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Difference in clinical courses and causes of COVID-19-related deaths in hospitalized patients infected with omicron and delta variants: A retrospective study in Japan

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Abstract: Despite the lower rate of severe illness associated with the omicron variant than the delta variant, more deaths have occurred among patients with mild-to-moderate COVID-19 in Japan since the omicron variant surge during the sixth wave. This study aimed to elucidate the background, clinical course, and causes of death in patients with COVID-19. We conducted a retrospective observational study on patients with COVID-19 admitted to the National Center for Global Health and Medicine who subsequently died during the delta (July–September 2021) and omicron variant outbreaks (December 2021–August 2022). Among the 20 patients who died during the delta variant epidemic, the main causes of death were pneumonia (n = 16, 80%), preadmission complications (n = 3, 15%), and complications occurring during hospitalization (n = 1, 5%). However, during the omicron variant epidemic, 7/24 patients (29%) died of pneumonia, 11 (46%) died of complications before admission, and 6 (25%) died of complications during admission. During the omicron variant outbreak, two-thirds of the COVID-19 deaths during hospitalization were not primarily caused by pneumonia, unlike the delta variant outbreak, during which pneumonia had a greater impact on mortality. As patient demographics and clinical pictures change, the establishment of medical infrastructure for patients with life-threatening comorbidities and careful monitoring of acute COVID-related complications are essential.

***Keywords*:** pneumonia, respiratory failure, comorbidities, disease progression, medical infrastructure, COVID-related complications

Introduction

The delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a higher severity rate than the previous variants (*1*). During the fifth wave, numerous severe COVID-19-related deaths were reported in Japan. The omicron variant has a lower severity rate than the delta variant (*2*). However, during the sixth wave and beyond, the number of deaths due to mild-to-moderate COVID-19 increased in Japan.

COVID-19 worsens complications like cardiovascular diseases, even in mild cases (*3*). In Japan, patients aged ≥ 60 years accounted for 74% of COVID-19 fatalities during the fifth wave (delta variant outbreak period). This rate increased to 95% during the sixth wave (omicron variant outbreak period), indicating that a higher proportion of older adults are affected (*4*). Nevertheless, a significant lack of understanding remains regarding the direct causes, background, and progression of COVID-19-related deaths, especially during the omicron variant outbreak.

Therefore, we conducted this retrospective observational study on patients with COVID-19 admitted to the National Center for Global Health and Medicine (NCGM) who subsequently died during both the delta and omicron variant outbreaks to elucidate the clinical

course and causes of death.

Patients and Methods

Age, sex, preexisting comorbidities, activities of daily living (ADL) status before hospitalization, COVID-19 vaccination history, complications during hospitalization, cause of death categorized according to the International Statistical Classification of Disease and Related Health Problems (ICD-10), and clinical course were compared and described for patients admitted to the NCGM during the delta (July 2021–September 2021) and omicron variant outbreak (December 2021–August 2022) periods, who were diagnosed with SARS-CoV-2 infection based on positive microbiological testing and subsequently died during hospitalization.

Additionally, we classified the causes of death into three groups: *i*) respiratory failure due to pneumonia, *ii*) exacerbation of preexisting comorbidities before hospitalization, and *iii*) complications that occurred during hospitalization. Clinical course descriptions of 5 representative cases are provided.

This study was reviewed and approved by the Ethics Committee of the Center Hospital of the National Center for Global Health and Medicine (NCGM-S-004634-00) on the condition that a document that declares an opt-out policy by which any patient and/or relatives could refuse to be included in this study was uploaded on the web page of the Center Hospital of the NCGM. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Among the patients with COVID-19 admitted during the delta and omicron variant outbreaks, 20 and 24 died during hospitalization, respectively. The median age (interquartile range) was 63.0 years (55.3–78.0) and 74.5 years (68.3–85.3), with 9 (45%) and 18 (75%) being males, respectively. Regarding COVID-19 vaccination history during the delta variant outbreak, 1 patient (5%) had received 2 doses, 2 patients (10%) had received 1 dose, 13 patients (65%) had no vaccination history, and 4 patients (20%) had unknown vaccination histories (Table 1). During the omicron variant outbreak, 4 patients (17%) had received 3 doses, 6 patients (25%) had received two doses, 8 patients (33%) had no vaccination history, and 6 patients (25%) had unknown vaccination histories.

