Original article

Smoking and severe illness in hospitalized COVID-19 patients in Japan

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Abstract

Background: The aim of this study was to identify associations between smoking status
and the severity of COVID-19, using a large-scale data registry of hospitalized COVID-19
patients in Japan (COVIREGI-JP), and to explore the reasons for the inconsistent results
previously reported on this subject.

Methods: The analysis included 17 666 COVID-19 inpatients aged 20–89 years (10 250
men and 7416 women). We graded the severity of COVID-19 (grades 0 to 5) according to
the most intensive treatment required during hospitalization. The smoking status of
severe grades 3/4/5 (invasive mechanical ventilation/extracorporeal membrane oxygena-
tion/death) and separately of grade 5 (death) were compared with that of grade 0 (no
oxygen, reference group) using multiple logistic regression. Results were expressed
as odds ratios (OR) and 95% confidence intervals (CI) adjusted for age and other factors
considering the potential intermediate effects of comorbidities.

Results: Among men, former smoking significantly increased the risk of grade 3/4/5 and
grade 5, using grade 0 as a reference group, with age- and admission-date-adjusted
ORs (95% CI) of 1.51 (1.18–1.93) and 1.65 (1.22–2.24), respectively. An additional
adjustment for comorbidities weakened the ORs. Similar results were seen for women.

Current smoking did not significantly increase the risk of grade 3/4/5 and grade 5 in either sex.

Conclusions: The severity of COVID-19 was not associated with current or former smoking per se but with the comorbidities caused by smoking. Thus, smoking cessation is likely to be a key factor for preventing smoking-related disease and hence for reducing the risk of severe COVID-19.

Key words: COVID-19, infectious disease, smoking

Key Messages

- COVIREGI-JP is a large-scale data registry of hospitalized COVID-19 patients in Japan.
- In this observational study using COVIREGI-JP, former smoking but not current smoking significantly increased the risk of COVID-19 severity in both sexes.
- The cause of severe COVID-19 is not smoking per se but is smoking-related disease.
- Smoking cessation may be a key factor for preventing smoking-related disease and thereby reducing the risk of severe COVID-19.

Introduction

Many studies that analyzed the causes of morbidity, severity and mortality of coronavirus disease 2019 (COVID-19) have been published from various countries,[1–9] although they have not yet yielded consistent results regarding the impact of smoking. Whereas several studies indicated that current and former smoking was associated with worse progression and severe symptoms of COVID-19, with increased hospital admission and death,[2,4,5,9–12] other studies with contradictory evidence have appeared, notably those indicating that current smoking is actually associated with a lower risk of COVID-19-related death.[8] Furthermore, an unknown smoking status was associated with increased risks of hospital admission and severe symptoms.[11] The reasons for such discrepancies may be due to the small number of participants in most studies,[2–4,6] non-separation of current and former smoking[2,3,6] and lack of adjustment for confounding factors such as sex, age, date of admission and comorbidities.[4] To date, there have been few detailed large-scale data analyses focusing on the association between smoking status and severity of COVID-19. Therefore, we conducted the current study to investigate the effect of smoking status on the severity of COVID-19, using a large-scale registry of data on hospitalized COVID-19 patients in Japan (COVIREGI-JP). We divided these patients into four groups according to smoking status (never smokers, former smokers, current smokers and unknown), considering sex, age, date of admission and comorbidities.

Methods

This study was approved by the National Center for Global Health and Medicine (NCGM) ethics review (NCGM-G-003494–0).

Study design

This study used data from COVIREGI-JP, a large-scale registry of hospitalized COVID-19 patients in Japan, which contains data on patients' characteristics and clinical course during hospitalization (e.g. admission and discharge dates, treatment methods and dates, survival or death). Prior to the beginning of this work, we informed the registry on the website of the National Center for Global Health and Medicine (the primary investigator's affiliation), the webinar for journalists, press release etc. and asked hospitals to participate in COVIREGI-JP and register the patients' information voluntarily. A total of 531 hospitals was involved with this registry system. The details have been reported elsewhere.[13–15] The inclusion criteria for enrolment were: (i) a positive SARS-CoV-2 test[13]; and (ii) inpatient treatment at a health care facility. If a patient had a history of multiple COVID-19 hospitalizations and met the aforementioned inclusion criteria, each admission was included separately in the registry. However, those data were excluded from the current analysis because the multiple hospitalization data for a particular patient could not be linked and therefore the

most intensive treatment during hospitalization, which was the outcome criterion for the present study, could not be identified. This was to avoid the inclusion of duplicate data.

