Clinical Characteristics of COVID-19 in Nagano Prefecture : An Epidemiological Survey Including Data from Wave 1 to Wave 4

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Purpose : This study aimed to evaluate the clinical characteristics of patients with coronavirus disease 2019 (COVID-19) hospitalized in the Nagano Prefecture during Waves 1-4 of the COVID-19 pandemic and identify the factors strongly associated with the duration of hospitalization and mortality using data from a database comprising hospital discharge summaries.

Methods : In this retrospective study, we reviewed the database of Infection control measures department, Nagano Prefectural Government, utilizing medical records from 2,521 COVID-19 patients hospitalized during waves 1 and 4 (peaks in early April 2020 and May 2021). Risk factors for prolonged hospitalization and mortality risk were analysed using multivariate logistic regression.

Results : The data of 76, 259, 1137, and 1049 patients hospitalized during Waves 1, 2, 3, and 4, respectively, were analyzed. The average age of the patients who died of COVID-19 was 86 years, with males accounting for the majority of cases. Old age, male sex, smoking history, and the presence of chronic heart failure (CHF) and chronic kidney disease (CKD) were associated with prolonged hospitalization. Old age and the presence of CKD showed significant associations with mortality.

Conclusions : Patients with risk factors were older and had a prolonged duration of hospitalization, indicating that age and CKD are independent risk factors for prolonged hospitalization and mortality in patients with COVID-19 in the Nagano Prefecture. Preventing the incidence of COVID-19 in older patients and those with impaired renal function would shorten the hospitalization duration and improve prognosis. *Shinshu Med J 73 : 25—36, 2025*

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I Introduction

The novel coronavirus disease 2019 (COVID-19) has spread rapidly worldwide since its outbreak in mid-December 2019[1]. COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2], the variants of which have caused multiple epidemics[3]. Assessing the prevalence of the epidemic in Japan in May 2023 revealed eight separate waves of outbreak. The peaks of waves 1, 2, 3, and 4 occurred in early April 2020, mid-June to early August 2020, early January 2021, and May 2021, respectively. Wave 5 revolved around delta stocks, with its zenith culminating in August 2021. The peaks of waves 6 (dominated by the Omicron strain), 7, and 8 occurred in February 2022, late July 2022, and January 2023, respectively[4)5)].

The emergence of mutant strains and recurrent outbreaks have led to changes in the clinical manifestations of COVID-19. The number of patients presenting with severe deterioration has decreased since

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the replacement of the previously prevalent strain with the omicron variant at the end of 2021. However, changes in the long-term incidence, clinical manifestations, and risk factors must be monitored owing to the high-risk nature of COVID-19. An epidemiological survey of patients hospitalized with COVID-19 in Nagano Prefecture from Waves 1-4 was conducted by the Infection Control Measures Department of the Nagano Prefectural Government. A database comprising the anonymized patient discharge summaries was created.

Several reports have emphasized the importance of the early detection of the risk factors for prolonged hospitalization, severity, and mortality in patients with COVID-19[6)-8)]. This study aimed to investigate the clinical features of the patients hospitalized with COVID-19 and those who died of the disease in Nagano Prefecture during the first four waves. Furthermore, data acquired from the database was used to identify the variables strongly correlated with mortality and duration of hospitalization. The clinical features and risk factors associated with the duration of hospitalization and mortality during Waves 1-4 of the COVID-19 pandemic in Nagano, Japan, were also investigated. Analyzing risk factors for waves 1-4 of the early COVID-19 pandemic leads to understanding what types of patients at particular risk should have received attention in terms of infection prevention in order to reduce hospital stays and deaths at a time when effective antiviral drugs did not yet exist.

Ⅱ Patients and Methods

A Data collection

Real-time reverse-transcription polymerase chain reaction assays or antigen testing of nasal or pharyngeal swab specimens were performed to confirm the diagnosis of COVID-19. The anonymized discharge summaries of patients with COVID-19 collected by the Infection Control Measures Department included the following data : age, sex, duration of hospitalization, presence of COVID-19 and secondary diseases at the time of hospitalization, severity of COVID-19 at the time of admission, maximum severity during hospitalization, outcomes cause of death, underlying diseases that may be potential risk factors for COVID-19, smoking history, symptoms, changes in the activities of daily living (ADL) before and after hospitalization, height, weight, body mass index (BMI), vital signs, blood test and imaging findings, respiratory management during hospitalization, and drug therapy. The name of the hospital where the patient was admitted and the date of admission and discharge were not disclosed to maintain anonymity. Regarding recording of background diseases, the words of background diseases were collected from each discharge summary. Each underlying disease's presence or absence was determined by conducting interviews at each medical facility.

