

Comorbidities as Risk Factors for Severe Disease in Hospitalized Elderly COVID-19 Patients by Different Age-Groups in Japan

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Keywords

Coronavirus disease 2019 · Severe acute respiratory coronavirus 2 · Older people · Inpatients · Risk factors

Abstract

Introduction: Old age is an independent risk factor (RF) for severe COVID-19; evidence for clinico-epidemiological characteristics among elderly COVID-19 patients is scarce. We aimed to analyze clinical and epidemiological characteristics and comorbidities associated with COVID-19 inpatients in age-stratified populations of an elderly COVID-19 cohort. **Methods:** We conducted a retrospective cohort study, using nationwide registry data of COVID-19 patients hospitalized before October 31, 2020 (major information entered in the registry as of December 28, 2020). Participants were divided by age according to the Japan Geriatrics Society and the Japan Gerontological Society: pre-old (65–74 years), old (75–89 years), and super-old (≥ 90 years). Multivariable logistic regression (MLR) analyses were conducted to identify stratified risk and relationships with comorbidities associated

with worse outcomes in different age-groups of elderly patients. Demographics and supportive care were evaluated by category. **Results:** Data of 4,701 patients from 444 hospitals were included. Most patients (79.3%) had at least one comorbidity; the proportion of patients with hypertension was high in all categories. The proportion of patients with dementia, cardiovascular disease, and cerebrovascular disease increased with age. The percentage of patients who underwent invasive mechanical ventilation/extracorporeal membrane oxygenation was lower in the super-old group. In total, 11.5% of patients died (5.3%, pre-old; 15.2%, old; and 22.4%, super-old). MLR showed that the risk of critical illness differed among age-groups. Male sex was a significant RF in all ages. Collagen disease, moderate to severe renal disorder, and dialysis were significant RFs in older patients, while hematological malignancies and metastatic tumors were more important RFs for severe disease in relatively younger patients. Most of the RFs for critical illnesses were associated with death. **Conclusion:** Differences in the epidemiological and clinical characteristics among the different age-groups were found.

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Introduction

Severe acute respiratory coronavirus 2 first emerged in Wuhan, China, in December 2019, and the ongoing outbreak of COVID-19 has been a global concern [1]. To date, Japan has passed through the first and second waves [2] and has now progressed to the third wave of COVID-19 [3]. The proportion of the elderly among all patients was higher in the first wave than that in the second wave, with higher mortality. Conversely, the second wave was characterized by a relatively low mortality rate and a large proportion of young people being infected, although the total number of infections is slightly larger than that in the first wave [2]. Regarding the third wave, since late October 2020, the number of patients recorded was more than 7,000 cases in a single day [4], breaking Japan's daily record. High-risk populations, including residents of long-term care welfare facilities for the elderly, have also been greatly affected by the pandemic.

Present evidence implies that certain conditions are associated with the risk of severe COVID-19. As patients age, the disease causes a more severe state [5–7]. In addition, a higher mortality rate was found in patients with underlying conditions [8]. Japan is a country with a “super-aged society,” and the average life expectancy in 2019 ranked highly in the world: 87.4 years for women and 81.4 years for men [9]. While old age contributes to disease severity, the epidemiological characteristics of COVID-19 in elderly patients, including the very elderly population, remain unclear. In addition, evidence for stratified risk analysis and relationships with comorbidities in worse outcomes among the very elderly remains scarce. In this study, in an age-stratified COVID-19 elderly cohort in a nationwide registry in Japan, we aimed to elucidate the following: how clinical and epidemiological characteristics differ and what comorbidities are associated with severe COVID-19 in each age-group of elderly inpatients.

Materials and Methods

Data Collection and the Case Report Form

We used data from the COVID-19 Registry Japan (COVIRE-GI-JP) [10]. The details of data collection and the case report form are described elsewhere [10]. The study data were collected and managed using Research Electronic Data Capture, a secure, Web-based data capture application hosted at the Joint Center for Researchers, Associates and Clinicians (JCRAC) Data Centre of the National Center for Global Health and Medicine (NCGM) [11]. We used data from hospitalized cases before October 31, 2020, and all major data items as of December 28, 2020, similar to a previous report [10].

Comorbidities

Several comorbidities were summarized for tabulation and multivariable logistic regression (MLR) as follows: cardiovascular disease, myocardial infarction, and congestive heart failure; chronic respiratory disease – chronic obstructive pulmonary disease and chronic lung disease; renal disease or dialysis, moderate to severe renal disorder, and maintenance hemodialysis before hospitalization; and leukemia/lymphoma. Body mass index (BMI) ≥ 25 was considered obese.