During the delta variant outbreak, cause *i*) respiratory failure due to pneumoniae accounted for the death of 16 patients (80%), cause *ii*) exacerbation of preexisting comorbidities before hospitalization for the death of 3 patients (15%), and cause *iii*) complications that occurred during hospitalization for the death of 1 patient (5%). However, during the omicron variant outbreak, cause *i*) respiratory failure due to pneumoniae accounted for the death of 7 patients (29%), *ii*) exacerbation of preexisting complications for 11 patients (46%), and *iii*) complications during hospitalization for 6 patients (25%). Out of the 16 patients who died due to respiratory failure due to pneumonia during the delta variant outbreak and 7 patients during the omicron variant outbreak, chest computed tomography (CT) scans performed at the end of hospitalization revealed lesions primarily centered around the bronchi and its surroundings in 1 (6%) and 4 patients (57%) in the delta variant outbreak group. Meanwhile, lesions primarily centered around the lung interstitium were observed in 15 (94%) and 3 (43%) patients, respectively.

In addition to this classification of causes of death, we summarized the age, sex, underlying comorbidities, pre-hospitalization ADL, COVID-19 vaccination history, complications that occurred during hospitalization, and statistical classification of diseases, disabilities, and causes of death (ICD-10) for each patient in Table 1 and Table 2. In total, 5 representative cases were selected from the 3 causes of death groups, and their clinical courses are described below.

Case 1: Respiratory failure due to pneumonia (COVID-19 pneumonia)

A male in his 80s with a medical history of myocardial infarction treated with percutaneous coronary intervention, type 2 diabetes, and hypertension had trouble moving while in his home bathtub and was urgently transported to the hospital. The patient did not receive the COVID-19 vaccine. Upon initial assessment, he exhibited poor oxygenation. Treatment was initiated with high-flow nasal cannula therapy, 2 mg/kg methylprednisolone (no remdesivir was administered due to hepatic and renal dysfunction), heparin, and antibiotics. On the third day in hospital, his respiratory condition worsened, necessitating noninvasive positive pressure ventilation (NPPV) and the initiation of tocilizumab therapy. Despite receiving pulse therapy with methylprednisolone at a dose of 250 mg starting on the 11th day, the patient's symptoms did not improve, leading to the worsening of respiratory failure on the 33rd day after death.

Case 2: Respiratory failure due to pneumonia (aspiration pneumonia)

A male in his 90s had a history of pulmonary emphysema, right leg block, and disuse syndrome. While attending the day-care facility, the patient contracted COVID-19 and was admitted on the fourth day of illness with a diagnosis of severe COVID-19. Treatment was initiated with remdesivir, dexamethasone, and heparin. Due to difficulty with oral intake, the patient experienced recurrent episodes of aspiration pneumonia after admission. Intravenous fluid therapy was maintained, but

Table 1. Primary causes of death in patients with COVID-19 admitted during the delta variant outbreak, characteristics, preexisting comorbidities, and complications during hospitalization (*n* = 20)