Age, sex, smoking history, and the presence of underlying disease were considered while selecting explanatory variables for multivariate analysis as the complete data for these variables were available for all 2521 patients with no missing values. Data regarding specific details, such as the number of cigarettes smoked per day and the duration of smoking, were missing as the database only recorded whether individuals were smokers. A significant amount of data regarding blood test and imaging findings were also missing as the database was created by gathering discharge summaries from various medical institutions. Consequently, considering these findings as potential explanatory variables in multivariate analysis was not possible.

B Study participants and setting

The database comprising the epidemiological data of the patients with COVID-19 treated at medical institutions in Nagano Prefecture created by the Nagano Prefectural Infection Control Measures Department was utilized in this retrospective study. The department was in charge of the database, from which we extracted and analyzed the data we needed for our study. The data of inpatients diagnosed with COVID-19 from Waves 1-4 were included in the database. The severity of illness was classified as follows according to the guidelines for treating COVID-19 published by the Japan Ministry of Health, Labour and Welfare : mild, peripheral oxygen saturation (SpO_2) ≥96 % ; moderate, SpO_2<96 % or symptoms of dyspnea or complications of pneumonia ; and severe, admission to intensive care unit (ICU) or ventilator required[9]. It was not possible to know the number of outpatients at the time of this study because it only gathered summary data on hospitalized patients. Therefore, the percentage of hospitalized patients relative to the total number of infected individuals in Nagano Prefecture could not be determined. The public health facility or the doctor in charge decided who was eligible for hospitalization.

C Statistical analyses

Descriptive data are presented as mean ± standard deviation (SD), along with percentages for categorical data. The explanatory variables included in the multiple regression analysis of duration of hospitalization were age ; sex ; smoking history ; hypertension ; and the presence of cardiovascular disease, chronic heart failure (CHF), arrhythmia, liver disease, malignant tumors, chronic obstructive pulmonary disease (COPD), bronchial asthma, diabetes, and chronic kidney disease (CKD). The determinants of the mortality risk of COVID-19 were determined via univariate logistic regression analysis followed by multivariate analysis. Univariate logistic regression analysis revealed that seven explanatory variables exhibited significance : age, hypertension, cardiovascular disease, CHF, arrhythmia, malignancy, and CKD. The selection of these variables was confirmed to be correct based on the findings of previous studies[10)-16)]. Variables with a p value <0.05 in the univariate analyses were considered for inclusion in the multivariate model. Regarding therapeutic drugs, including antiviral drugs and steroids, only the use or non-use was recorded in the database ; no information on specific dosage and administration was obtained, so they were not selected as items for multivariate analysis. Blood test and imaging findings could not be used as potential explanatory variables in the multivariate analysis owing to a large amount of data being missing. Statistical significance was set at $p<0.05$ using statistical software R (version 4.0.3 for Windows 64-bit ; http://www.r-project.org). **Fig. 1** was plotted using a software R package named “palmerpenguins”. We found that there was little patient data from the wave 1 and wave 2, making it challenging to do analysis by epidemic period. Instead, we used combined data from waves 1 through 4 to assess mortality and lengths of hospital admissions.

D Ethical considerations

This study was approved by the Institutional Review Board of the Shinshu University School of Medicine (approval number 5393, December 28, 2021). The requirement for obtaining written informed consent was waived owing to the use of de-identified retrospective data.

Ⅲ Results

A Patients

The anonymized discharge summary data of 2,521 patients with COVID-19 were available in the database. The number of patients per outbreak was as follows : Wave 1, 76 ; Wave 2, 259 ; Wave 3, 1137 ; and Wave 4, 1049 **(Table 1)**. The mean age of the patients was as follows : Wave 1, 44.5 (±18.6) ; Wave 2, 41.9 (±20.3) ; Wave 3, 56.9 (±19.8) ; and Wave 4, 58.2 (±20.4). The average duration of hospitalization was as follows : Wave 1, 24.8 days ; Wave 2, 11.6 days ; Wave 3, 11.8 days ; and Wave 4, 12.7 days. During Waves 1-4, the severity of disease was mild, moderate, and severe in 1224 (48.6 %), 1239 (49.1 %), and 57 (2.3 %) patients, respectively. The number of severe cases of COVID-19 at the time of hospitalization during each wave was as follows : Wave 1, five (6.6 %) ; Wave 2, two (0.8 %) ; Wave 3, 29 (2.6 %) ; and Wave 4, 21 (2.0 %). The prevalence of hypertension and diabetes was >10 % during Waves 1-4, with hypertension and diabetes affecting 465 (18.4 %) and 257 (10.2 %) patients, respectively.

