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Predictors of in-hospital mortality in elderly unvaccinated patients during SARS-CoV-2 Alpha variants epidemic

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SUMMARY

Background: COVID-19, caused by SARS-CoV-2, has caused a global pandemic. This study aimed to identify predictors of in-hospital mortality in unvaccinated elderly patients with COVID-19 by comparing various predictive factors between the survivors and non-survivors.

Methods: We retrospectively selected 132 unvaccinated patients aged over 65 years with COVID-19 at a hospital in Kanagawa, Japan, during SARS-CoV-2 Alpha variants epidemic. We compared the clinical characteristics, laboratory and radiological findings, treatment, and complications of the survivors and non-survivors. In logistic regression analysis, variables that were significant in the univariate analysis were subjected to multivariate analysis using the variable increase method.

Results: There were 119 and 13 patients in the survivor and non-survivor groups, respectively. Multivariate regression revealed increasing odds with the presence of ARDS and DIC (odd ratio (OR) = 16.35, 34.36; P=0.002, 0.001, respectively) and prolonged hospital stay (OR = 1.17; P=0.004).

Conclusions: We found the complications of ARDS and DIC and hospital length of stay to be independent predictors of in-hospital mortality in elderly unvaccinated patients with COVID-19. Establishing treatments and prevention methods for ARDS and DIC could result in lower mortality rates.

Introduction

An outbreak of unknown viral pneumonia was confirmed in Wuhan, China, in December 2019 [1,2]. It was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [3]. In February 2020, the World Health Organization (WHO) officially named the disease caused by the infection Coronavirus Disease 2019 (COVID-19) [3].

The first patient with COVID-19 in Japan was confirmed in January 2020, and the first outbreak occurred in February 2020 with 712 positive cases among the passengers of the Diamond Princess, a large luxury cruise ship that called the port of Yokohama in Kanagawa Prefecture [4]. Currently, the number of critically ill patients with COVID-19 is decreasing due to

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COVID-19 vaccination. However, the number of unwell unvaccinated patients is increasing due to the emergence of mutant strains.

Advanced age is a risk factor for COVID-19 mortality [2]. In Japan, mortality is less than 1% for people in their 50s or younger but increases with age. For people over 60, 70, and 80 years, it is 1.4%, 4.5%, and 12.3%, respectively [5]. Previous reports on the predictors of severity and mortality have shown that advanced age; male sex; smoking history; history of hypertension, diabetes mellitus, and ischemic heart disease; chest tightness/dyspnea; leukocytosis; lymphopenia; higher levels of serum lactate dehydrogenase (LDH), C-reactive protein (CRP), interleukin-6, procalcitonin (PCT), Krebs von den Lungen-6 (KL-6), ferritin, aspartate aminotransferase (AST), direct bilirubin, and D-dimer; lower levels of lymphocytes, number of affected pulmonary lobes on CT scan and high Sequential Organ Failure Assessment (SOFA) score are associated with mortality in COVID-19 [2,6–13].

During the SARS-CoV-2 Alpha variants epidemic, we conducted a retrospective statistical analysis of the predictors of in-hospital mortality in elderly unvaccinated patients over 65 years old.

Materials and methods

Study design, participants, and data collection

This retrospective study was conducted on elderly (≥65 years old) unvaccinated patients with COVID-19 who were discharged or died at a single hospital in Kanagawa, Japan, from February 2020 to June 2021. This hospital was one of the medical facilities in the Prefecture that proactively treats patients with moderate-to-severe infectious diseases. The diagnosis of COVID-19 was made according to the interim guidance of the WHO. Clinical data were extracted from electronic medical records in the hospital database. We divided all elderly unvaccinated patients over 65 years old with COVID-19 into two groups: non-survivor and survivor (Figure 1).

We compared age, sex, severity, smoking status, history, clinical symptoms, hospitalization progress, respiratory state, laboratory findings at admission, radiological findings, severity score (A-DROP, CURB-65, and SOFA), treatment content, and complications. This study was approved by the Atsugi City Hospital Ethics Committee (approval number, R3-09). All records were anonymized before analysis, and informed consent was obtained in most cases. When patients could not communicate effectively or had died, we provided detailed explanations to their family members and obtained verbal consent from them. This committee approved verbal consent to be obtained from the patients. We used the opt-out approach for patient recruitment. All patients agreed to participate in the study.

