022, one resident in the long-term care unit developed fever at Day 3 (Figure 1A) and was diagnosed with COVID-19 at Day 6. This triggered an active epidemiological investigation in Facility A on Day 6, including universal RT–PCR tests for all residents and staff. Seven COVID-19 cases (resident, n=4; staff, n=3) were identified, and an outbreak was recognized. During the outbreak period (between day 0 and day 41; Figure 1A), a total of 31 residents (39.2%) and 26 staff members (49.1%) in long-term care units were infected.

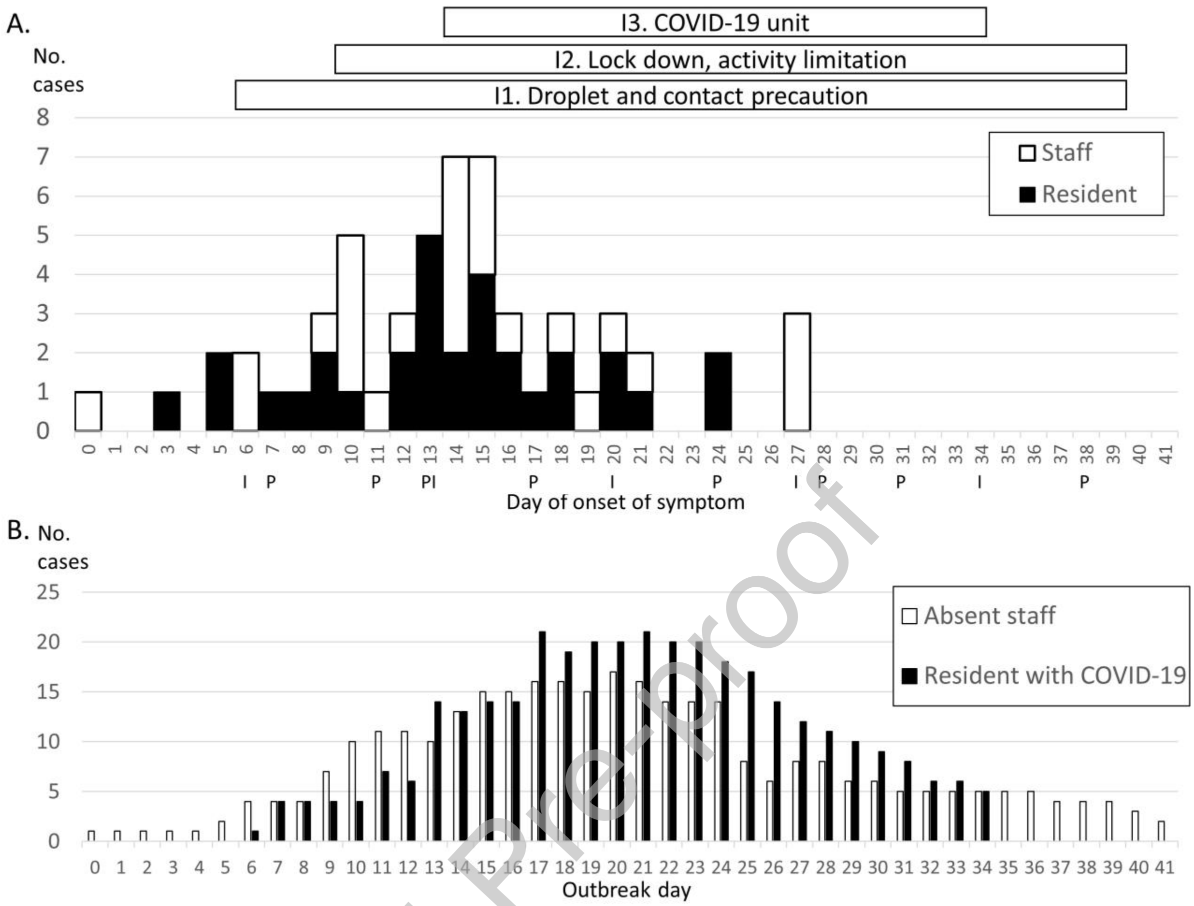

Figure 1. Epidemic curve and burden of the COVID-19 outbreak in long-term care units of the nursing home in Kyoto, Japan, February–March 2022. A) Epidemic curve and infection control measures. At the bottom of the graph, "P" indicates universal or targeted RT–PCR testing for residents and staff, and "I" indicates a visit by an infection control specialist (medical doctor) to the facility to improve infection control measures. A total of 628 specimens were tested by RT–PCR, and the specialist visited 5 times at a regular interval of once a week. The three main infection control measures included at the top of the graph were introduced on the following days (I1, Day 6; I2, Day 10; I3, Day 14). B) Number of residents with COVID-19 who were cared for in the facility and staff with COVID-19 who were absent due to isolation for COVID-19. On each day, the number of residents with COVID-19 after the day of COVID-19

diagnosis and before the end of the isolation day were counted.