Age Class

According to the Japan Geriatrics Society and the Japan Gerontological Society, age was divided into 3 categories: pre-old (65–74 years), old (75–89 years), and super-old (≥ 90 years) [12].

National Early Warning Score

National Early Warning Score (NEWS) is a validated early warning score system composed of 6 physiological measurements (respiratory rate, oxygen saturation, body temperature, systolic blood pressure, heart rate, and level of consciousness) to assess patients at risk for early exacerbation. The NEWS determines its triage category for a clinical alert, requiring clinician assessment based on the score level: a low score (1–4), a medium score (5–6), and a high score (7 or more) [13]. We displayed the clinical course of elderly COVID-19 patients and subdivided into each NEWS category at admission.

Respiratory Support during Hospitalization

Respiratory support during hospitalization was classified into 3 categories: no oxygen, oxygen, and invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO). Each category was defined by the following state of supplementary oxygen: no oxygen was supplied throughout hospitalization; oxygen – oxygen was supplied (including high-flow oxygen devices and non-IMV) during hospitalization; and IMV/ECO – IMV or ECMO was required during hospitalization. The amount of administered oxygen was grouped into bivariate variables: no/low and high. The no/low-dose group comprised those who received no oxygen, those who received oxygen by cannula, and those who received < 5 L of oxygen by a mask. The high-dose class comprised those who received ≥ 5 L of oxygen by a mask and those who received oxygen by a reservoir, high-flow oxygen device, or noninvasive/IMV. Severe illness was grouped into bivariate variables: severe and nonsevere. Patients who received a high dose of oxygen as defined above or died between 5 and 15 days after the onset were categorized as severe.

Statistical Analysis

Continuous variables are described as the medians and interquartile range and categorical variables in the number of cases and percentages. Comparisons among age-groups were conducted using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. MLR analyses were conducted to identify risk factors (RFs) for severe illness and factors associated with death. First, clinically important variables were investigated by study investigators. Variables of age, male sex, BMI, and comorbidities (cerebrovascular disease, collagen disease, dementia, diabetes, leukemia or lymphoma, liver disease, chronic lung disease or chronic obstructive pulmonary disease, myocardial infarction or congestive heart failure, metastatic sol-

Table 1. Patients' characteristics

	Pre-old	Old	Super-old	<i>p</i> value
Patients, <i>n</i>	2,085	2,174	442	
Demographics				
Sex				
Male	1,256 (60.4) ^a	1,061 (48.8)	134 (30.3)	<0.001
Female	825 (39.6)	1,112 (51.2)	308 (69.7)	
Age, years				
Median [IQR]	70 [67, 72]	81 [78, 85]	93 [91, 94]	<0.001
Smoking history				
Former or current smoker	913 (52.6)	643 (40.2)	63 (23.4)	<0.001
Drinking alcohol				
Daily (≥3 cans of beer per day)	184 (22.7)	68 (14.4)	2 (5.7)	<0.001
BMI				
Median [IQR]	23.4 [21.1, 25.9]	22.3 [19.8, 24.9]	20.2 [17.8, 22.6]	<0.001
Onset				
Yes (with symptom)	1,827 (90.9)	1,847 (87.4)	373 (87.4)	0.001
Days from the symptom onset to hospitalization				
Median [IQR]	5 [3, 8]	4 [2, 8]	3 [1, 6]	<0.001
Contact history within 14 days before the onset				
Contact with COVID-19 patients				
Yes	1,066 (58.9)	1,349 (69.6)	321 (79.9)	
No	743 (41.1)	590 (30.4)	81 (20.1)	
Stay in healthcare facilities where COVID-19 patients are admitted				
Yes	218 (11.3)	334 (16.6)	104 (24.5)	<0.001
Meals with more than 3 persons (except for family members/housemate)				
Yes	231 (16.7)	206 (13.8)	36 (11.6)	0.023
Stay in crowded space ^b				
Yes	298 (20.3)	213 (13.1)	18 (5.0)	<0.001
Conditions at admission				
NEWS				
0–4	1,082 (72.0)	984 (64.0)	196 (64.3)	
5–6	199 (13.2)	258 (16.8)	53 (17.4)	<0.001
7–	221 (14.7)	296 (19.2)	56 (18.4)	
Oxygen support				
No oxygen	1,636 (79.5)	1,570 (73.0)	329 (75.5)	
Oxygen administered	421 (20.5)	581 (27)	107 (24.5)	<0.001
Route of oxygen				
Cannula/mask/reservoir	354 (84.1)	508 (87.4)	106 (99.1)	
Nasal high flow	6 (1.4)	8 (1.4)	1 (0.9)	
Non-IMV or IMV	61 (14.5)	65 (11.2)	0 (0)	