Definitions

Fever was defined as an axillary temperature of at least 37.3°C. Severity was classified according to the Japanese guidelines as mild, moderate I, moderate II, and severe [14]. Mild was defined as having no respiratory symptoms; moderate I was defined as having respiratory symptoms, such as shortness of breath and/or pneumonia findings; moderate II was defined as requiring oxygen administration; and severe was defined as being managed in the intensive care unit and/or under mechanical ventilator. The CURB-65 and A-DROP scoring systems have been used to assess the severity of community-acquired pneumonia [15]. The CURB-65 score, proposed by the British Thoracic Society in 2003, aggregates scores for confusion; urea $>$ 7 mmol/L; respiratory rate $\geq$ 30 breaths/min; blood pressure (systolic $<$ 90 mmHg or diastolic $\leq$ 60 mmHg); and age $\geq$ 65 years [16]. The A-DROP scoring system, by the Japanese Respiratory Society, assesses the following parameters: age (male $\geq$ 70 years, female $\geq$ 75 years), dehydration (blood urea nitrogen $\geq$ 210 mg/L), respiratory failure (SaO2 $\leq$ 90% or PaO2 $\leq$ 60 mmHg), orientation disturbance (confusion), and low blood pressure (systolic blood pressure $\leq$ 90 mmHg) [17].

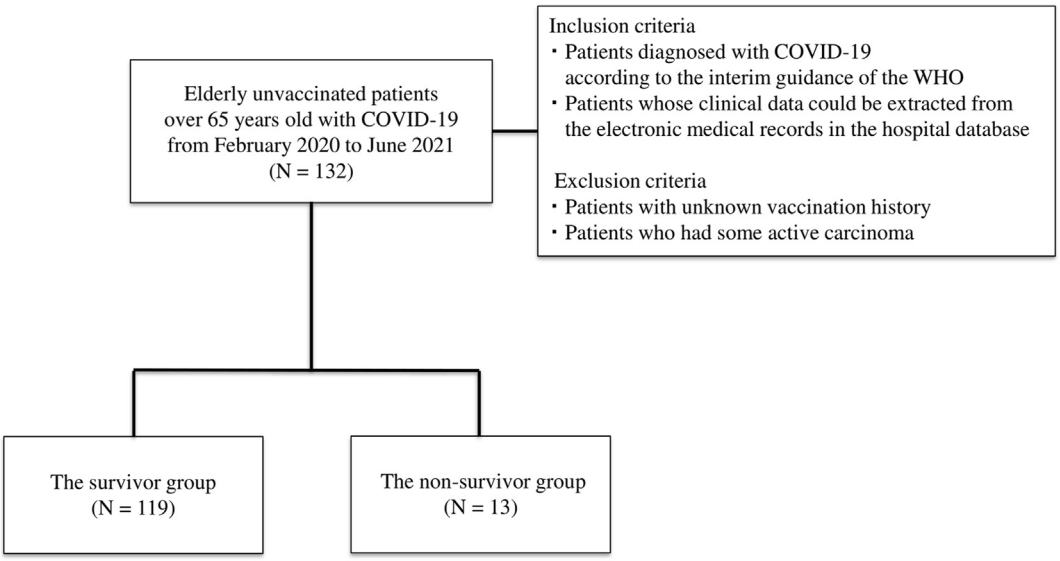

Figure 1. Of the 132 eligible patients diagnosed with COVID-19, 119 were classified into the survivor group and 13 into the nonsurvivor group.

Acute respiratory distress syndrome (ARDS) is an acute diffuse, inflammatory lung injury leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. ARDS was diagnosed according to the Berlin definition [18].

Sepsis is defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock as a life-threatening organ dysfunction caused by a dysregulated host response to infection [19–21]. Organ dysfunction is represented by an increase in the score of 2 points or more, which is associated with an in-hospital mortality greater than 10% [22].

The International Society on Thrombosis and Haemostasis (ISTH) has defined disseminated intravascular coagulation (DIC) as an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes [23]. DIC is a frequent complication in sepsis, and it can originate from and cause damage to the microvasculature. If sufficiently severe, it can cause organ dysfunction. Currently, the ISTH overt-DIC criteria are the global standard. Multiple organ dysfunction syndrome (MODS) was defined as the progressive physiological dysfunction of two or more organ systems where homeostasis cannot be maintained without intervention [24].

Steroid pulse therapy was defined as intravenous administration of 1000 mg methylprednisolone for 3 days, which is customary in Japan.