B Relationship between the duration of hospitalization and age

Fig. 1 presents the relationship of the duration of hospitalization and age with the severity **(Fig. 1A)**, outcome **(Fig. 1B)**, distribution by wave **(Fig. 1C)**, and patients with ≥1 risk factors **(Fig. 1D)** in Waves 1-4. Patients diagnosed with moderate disease at the time of admission were primarily middle-aged and older adults **(Fig. 1A)**, whereas those diagnosed with severe diseases were older. In terms of outcomes during Waves 1-4, 2,353 (93.3 %) patients recovered, 28 (1.1 %) patients were transferred to tertiary emergency

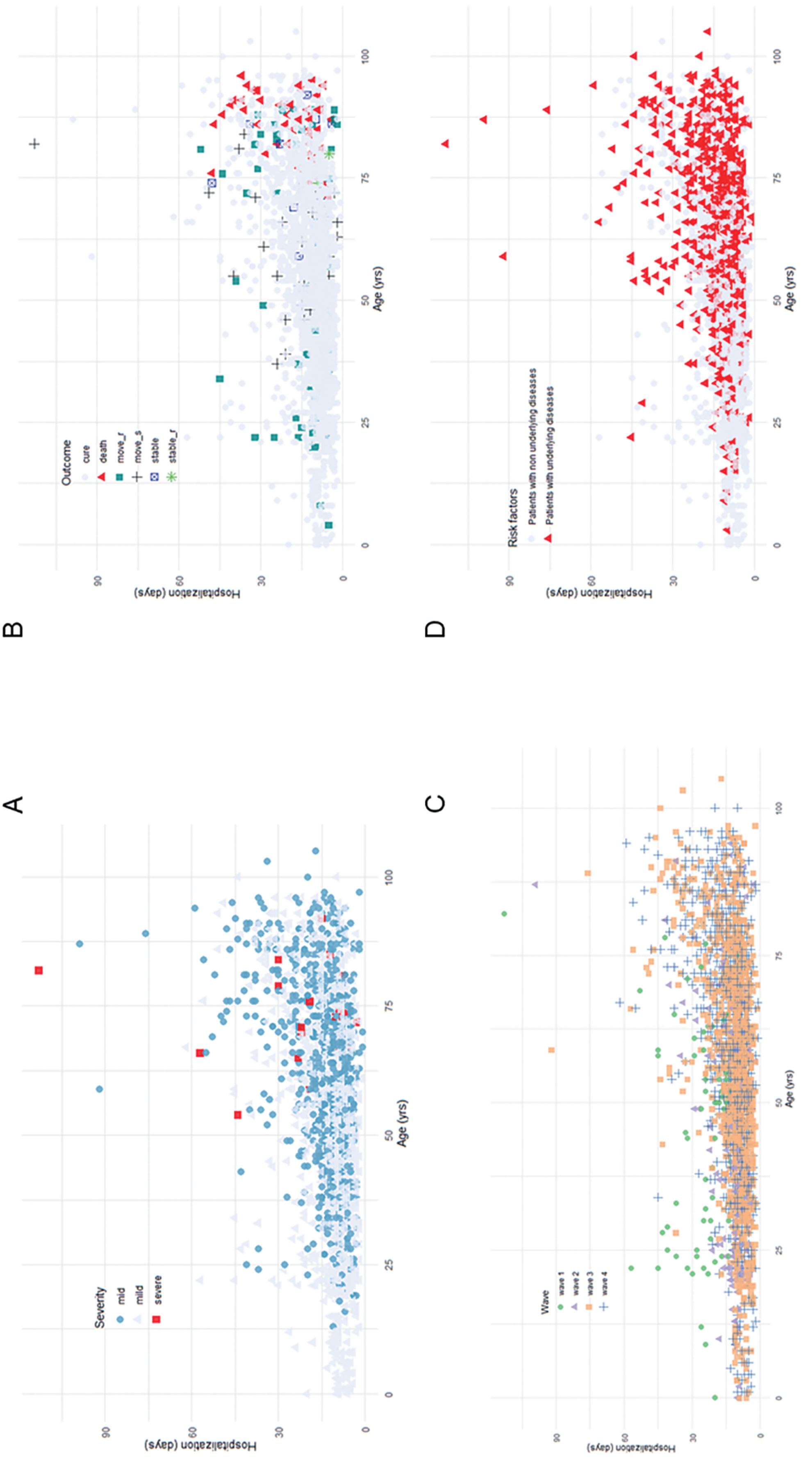
A
Severity
mid
mild
severe
Hospitalization (days)
Age (yrs)
B
Outcome
cure
death
move_r
move_s
stable
stable_r
C
Wave
wave 1
wave 2
wave 3
wave 4
D
Risk factors
Patients with non underlying diseases
Patients with underlying diseases