Cause of death	Age (years)	Sex	Number of vaccinations	ICD-10	Preexisting ADL	Preexisting comorbidities	Oxygen therapy	Complications during hospitalization
i) Pneumonia (*n* = 16)	20s	F	None	Respiratory infections	Independent	Hypertension, diabetes, obesity	ECMO	Progression of respiratory failure due to pneumonia
	30s	M	None	Respiratory infections	Independent	Obesity	Mechanical ventilation	Progression of respiratory failure due to pneumonia, emphysema, and pneumothorax
	50s	M	None	Respiratory infections	Independent	Myocardial infarction, diabetes, obesity	Mechanical ventilation	Progression of respiratory failure due to pneumonia
	50s	M	None	Respiratory infections	Independent	Rheumatoid arthritis, hypertension, diabetes, obesity	Mechanical ventilation	Progression of respiratory failure due to pneumonia
	50s	M	None	Respiratory infections	Independent	None	Mechanical ventilation	Progression of respiratory failure due to pneumonia
	50s	F	None	Respiratory infections	Independent	Diabetes, schizophrenia	Mechanical ventilation	Progression of respiratory failure due to pneumonia, *Pseudomonas aeruginosa* bacteremia
	60s	M	None	Respiratory infections	Independent	Nephritis in childhood	Mechanical ventilation	Respiratory failure progression due to pneumonia, pneumothorax, pyothorax, multiple organ failure
	60s	F	None	Respiratory infections	Independent	Diabetes, obesity	Mechanical ventilation	Respiratory failure progression due to pneumonia, mediastinum emphysema
	70s	M	None	Respiratory infections	Independent	Hypertension, atrial fibrillation, bronchial asthma	NPPV (No intubation request)	Respiratory failure progression due to pneumonia, atrial fibrillation, cerebral infarction, splenic infarction, gastrointestinal bleeding (under heparin use
	70s	M	2	Respiratory infections	Independent	Lymphoma, prostate cancer, hypertension	Mechanical ventilation	Respiratory failure progression due to pneumonia, suspected aspiration, pneumothorax
	70s	F	None	Respiratory infections	No record	None	NPPV (There was no key person, and due to the lack of expected improvement, intubation was not performed.)	Progression of respiratory failure due to pneumonia
	70s	F	None	Respiratory infections	Independent	Hypertension, hyperlipidemia, osteoporosis	HFNC (No intubation request)	Progression of respiratory failure due to pneumonia
	70s	F	None	Respiratory infections	Independent	Hypertension, HCV hepatitis	NPPV (No intubation request)	Progression of respiratory failure due to pneumonia
	70s	F	None	Respiratory infections	No record	None	NPPV	Respiratory failure progression due to pneumonia, malignant genital bleeding (under heparin use)
	70s	F	None	Respiratory infections	Daily support by helpers	SLE, Sjögren's syndrome, atrioventricular block	Mask	Aspiration pneumonia, pyelonephritis
	90s	M	1	Respiratory infections	Independent	After cholecystectomy	Reservoir mask (No intubation request)	Progression of respiratory failure due to pneumonia

Abbreviations: ADL, Activities of daily living. SLE, Systemic lupus erythematosus. ECMO, Extracorporeal membrane oxygenation. NPPV, Non-invasive positive pressure ventilation. HFNC, High-flow nasal cannula.

Table 1. Primary causes of death in patients with COVID-19 admitted during the delta variant outbreak, characteristics, preexisting comorbidities, and complications during hospitalization (*n* = 20) (continued)

Cause of death	Age (years)	Sex	Number of vaccinations	ICD-10	Preexisting ADL	Preexisting comorbidities	Oxygen therapy	Complications during hospitalization
ii) Preexisting comorbidities (*n* = 3)	30s	M	Unknown	Others	Independent	Acute traumatic subdural hematoma, cervical spine fracture (at the time of admission)	None (incubation only)	–
	50s	F	1	Respiratory failure	No record	Alcoholic cirrhosis (Child-Pugh C), esophageal varicose vein rupture, obesity	NPPV	Hypovolemic shock due to low albumin
	80s	F	Unknown	Cardiovascular diseases	Walk with a cane, eat without assistance	Rheumatoid arthritis, hypertension, acute myocardial infarction (at the time of admission)	None	–
iii) Complications during hospitalization (*n* = 1)	50s	F	None	Others	Independent	None	ECMO	Respiratory failure progression due to pneumonia, cerebral hemorrhage (under ECMO)

Abbreviations: ADL, Activities of daily living. SLE, Systemic lupus erythematosus. ECMO, Extracorporeal membrane oxygenation. NPPV, Non-invasive positive pressure ventilation. HFNC, High-flow nasal cannula.

the patient died on the 26th day due to respiratory failure caused by aspiration pneumonia.

Case 3: Exacerbation of preadmission complications

A woman in her 80s presented with severe valvular heart disease, chronic heart failure, and a history of stroke. The patient had received 3 doses of the COVID-19 vaccine. The patient was transported to our facility because of respiratory distress and was diagnosed with worsening chronic heart failure caused by severe valvular heart disease. Upon admission, the patient tested positive for SARS-CoV-2 by polymerase chain reaction. Respiratory failure, believed to be associated with heart failure, progressed, and the patient died on the fourth day of illness.