Infection control measures, including universal masking and eye protection in all units, contact precautions in the units with at least one COVID-19 case, education and monitoring of appropriate PPE use, high-touch surface decontamination using cleaning wipes, facility lockdown, physical distancing (staying in rooms) and limiting resident activity, and the construction of a separate COVID-19 unit were implemented sequentially (Figure 1A) through collaboration between infection control specialists from Kyoto University and the Health and Welfare Bureau of Kyoto City. In the collaboration, business continuity planning, which included limiting care for residents, was introduced to continue care for residents during the staff shortage; transportation of COVI D-19 patients to the acute care hospitals was managed, and home-visit medical care at the facility (oral and intravenous antivirals and home-oxygen therapy) was employed. The COVID-19 unit was placed in the area of unit D, and short-term care units and airborne precautions were added due to the need for potential aerosol-generating maneuvers, including sputum aspiration. Regular RT-PCR screening of residents and staff (universal or targeted to the units with COVID-19 cases) was also performed once or twice per week (Figure 1A). During the outbreak period, 628 specimens were tested, and an infection control specialist visited 5 times to improve the infection control measures. Following the negative RT-PCR results for all residents and staff on day 38, the infection control measures were terminated on day 39.

Characteristics and outcomes of the COVID-19 cases

Table 1 shows that the residents in the long-term care units were older with a median age of 89, were mostly female (83.5%), and were mildly to moderately frail (Clinical Frailty Scale, IQR 5-6). All residents had dementia, but underlying medical conditions were not common (Charlson Comorbidity Index, IQR 1-2). No residents received immunosuppressive treatment or were current smokers. These clinical characteristics were not significantly different between COVID-19 patients and uninfected residents (Table 1).

Table 1. Characteristics of 79 residents in long-term care units of the nursing home in Kyoto, Japan, February–March 2020.

Characteristic	All residents (n=79)	COVID-19 cases (n=31)	Uninfected residents (n=48)	P value
Age, years, median (IQR)	89 (86-93)	89 (86-92)	89 (86.75-93)	0.86
Male sex	13 (16.5%)	6 (19.4%)	7 (14.6%)	0.76
Clinical Frailty Scale, median (IQR)	6 (5-6)	5 (5-6)	6 (5-6)	0.55
Charlson Comorbidity index, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0.52
Dementia	79 (100%)	31 (100%)	48 (100%)	NC
Diabetes	6 (7.6%)	2 (6.5%)	4 (8.3%)	1
Chronic heart failure	13 (16.5%)	4 (12.9%)	9 (18.8%)	0.55
Chronic pulmonary disease	4 (5.1%)	3 (9.7%)	1 (2.1%)	0.29
Renal disease	2 (2.5%)	0 (0%)	2 (4.2%)	0.52
Solid tumor	4 (5.1%)	1 (3.2%)	3 (6.3%)	0.15
Vaccination (2 doses)	79 (100%)	31 (100%)	48 (100%)	NC
Days since the last dose of a vaccine, median (IQR)	234 (232-236)	233 (232-235)	233 (232-235)	0.47
Unit				
A	23 (29.1%)	1 (3.2%)	22 (45.8%)	<0.001
B	19 (24.1%)	15 (48.4%)	4 (8.3%)	<0.001

C	23 (29.1%)	10 (32.3%)	13 (27.1%)	0.62
D	14 (17.7%)	5 (16.1%)	9 (18.8%)	1

IQR, interquartile range; NC, not calculated.

The residents in unit B were most frequently infected with COVID-19, followed by the residents in units C, D, and A. The characteristics of the staff are shown in Table S1.