Fig. 1

Fig. 1 Fig. 1 depicts the visual distribution of the severity and outcome of the patients hospitalized with coronavirus disease 2019 (COVID-19) during Waves 1-4, and underlying diseases.
Fig. 1A displays the severity of COVID-19 hospitalizations from Waves 1-4. From a graphical point of view, individuals with moderate symptoms, depicted in dark blue color, are more evenly spread across the categories of middle-aged and older individuals compared with individuals with mild symptoms, depicted in light blue color. Patients with severe symptoms were typically older than 50 years.
Fig. 1B illustrates the patient outcomes. The light blue circles indicate patients successfully recovered and were discharged from the hospital. The red triangles represent the deceased patients. The crosses represent patients who deteriorated and were transferred to another medical facility. The green squares represent patients whose condition stabilized. The blue squares patients transferred to the hospital for rehabilitation. The yellow-green asterisks represent patients who required continued hospitalization even after being cured from COVID-19. The patients requiring transfer were distributed across various age groups, ranging from young to older adults, and had been hospitalized for＞2 weeks.
Fig. 1C presents the patients in each wave using different symbols : Wave 1, green circle ; Wave 2, purple triangle ; Wave 3, green square ; and Wave 4, blue cross. Observing the patients in Wave 1 (depicted as green circles) revealed that a significant number of individuals were admitted to the hospital for ＞14 days. This encompassed a wide age range, ranging from young to older patients.
The red triangles in Fig. 1D represent patients with ≥1 underlying diseases. Visually, the patients with underlying diseases are predominantly individuals aged ≥50 years, and a significant number of patients with exceptionally extended hospital stays have underlying diseases.

medical facilities owing to severe illness, 90 (3.6 %) patients were transferred for rehabilitation, and 50 (2.0 %) patients died **(Table 1)**. Although the majority of patients who died were older adults, the patients transferred for rehabilitation were distributed across all age groups **(Fig. 1B)**.

Fig. 1C presents the correlation between age and the duration of hospitalization for each wave. Among young patients, the patients diagnosed with COVID-19 during Wave 1 (green circle) included those hospitalized for＞1 month. Older patients were hospitalized for extended periods during waves 2-4. **Fig. 1D** presents the relationship between the duration of hospitalization and age among patients with ≥1 underlying diseases (red triangles), indicating that patients hospitalized for＞1 month had some risk factors.

C Comparison between the patients who died during waves 3 and 4

Table 2 provides a concise summary of the clinical characteristics of the patients who died during waves 3 and 4. The number of deaths during each wave was as follows : Wave 1, one ; Wave 2, zero ; Wave 3, 30 ; and Wave 4, 19. Nineteen (63.3 %) and 11 (36.7 %) of the patients who died during Wave 3 were males and females, respectively. Twelve (63.2 %) and seven (36.8 %) of the patients who died during Wave 4 were males and females, respectively. The severity of disease at the time of admission was moderate in 25 (83.3 %) and 15 (78.9 %) cases during waves 3 and 4, respectively. The use of favipiravir, initially anticipated to be efficacious against COVID-19, among the deceased patients declined from Waves 1-4 ; in contrast, the use of remdesivir increased. Furthermore, steroids were administered more frequently than antiviral drugs, with 21 (70.0 %) and 12 (63.2 %) patients receiving dexamethasone during Waves 3 and 4, respectively.

D Analysis of the variables affecting the duration of hospitalization

Multiple regression analysis performed using age, sex, smoking, and underlying disease as explanatory variables revealed that the duration of hospitalization was associated with age ; sex ; smoking history ; and the presence of CHF, COPD, and CKD **(Table 3)**.