The age range of patients for this analysis was restricted to between 20 and 89 years because the prevalence of smoking was very low in patients <20 years of age (due to smoking being prohibited by law). Very old patients ≥90 years were also excluded because their prognosis may be strongly affected by many factors other than smoking history. Non-Japanese citizens were also excluded to minimize the potential effects of ethnicity.

Dataset

We used the following data items that had been entered as of 26 February 2021: demographic and epidemiological characteristics, comorbidities, outcome at discharge and supportive care during hospitalization. Smoking history was recorded in four categories: current smoker (smoking until just before the onset of COVID-19), former smoker, never smoker and unknown. If the information of smoking status was not obtained, it was treated as 'unknown'. The major reason for assigning 'unknown' smoking status was that the interviewers were unable to question patients with very severe symptoms at the time of admission, or could not interview the family members as proxies because they were not allowed to accompany the patient at admission in order to limit infection. Data on the number of cigarettes smoked per day were also not available. Data on comorbidities were acquired from patient medical records, as entered by the medical staff at each hospital. Comorbidity was defined as diseases contracted before hospitalization and persisting at admission. Detailed criteria for the definition of comorbidities were not determined specifically for this study.

Patients

There were 29 066 patients registered in the COVIREGI-JP who were hospitalized between 3 January 2020 and 26 February 2021 and were discharged or dead by 27 February 2021. Patients were excluded from the analysis in the following order: non-Japanese citizens ($n = 3355$), sex missing ($n = 22$), outside of the age range 20–89 ($n = 2215$), transferred from another hospital ($n = 2781$), transferred to another hospital ($n = 1754$), still hospitalized ($n = 1093$), treatment procedures missing ($n = 82$) and admission and/or discharge dates missing ($n = 98$). Finally therefore, the analysis included 17 666 patients aged 20–89 years (10 250 men and 7416 women) ([Figure 1](#) and [Table 1](#), left-hand columns).
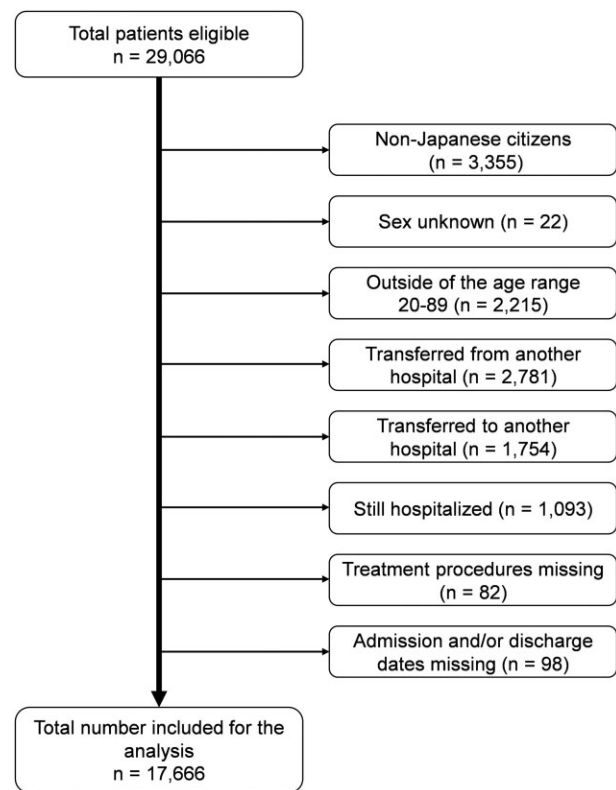

Figure 1 Population flow chart, showing the selection of patients for inclusion in the analysis

Definition of disease grade

We graded the severity of COVID-19 according to the most intensive treatment received or death during hospitalization, as shown in the header of [Table 1](#), as follows: grade 0 (no oxygen, i.e. patients were never supported with supplemental oxygen); grade 1 (patients were supported with noninvasive mechanical ventilation or supplemental oxygen); grade 2 [patients supported with high-flow oxygen or non-invasive positive pressure ventilation (NIPPV)]; grade 3 [invasive mechanical ventilation (IMV)]; grade 4 [extracorporeal membrane oxygenation (ECMO)]; grade 5 (death during hospitalization regardless of treatment). We considered pooled grades 3, 4 and 5 as 'severe' for these analyses, but also in addition analyzed grade 5 (death) separately.