All 31 residents with COVID-19 were symptomatic. The index case (the first test-positive resident) presented fever without hypoxemia, visited an emergency department, and was admitted. Fourteen residents were severely ill with < 94% oxygen saturation (Table 2) and were eligible for immediate hospitalization by the Japanese COVID-19 treatment guideline.

Table 2. Disease severity and treatment of 31 COVID-19 cases among residents in long-term care units

Variables	COVID-19 cases (n=31)	Nonsurvivors (n=8)	Survivors (n=23)	P value
Severity				
Mild, symptomatic without hypoxemia	15 (48.4%)	2 (25.0%)	13 (56.5%)	0.15
Moderate, hypoxemic, SpO_2 ≥94%	2 (6.5%)	0	2 (8.7%)	1
Severe, hypoxemic, SpO_2 <94%	14 (45.2%)	6 (75.0%)	8 (34.8%)	0.28
Treatment				
Hospitalized	4 (12.9%)	1 (12.5%)	3 (13.0%)	1
Non-hospitalized				
Oral antiviral drugs*	22 (67.7%)	4 (50.0%)	18 (78.3%)	0.19

Intravenous neutralizing monoclonal antibodies[†]	5 (16.1%)	0	5 (21.7%)	0.29
Home oxygen therapy	3 (9.7%)	1 (12.5%)	2 (8.7%)	1

[*] All cases received molnupiravir 1–8 days after onset (median 4.5 days). Three nonsurvivors and 15 survivors received treatment within 5 days of onset.

[†] All cases received sotrovimab, in addition to molnupiravir, 6–11 days after onset (median 7 days). Three patients received treatment within 7 days of onset.

Of these residents, only three were admitted, and one was transferred to the hospital by ambulance but was returned to the facility because of insufficient beds for COVID-19 patients. The other 10 residents could not be transferred to hospitals because the bed control center of Kyoto Prefecture, which managed hospitalization of COVID-19 patients in Kyoto City, decided not to transfer due to a shortage of beds. The presence of pneumonia could not be determined because X-ray equipment was not available at the facility. Two-thirds of residents received an oral antiviral drug (molnupiravir), but some had difficulties taking medicine due to poor general condition and dysphasia. Intravenous neutralizing monoclonal antibody (sotrovimab) was administered for five severe residents, but visiting health care professionals had difficulties placing catheters and maintaining drip lines.

Within 90 days of outbreak onset, eight COVID-19 residents (25.8%) and three uninfected residents (6.2%) died (P=0.02 by Fisher's exact test, Table 3; P=0.02 by log-rank test, Figure S1).

Table 3. Outcomes of residents in long-term care units

Characteristic	COVID-19 cases (n=31)	Uninfected residents (n=48)	P value
90-day mortality during the outbreak day 0	8 (25.8%)	3 (6.2%)	0.02

and 90			
Any morbidity during the outbreak period*			
(Day 0–41)	15 (48.4%)	4 (8.3%)	<0.001
Decreased activities of daily living	14 (45.2%)	0	<0.001
Bedridden	7 (22.6%)	0	<0.001
Development of a pressure injury†	5 (16.1%)	4 (8.3%)	0.30
Progression of dementia	6 (19.4%)	0	0.003
Decreased oral intake	6 (19.4%)	0	0.003

* Among deceased residents, two residents with COVID-19 and one uninfected resident had morbidities.

† The sacral region was the most common (n=4 and n=3 for residents with COVID-19 and uninfected residents, respectively), followed by the heel (n=1 each).

COVID-19 infection was significantly associated with mortality within 90 days of outbreak onset in a multivariate Cox proportional hazards regression analysis (hazard ratio, 6.99 [95% confidence interval, 1.65–29.6], Table S2). Among the eight residents with COVID-19 who died, two died 6 and 8 days after onset (during the disease course; Table S3). The other three patients who were severely dehydrated due to fever and decreased oral intake during their illness died 12–19 days after onset. The other three patients who became severely frail and had decreased oral intake after recovery from COVID-19 died 17–68 days after onset. Of these deaths, 5 residents with severe conditions could not be hospitalized. All three uninfected residents died of old age.

During the outbreak period, almost half of the residents with COVID-19 had one or more comorbidities, including decreased activities of daily living, development of pressure injuries, progression of dementia, and decreased oral intake (Table 3). Four uninfected residents (8.3%) also developed pressure injuries, while no residents had active pressure injuries before the outbreak.