E Mortality risk factors for patients with COVID-19

Table 4 summarizes the results of the univariate and multivariate logistic regression analyses of the risk factors for mortality in patients with COVID-19, including underlying diseases, smoking status, age, and sex. Univariate analysis revealed that older age and the presence of hypertension, cardiovascular disease, CHF, arrhythmia, malignancy, and CKD showed significant associations with mortality. Multivariate

Table 1　Demographic and clinical characteristics of the patients according to the waves of the COVID-19 pandemic

Demographics	All patients (n＝2521)	Wave 1 (n＝76)	Wave 2 (n＝259)	Wave 3 (n＝1137)	Wave 4 (n＝1049)
Age (year), mean (SD)	55.5 (20.7)	44.5 (18.6)	41.9 (20.3)	56.9 (19.8)	58.2 (20.4)
≧65 years, n (%)	892 (35.4%)	11 (14.5%)	37 (14.3%)	429 (37.7%)	415 (39.6%)
Male, n (%)	1353 (53.7%)	44 (57.9%)	140(54.1%)	576 (50.7%)	593 (56.5%)
Female, n (%)	1168 (46.3%)	32 (42.1%)	119 (45.9%)	561 (49.3%)	456 (43.5%)
Smoking experience, n (%)	406 (16.1%)	14 (18.4%)	59 (22.0%)	179 (15.7%)	154 (14.7%)
Duration of hospitalization (day), mean (SD)	12.6 (8.8)	24.8 (14.9)	11.6 (8.1)	11.8 (8.3)	12.7 (8.2)
Underlying diseases					
Hypertension, n (%)	465 (18.4%)	10 (13.2%)	31 (12.0%)	241 (21.2%)	183 (17.4%)
Cardiovascular disease, n (%)	84 (3.3%)	3 (4.0%)	5 (1.9%)	41 (3.6%)	35 (3.4%)
CHF, n (%)	84 (3.3%)	84 (3.3%)	84 (3.3%)	84 (3.3%)	84 (3.3%)
Arrhythmia, n (%)	47 (1.9%)	2 (2.6%)	5 (1.9%)	20 (1.8%)	20 (1.9%)
Liver disease, n (%)	49 (1.9%)	1 (1.3%)	11 (4.2%)	16 (1.4%)	21 (2.0%)
Malignancy, n (%)	94 (3.7%)	5 (6.6%)	8 (3.1%)	44 (3.9%)	37 (3.6%)
COPD, n (%)	21 (0.8%)	0 (0.0%)	1 (0.4%)	12 (1.1%)	37 (3.5%)
Asthma, n (%)	88 (3.5%)	1 (1.3%)	10 (3.9%)	46 (4.0%)	31 (3.0%)
Diabetes, n (%)	257 (10.2%)	10 (13.2%)	24 (9.3%)	122 (10.7%)	101 (9.7%)
CKD, n (%)	36 (1.4%)	1 (1.3%)	5 (1.9%)	19 (1.7%)	11 (1.0%)
Severity (At the time of hospitalization)					
Mild, n (%)	1224 (48.6%)	41 (53.9%)	191 (73.7%)	551 (48.5%)	441 (42.0%)
Moderate, n (%)	1239 (49.1%)	30 (39.5%)	66 (25.5%)	557 (49.0%)	587 (56.0%)
Severe, n (%)	57 (2.3%)	5 (6.6%)	2 (0.8%)	29 (2.6%)	21 (2.0%)
Outcome					
Discharge, n (%)	2353 (93.3%)	65 (85.5%)	238 (91.9%)	1048 (92.2%)	1002 (95.5%)
Hospital transfer (due to severe status), n (%)	28 (1.1%)	7 (9.2%)	6 (2.3%)	8 (0.7%)	7 (0.7%)
Hospital transfer (for rehabilitation) , n (%)	90 (3.6%)	4 (5.3%)	14 (5.4%)	51 (4.5%)	21 (2.0%)
Death, n (%)	50 (2.0%)	0 (0.0%)	1 (0.4%)	30 (2.6%)	19 (1.8%)
Treatment					
Favipiravir, n (%)	429 (17.0%)	35 (46.1%)	57 (22.0%)	248 (21.8%)	89 (8.5%)
Remdesivir, n (%)	205 (8.1%)	0 (0.0%)	10 (3.9%)	61 (5.4%)	134 (12.8%)
Dexamethasone, n (%)	549 (21.8%)	1 (1.3%)	33 (12.7%)	291 (25.6%)	224 (21.4%)
Methylprednisolone pulse, n (%)	71 (2.8%)	7 (9.2%)	8 (3.1%)	27 (2.4%)	29 (2.8%)
Ciclesonide, n (%)	180 (7.1%)	35 (46.1%)	56 (21.6%)	87 (7.7%)	2 (0.2%)
Tocilizumab, n (%), n (%)	21 (0.8%)	1 (1.3%)	5 (1.9%)	12 (1.1%)	3 (0.3%)
anticoagulant, n (%)	320 (12.7%)	10 (13.2%)	21 (8.1%)	184 (16.2%)	105 (10.0%)