IQR, interquartile range. ^aThe denominator in each category depends on the number of missing values. ^bCrowded space: sport gym, live music house, karaoke, game center, buffet, indoor party, conference, nightclub/bar, among others.

id tumor, paralysis, peptic ulcer, peripheral vascular disease, renal disease or dialysis, and solid tumor) were selected, and their multicollinearity was assessed by the variance inflation factor. When multicollinearity was observed (variance inflation factor > 3), variables more associated with increased risk were chosen (however, no variables showed apparent collinearity in the following analysis). The variables of age, male sex, BMI, and comorbidities were included in the overall analysis and male sex, BMI, and comorbidities in the analysis within each age class. Forward stepwise logistic analysis was carried out when the

number of patients was limited, and all the relevant variables could not be employed; the RFs were further selected based on AIC. R version 4.0.2 (R Core Team [14]) was used for all statistical analyses in this study.

Ethics

This study was approved by the NCGM Ethics Review.

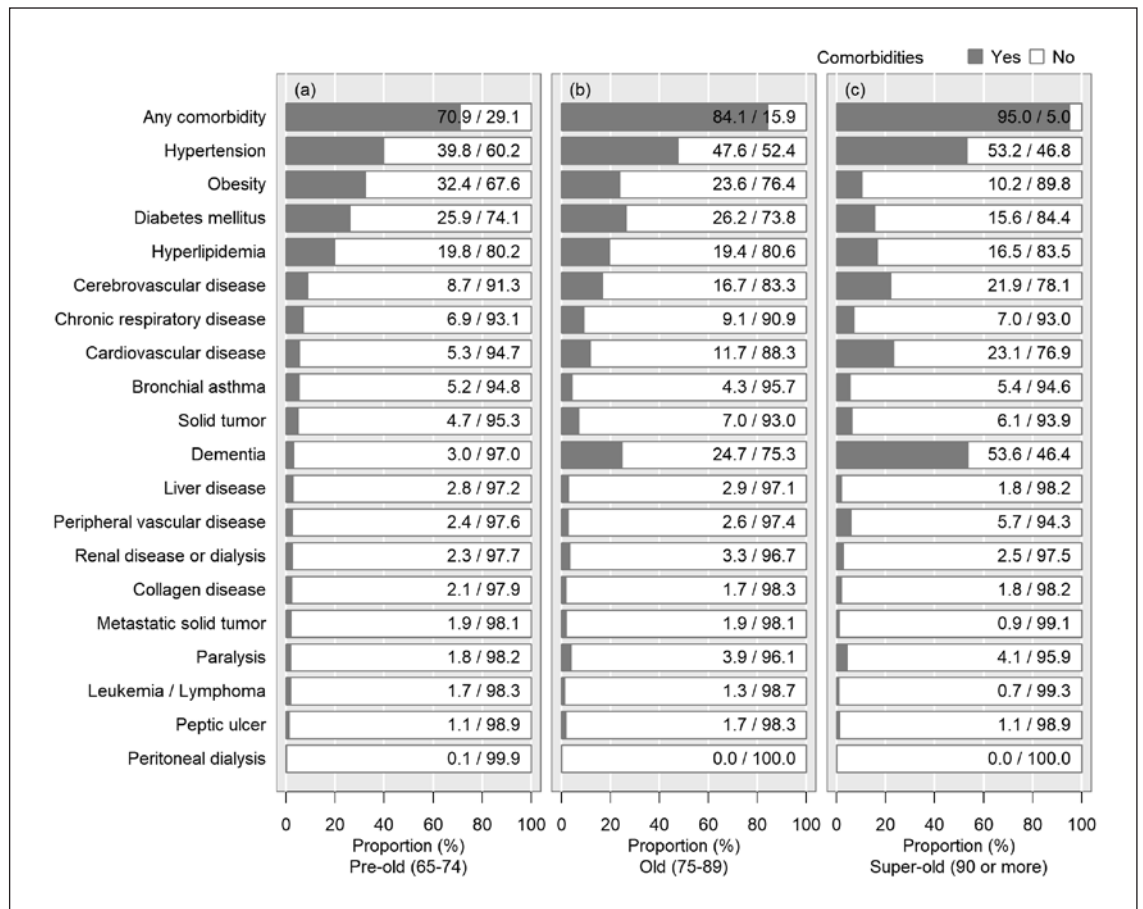


Fig. 1. a–c Comorbidities. The presence/absence of comorbidities reported at admission. Obesity was defined as a BMI of ≥ 25 .