Statistical analysis

The frequency distributions of COVID-19 grades and other categorical data are shown as percentages. The chi square test was used to compare percentage values between groups. Continuous variables were summarized as mean, standard deviation (SD) and range. The smoking status of patients with severe grade disease 3/4/5 (invasive mechanical ventilation/extracorporeal membrane oxygenation/

Table 1 Definition of severity grade according to the most intensive treatment or death, and frequency of each grade by sex and age groups among COVID-19 patients registered in Japan

Age (years)	N	Grade					
		0: no oxygen	1: nasal cannula/oxygen masks	2: high-flow oxygen devices/NIPPV	3: invasive mechanical ventilation	4: ECMO	5: death (regardless of treatment)
Men							
20–29	1444	97.1%	2.6%	0.1%	0.2%	0.0%	0.0%
30–39	1338	89.2%	9.6%	0.8%	0.4%	0.1%	0.0%
40–49	1738	78.9%	17.6%	2.0%	1.1%	0.3%	0.1%
50–59	2010	69.0%	25.7%	2.4%	2.0%	0.3%	0.5%
60–69	1601	55.7%	34.0%	3.6%	2.9%	0.1%	3.7%
70–79	1380	49.6%	34.9%	3.6%	2.1%	0.2%	9.6%
80–89	739	39.2%	33.0%	2.0%	0.3%	0.0%	25.4%
Total	10 250	70.4%	22.0%	2.1%	1.4%	0.2%	3.8%
Women							
20–29	1301	98.2%	1.6%	0.1%	0.1%	0.0%	0.0%
30–39	875	96.6%	3.2%	0.1%	0.1%	0.0%	0.0%
40–49	932	91.4%	7.3%	0.6%	0.2%	0.0%	0.4%
50–59	1124	83.7%	14.9%	0.6%	0.4%	0.0%	0.4%
60–69	1014	73.6%	22.8%	1.3%	1.2%	0.0%	1.2%
70–79	1187	65.5%	28.1%	1.9%	0.5%	0.0%	4.0%
80–89	983	52.9%	33.7%	1.7%	0.2%	0.0%	11.5%
Total	7416	80.4%	15.9%	0.9%	0.4%	0.0%	2.4%

Percentage values are for row.

NIPPV, non-invasive positive pressure ventilation; ECMO, extracorporeal membrane oxygenation.

death) and separately with grade 5 (death) was compared with that of grade 0 (no oxygen, reference group) using multiple logistic regression and expressed as odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, date of admission and comorbidities. Because there were too many types of comorbidities (25 diseases), the adjusted comorbidities were selected by a stepwise procedure using $P < 0.10$ for entry and removal. Grades 1 and 2 were excluded from the primary analysis in order to focus on the risk of severe grades (3 and above) by comparing with grade 0. Since the inclusion of grades 1 and 2 may obscure the association between smoking status and the severity of COVID-19, the ORs of grades 1/2/3/4/5, and 2/3/4/5 using grade 0 as a reference group, were also calculated for the sensitivity analyses. The entire observation period was divided into seven periods at 2-month intervals, and the date of admission was categorized among them and coded as dummy variables for statistical adjustment. We did not employ a survival-time analysis such as Cox-proportional hazards modelling considering the length of hospitalization, because it was clear that the duration of hospitalization (days) and the grade (0 to 5) were correlated (Spearman's rank correlation coefficient = 0.394). Men and women were separately analyzed because the prevalence of smoking is markedly lower in women than in men

in the general Japanese population.[16] A two-sided *P*-value of <0.05 was considered to be statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

The mean duration of hospitalization including the day of admission was 12.9 days (range: 1 to 201) for patients admitted to hospital because of a positive test for SARS-CoV-2. The frequency of COVID-19 severity grade by sex and age groups is summarized in Table 1. The lowest grade 0 (no oxygen) was the most prevalent, accounting for 70.4% of men and 80.4% of women. Severe grades 3 and 4 in patients aged ≥70 years were less frequent than in 60–69-year-olds, whereas the case fatality rate was very high especially in 80–89-year-olds (25.4% of men and 11.5% of women).