CKD, Chronic Kidney Disease；CHF, Chronic heart failure；COPD, chronic obstructive pulmonary disease

Table 2　Summary of the patients who died during Waves 3 and 4

Demographics	All patients (n＝49)	Wave 3 (n＝30)	Wave 4 (n＝19)
Age (year), mean (SD)	86.0 (6.6)	86.0 (6.9)	85.0 (6.3)
≧65 (year), n (%)	49 (100.0%)	30 (100.0%)	19 (100.0%)
Male, n (%)	31 (63.3%)	19 (63.3%)	12 (63.2%)
Female, n (%)	18 (36.7%)	11 (36.7%)	7 (36.8%)
Smoking experience, n (%)	12 (24.5%)	9 (30.0%)	3 (15.8%)
Length of hospital stay (day), mean (SD)	20.2 (12.4)	21.0 (13.1)	19.0 (11.4)
Underlying diseases			
Hypertension, n (%)	21 (42.9%)	13 (43.3%)	8 (42.1%)
Cardiovascular disease, n (%)	6 (12.2%)	4 (13.3%)	2 (10.5%)
CHF, n (%)	4 (8.2%)	3 (10.0%)	1 (5.3%)
Arrhythmia, n (%)	4 (8.2%)	4 (13.3%)	0 (0.0%)
Liver disease, n (%)	1 (2.0%)	1 (3.3%)	0 (0.0%)
Malignancy, n (%)	5 (10.2%)	3 (10.0%)	2 (10.5%)
COPD, n (%)	1 (2.0%)	1 (3.3%)	0 (0.0%)
Asthma, n (%)	4 (8.2%)	4 (13.3%)	0 (0.0%)
Diabetes, n (%)	9 (18.4%)	6 (20.0%)	3 (15.8%)
CKD, n (%)	6 (12.2%)	4 (13.3%)	2 (10.5%)
Severity at admission			
Mild, n (%)	5 (10.2%)	2 (6.7%)	3 (15.8%)
Moderate, n (%)	40 (81.6%)	25 (83.3%)	15 (78.9%)
Severe, n (%)	4 (8.2%)	3 (10.0%)	1 (5.3%)
Treatment			
Favipiravir, n (%)	15 (30.6%)	11 (36.7%)	4 (21.1%)
Remdesivir, n (%)	6 (12.2%)	1 (3.3%)	5 (26.3%)
Dexamethasone, n (%)	33 (67.3%)	21 (70.0%)	12 (63.2%)
Methylprednisolone pulse, n (%)	14 (7.7%)	7 (23.3%)	7 (36.8%)
anticoagulant, n (%)	17 (34.7%)	10 (33.3%)	7 (36.8%)

CKD, Chronic Kidney Disease ; CHF, Chronic heart failure ; COPD, chronic obstructive pulmonary disease

logistic regression analysis indicated that older age and the presence of CKD showed significant correlations with mortality due to COVID-19.

Ⅳ　Discussion

This is the first report to utilize a database based on the discharge summaries of patients with COVID-19 to identify the underlying diseases related to the duration of hospitalization and deaths in Nagano Prefecture through Waves 1-4. The patients hospitalized with COVID-19 during waves 1-4 were older and had ≥1 underlying disease. CHF, COPD, CKD, older age, male sex, and smoking history were correlated with a prolonged duration of hospitalization. The deceased inpatients whose cause of death was COVID-19 were older, with an average age of 86 years. Moreover, mul-

Table 3 Multiple regression analysis of age, sex, smoking history, and comorbities for predicting the duration of hospitalization for coronavirus disease 2019