Case 4: Exacerbation of preadmission complications

A man in his 60s with stage 4 advanced small cell lung cancer received supportive care. He called for emergency assistance because of respiratory distress and was hospitalized. Although the patient had planned to be transferred to a hospice, on the 6th day of illness the patient came in close contact with a patient with COVID-19, and on the 7th day, the patient was diagnosed as an asymptomatic carrier of SARS-CoV-2. The patient was treated with a 3-day course of remdesivir to prevent severe disease progression. The patient experienced severe cancer-related pain, nausea, and fatigue, and sedation was initiated on the 8th day. The patient died on the 11th day.

Case 5: Complications during hospitalization

The patient was a male in his 80s with a history of hypertension, atrial fibrillation, and chronic obstructive pulmonary disease. The patient had received 2 doses of the COVID-19 vaccine. The patient developed a fever and cough, which led to hospital admission on the fourth day of illness with a diagnosis of moderate COVID-19 and chronic interstitial pneumonia. Remdesivir and antibiotics were administered. The following day, the patient required supplemental oxygen, and methylprednisolone treatment (250 mg) was initiated. However, pneumonia worsened, and pulse therapy with 1 g methylprednisolone and various immunosuppressive agents (cyclophosphamide, bortezomib, and tacrolimus) were administered sequentially. On the 11th day of illness, the patient developed heart failure, which improved with the initiation of diuretics and NPPV. On the 24th day, the patient was diagnosed with acute exacerbation of heart failure and hypotension with ST-elevation myocardial infarction. Due to respiratory distress, coronary artery catheterization was not performed, and the patient died on the 26th day due to worsening heart failure.

Table 2. Primary causes of death in patients with COVID-19 admitted during the omicron variant outbreak, characteristics, preexisting comorbidities, and complications during hospitalization (*n* = 24)

Cause of death	Age (years)	Sex	Number of vaccinations	ICD-10	Preexisting ADL	Preexisting comorbidities	Oxygen therapy	Complications during hospitalization
i) Pneumonia (*n* = 7)	60s	M	2	Respiratory infections	Independent	Hypertension, chronic kidney disease	NPPV	Pneumothorax, mediastinal emphysema
	70s	M	2	Respiratory infections	Independent	Diabetes, lung squamous cell carcinoma, MPA, chronic kidney disease	HFNC	Aspiration pneumonia, *Pseudomonas aeruginosa* pneumonia, acute myocardial infarction
	80s	F	Unknown	Respiratory infections	Requiring long-term care level 3*, walk with supervision	Rheumatoid arthritis, Parkinson's disease, after heart valve replacement	NPPV	Aspiration pneumonia, pulmonary pyogenic disease
	80s	M	None	Respiratory infections	Independent	Hypertension, diabetes, myocardial infarction, dyslipidemia	NPPV	Disseminated intravascular coagulation syndrome, multiple organ failure
	80s	M	Unknown	Respiratory infections	Needs long-term care level 4, requiring partial assistance with bathing and dressing	Normal pressure hydrocephalus, postoperative bladder cancer, angina pectoris, dementia	HFNC	Aspiration pneumonia
	90s	M	None	Respiratory infections	Cognitive impairment, requiring long-term care level 2	Emphysema, right bundle branch block	Reservoir mask	Aspiration pneumonia
	90s	M	2	Respiratory infections	Walking with assistance, requiring long-term care level 2	Hypertension, cerebral infarction, chronic kidney disease	Nasal cannula	Aspiration pneumonia
ii) Preexisting comorbidities (*n* = 11)	40s	M	Unknown	Others	Unknown	Alcoholic cirrhosis	None	Rupture of varicose vein in colon
	50s	M	3	Cardiovascular diseases	Independent	Sarcoidosis, chronic kidney disease	HFNC	Exacerbation of heart failure
	50s	M	None	Others	Independent	Polycystic Kidney, chronic kidney disease	None	MSSA bacteremia, uremia
	60s	M	Unknown	Malignant neoplasms	Requiring long-term care level 3	HIV infection, multiple metastases of gastric cancer, diabetes, hypertension	Nasal cannula	Hemorrhage from tumor, anemia
	60s	F	Unknown	Malignant neoplasms	Unknown	Multiple metastasis of rectal cancer, hypertension	None	Hemorrhage from tumor
	60s	M	None	Malignant neoplasms	Unknown	Multiple metastases of small cell lung cancer, hypertension	None	
	70s	M	Unknown	Malignant neoplasms	Unknown	Multiple metastases of liver cancer, heart failure	Nasal cannula	Exacerbation of heart failure