The ages, smoking status, body mass index (BMI) and prevalence of comorbidities in these COVID-19 patients are shown in Table 2. The mean age was 52.3 years for men and 54.0 years for women. The mean BMI was 24.9 kg/m² for men and 22.8 kg/m² for women. The frequency of the four smoking categories—current, former, never and 'unknown'—were 23.4%, 29.2%, 34.5% and 13.0%, respectively, for men and 10.6%, 10.4%, 62.9%

Table 2 Basic characteristics and comorbidities of the COVID-19 patients registered in Japan

	Men (n = 10 250)		Women (n = 7416)	
	n	%	n	%
Age (20–89 years)				
Mean ± standard variation		52.3 ± 18.1		54.0 ± 20.6
Smoking history[a]				
Currently smoking (until shortly before the onset of symptoms)	2395	23.4% (26.9%)	784	10.6% (12.6%)
Former smoking	2988	29.2% (33.5%)	771	10.4% (12.4%)
Never smoking	3534	34.5% (39.6%)	4663	62.9% (75.0%)
Unknown	1333	13.0%	1198	16.2%
BMI (kg/m^2)[b]				
Mean ± standard variation		24.9 ± 4.4		22.8 ± 4.5
Comorbidities				
Myocardial infarction	211	2.1%	51	0.7%
Congestive heart failure	162	1.6%	123	1.7%
Peripheral vascular disease	123	1.2%	59	0.8%
Cerebrovascular disorders	422	4.1%	322	4.3%
Hemiplegia	72	0.7%	57	0.8%
Dementia	259	2.5%	473	6.4%
COPD	260	2.5%	41	0.6%
Chronic lung diseases other than COPD	129	1.3%	55	0.7%
Bronchial asthma	454	4.4%	506	6.8%
Mild liver disease	260	2.5%	82	1.1%
Moderate to severe liver dysfunction (cirrhosis with portal hypertension)	38	0.4%	7	0.1%
Peptic ulcer	81	0.8%	37	0.5%
Hypertension	2690	26.2%	1710	23.1%
Hyperlipidaemia	1341	13.1%	918	12.4%
Mild diabetes	1482	14.5%	656	8.8%
Severe diabetes	200	2.0%	64	0.9%
Diabetes mellitus (mild and severe)	1682	16.4%	720	9.7%
Obesity	706	6.9%	281	3.8%
Moderate to severe renal dysfunction (creatinine ≥3 mg/dL, during dialysis, after kidney transplant, urinary nephropathy)	96	0.9%	43	0.6%
Maintenance haemodialysis before hospitalization	59	0.6%	26	0.4%
Solid cancers	306	3.0%	216	2.9%
Leukaemia	28	0.3%	12	0.2%
Lymphoma	45	0.4%	21	0.3%
Metastatic solid cancers	90	0.9%	49	0.7%
Connective tissue disease	71	0.7%	123	1.7%
HIV infection	34	0.3%	0	0.0%

BMI, body mass index; COPD, chronic obstructive pulmonary disease.
[a]Percentage values in parentheses are for excluding the 'unknown' category.
[b]BMI was missing for 16.5% and 18.4% of men and women, respectively.

and 16.2% for women. Many patients had hypertension (26.2% of men and 23.1% of women), hyperlipidaemia (13.1% of men and 12.4% of women), diabetes (16.4% of men and 9.7% of women) and obesity (6.9% of men and 3.8% of women) as comorbidities.

The risks of grade 3/4/5 disease (IMV/ECMO/death) and grade 5 (death) were mostly higher in men than in women (except for the very small number of deaths in the 40–49-year-old group) and increased as the age increased in both sexes (data not shown).