Results

Patients' Characteristics

Data from 4,701 patients from 444 hospitals were included. Of them, 2,085 (44.3%) were pre-old, 2,174 (46.2%) were old, and 442 (9.4%) were super-old. Due to missing values, the number of cases included in the following analyses might vary. Patient demographics and clinical characteristics are shown in Table 1 and Figure 1, respectively. The sex ratio of cases was almost equal (2,451 [52.2%] males and 2,245 [47.8%] females); however, the ratio in each age class varied, and more males were enrolled in the pre-old group (1,256 [60.4%]), and more females in the super-old group (308 [69.7%]).

The NEWS on admission was < 4 in 2,262 (67.6%) patients. A total of 3,535 (76.1%) patients did not require additional oxygen on admission.

The number of patients who had contact with COVID-19 patients within 14 days before the onset was 2,736 (65.9%), and the proportion tended to increase with age. Within 14 days of the symptom onset, there were 473 cases (14.9%) who had group meals, defined as having meals with more than 3 persons except for family members, and 529 cases (15.3%) who stayed in crowded spaces. The proportions in each age-group tended to decrease with increasing age. Conversely, the proportion of elderly patients staying in healthcare facilities increased with age.

Most patients (3,726 [79.3%]) had at least one comorbidity, and the proportion of patients with hypertension was high in all age-groups. The proportion of patients with dementia, cardiovascular disease, and cerebrovascular disease increased with age.

Table 2. Supportive care during hospitalization and outcome

	Pre-old	Old	Super-old	p value
Patients, n	2,085	2,174	442	
Severity during hospitalization				
Severity during hospitalization				
No oxygen	1,082 (52) ^a	856 (39.4)	190 (43)	<0.001
Oxygen	773 (37.1)	1,091 (50.3)	244 (55.2)	
IMV/ECMO	227 (10.9)	224 (10.3)	8 (1.8)	
Outcome at discharge				
Outcome				
Discharge or transfer	1,974 (94.7)	1,843 (84.8)	342 (77.6)	<0.001
Dead	110 (5.3)	330 (15.2)	99 (22.4)	
Details of outcome				
Discharge	1,540 (73.9)	1,070 (49.2)	118 (26.8)	
Transfer to a different hospital	383 (18.4)	546 (25.1)	119 (27)	
Transfer to a nonmedical facility	28 (1.3)	28 (1.3)	7 (1.6)	
Transfer to a long-term care facility	23 (1.1)	199 (9.2)	98 (22.2)	
Tracheotomy				
Yes	37 (1.9)	27 (1.5)	0 (0)	<0.001
Self-care ability				
Stable or improved	1,701 (88.3)	1,380 (77.6)	251 (77)	<0.001
Worsened	225 (11.7)	399 (22.4)	75 (23.0)	
Supportive therapy during hospitalization				
Stay in the ICU				
Yes	299 (14.3)	324 (14.9)	30 (6.8)	<0.001
Oxygen support				
No oxygen	1,082 (52)	856 (39.4)	190 (43)	<0.001
Oxygen administered	1,000 (48)	1,315 (60.6)	252 (57)	
Route of oxygen				
High-flow nasal cannula	64 (6.4)	102 (7.8)	12 (4.8)	
Non-IMV	31 (3.1)	39 (3)	7 (2.8)	
IMV	197 (19.7)	219 (16.7)	8 (3.2)	
ECMO	30 (3)	5 (0.4)	0 (0)	
Other	678 (67.8)	950 (72.2)	225 (89.3)	
Number of the death after oxygen support				
High-flow nasal cannula	7 (10.9)	36 (35.3)	5 (41.7)	
Non-IMV	4 (12.9)	13 (33.3)	4 (57.1)	
IMV	48 (24.4)	100 (45.7)	6 (75)	
ECMO	15 (50)	2 (40)	0 (-)	
Inotropic				
Yes	117 (5.6)	144 (6.6)	8 (1.8)	<0.001
RRT or dialysis				
Yes	61 (2.9)	56 (2.6)	1 (0.2)	<0.001
Blood transfusion				
Yes	109 (5.2)	120 (5.5)	15 (3.4)	0.181

RRT, renal replacement therapy; ICU, intensive care unit. ^aThe denominator in each category depends on the number of missing values.