Statistical analysis

Continuous quantitative data, which were assumed to be normally distributed in the intergroup comparison, are expressed as the mean ± standard deviation and were tested using the unpaired *t*-test. Data with a non-normal distribution are expressed as the median (interquartile range) or the number of patients (%) and were tested using the Mann–Whitney *U* test. Categorical data are expressed as the number of patients (%) and were tested using Fisher's exact test. In logistic regression analysis, variables that were significant in the univariate analysis were subjected to multivariate analysis using the variable increase method (probability ratio). $P<0.05$ indicated statistical significance. Statistical analyses were performed using the SPSS software, version 23.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

A total of 132 elderly unvaccinated patients were enrolled in this study; 119 were in the survivor group and 13 were in the non-survivor group. The overall mortality rate was 9.8% (13/132). As shown in Table I, there were no statistically significant differences between the groups in either age or sex, although the non-survivors tended to be older (mean age: 80.8 ± 6.7 vs. 77.1 ± 0.9, $P=0.104$). On the other hand, there were statistically significant differences in severity classification ($P<0.001$). The non-survivors had a higher frequency in almost all comorbidities than survivors; however, only hypertension reached a statistically significant difference (92% vs. 53%, $P=0.007$). The number of days from onset to hospitalization, the start of treatment, and oxygen inhalation tended to be longer in the survivor group (5.7 ± 3.7 vs. 4.2 ± 3.0, $P=0.147$, 7.2 ± 3.6 vs. 4.4 ± 2.9, $P=0.008$, 9.2 ± 5.9 vs. 5.2 ± 2.5, $P=0.021$, respectively), and the hospital length of stay was longer in the non-survivor group (14.8 ± 5.5 vs. 24.5 ± 14.0, $P<0.001$).

In the laboratory data, there were significant differences in serum AST, Cr, CRP, and ferritin levels on admission (Table II). In radiological findings on admission, there was a significant difference in bilateral shadows (58% vs. 92%, $P=0.016$).

Drug treatments (Table III) showed significant differences in patients who had corticosteroid and steroid pulse therapy ($P=0.031$, <0.001, respectively). Regarding complications, ARDS, sepsis, DIC, and MODS were more common in the non-survivor group ($P<0.001$, <0.001, <0.001, 0.025, respectively), and ARDS was particularly high at 77% in the non-survivors.

In univariate analysis, as shown in Table IV, severity classification; activity ability (bedridden); comorbidity (hypertension); days from onset to the start of treatment and oxygen inhalation; hospital length of stay; measured SpO2 value on room air; severity score (A-DROP, CURB-65, and SOFA); serum AST, LDH, CRP, and ferritin; bilateral shadow on radiological images; and complications of ARDS, sepsis, DIC, and MODS could be the in-hospital mortality predictors. In multivariate analysis, hospital length of stay, ARDS, and DIC were statistically associated with mortality (odds ratio (OR) = 1.17, 16.35, 34.36, $P=0.004$, 0.002, 0.001, respectively) (Table V).

Discussion

This retrospective study revealed that ARDS and DIC complications and hospital length of stay were independent predictors of in-hospital mortality in elderly unvaccinated patients with COVID-19. The establishment of efficient treatment and prevention methods for ARDS and DIC complications in the future could reduce their respective mortality rates. Prone positioning, which offers several physiologic and clinical benefits, including improving hypoxemia, matching ventilation with perfusion, and reducing regional hyperinflation, reduces mortality due to ARDS [25]. Prone position therapy has been reported to contribute to the improvement of oxygenation in patients with COVID-19 with respiratory failure [26]. The European Respiratory Society also recommends prone position therapy for patients with COVID-19 [27]. However, evidence about prone position therapy being an effective preventive treatment modality for ARDS is still insufficient, and further research is thus warranted.