Table 3 shows the association between smoking status and severity of COVID-19. Among men, former smokers had a significantly increased risk of grade 3/4/5 and grade 5, using grade 0 as a reference group, with age- and date of admission-adjusted ORs (95% CI) of 1.51 (1.18–1.93) and 1.65 (1.22–2.24), respectively. Similarly among women, increased risks were seen for grade 3/4/5 and grade 5, using grade 0 as a reference group, with age- and date of admission-adjusted ORs (95%CI) of 1.94 (1.20–3.15) and 1.79 (1.03–3.10), respectively. Current smokers did not have a significantly increased risk of grade 3/4/5 and grade 5, using grade 0 as a reference group, in either sex, whereas the risk of grade 3/4/5 and grade 5 in the 'unknown' group was elevated in both men and women. For women, current smokers unexpectedly had a significantly decreased risk of experiencing grade 3/4/5; the OR adjusted for age, period and comorbidities, using grade 0 as a reference group, was 0.21 (0.05–0.97). In the same manner, we also compared grade 0 and grade 1/2/3/4/5 as a sensitivity analysis and obtained similar results.

To examine the potential reasons why the risks of severe COVID-19 were increased in former but not current smokers, additional analyses were conducted on the inter-relationships among COVID-19, comorbidities and smoking. Supplementary Table S1, available as Supplementary data at *IJE* online, shows associations between comorbidity and severe COVID-19. The risks of grade 3/4/5 disease were significantly increased in the presence of certain comorbidities such as congestive heart failure, cerebrovascular disorders, chronic lung diseases, liver diseases, diabetes (mild and severe), obesity, solid cancers, leukaemia, metastatic solid cancers and connective tissue disease in both men and women. Similar results were observed for grade 5, although some were not statistically significant, possibly because of the small number of deaths (data not shown). Supplementary Table S2, available as Supplementary data at *IJE* online, shows the OR for the presence of comorbidities according to smoking status. Some comorbidities were more prevalent in smokers, especially in former smokers as compared with never smokers, suggesting that a certain proportion of former smokers had quit because of the occurrence of the comorbidity. After additional adjustment for comorbidities, the risks of grade 3/4/5 and grade 5 disease in former smokers were weakened (Table 3), e.g. 1.51 (1.18–1.93) was reduced to 1.32 (1.01–1.71) in men and 1.94 (1.20–3.15) to 1.40 (0.81–2.44) in women for grade 3/4/5.

Discussion

In this study, we defined the severity of COVID-19 by grading patients according to the most intensive treatment they received during hospitalization, or death, and examined the association between smoking status and the risk of severe illness, taking the effects of sex, age, date of admission and comorbidities into account among patients admitted to hospital who tested positive for SARS-CoV-2.

After adjusting for age and date of admission, former smokers were found to be at greater risk than never-smokers not only for severe COVID-19 (grade 3/4/5) but also for several comorbidities in both men and women. Life-threatening illness can cause smokers to quit and can thereby distort death rates among current and former smokers in opposite ways.[17] A prospective cohort study in Japan showed that the risk of death among those who ceased smoking due to other disease was higher than among continuing smokers.[18] Therefore, the associations between smoking status and the severity or prognosis of COVID-19 should be carefully interpreted, considering such distortion caused by comorbidities among current and former smokers. In our study, the increased risk of severe COVID-19 among former smokers was explained to some extent by the presence of comorbidities, because adjustment for comorbidities weakened the ORs. In other words, comorbidities were mediating factors in the association between former smoking and the severity of COVID-19. Similar to our results, a British study by Williamson *et al.* reported an increased risk of COVID-19-related deaths among former smokers.[8] Sex- and age-adjusted hazard ratios (95% CIs) were 1.14 (1.05–1.23) and 1.43 (1.37–1.49) for current and former smokers, respectively, as compared with never smokers in that study; after being fully adjusted for patients' characteristics, including history of other disease, especially chronic respiratory disease, hazard ratios were decreased to 0.89 (0.82–0.97) and 1.19 (1.14–1.24). It was hypothesized that it was likely that the comorbidities mediated many of the observed effects of smoking on COVID-19-related deaths.[8] Petrilli et al. also showed that former smoking increased the risk of critical illness among inpatients with COVID-19, in an unadjusted analysis.[11] However, after adjustment for patients' characteristics including comorbidities, the increased risk was no longer seen. The adjusted variables were very similar between the study of Petrilli *et al.* and ours, except that ethnicity was almost completely homogeneous in our study. The weakened but still significant elevation of ORs after adjusting for comorbidities may be at least partly because of the presence of unmeasured or non-medicated comorbidities (e.g. registry data on diabetes did not include those with dietary therapy only) and unknown confounders. Another reason may be that if data are more frequently missing for former and current smokers than never smokers among patients with grade 3/4/5, the observed risk of severe COVID-19 for former and current smokers would