Supportive Care and Outcomes

Among 4,695 patients, 2,128 (45.3%) did not require additional oxygen during hospitalization (Table 2). The number of patients who received oxygen during hospitalization was 2,567 (54.7%) and that of who underwent IMV/ECMO was 459 (17.9%). Among those who re-

ceived supportive oxygen through high-flow devices or IMV, 48 (27.0%) and 154 (36.3%) patients died, respectively. A total of 4,159 (88.5%) patients were discharged or transferred to different hospitals, nonmedical facilities, or long-term care facilities.

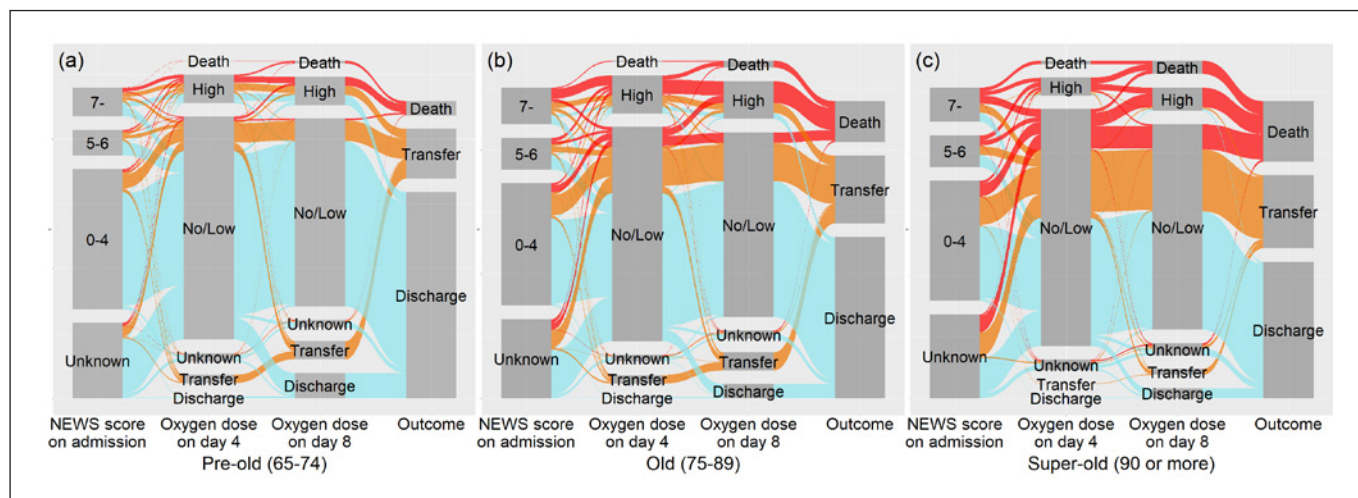


Fig. 2. a–c Progression of patients' severity and administration of supportive oxygen on day 4/8 after admission. A no/low oxygen dose consisted of those who received no oxygen, those who received oxygen by cannula, and those who received <5 L of oxygen by mask. A high oxygen dose consisted of those who received \geq 5 L of oxygen by a mask and those who received oxygen by a reservoir, high-flow oxygen device, or non-IMV/IMV.

Figure 2 illustrates the progression of severity and dose of administered oxygen on days 4 and 8 after admission. Many of the patients with a NEWS lower than 4 were discharged; however, the proportion of patients discharged tended to decrease with increasing age. The proportion of patients who died among those with a NEWS of >7 increased with age. In the pre-old group, more than 50% of the patients were discharged or transferred to other hospitals after receiving a high dose of oxygen on days 4 or 8. In contrast, most of the patients who received a high dose of oxygen died in the super-old group (23 [79.3%] on day 4 and 32 [84.2%] on day 8).

RFs for Severe Illness

RFs for severe illness are listed in Figure 3. Overall, age (OR 1.05 [1.04, 1.07]) and sex (OR 2.23 [1.80, 2.77]) were considered to increase risk. Among the comorbidities, obesity (BMI \geq 25) (OR 2.05 [1.65, 2.55]), collagen disease (OR 2.77 [1.50, 5.01]), diabetes (OR 1.41 [1.14, 1.74]), liver disease (OR 1.89 [1.14, 3.09]), leukemia and lymphoma (OR 3.63 [1.85, 6.96]), chronic respiratory disease (OR 1.87 [1.37, 2.55]), metastatic solid tumor (OR 2.44 [1.29, 4.51]), and renal disease or dialysis (OR 2.28 [1.37, 3.75]) were found to be significant RFs. Multivariate logistic regression in the pre-old and the old classes showed a similar trend. In the super-old group, collagen disease, renal disease or dialysis, and sex were selected after stepwise analysis. In addition, it was shown that male sex was a RF for all age-groups. Most of the significant factors in Fig-

ure 3 were also considered to be RFs associated with death (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000521000). Among them, sex was significant in all age-groups.