Multiple regression analysis			
Variables	regression coefficient (standard error)	t-value	p value
Age (years)	0.138 (0.009)	15.990	＜0.0001
Sex	−1.031 (0.340)	−3.028	0.002
Smoking	−1.413 (0.465)	−3.040	0.002
Underlying disease			
Hypertension	−0.508 (0.472)	−1.078	0.281
Cardiovascular disease	0.403 (0.945)	0.426	0.700
CHF	3.255 (1.429)	2.277	0.022
Arrhythmia	−2.405 (1.254)	−1.917	0.055
Liver disease	−1.817 (1.205)	−1.509	0.131
Malignancy	0.716 (0.883)	0.810	0.418
COPD	4.548 (1.849)	2.460	0.014
Asthma	1.434 (0.903)	1.588	0.112
Diabetes	1.0267 (0.569)	1.805	0.071
CKD	6.357 (1.419)	4.481	＜0.0001

Note : Bold values indicate statistical significance. Abbreviations : CKD, Chronic Kidney Disease ; CHF, Chronic heart failure ; COPD, chronic obstructive pulmonary disease

tivariate logistic regression analysis revealed a significant correlation between mortality due to COVID-19 and factors such as old age and the presence of CKD. Based on the differences and similarities between previously published papers and the results of this study in Nagano Prefecture, we attempted to understand what diseases required particular attention in preventing COVID-19 infection in Nagano Prefecture.

The majority of patients hospitalized with COVID-19 in Nagano Prefecture during Waves 1-4 of the COVID-19 pandemic who exhibited moderate-to-severe symptoms were older or middle-aged adults with at least one underlying disease **(Table 1, Fig. 1)**. The number of hospitalized patients, severity, duration of hospitalization, and treatment drugs changed dramatically from Wave 1 to Wave 4. These changes are consistent with those reported by previous retrospective studies conducted in other prefectures during the same period[4)5)]. A substantial increase in the number and mean age of patients hospitalized with COVID-19 was observed during Wave 3, rising from 41.9 during Wave 2 to 56.9 years during Wave 3. In contrast, the

Table 4　Univariate and multivariate logistic regression analyses of mortality risk factors for patients with coronavirus disease including age, sex, smoking history, and underlying disease

Univariate logistic regression analysis			
Variates	Odds ratio	95% CI	p value
Age (years)	1.148	1.115-1.187	＜0.0001
Sex	0.705	0.389-1.244	0.235
Smoking	1.665	1.001-1.004	0.129
Underlying disease			
Hypertension	3.306	1.846-5.824	＜0.0001
Cardiovascular disease	4.184	1.562-9.407	＜0.001
CHF	6.628	1.917-17.573	＜0.0001
Arrhythmia	4.910	1.435-12.774	＜0.001
Liver disease	1.030	0.058-4.862	0.977
Malignancy	2.974	1.012-7.011	＜0.05
COPD	2.501	0.138-12.377	0.376
Asthma	2.471	0.733-6.257	0.090
Diabetes	1.968	0.887-3.914	0.070
CKD	11.095	4.007-26.345	＜0.0001

Multi logistic regression analysis			
Variables	Odds ratio	95% CI	p value
Age (years)	1.146	1.112 - 1.186	＜0.001
Underlying disease			
Hypertension	1.162	0.596 - 2.209	0.652
Cardiovascular disease	0.947	0.311 - 2.464	0.916
CHF	0.839	0.221 - 2.523	0.774
Arrhythmia	1.731	0.432 - 5.481	0.389
Malignancy	1.201	0.365 - 3.215	0.737
CKD	3.957	1.217 - 1.151	0.015

Note : Bold values indicate statistical significance. Abbreviations : CKD, Chronic Kidney Disease ; CHF, Chronic heart failure ; COPD, chronic obstructive pulmonary disease

average duration of hospitalization decreased from 24.8 days during the first wave to 11.6 days during the second wave. **Table 1** and **Fig. 1C** demonstrate that younger patients who were severely ill were hospitalized for extended periods during Wave 1 ; however, these patients did not die. The availability of guidelines and an understanding of the duration of viral shedding, verified via epidemiological surveys primarily conducted by public health centers, have enhanced treatment approaches and reduced the average duration of hospitalization. The mortality rate was maintained at approximately 2 % during Waves 3 and 4 as the proportion of patients with moderate symptoms increased gradually from Wave 3 to Wave 4. The increase in long-term hospitalization after Wave 3 can be attributed to several factors. In addition to the increase in the number of hospitalizations caused by nosocomial infections, there have been reports of hospitalization periods that include the treatment of the underlying disease, as well as hospitalization until the PCR test results are negative. The prefecture and a panel of experts actively encouraged discharging patients on the standard discharge date and transferring to another hospital during Wave 4 to secure a sufficient number of inpatient beds. Older patients were hospitalized for a prolonged duration even after the third wave **(Fig. 1C)**. Prolonged hospitalization may not necessarily be due to the severity of the disease **(Fig. 1A)**. Hospitalization may be caused by a decline in ADL and exacerbation of complications triggered by infection in older adults even if the severity of COVID-19 is mild.