Regarding the increase in mortality rate due to DIC, another study also reported that the rate of COVID-19 complicated by DIC is 0.6% for survivors and 71.4% for non-survivors [28]. As with our study, the incidence of DIC leads to high mortality rates. COVID-19 is known to cause abnormal thrombotic fibrinolysis due to excessive inflammation and vascular endothelial cell damage. Complications of thrombosis and an increase in D-dimer may indicate a poor prognosis [2,10]. Currently, low-molecular-weight heparin treatment is recommended for preventing thrombosis in patients with COVID-19 [29]. In an interesting study, Tang *et al.* reported that heparin anticoagulant therapy lowers the mortality rate in patients with COVID-19 with markedly elevated D-dimer concentrations [30]. Nafamostat, a serine proteinase inhibitor, has antithrombin, antiplasmin, and antitrypsin effects. It has been used at times to treat DIC or pancreatitis and may effectively block the

Table I
Comparison of clinical characteristics between survivors and nonsurvivors

	Survivors (*N*=119)	Nonsurvivors (*N*=13)	*P*-value
Age, years	77.1 ± 0.9	80.8 ± 6.7	0.104
Sex			0.561
Male	70 (59)	9 (69)	
Female	49 (41)	4 (31)	
Severity classification on admission			<0.001
Mild	21 (18)	0 (0)	
Moderate I	72 (60)	4 (31)	
Moderate II	25 (21)	9 (69)	
Severe	1 (1)	0 (0)	
Comorbidity			
Hypertension	63 (53)	12 (92)	0.007
Diabetes mellitus	42 (35)	2 (15)	0.218
Coronary heart disease	22 (19)	4 (31)	0.285
Chronic kidney disease	14 (12)	4 (31)	0.079
Chronic obstructive lung disease	29 (24)	4 (31)	0.736
Cerebrovascular disease	16 (13)	4 (31)	0.111
Carcinoma	21 (18)	3 (23)	0.704
Hemodialysis management	4 (3)	1 (8)	0.410
Current smoker	47 (40)	8 (62)	0.147
Clinical course			
Days from onset to hospitalization	5.7 ± 3.7	4.2 ± 3.0	0.147
Days from onset to the start of treatment	7.2 ± 3.6	4.4 ± 2.9	0.008
Days from onset to the start of oxygen inhalation	9.2 ± 5.9	5.2 ± 2.5	0.021
Hospital length of stay, days	14.8 ± 5.5	24.5 ± 14.0	<0.001
Symptoms			
Fever	91 (77)	13 (100)	0.069
Cough	74 (62)	12 (92)	0.033
Sputum	58 (49)	12 (92)	0.003
Nasal discharge	14 (12)	8 (62)	<0.001
Sore throat	24 (20)	8 (62)	0.003
Headache	15 (13)	6 (46)	0.007
Appetite loss	52 (44)	11 (85)	0.007
Diarrhea	9 (8)	2 (15)	0.296
Shortness of breath	28 (24)	10 (77)	<0.001
Measured SpO_2 value on room air			0.001
SpO_2 ≧ 93%	26 (22)	9 (69)	
SpO_2 ≦ 92%	93 (78)	4 (31)	
A-DROP score			0.002
0 points	15 (13)	0 (0)	
1—2 points	95 (80)	8 (62)	
3 points	5 (4)	3 (23)	
4—5 points	4 (3)	2 (15)	
CURB-65 score			<0.001
0—1 points	71 (60)	1 (8)	
2 points	39 (33)	8 (81)	
3—5 points	9 (8)	4 (31)	
SOFA score			0.008
0—1 points	90 (76)	5 (39)	
≧2 points	29 (24)	8 (61)	

Values are presented as number (%) or mean ± standard error.
Abbreviation: SpO_2, peripheral arterial oxygen saturation.

requisite viral entry process for SARS-CoV-2 [31]. Heparin and nafamostat combination therapy might prove to have a therapeutic effect on the complication of DIC in patients with COVID-19.

There are differences between this study and previous reports on COVID-19 mortality predictors. Firstly, in Japan, vaccination was delayed compared to other countries, so all patients in this study were unvaccinated. Also, reflecting Japan's aging society, this study included many patients aged 80 or over. Further, this study was affected by the supply restrictions of remdesivir but included many patients treated with favipiravir, which was developed in Japan. On the other

Table II
Comparison of laboratory and radiological findings between survivors and nonsurvivors