Administered Drug

The data for the administered drug are summarized in online supplementary Figure 1. Steroids were most likely to be used in the old (32.8%), pre-old (26.4%), and super-old (23.9%) groups. Remdesivir was used less frequently in the super-elderly (9.7%) than in the other 2 groups (pre-old, 17.8%; old, 19%). Favipiravir was used similarly among the groups (66.5–68.2%).

Discussion

Our study revealed clear differences in epidemiological and clinical characteristics among the different age-groups. When discussing the risk of infectious diseases, populations aged 60 or 65 years or older have been grouped together as elderly [15]. The prognosis in populations aged 65 years and older is worse than that in younger populations, and the elderly population is generally at higher risks [16–18]. Conversely, Japan is one of the super-aging societies in the world, with 15.6 million men (25.4%) and 20.2 million women (31.3%) aged 65 years and over, accounting for 28.4% of the total population [19]. The pre-old population in this study was tradi-

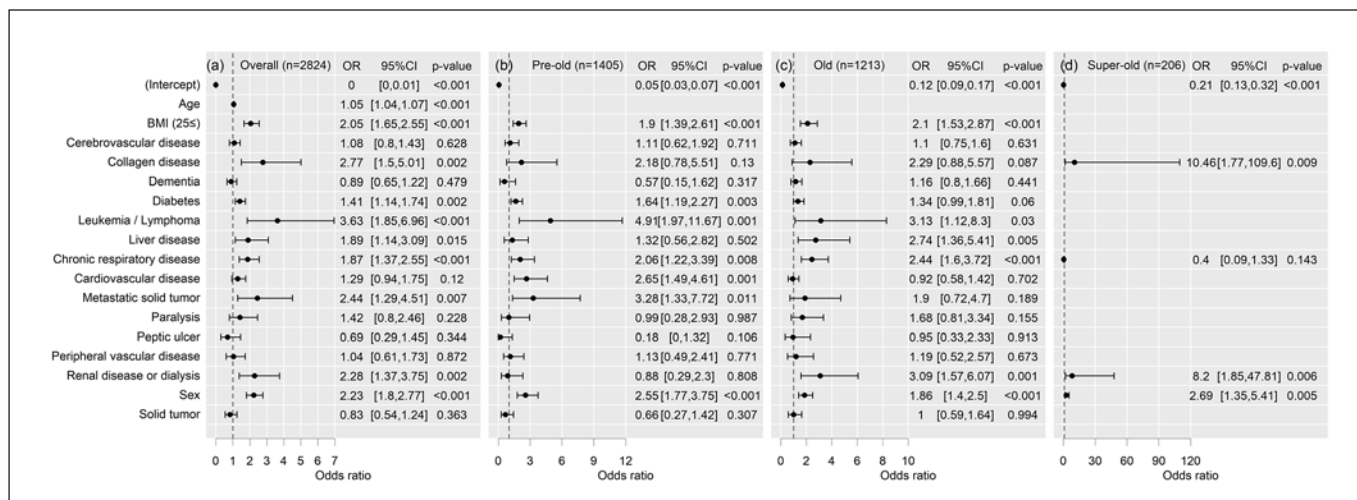


Fig. 3. a-d RFs for severe illness among elderly patients. Cardiovascular disease: myocardial infarction and congestive heart failure. Chronic respiratory disease: COPD and chronic lung disease. Renal disease or dialysis: moderate to severe renal disorder and maintenance hemodialysis before hospitalization. COPD, chronic obstructive pulmonary disease.

tionally considered to be the elderly; however, many of them are still active in society. Therefore, the heterogeneity of health and activity status makes it difficult to discuss the group aged ≥ 65 years. Thus, we divided the elderly population of Japan into 3 groups: pre-old (65–74 years), old (75–89 years), and super-old (≥ 90 years) and investigated RFs, treatments, outcomes, and their differences within and among these groups.

The epidemiological characteristics before infection were different among each age-group. The pre-old group was more likely to have eaten out with nonfamily members (16.7%) and to have been in crowded spaces (20.3%). Although it is unclear where the actual infection occurred, the pre-old population in Japan is usually still active, suggesting that the infection might be transmitted through social activities. On the other hand, more patients in the old and the super-old groups had stayed in healthcare facilities where COVID-19 patients were admitted within 14 days prior to the symptom onset. In particular, the proportion of such cases in the super-old group was 24.5%, which might reflect the impact of nosocomial infections in the super-old group, which has been frequently reported in the current COVID-19 outbreak [20, 21].