Table 2. Primary causes of death in patients with COVID-19 admitted during the omicron variant outbreak, characteristics, preexisting comorbidities, and complications during hospitalization (*n* = 24) (continued)

Cause of death	Age (years)	Sex	Number of vaccinations	ICD-10	Preexisting ADL	Preexisting comorbidities	Oxygen therapy	Complications during hospitalization
	70s	M	None	Malignant neoplasms	Independent	Transverse colon cancer multiple metastases, Bowel obstruction, Obesity	Nasal cannula	Transverse colon ileus, multiorgan failure
	70s	F	3	Others	Independent	Diabetes, extensive cerebral infarction	Nasal cannula	Brain herniation
	80s	F	3	Cardiovascular diseases	Independent	Valvular disease, heart failure, cerebral infarction	NPPV	Exacerbation of heart failure
iii) Complications during hospitalization (*n* = 6)	90s	F	3	Cardiovascular diseases	Requiring long-term care level 4, Walking only indoors with assistance	Valvular disease, heart failure, chronic kidney disease, hypertension	None	Acute pyelonephritis, exacerbation of heart failure, renal failure
	60s	M	2	Others	Independent	Obesity, hypertension	NPPV	Iliopsoas hematoma, hemorrhagic shock, acute renal failure
	60s	M	2	Cardiovascular diseases	Independent	Esophageal cancer, hypertension, transient ischemic attack	None	Aortic rupture
	70s	M	None	Others	Independent	Interstitial pneumonia, thymoma	Mechanical ventilation	Intracranial hemorrhage
	70s	M	None	Respiratory infections	Independent	Hypertension, diabetes	Mechanical ventilation	Bacteremia, septic shock, acute respiratory distress syndrome, acute renal dysfunction, ventilator-associated pneumonia
	80s	M	2	Cardiovascular diseases	Requiring long-term care level 2, requires partial assistance with excretion	Interstitial pneumonia, chronic obstructive pulmonary disease, atrial fibrillation, hypertension	NPPV	Acute myocardial infarction
	90s	F	None	Others	Requiring long-term care level 5, use a wheelchair	Polymyalgia rheumatoid arthritis, bullous pemphigoid, cerebral infarction	Reservoir mask	Bacteremia, pyelonephritis, bacterial pneumonia, pneumothorax, bleeding from gastric and duodenal ulcers

Abbreviations: ADL, Activities of daily living. MPA, microscopic polyangiitis. NPPV, Non-invasive positive pressure ventilation. HFNC, High-flow nasal cannula. MSSA, Methicillin-Susceptible Staphylococcus Aureus.
*Types of long-term care: Care Level 1: A person faces difficulty in performing essential daily life activities by himself/herself. One person's ability to handle task-based activities in daily life is lower than that of patients in the Support Required 2 category. Care Level 2: The person is in a state similar to that detailed under Care Level 1 but requires more care to be able to perform essential daily life activities. Care Level 3: Compared with the state of Care Level 2, a person's abilities to perform essential daily life activities and task-based activities were significantly lower. Consequently, they require almost constant care. Care Level 4: The person is in a state similar to that detailed in Care Level 3, but his/her ability to act is lower. As a result, they face difficulties in living without constant care. Care Level 5: The person's ability to act is even lower than that of patients in the Care Level 4 category. Consequently, they require constant care.

Discussion

In addition to describing the clinical course of the disease in patients, the cases were classified into three groups based on the primary cause of death: *i*) pneumonia (including COVID-19 pneumonia and aspiration pneumonia), *ii*) exacerbation of preadmission complications, and *iii*) complications that occurred during hospitalization.