The majority of the residents (96.2%) and all staff received the second dose of the BNT162b mRNA COVID-19 vaccine more than 6 months before the outbreak. There was no significant difference in the days since the last vaccine dose to the outbreak between residents with and without COVID-19 (Table 1). No residents or staff contracted COVID-19 before the outbreak.

The characteristics of staff with and without COVID-19 are shown in Table S1. Twenty-five staff members with COVID-19 had mild disease and improved without hospitalization. The other staff member was asymptomatic.

Genome analysis

During the outbreak period, genome data for 23 residents and 15 staff members in long-term care units and 3 others were obtained. All genomes from the 38 cases in long-term care units belonged to BA.1.1.2. Of these, 23 (60.5%) genomes obtained from residents and staff who worked in various units were identical (cluster Ic) and included those from the staff who presented the earliest onset date (Figure 2).

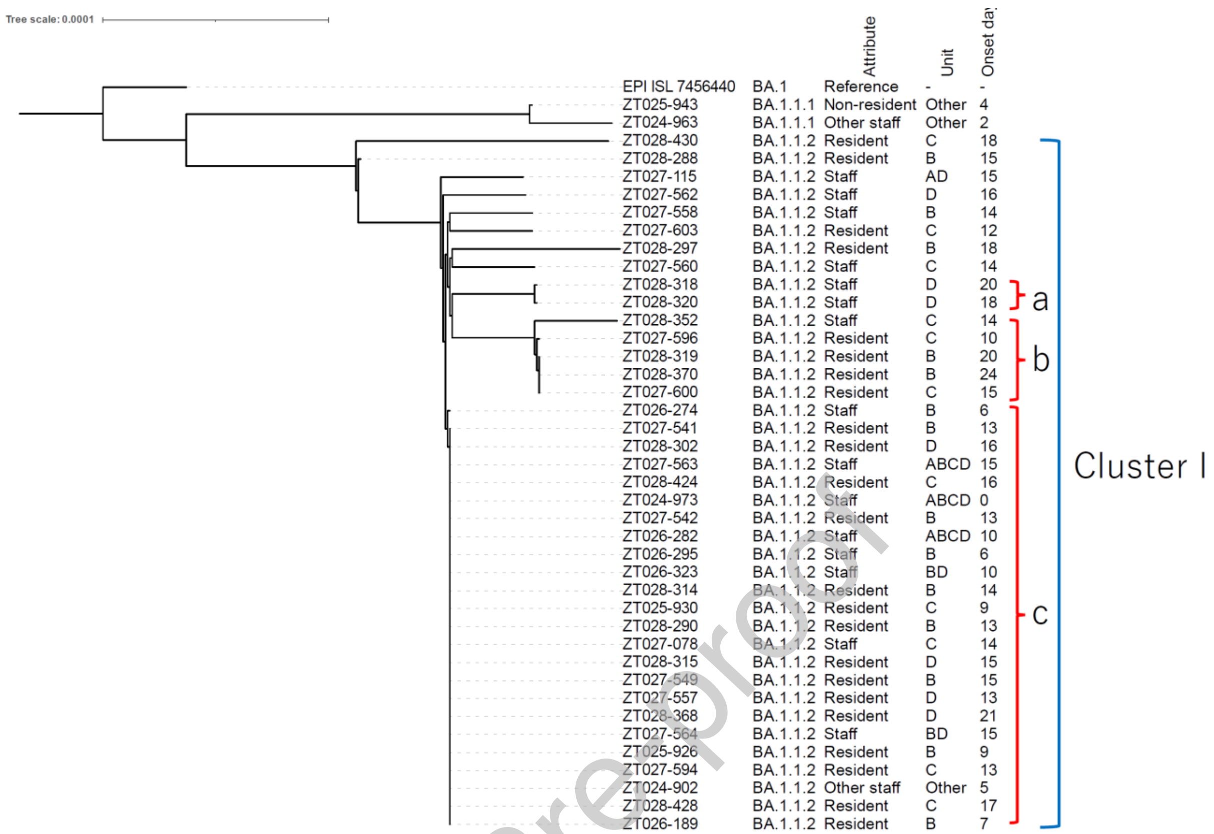

Figure 2. A maximum-likelihood phylogenetic tree of SARS-CoV-2 genomes obtained from 41 COVID-19 cases in a long-term care facility in Kyoto, Japan, February–March 2022. The tree was constructed with the best-fit nucleotide substitution model of F81+F+I determined by ModelFinder of IQ-TREE. The tree is rooted with the reference strain of the Omicron variant (BA.1; EPI_ISL_7456440). Branch supports were assessed by 1000 replicates and are shown as SH-like approximate likelihood ratio test support (%)/ultrafast bootstrap support (%). Bootstrap values were calculated using 1000 replicates of the SH-like approximate likelihood ratio test and the ultrafast bootstrap test and are shown under branches in the corresponding order (%). Genomes were obtained from 23 residents and 15 staff members in long-term care units and 3 others from the other division of the facility.

The other genomes showed 1–4 single nucleotide polymorphisms (SNPs) in the cluster Ic genomes. One genome obtained from a staff member in a different division of the facility was also identical to that of cluster Ic, but the staff member was a household member of one of the staff of a long-term care unit with the cluster Ic genome. Two genomes obtained from a daycare participant and a staff member belonged to BA.1.1.1.

Economic impact

The number of residents decreased after the recognition of the outbreak on day 6 and lasted for at least 14 days after the end of the outbreak (day 55). A total of 355 and 278 resident-days in long-term and short-term units were lost, respectively, and corresponded to $77,000 (at a rate of 1 dollar = 100 yen). The additional cost for equipment purchases was $9,500 and $5,100 for disposal. The overall labor costs were $1,000 lower in the outbreak months (February–March 2022) than in the 2 months prior to the outbreak (December 2021 and January 2022). The additional overtime pay was $2,800 and the reduction in labor costs due to the absence of staff with COVID-19 was $3,800. Additional staff were not employed during the outbreak.

Discussion