The proportion of elderly patients who required oxygenation at admission and during hospitalization was lower in our study than that in a prior study [22], which means that our study had milder cases. This could be due to the specific situation in Japan during the study period,

where medical capacity was not overwhelmed, and long-term care facilities and home care schemes were still insufficient. Under these circumstances, most elderly patients were admitted to the hospital, regardless of the severity of COVID-19. Therefore, even milder cases had an opportunity to be hospitalized.

In the elderly, besides death in the acute phase caused by COVID-19, deaths due to various complications after COVID-19 can occur. Therefore, in this study, we considered it necessary to analyze a broader range of serious conditions, not just death, to identify the RFs associated with severe acute COVID-19. Thus, patients who received high-dose oxygen or died between 5 and 15 days after the onset of illness were considered to be severely ill, and the RFs among them were examined. The RFs of severe disease in elderly patients as a whole were male sex, age, obesity, collagen disease, diabetes, liver disease, leukemia/lymphoma, chronic respiratory disease, metastatic cancer, and moderate to severe renal dysfunction/dialysis. A previous meta-analysis showed that patients aged 70 years and above have higher risks of COVID-19 in different severity stages [23], and overlapping comorbidities with our study results revealed RFs for severe disease [24, 25]. The same conditions were also identified as being associated with severe diseases in a large, hospitalized patient cohort in Japan [10]. On the other hand, when assessing the RFs associated with severe disease by different age-groups, not all ages were uniform, and RFs associated with severe disease varied between different age-groups.

These results suggest that comorbidities contributed to the severity of elderly COVID-19 patients in a complex manner.

MLR showed that male sex was a common RF in all ages of elderly patients. The ratio of females to males in the elderly population in Japan is 1:1.09 in the pre-old, 1:1.41 in the old, and 1:3 in the super-old population, and the ratio of females to males tends to increase with increased age. The proportion of females in this study was higher in the super-old population (69.7% compared to 30.3% for males), possibly suggesting that the different lifetime between men and women is reflected in the number of COVID-19 cases. Conversely, more males (60.4%) than females (39.6%) were admitted to the pre-old age-group. In this age-group, 76.3% of men and 62.5% of women had at least one underlying disease, and the NEWS at the time of admission was 3 [1, 5] for men and 2 [0, 4] for women, suggesting that more males were hospitalized as symptomatic patients. These results suggest an increased risk of acquiring infection and an increased likelihood of severe disease in elderly men in our cohort. Biological, psychological, and behavioral factors have been suggested to increase the risk of infection, mortality, and disease severity in men [26, 27].

Hematological malignancies, including leukemia and lymphoma, and metastatic tumors were important RFs for severe disease in the elderly, but they dropped out of the list in the super-elderly. These results might be because there were fewer cases of these diseases in older patients; however, the previous study also suggested a worse outcome in younger hematological malignancy patients with COVID-19 than that in older patients [28]. According to a multicenter cohort study in Italy, the standardized mortality ratio was 2.04% (95% confidence interval, 1.77–2.34) in COVID-19 patients with hematological malignancies, compared with the general Italian population with COVID-19 [28]. In addition, in their cohort of COVID-19 patients with hematological malignancies, the standardized mortality in patients younger than 70 years was higher than that in patients aged 70 years or older (3.72 compared to 1.71). Patients younger than 70 years could be eligible for definitive treatments, including hematopoietic stem-cell transplantation. Therefore, the differences in outcomes at younger ages may be influenced by the treatment of hematological malignancies. A prior prospective cohort study showed high mortality in COVID-19 patients with metastatic tumors [29]. Older age was associated with higher mortality in cancer patients [30], but there is a lack of research on which age-groups in the elderly patients specifically contribute to

poor prognosis. Although this is beyond the scope of our study, further investigation of the differences in cancer types and treatments by different age-groups may provide new insights.

Collagen disease and moderate to severe renal dysfunction/dialysis were major risks for severe disease in older patients. Former robust data of clinical outcomes in COVID-19 patients with collagen diseases are insufficient [31]. Some reports suggested that rheumatic diseases did not change the mortality in COVID-19 but tended to increase the risk of respiratory failure [32, 33]. According to a study from the COVID-19 Global Rheumatology Alliance, the use of high-dose glucocorticoids (≥ 10 mg/day of prednisolone-equivalent) was associated with hospitalization [34]. Conversely, the use of conventional disease-modifying antirheumatic drugs alone or in combination with biologics/Janus kinase inhibitors was not related to hospitalization. The activity of collagen diseases and drug use has not been investigated in this study and needs to be confirmed in more detail in the future. Patients with chronic renal dysfunction or receiving maintenance dialysis were shown to be highly vulnerable to COVID-19, resulting in a death rate of over 20% [35–37]. Moreover, multiple concomitant comorbidities with end-stage renal disease could increase the risk of poor outcomes in COVID-19 patients.