Deaths due to pneumonia

In total, 16/20 patients (80%) who died during the delta variant epidemic and 7/24 patients (29%) who died during the omicron outbreak died of pneumonia. The pneumonia group was broadly divided into patients with lesions mainly in the bronchi and surrounding areas and those with lesions mainly in the pulmonary interstitium. In typical viral pneumonia caused by SARS-CoV-2 infection, lesions in the pulmonary interstitium are observed on chest CT scans (*5*). In contrast, in cases where lesions were found in the bronchi and peribronchial centers, the patient likely developed pneumonia secondary to the SARS-CoV-2 infection. The impact of aspiration should also be considered based on the patient's age, ADL, and underlying diseases.

Moreover, 15/20 patients who died during the delta variant epidemic had lesions mainly in the pulmonary interstitium, suggesting that most patients during the delta variant epidemic died due to the progression of viral pneumonia caused by SARS-CoV-2 infection. In animal models, the omicron variant (B.1.1.529) was reported to have similar nasal growth potential as the delta variant (B.1.617.2) but lower growth potential and pathogenicity in the lungs (*6*). In addition, omicron variants replicate rapidly in human airway models and ex vivo cultures of human bronchioles. However, their replication efficiency is reduced in human alveolar models and ex vivo cultures of human lungs (*7*). These findings indicate that omicron variants tend to infect the upper respiratory tract rather than the lungs, which is consistent with the results of previous studies.

Death due to factors other than pneumonia

During the delta epidemic, 4/ 20 patients died from causes other than pneumonia, and during the omicron epidemic, 17/24 patients died from complications before or during hospitalization. In both groups, the deterioration of the general condition due to the SARS-CoV-2 infection may have affected the disease course.

Deaths due to preexisting comorbidities

Among the patients who died from causes other than pneumonia during the omicron variant outbreak, 11 patients (46%) died due to the exacerbation of preexisting comorbidities, representing the highest proportion. These cases involved patients infected with SARS-CoV-2 with severe underlying conditions. The breakdown of these comorbidities included 4 cases of heart failure, 4 cases of malignancy, 1 case of hepatic dysfunction, 1 case of renal dysfunction, and 1 case of extensive cerebral infarction. Worsening underlying conditions, such as cancer and cardiovascular diseases, were considered the primary cause of death. Three deaths were attributed to preexisting comorbidities during the delta variant outbreak: traumatic subdural hematoma, decompensated liver cirrhosis, and acute myocardial infarction.

From the early stages of COVID-19 to the delta variant outbreak, pneumonia accounted for most deaths, necessitating the establishment of facilities capable of managing patients with severe respiratory failure. However, during the omicron variant outbreak, infection control measures must be prioritized for patients with preexisting comorbidities who are at high risk of approaching the end of life before hospital admission.

Deaths due to complications during hospitalization

Factors other than preexisting comorbidities, such as infections, bleeding, and cardiovascular diseases, are the main causes of death among the complications that occur during hospitalization. During the delta variant outbreak, 1 patient died from complications that emerged during hospitalization, and during the omicron variant outbreak, 6 patients died.

Out of the 6 patients who died from complications during the omicron variant outbreak, 4 succumbed to cardiovascular events. The causes of death were hemorrhagic shock due to iliopsoas hematoma, cerebral hemorrhage, aortic dissection, and acute myocardial infarction. The remaining 2 patients died from acute respiratory distress syndrome and septicemia caused by pyelonephritis. Out of these 6 patients, 4 were completely independent in ADL before admission, and 1 required only mild support. No in-hospital deaths were anticipated during admission.

During the omicron variant outbreak, patients with COVID-19 admitted to the hospital who subsequently died showed a notable prevalence of cardiovascular diseases. From a wider standpoint, excess mortality from cardiovascular diseases has been reported domestically and internationally. Nishiura *et al*. (*8*) predicted a significant increase in selective deaths attributed to cardiovascular diseases and senility in Japan during the 2022 fiscal year. Nomura *et al*. (*9*) reported excess mortality due to cardiovascular diseases, respiratory diseases, malignancies, and senility in 2021. Globally, previous reports have indicated a higher incidence of cardiovascular complications in patients with COVID-19 (*10*).