The COVID-19 outbreak due to the Omicron BA.1 variant in this nursing home was associated with a significantly higher 90-day mortality rate (25.8%) among the residents with COVID-19 in the long-term units than among uninfected residents (6.2%). Among these residents with COVID-19 who died, 6.5% died during the disease course, and COVID-19 was considered the direct cause of death. This value is comparable to the reported mortality rate of 4.6% among patients >80 years of age in Kyoto Prefecture during the sixth wave (December 2021–May 2022), which included the outbreak period and when Omicron BA.1 was prevalent (11). However, 16.1% of the total mortality resulted from patients who presented severe disease and could not be hospitalized (including a patient who died during the disease course; Table S3). During the outbreak period, the bed occupancy rates of COVID-19 inpatients were high, and there were frequent difficulties in ambulance transportation (Figure S2). It might be possible that a part of the observed excess mortality could have been lowered if appropriate medical care had been given. A review of outbreaks in LTCFs (mostly skilled nursing facilities) reported a high average mortality rate of 21% (range, 1–34%) (12). However, these outbreaks occurred in the prevaccine era in 2020 and cannot be directly compared with the present outbreak.

Risk factors for hospitalization, progression to severe disease and mortality included old age, underlying comorbidities, vaccination status, and SARS-CoV-2 variants (13-15). The residents in Facility A were elderly individuals, but comorbidities were not prevalent (Table 1). Omicron is associated with lower risks of hospitalization and death than Delta (14), even in those aged >80 years (at an adjusted hazard ratio of 0.47 for hospitalization) (15). In Japan, the reported mortality rates among those aged >80 years were 5.1% during the fifth wave when Delta was prevalent and 4.1% during the sixth wave with Omicron (6). Vaccination lowers the risk of SARS-CoV-2 infection, progression to severe disease and mortality (14, 16). A study in the US reported that the in-hospital mortality rates of unvaccinated and vaccinated adults infected with Omicron were 9.2% and 5.1%, respectively (14). However, vaccine effectiveness against Omicron is lower than that against Alpha, Delta, and non-VOCs, which is probably related to Omicron's potential mutations for immune escape and waning immunity of hosts (16, 17). Worldwide data indicate that mortality related to COVID-19 outbreaks in LTCFs decreased after the initiation of vaccination, but the most recent data representing infection due to the Omicron variant show an increase in mortality, although it varies among countries (1). A booster dose of the BNT162b2 or mRNA-1273 vaccine is reported to restore the effectiveness against Omicron (16, 18). Approximately 8 months have passed since the residents and staff in Facility A received 2 doses of a vaccine, and a booster shot was planned during the outbreak period; thus, no residents or staff had received the booster shot at the time of the outbreak, which might have contributed to the deteriorating outcomes of the outbreak.