	Survivors (*N*=119)	Nonsurvivors (*N*=13)	*P*-value
Laboratory data on admission			
WBC, $\times 10^9$ per L	5471 ± 2715	5892 ± 1976	0.588
Lymphocyte count, $\times 10^9$ per L	887 ± 447	796 ± 668	0.514
D-dimer, μg/mL	2.1 ± 3.8	3.4 ± 5.6	0.276
AST, U/L	35 ± 19	50 ± 27	0.011
ALT, U/L	24 ± 17	29 ± 16	0.302
LDH, U/L	273 ± 87	362 ± 137	0.001
Albumin, g/L	3.4 ± 0.6	3.1 ± 0.6	0.141
Cr, mg/dL	1.1 ± 1.1	1.9 ± 2.9	0.039
CRP, mg/dL	5.2 ± 5.1	9.9 ± 9.3	0.005
PCT, ng/mL	0.2 ± 0.9	0.4 ± 0.7	0.421
Ferritin, μg/L	516 ± 652	1018 ± 868	0.031
KL-6, U/mL	333 ± 183	443 ± 353	0.105
Radiological findings on admission			
Isolated ground-glass opacity	28 (24)	2 (15)	0.732
Multiple ground-glass opacity	73 (61)	11 (85)	0.132
Consolidation	45 (38)	8 (62)	0.136
Pleural effusion	4 (3)	1 (8)	0.410
Unilateral distribution	34 (29)	1 (8)	0.183
Bilateral distribution	69 (58)	12 (92)	0.016

Values are presented as number (%) or mean ± standard error.
Abbreviations: WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Cr, creatinine; ALP, alkaline phosphatase; CRP, C-reactive protein; PCT, procalcitonin; KL-6, Krebs von den Lungen-6.

hand, tocilizumab was not approved for insurance use in Japan, so no patient used it in this study. The most used drugs for COVID-19 in our hospital were corticosteroids. Therefore, we were able to compare the use and frequency of steroid pulse therapy and the steroid medication period. Antibiotics were more commonly used in the non-survivor group compared with the survivor group (92% vs. 37%, $P<0.001$), and penicillin or carbapenem were mainly selected. Antibiotics were utilized owing to the coexistence of some bacterial infections with ARDS and DIC complications.

Table III
Comparison of treatments and complications between survivors and nonsurvivors

	Survivors (*N*=119)	Nonsurvivors (*N*=13)	*P*-value
Treatments and management during hospitalization			
Corticosteroids	72 (61)	12 (92)	0.031
Steroid pulse therapy	31 (26)	11 (85)	<0.001
Number of steroid pulse therapy courses	0.4 ± 0.7	1.7 ± 1.1	<0.001
Days of steroid use	11.1 ± 13.3	19.5 ± 13.5	0.033
Lopinavir/ritonavir	2 (2)	0 (0)	>0.999
Ciclesonide inhalation	22 (19)	3 (23)	0.711
Favipiravir	33 (28)	7 (54)	0.063
Remdesivir	0 (0)	1 (8)	0.098
Antibiotics	44 (37)	12 (92)	<0.001
Prone position therapy	69 (58)	11 (85)	0.077
Nasal high flow	32 (27)	11 (85)	<0.001
Noninvasive ventilator	6 (5)	4 (31)	0.009
Invasive ventilator	2 (2)	2 (15)	0.048
Complications			
ARDS	14 (12)	10 (77)	<0.001
Sepsis	8 (7)	7 (54)	<0.001
DIC	3 (3)	7 (54)	<0.001
MODS	9 (8)	4 (31)	0.025

Values are presented as number (%) or mean ± standard error.
Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome.

Table IV
Univariate analysis of mortality risk factors for unvaccinated elderly patients with COVID-19