COVID-19 is associated with an increased risk of cardiovascular diseases, potentially leading to

myocarditis, acute coronary syndrome, atherosclerosis, heart failure, thromboembolic events, and arrhythmias. The acute phase of COVID-19 and its long-term effects after acute infection may contribute to increased hospitalization and mortality rates in patients with cardiovascular diseases (*11*). A meta-analysis of 17 cohort studies involving 5815 patients showed that the most common cardiovascular complications are heart failure, myocardial injury, arrhythmias, and acute coronary syndromes (*12*). Even in mild cases, an increased risk of cardiovascular diseases for up to 1 year has been reported, with higher rates of heart failure and stroke (*3*).

The findings of this study corroborate those of previous studies from a broader perspective, indicating the prevalence of cardiovascular complications in COVID-19 cases. However, many aspects of COVID-19 pathogenesis remain unclear. Therefore, data that can contribute to our understanding of the disease and excess mortality can be obtained by collecting epidemiological data on the causes of death, including events with unclear associations with COVID-19. Consequently, starting from April 2023, Japan has revised the case reporting form for COVID-19 Registry Japan (COVIREGI-JP) to collect detailed information on patients who have succumbed to COVID-19, aiming to gather comprehensive data.

In addition to the direct impact on organs caused by COVID-19 infection, observations have pointed to secondary changes, including disruptions in healthcare access due to medical system breakdown and lifestyle alterations, as contributing factors. Brant *et al*. (*13*) reported changes in cardiovascular disease mortality rates in 6 major cities in Brazil. Mortality rates varied, ranging from +46.1% (Manaus) to -7.1% (Rio de Janeiro), with more pronounced effects observed in areas where the healthcare system serving the most socioeconomically disadvantaged populations collapsed. In Brazil's most affected northern region, Jardim *et al*. (*14*) estimated a 2.5-fold excess mortality increase in cardiovascular disease-related mortality in 2020. Several other studies have suggested that barriers to healthcare access contribute to increased cardiovascular diseases (*15, 16*).

Reports on the strain on Japanese medical infrastructure up until the delta variant surge and the fourth wave indicated no overwhelming numbers of COVID-19 cases beyond the capacity of acceptance and no depletion of medical equipment such as ventilators. Thus, it was inferred that the Infection control team capacity was not exceeded. However, during the fourth wave, there were indications of excess mortality for the first time, suggesting a potential reflection of strain on medical institutions. Whether appropriate access to medical facilities is sufficient during the peak of infection spread remains unclear. During the fifth and sixth waves, an increase in difficult cases of emergency transport was noted alongside a rise in the number of infected patients, pointing to the possibility of strain on medical infrastructure (*17*).

The limitations of this study were as follows. The analysis was limited to hospitalized patients from a single facility in Japan, making it difficult to directly extrapolate the results to the causes and backgrounds of COVID-19-related deaths in all patients. As we did not observe the causes and backgrounds of the patients who received at-home treatment, their characteristics may differ from those of hospitalized patients. Therefore, we plan to conduct future observational studies involving multiple facilities. Additionally, we did not conduct a comparison with surviving patients, and the causal relationship between patient background and cause of death remains unclear. Furthermore, as the period following the omicron variant outbreak is expected to show continued circulation of different variants, the trends observed in this study may change under the influence of different variants.

In conclusion, from the early stages of COVID-19 to the delta variant outbreak, numerous cases of severe respiratory failure caused by the typical SARS-CoV-2 infection leading to viral pneumonia were reported. Establishing medical systems capable of treating patients with severe respiratory failure was crucial during this period. However, during the omicron variant outbreak, approximately two-thirds of the deceased patients at our hospital had non-pneumonia-related conditions as the primary cause of death, exhibiting a different clinical profile compared with the delta variant cases.

Moving forward, we aim to adapt our medical systems by considering these changing patient profiles and continue to collect data at the macro level. We hope that this study, which observed changes in the number of deceased patients between delta and omicron variant outbreaks, will be the starting point for further understanding of the pathogenesis of the disease.

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