Residents infected with COVID-19 also frequently had morbidities or increased frailty compared with uninfected residents (Table 3). This fact indicates that in nursing home residents, COVID-19 significantly increases frailty and limits quality of life. In addition, some patients might have "long COVID" conditions that could affect mortality and morbidity (19). Fatigue was a dominant feature of long COVID conditions. Although we could not follow these consequences for a long period or assess subjective symptoms due to cognitive impairment, studies indicated a 10–55% prevalence at 8–11 weeks after onset (19). Residents in nursing homes are considered at high risk of developing pressure injuries (20). No residents suffered from pressure injuries before the outbreak under routine prevention measures taken at the facility. During the outbreak, pressure injuries occurred in residents with or without COVID-19, probably due to a decreased frequency of repositioning and skin care under a staff shortage. This illustrated possible adverse effects of the outbreak on the residents.

Even under stringent visitation restrictions, as in Facility A, COVID-19 can be introduced into LTCFs by health care workers (12), which was supported by genomic data (21). In this study, the outbreak was also supported by genome analysis (Figure 2). Once introduced into LTCFs, rapid and widespread transmission has been reported because of difficulty in diagnosis, e.g., the lack of typical symptoms and presence of asymptomatic or presymptomatic cases, and in employing recommended infection control measures such as physical distancing and isolation due to dementia in the absence of trained infection control specialists (21, 22). Severe cognitive impairment, renal disease, and obesity were associated with SARS-CoV-2 positivity in LTCF outbreaks (12). In Facility A, no significant difference was observed between infected and uninfected residents except for the units (Table 1). Residents stayed in their corresponding units, but 14 staff members, 9 of whom were infected, provided care in various units. These staff members might have contributed to spreading the virus across units.

The appropriate use of PPE is one of the key measures for the containment of outbreaks (23). Staff trainings on donning and doffing PPE and appropriate timing of hand hygiene were conducted; however, we could not perform regular monitoring or provide regular feedback. Isolation and cohorting followed by universal testing during LTCF outbreaks were effective in mitigating outbreaks (12, 24). In Facility A, extensive RT-PCR testing for residents and staff was performed until no new cases were detected. However, not all residents with COVID-19 were isolated in a single room or cohorted, partly due to the increasing number of cases and a lack of leadership for timely infection control measures until a separate COVID-19 unit was opened on Day 14 of the outbreak. These interventions might be needed for the early containment of outbreaks.

The limitations of this study included the absence of detailed clinical characteristics of residents (e.g., comorbidities, care), assessments of infection control measures at baseline and during the outbreak (e.g., compliance with hand hygiene and PPE guidelines), routine RT-PCR screening of residents, and genomic data from all infected cases due to different testing locations. We did not have data on SARS-CoV-2 IgG antibody levels against the spike protein and could not determine which residents or staff were unresponsive to two doses of the vaccine. The strengths of this study included comprehensive epidemiological characterization of the outbreak with genomic data support.

Conclusions

As a result of the management of a large number of residents with COVID-19 in a LTCF that did not provide medical care under the staff shortage, we observed high mortality and morbidity among the residents with COVID-19, morbidity among uninfected residents, and an economic impact to the facility, although residents and staff were fully vaccinated and the less virulent Omicron variant was the cause of infection. In our opinion, it is important to avoid the management and treatment of severe COVID-19 cases in LTCFs, especially in the case of a shortage of staff, including nurses, and to improve medical care systems for COVID-19 cases in LTCFs, including the establishment of a robust case management and transportation system, even when the bed occupancy rate for COVID-19 patients is high. Other interventions, including booster shots and effective infection control interventions (before and after outbreaks), are also needed for the prevention of outbreaks and improvement of outcomes of COVID-19 due to new VOCs that may be associated with reduced vaccine effectiveness and higher transmissibility and/or disease severity.