Table 3 Association between smoking status and severity grades of COVID-19

Sex / Smoking history	Grade 0 (no oxygen)	Grade 1/2/3/4/5 OR (95% CI) Adjusted for age and date of admission[a]	Grade 1/2/3/4/5 OR (95% CI) Adjusted for age, date of admission and comorbidities[a,b]	Grade 2/3/4/5 OR (95% CI) Adjusted for age and date of admission[a]	Grade 2/3/4/5 OR (95% CI) Adjusted for age, date of admission and comorbidities[a,b]	Grade 3/4/5 (IMV/ECMO/death) OR (95% CI) Adjusted for age and date of admission[a]	Grade 3/4/5 OR (95% CI) Adjusted for age, date of admission and comorbidities[a,b]	Grade 5 (death) OR (95% CI) Adjusted for age and date of admission[a]	Grade 5 (death) OR (95% CI) Adjusted for age, date of admission and comorbidities[a,b]
Men	n=7219	n=3031		n=772		n=554		n=392	
Current smoker	26.4%	16.1% 0.92 (0.81–1.06)	0.87 (0.76–1.00)	12.4% 0.99 (0.76–1.30)	0.89 (0.67–1.17)	11.4% 1.19 (0.85–1.66)	1.02 (0.72–1.45)	8.7% 1.44 (0.92–2.25)	1.41 (0.89–2.25)
Former smoker	24.3%	40.8% **1.29 (1.15–1.45)**	**1.22 (1.08–1.37)**	42.4% **1.43 (1.17–1.75)**	**1.29 (1.04–1.59)**	41.2% **1.51 (1.18–1.93)**	**1.32 (1.01–1.71)**	41.1% **1.65 (1.22–2.24)**	**1.50 (1.09–2.06)**
Never smoker	36.6%	29.5% 1 (reference)	1 (reference)	27.2% 1 (reference)	1 (reference)	25.1% 1 (reference)	1 (reference)	23.0% 1 (reference)	1 (reference)
Unknown	12.7%	13.7% 1.04 (0.90–1.22)	1.05 (0.90–1.23)	18.0% **1.33 (1.03–1.71)**	1.23 (0.94–1.61)	22.4% **1.76 (1.32–2.35)**	**1.58 (1.16–2.16)**	27.3% **2.42 (1.72–3.41)**	**2.37 (1.65–3.41)**
Women	n=5959	n=1457		n=276		n=209		n=181	
Current smoker	12.0%	4.9% 0.98 (0.74–1.29)	0.90 (0.67–1.20)	2.5% 0.73 (0.33–1.60)	0.61 (0.26–1.41)	1.0% 0.31 (0.08–1.29)	**0.21 (0.05–0.97)**	1.1% 0.43 (0.10–1.80)	0.43 (0.10–1.80)[c]
Former smoker	9.5%	13.9% **1.70 (1.40–2.06)**	**1.56 (1.28–1.91)**	13.8% **2.18 (1.47–3.23)**	**1.73 (1.12–2.67)**	11.5% **1.94 (1.20–3.15)**	1.40 (0.81–2.44)	9.9% **1.79 (1.03–3.10)**	**1.79 (1.03–3.10)[c]**
Never smoker	63.4%	60.7% 1 (reference)	1 (reference)	56.2% 1 (reference)	1 (reference)	56.0% 1 (reference)	1 (reference)	56.9% 1 (reference)	1 (reference)[c]
Unknown	15.1%	20.5% **1.20 (1.02–1.42)**	**1.21 (1.02–1.43)**	27.5% **1.52 (1.12–2.06)**	**1.42 (1.02–1.96)**	31.6% **1.72 (1.23–2.41)**	**1.61 (1.12–2.31)**	32.0% **1.63 (1.14–2.34)**	**1.63 (1.14–2.34)[c]**

Percentage values are for column.

IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

[a]Odds ratio (OR) and 95% confidence interval (CI) for each grade (using 'Grade 0' as reference) according to smoking history by a multiple logistic regression model; 10-year dummy variables were used to adjust for age; dummy variables for 2-month intervals were used to adjust for date of admission. ORs (95% CIs) marked with bold indicate statistically significant at $p<0.05$.

[b]Comorbidities were selected by a stepwise procedure using $P <0.10$ for entry and removal.

[c]None of the comorbidities were selected for adjustment.

be biased in the preventative direction. This explanation is possible because there were more missing data on smoking status for patients in the grade 3/4/5 than grade 0 groups (Table 3).

On the other hand, the risk of severe COVID-19 among current smokers was not as high as in former smokers. In a meta-analysis, significantly increased unadjusted ORs of severe COVID-19 for former and current smokers were reported.[19] As compared with current smokers, the pooled unadjusted OR was 1.85 (95% CI: 1.33–2.55) for former smokers whereas that for never smokers was not significant.[19] These results of a higher OR for former than current smokers were similar to those seen in our study. This may be due to current smokers not 'yet' being afflicted with the comorbidities that former smokers already had. Alternatively, ORs for current smoking may be biased in the preventative direction due to missing data, as explained above. Whether or not current smoking itself is directly related to the current risk of severe grade of COVID-19, it is reasonable to expect an increased risk of severe COVID-19 in the future because current smoking is an established risk factor for those different diseases including cardiovascular diseases, cancer and lung diseases that do increase the risk of severe COVID-19.

The group with 'unknown' smoking status had a significantly increased risk of severe COVID-19 as compared with never smokers. To determine the reason for this, the clinical characteristics of the 'unknown' smoking group were carefully examined. It was found that the proportion of 'unknowns' was significantly higher in patients who were treated by IMV/ECMO or died shortly after admission (within about 4 days) relative to all the other patients (36.8% and 14.2%, respectively, $P < 0.0001$) (not shown in the table). In all likelihood, information on smoking habits of patients who were suffering from severe COVID-19 already early after admission was unobtainable, and thus the risk of severe disease in the 'unknown' group was high. In other words, the observed association between 'unknown' smoking status and elevated risk of grade 3/4/5 was an example of 'reverse causality', i.e. patients with severe illness of COVID-19 could not be asked about their smoking status. Therefore, risk analyses for the severity of COVID-19 due to smoking should be carefully performed, particularly considering the reasons for both smoking cessation and an unknown smoking status. Petrilli *et al.* reported that an unknown smoking status was associated with an approximately 1.4-fold increased risk of both hospitalization and critical illness due to COVID-19.[11] Williamson *et al.* included patients with an unknown smoking status in the non-smoker group in their primary analysis, on the assumption that smoking would be likely to be recorded if present, and a sensitivity analysis showed the estimates were robust to the assumption.[8]

When examining the association between smoking status and COVID-19, there are three possible situations,. that is, A: becoming infected; B: having more severe disease leading to hospitalization or death; and C: getting worse given hospitalization with a positive SARS-CoV-2 test. Although former smoking was related to worse prognosis of COVID-19 among the hospitalized patients in our study (situation C), it was unknown whether smoking status was related to the risk of SARS-CoV-2 infection in the first place. Therefore, as an additional exploratory analysis for situation A, we compared the smoking status of our COVID-19 patients with data from the National Health and Nutrition Survey (NHNS) 2018,[16] which is a survey of a representative sample of the Japanese population, as a case-control study. Because all patients who tested positive for SARS-CoV-2 were hospitalized before 13 November 2020, according to the national policy in Japan, data of patients who were admitted before this day (2819 men and 3067 women, excluding 'unknown' smoking status) were used to assess the risk of infection. The age- and prefecture-adjusted ORs (95% CIs) of hospital admission due to COVID-19 were 5.64 (4.86–6.55) in men and 3.67 (2.95–4.58) in women for former smokers and 1.40 (1.24–1.57) in men and 1.70 (1.43–2.02) in women for current smokers. These results should be carefully interpreted especially regarding the weak ORs for current smoking because the details of the questionnaire about smoking in NHNS-2018 are different from the COVIREGI-JP and the 'unknown' smoking category was excluded from the latter. However, the marked increase in ORs for former smoking may suggest enhanced susceptibility to COVID-19 infection among former smokers. There are few studies that examined the risk of COVID-19 infection (situation A) in relation to smoking status. A case-control study to examine the risk of contracting COVID-19 according to smoking was conducted in health care workers in India.[20] There was no significant increase in the risk of COVID-19 according to smoking [adjusted relative risk for smokers (95% CI) = 1.09 (0.58–2.07)]. Further studies are necessary to resolve this issue.