Dementia was not detected as a RF for severe COVID-19 in our study. However, previous COVID-19 studies showed that dementia was associated with higher risks for hospitalization and death due to COVID-19 [38, 39]. On the other hand, some studies reported that dementia was not associated with higher mortality in super-elderly patients [40, 41]. There are several possible explanations for the dissociation between these analyses. First, in super-elderly patients, mortality from other comorbidities may be higher, and the impact of dementia may be less. Next, elderly patients may not only become severely ill in the acute phase of COVID-19 but may also become severely ill from new hospital-acquired complications in the late stage from the onset of COVID-19. In our study, to distinguish early severe disease caused by COVID-19 from other complications in the late stage, we used the most severe condition within 15 days of admission as an indicator of severe disease. Our results might suggest that many elderly patients become severely ill due to subsequent complications rather than COVID-19 itself. Finally, in Japan, the local health center takes responsibility for the indications for hospitalization of COVID-19 patients. During the period of data collection, the hospitalization threshold for the elderly was low. In addition, all hospi-

talization and treatment costs were paid by the government. This background might lead to less unmeasured confounding (e.g., socioeconomic determinants), which might affect the outcome of COVID-19 patients with dementia in other studies.

In our study, the older the patient, the worse the prognosis. Not only did the percentage of deaths increase, but the percentage of patients who could be discharged home also decreased. Conversely, supportive care also varied by age, with invasive procedures, including IMV, being applied less frequently with increasing age, with approximately 10% of pre-old and old patients receiving IMV, compared to only 1.8% of super-old patients. To our knowledge, previous data on the super-old cohort are not available; however, the data from Korea using different age categories suggest that patients ≥ 80 years of age were less likely to receive IMV than those of 65–69 or 70–79 years of age [42]. The previous data also suggested that more than half of the patients were deceased despite receiving IMV [42, 43]. Decision-making regarding the treatment of the elderly involves several factors, including proficiency of medical personnel, harm/benefits of the treatment, expected prognosis, and the patient's preference regarding care [44]. Furthermore, in many regions, medical resources have been another issue in the current outbreak [45–48]. Future studies are needed to determine the factors that influence the extent to which clinicians provide treatment in elderly patients.

There were some limitations because of the observational nature of the study [11]. The data entered in this registry were from patients who were discharged from medical institutions, which may not reflect the situation of some patients who needed to be hospitalized for a long time. In addition, specific treatments, including medicines for each disease, were not investigated, which may not reflect the heterogeneity of the population with certain comorbidities. Finally, the data registered in our study were insufficient to analyze the association between frailty and the degree of dependence of the elderly and RFs for severe COVID-19. Previous studies have suggested that these indicators could be independent RFs for severe COVID-19 in the elderly [49, 50]. Especially in the very elderly, these indicators may be important in predicting the prognosis of COVID-19.

In conclusion, in the elderly population, there were differences in epidemiological and clinical characteristics among the different age-groups. The optimal management of COVID-19 in the elderly requires further study.

Acknowledgment

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Statement of Ethics

Our study data were provided by Research Electronic Data Capture, a secure, Web-based data capture application hosted at the JCRAC Data Center of the NCGM. The opt-out recruitment method was applied, and informed consents for individuals were waived as approved by the NCGM Ethics Review. Information about the entire research was disclosed through the website (<https://covid-registry.ncgm.go.jp/>). This study was approved by the NCGM Ethics Review (approval number: NCGM-G-003494-0).

Conflict of Interest Statement

H. Ohtsu reports personal fees as a statistician and as an external consultant for clinical trials from EPS International, outside the submitted work. S. Saito reports grants from Shionogi outside the submitted work. The other authors have no conflicts of interest to disclose.

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Author Contributions

Y. Asai, H. Nomoto, and K. Hayakawa developed the concept and design and had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Y. Asai and S. Tsuzuki were responsible for the statistical analysis. N. Matsunaga, S. Tsuzuki, M. Terada, H. Ohtsu, K. Kitajima, K. Suzuki, S. Saito, F. Saito, K. Nakamura, T. Suzuki, and S. Morioka provided administrative, technical, or material support. N. Ohmagari supervised the study. All the authors critically revised the manuscript for important intellectual content.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the privacy of research participants and sites but are available upon reasonable request. Data on an individual level are shared with limitations to participating healthcare facilities through applications to the COVIREGI-JP.

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