Author contributions

Y.M. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y.M. and M.N. conceived and designed the study. All authors contributed materials and data collection. Y.M. performed the experiments and analyzed the data. Y.M. drafted the manuscript, and all authors reviewed and approved the final version of the manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

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References

1. Comas-Herrera A MJ, Byrd W, Lorenz-Dant K, Patel D, Pharoah D (eds.). LTCcovid International living report on COVID-19 and Long-Term Care[cited 2022 May 16]. Available from: https://ltccovid.org/international-living-report-covid-ltc/.

2. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl

J Med. 2020 May 28;382(22):2081-90.

3. White EM, Kosar CM, Feifer RA, Blackman C, Gravenstein S, Ouslander J, et al. Variation in SARS-CoV-2 Prevalence in U.S. Skilled Nursing Facilities. J Am Geriatr Soc. 2020 Oct;68(10):2167-73.

4. Du Z, Hong H, Wang S, Ma L, Liu C, Bai Y, et al. Reproduction Number of the Omicron Variant Triples That of the Delta Variant. Viruses. 2022 Apr 15;14(4).

5. World Health Organization. Tracking SARS-CoV-2 variants[cited 2021 July 13]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.

6. Ministry of Health, Labour and Welfare. Materials of COVID-19 measures advisory board [in Japanese][cited 2022 Apr 11]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00256.html.

7. Nagao M, Matsumura Y, Yamamoto M, Shinohara K, Yukawa S, Noguchi T, et al. Analysis of a city-wide COVID-19 prevention strategy for aged-care facilities during third and fifth waves of COVID-19 in Kyoto City, Kyoto, Japan. Influenza Other Respir Viruses. 2022 Mar 9.

8. National Institute of Infectious Diseases. Manual for Active Epidemiological Surveillance of Patients with Novel Coronavirus Infection (Provisional Version)2020 [cited 2022 Apr 11]. Available from: https://www.niid.go.jp/niid/images/epi/corona/2019nCoV-02-200227-en.pdf.

9. Matsumura Y, Shimizu T, Noguchi T, Nakano S, Yamamoto M, Nagao M. Comparison of 12 Molecular Detection Assays for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). J Mol Diagn. 2021 02;23(2):164-70.

10. Rambaut A, Holmes EC, O'Toole A, Hill V, McCrone JT, Ruis C, et al. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. Nat Microbiol. 2020 Nov;5(11):1403-7.

11. Kyoto Prefecture. Situation of beds occupancy rate [in Japanese][cited 2022 May 6]. Available from: https://www.pref.kyoto.jp/kentai/corona/tassei_jyokyo.html.

12. Gmehlin CG, Munoz-Price LS. Coronavirus disease 2019 (COVID-19) in long-term care facilities: A review of epidemiology, clinical presentations, and containment interventions. Infect Control Hosp Epidemiol. 2022 Apr;43(4):504-9.

13. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021 Feb;76(2):428-55.

14. Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ. 2022;376:e069761.

15. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet. 2022 Apr 2;399(10332):1303-12.

16. Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect. 2022 Feb;28(2):202-21.

17. Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med. 2022 Feb 21.

18. Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, et al. Association Between 3 Doses of mRNA COVID-19 Vaccine and Symptomatic Infection Caused by the SARS-CoV-2 Omicron and Delta Variants. JAMA. 2022 Feb 15;327(7):639-51.

19. Sandler CX, Wyller VBB, Moss-Morris R, Buchwald D, Crawley E, Hautvast J, et al. Long COVID and Post-infective Fatigue Syndrome: A Review. Open Forum Infect Dis. 2021 Oct;8(10):ofab440.

20. Smith DM. Pressure ulcers in the nursing home. Ann Intern Med. 1995 Sep 15;123(6):433-42.

21. Graham NSN, Junghans C, Downes R, Sendall C, Lai H, McKirdy A, et al.

SARS-CoV-2 infection, clinical features and outcome of COVID-19 in United Kingdom nursing homes. J Infect. 2020 Sep;81(3):411-9.

22. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 3;69(13):377-81.

23. World Health Organization. Infection prevention and control guidance for long-term care facilities in the context of COVID-19 update2021 [cited 2022 June 4]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC_long_term_care-2021.1.

24. Psevdos G, Papamanoli A, Barrett N, Bailey L, Thorne M, Ford F, et al. Halting a SARS-CoV-2 outbreak in a US Veterans Affairs nursing home. Am J Infect Control. 2021 Jan;49(1):115-9.