Studies have also been conducted to determine the association between smoking and more severe disease leading to hospitalization or death due to COVID-19 (situation B). In the study by Petrilli *et al.*, former and current smokers had significantly decreased risks of hospital admission compared with never smokers, as mentioned above.[11] Williamson *et al.* reported that sex- and age-adjusted risks of COVID-19 significantly increased for both former smokers and current smokers as compared with never smokers. After adjusting for patients' characteristics

including comorbidities, the significantly increased risk for former smokers still remained, but the risk for current smokers became significantly lower.[8] In a study by Camille *et al.*, former smokers showed a significant increase and current smokers showed a non-significant increase in the risk of hospitalization for COVID-19 compared with never smokers after adjustment for patients' characteristics including comorbidities.[21]

Our primary analysis (situation C) showed that former smoking was associated with a significantly increased risk of more severe disease in COVID-19 inpatients. Petrilli *et al.* found that former smokers and current smokers did not have a significantly increased risk of critical COVID-19 illness compared with non-smokers among hospitalized COVID-19 patients, but that 'unknowns' did have.[11]

Taken together, these reports regarding associations between smoking status and COVID-19 are inconsistent in situations A, B and C. The reasons may include the fact that smoking status was not necessarily subdivided into non-smokers, former smokers, current smokers and 'unknown', and that adjusted confounding factors varied in the different studies. To unequivocally clarify this issue, a meta-analysis would be necessary considering the abovementioned factors, i.e. the situations A, B and C; smoking categories, especially former smoking and 'unknown'; adjustment for confounding factors essentially age and sex; and the potential mediating effects of comorbidities.

A limitation of the current study is that the number of cigarettes smoked, duration of smoking, type of cigarette products (e.g. electronic cigarettes) and passive smoking could not be investigated. Furthermore, as mentioned in the Methods, we had to exclude those patients who moved in or out of the hospital when we did not know the most intensive treatment, and to avoid the inclusion of duplicate data. On the other hand, our study has multiple strengths. The first is that we used large-scale data of 10 250 men and 7416 women. Second, we divided the smoking status into four categories considering comorbidities. This enabled us to reveal that former smoking and unknown smoking status may have special relevance.

In conclusion, former smokers were at high risk of severe COVID-19. This association could be explained as follows: (i) smokers are likely to suffer from smoking-related diseases such as cardiovascular disease, cancer and lung disease; (ii) smokers with these diseases may cease smoking due to being afflicted with them; and (iii) comorbid diseases increase the severity of COVID-19. Thus, the reason for severe COVID-19 would not be smoking cessation itself but the presence of smoking-related diseases that could have motivated the patient to quit smoking. Along these lines, it is reasonable to expect current smokers to be at increased risk of severe COVID-19 in the future because their current smoking is an established risk factor for the various different diseases that increase the risk of severe COVID-19. Smoking cessation may be a key factor to prevent smoking-related diseases and thereby to reduce the risk of severe COVID-19.

Author Contributions

YM takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript. TY, KH, NM, HO, SS, MT, SS and NO researched data. YM, TY, KH, NM, HO, SS, MT, SS, SM, SK, TM, HH, AK and NO contributed to discussions. YM wrote the manuscript. TY, KH, SS, MT and TM reviewed and edited the manuscript. All authors read and approved the final manuscript.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of Interest

None declared.

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