The duration of hospitalization was associated with old age ; male sex ; smoking history, and the presence of CHF, COPD, and CKD in the present study. Heart failure is a major risk factor for COVID-19[12]. Patients with COPD are susceptible to mortality and hospitalization owing to COVID-19[17]. A substantial increase in COVID-19-related mortality has been associated with CKD, particularly in patients with kidney failure who have undergone kidney transplantation[16]. Papadopoulos et al. reported that decreased testosterone levels are associated with an increase in the severity of COVID-19 in older males[18]. Although the relationship between smoking history and the incidence of COVID-19 was uncertain in the early stages of the COVID-19 pandemic, recent large-scale studies have demonstrated that smoking history is a risk factor for hospitalization and death due to COVID-19[19)-21]. A recent review revealed that diabetes mellitus is associated with mortality and the severity of COVID-19[22]. However, no such correlation between the duration of hospitalization and diabetes mellitus was observed in the multiple regression analysis performed in the present study. This may be attributed to the possibility that critically ill patients with COVID-19 who have diabetes mellitus as an underlying disease could die suddenly during hospitalization. Furthermore, hospital stays are not always correlated with the severity of illness. It is possible that the severity of diabetes was not assessed in the present study, which could have led to an underestimation of the actual effects of the disease.

Multivariate logistic regression analysis revealed that old age and CKD were significant risk factors for COVID-19-related mortality during Waves 1-4. CKD, along with renal function biomarkers (such as BUN), is a risk factor for severe COVID-19 and death[23]. A previous case-control study of patients hospitalized with COVID-19 in Nagano Prefecture that targeted patients during the same wave as the present study revealed that BUN, age, and BMI are risk factors for requiring oxygen administration[24]. A registry study conducted in Sweden revealed that patients with COVID-19 who have underlying cardiorenal disease had a significantly poor prognosis from Wave 1 to Wave 3 (January 2020 to September 2021) of the COVID-19 outbreak[25]. Avotins et al. reported that a low GFRcys/GFRcr ratio is associated with an increase in COVID-19-related mortality among hospitalized patients[26]. Thus, accurate evaluation of renal function at the time of diagnosis and follow-up may aid in predicting the severity and prognosis of COVID-19. Logistic regression analysis revealed that CKD is a risk factor for mortality, consistent with the findings of earlier reports[27]. However, the exact cause and severity of CKD remain unknown owing to the limitations of the database, such as the absence of urinary findings. Building a database that evaluates the severity of CKD will facilitate the planning of epidemiological studies that examine the risk factors for newly emerging infectious diseases.

The present study has certain limitations. First, the data used in this study were part of a database created by the Nagano Prefecture Disease Control Division by gathering the anonymized discharge summaries of medical institutions in Nagano Prefecture. Consequently, data regarding several parameters, especially those pertaining to blood test parameters, were missing as the format of the discharge summary at each medical institution was not standardized. Thus, using blood test biomarkers or imaging findings as explanatory variables in the multivariate analysis of the duration of hospitalization and death was not possible. Another limitation is that the underlying diseases recorded in the database, such as arrhythmias and atrial fibrillation, may not have been precisely categorized. Patient information in the database was mainly focused on the time of initial admission. Therefore, information regarding the follow-up of the patients could not be obtained. Furthermore, the effect of vaccinations was not assessed as the majority of patients hospitalized during the first four waves of the pandemic were not yet vaccinated. Also, the database did not include information about oral medications taken by hospitalized patients for underlying diseases, making it impossible to examine the relationship between commonly used drugs and duration of hospitalization or mortality.

V Conclusion

This study provides an overview of the characteristics of the COVID-19 outbreak in Nagano Prefecture during the first four waves of the COVID-19 pandemic. This study also demonstrated that old age and CKD were independent risk factors for mortality in patients with COVID-19 during the first four waves. Preventing the incidence of COVID-19 among older patients and those with CKD is crucial for improving prognosis. Aggressive infection prevention should be considered for these high-risk patients.

Conflict of Interest

The authors declare that they have no competing interests.

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