	OR	95% CI	*P*-value
Age, years	1.061	0.987–1.141	0.109
Male sex (vs. female)	1.575	0.459–5.405	0.470
Severity classification	5.297	1.839–15.258	0.002
Comorbidity present			
Hypertension	10.667	1.344–84.659	0.025
Diabetes mellitus	0.333	0.071–1.575	0.166
Coronary heart disease	1.960	0.553–6.946	0.297
Chronic kidney disease	3.333	0.906–12.269	0.070
Chronic obstructive lung disease	1.379	0.395–4.814	0.614
Cerebrovascular disease	2.861	0.787–10.396	0.110
Inactive carcinoma	1.400	0.354–5.529	0.631
Hemodialysis management	2.396	0.247–23.203	0.451
Current smoker (vs. nonsmoker)	2.451	0.756–7.947	0.135
Clinical course			
Days from onset to hospitalization	0.872	0.716–1.063	0.175
Days from onset to the start of treatment	0.726	0.563–0.936	0.013
Days from onset to the start of oxygen inhalation	0.673	0.510–0.887	0.005
Hospital length of stay, days	1.139	1.057–1.228	<0.001
Measured SpO_2 value on room air			
SpO_2 ≧ 93% (vs. ≦ 92%)	0.124	0.035–0.436	0.001
Severity score			
A-DROP	3.24	1.477–7.107	0.003
CURB-65	4.63	1.935–11.08	0.001
SOFA	4.96	1.506–16.374	0.008
Laboratory data on admission			
WBC, $\times 10^9$ per L	1.000	0.999–1.000	0.587
Lymphocyte count, $\times 10^9$ per L	1.000	0.998–1.001	0.510
D-dimer, μg/mL	1.059	0.952–1.179	0.291
AST, U/L	1.026	1.004–1.049	0.019
ALT, U/L	1.014	0.987–1.042	0.309
LDH, U/L	1.008	1.002–1.013	0.005
Albumin, g/L	0.516	0.212–1.255	0.144
Cr, mg/dL	1.281	0.970–1.691	0.081
CRP, mg/dL	1.112	1.024–1.207	0.012
PCT, ng/mL	1.204	0.741–1.957	0.453
Ferritin, μg/L	1.001	1.000–1.002	0.043
KL-6, U/mL	1.002	0.999–1.004	0.128
Radiological findings on admission			
Isolated ground-glass opacity	0.59	0.124–2.826	0.510
Multiple ground-glass opacities	3.46	0.735–16.348	0.116
Consolidation	2.63	0.811–8.539	0.107
Pleural effusion	2.39	0.247–23.203	0.451
Unilateral distribution	0.20	0.026–1.665	0.139
Bilateral distribution	8.69	1.095–69.064	0.041
Complications			
ARDS	25.00	6.131–101.946	<0.001
Sepsis	16.18	4.388–59.712	<0.001
DIC	45.1	9.273–219.444	<0.001
MODS	5.43	1.395–21.159	0.015

Abbreviations: SpO_2, peripheral arterial oxygen saturation; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Cr, creatinine; ALP, alkaline phosphatase; CRP, C-reactive protein; PCT, procalcitonin; KL-6, Krebs von den Lungen-6; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome; CI, confidence interval; OR, odds ratio.

Our study has certain limitations. First, owing to the retrospective nature of the study it is prone to biases and all laboratory tests, including serum PCT, KL-6, and ferritin tests, were not conducted for each patient. This might have resulted in the underestimation of in-hospital mortality due to COVID-19. Second, the insufficient supply of antiviral medications, suboptimal adherence to standard COVID-19 treatment, and the use of high-dose corticosteroids, such as in repeated steroid

Table V
Multivariate analysis of risk factors of mortality among unvaccinated elderly patients with COVID-19

	OR	95% CI	*P*-value
Hospital length of stay, days	1.17	1.052—1.302	0.004
ARDS	16.35	2.730—97.940	0.002
DIC	34.36	34.365—4.119	0.001

Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; CI, confidence interval; OR, odds ratio.

pulse therapy, may have contributed to unfavorable clinical outcomes in some patients. Third, we could not analyze the impact of mutant strains on mortality risk due to the unavailability of genome sequencing data for SARS-CoV-2 at our hospital. Fourth, the limited sample size may have influenced the interpretation of our findings. Furthermore, there was a significant difference in the number of survivors and non-survivors in the study. Finally, as our hospital is a medical institution that focuses on treating patients with moderate-to-severe respiratory symptoms, many patients with relatively more severe diseases may have been included in the study.

However, we believe that our study population is representative of cases diagnosed and treated in Japan at the time. Also, despite these factors, this study has valuable implications for assessing the mortality of COVID-19 in elderly unvaccinated patients. We hope that predictors of mortality will be identified in larger clinical trials in the future.

Conclusions

The complications of ARDS and DIC and prolonged hospital stays are associated with higher in-hospital mortality in elderly unvaccinated patients with COVID-19. The prevention of these complications and shortened hospital stay might contribute to lower mortality rates.

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Credit author statement

Zenya Saito: Conceptualization, Original draft, Writing, Reviewing and Editing.

Shota Uchiyama: Data collection, investigation, reviewing final manuscript.

Saiko Nishioka: Data collection, investigation, reviewing final manuscript.

Kentaro Tamura: Data collection, investigation, reviewing final manuscript.

Nobumasa Tamura: Data collection, investigation, reviewing final manuscript.

Kazuyoshi Kuwano: Validation, Methodology, Data analysis, Supervision.

Conflict of interest statement

The authors declare that they have no competing interests.

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