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Impact of accumulative smoking exposure and chronic obstructive pulmonary disease on COVID-19 outcomes: report based on findings from the Japan COVID-19 task force

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ABSTRACT

Objectives: Smoking and chronic obstructive pulmonary disease (COPD) are risk factors for severe COVID-19. However, limited literature exists on the effect of COPD and smoking on COVID-19 outcomes. This study examined the impact of smoking exposure in pack-years (PY) and COPD on COVID-19 outcomes among smokers in Japan.

Methods: The study included 1266 smokers enrolled by the Japan COVID-19 task force between February 2020 and December 2021. PY and COPD status was self-reported by patients. Patients were classified into the non-COPD (n = 1151) and COPD (n = 115) groups; the non-COPD group was further classified into <10 PY (n = 293), 10-30 PY (n = 497), and >30 PY (n = 361). The study outcome was the need for invasive mechanical ventilation (IMV).

Results: The incidence of IMV increased with increasing PY and was highest in the COPD group (<10 PY = 7.8%, 10-30 PY = 12.3%, >30 PY = 15.2%, COPD = 26.1%; *P* <0.001). A significant association was found for IMV requirement in the >30 PY and COPD groups through univariate (odds ratio [OR]: >30 PY = 2.11, COPD = 4.14) and multivariate (OR: >30 PY = 2.38; COPD = 7.94) analyses. Increasing PY number was also associated with increased IMV requirement in patients aged <65 years.

Conclusion: Cumulative smoking exposure was positively associated with COVID-19 outcomes in smokers.

Introduction

COVID-19 caused by SARS-CoV-2, has spread worldwide despite infection-control efforts, resulting in many cases and deaths [1,2]. The risk factors for COVID-19 include older age (>65 years) [3], male sex [4], obesity [5], and cardiovascular risk factors, such as hypertension and diabetes mellitus [6].

Although smoking rates have been decreasing on average annually worldwide, one in four to five adults will still reportedly be habitual smokers by the year 2022 [7]. Smoking is known to affect the severity of various bacterial and viral infections. Current and previous smokers are more likely to develop community-acquired pneumonia [8], invasive pneumococcal disease, and severe influenza [9] compared to never-smokers. Furthermore, smokers have a higher risk of mortality from Middle East respiratory syndrome coronavirus compared to never-smokers [10]. Several large-scale studies have demonstrated that smoking worsens the prognosis of COVID-19. Tortolero *et al.* [11] reported that a history of smoking was significantly associated with COVID-19 fatality after adjusting for age, sex, and ethnicity. Hou *et al.* [12] reported smoking to be associated with an increased risk of mortality in patients with COVID-19 (pooled relative risk: 1.19, 95% CI:1.12-1.27) in a meta-analysis comprising 73 references. However, the effect of smoking on COVID-19 remains controversial with regard to smoking status (current vs past smoking). Several reports have stated that current smoking was not associated with severe COVID-19 [13,14]; moreover, a large-scale observational study from Japan reported that only past smoking increased the risk of severity of COVID-19 in males, while current smoking did not [15]. However, Lacedonia *et al.* [16] reported that generally, COVID-19 patients with COPD had a higher 30-day all-cause mortality than non-COPD patients, mainly due to the presence of other comorbidities.

Several studies have focused on the relationship between smoking status and COVID-19 disease severity; however, only one study from the United States has reported on this relationship as a quantity-reaction relation [17]. The study demonstrated that patients who smoked more than 30 pack-years (PY) had a 2.25 times higher risk of hospitalization and were 1.89 times more likely to die following the diagnosis of COVID-19 compared to never-smokers [17]. However, no previous studies have compared the impact of smoking intensity and chronic obstructive pulmonary disease (COPD) status on COVID-19 severity.

We hypothesized that COPD would affect COVID-19 outcomes independently of or more strongly than smoking intensity, which has a dose-dependent relationship among smokers. Hence, the aim of this study was to compare the effects of smoking accumulation and COPD on COVID-19 outcomes.

Methods

Study design

The detailed study protocol is described elsewhere [18]. Briefly, the patients admitted with a diagnosis of COVID-19 in more than 70 participating facilities of the Japan COVID-19 task force between February 2020 and December 2021 were included in this study. Written or oral informed consent was obtained from all the patients, and the study was approved by the ethics committee of the Keio University School of Medicine (Approval No. 2020061) and the ethics committee at each facility. COPD complications were defined based on patients' self-reports during hospitalization. Figure 1 illustrates the consort diagram. Of the 3424 patients, those meeting the following criteria were excluded: incomplete medical records concerning smoking status (n = 467), COPD complications (n = 33), and never-smokers (n = 1675).

Therefore, 1266 patients with a smoking habit were included in this analysis (Figure 1). The patients were divided into the following four groups: non-COPD group with PY <10 (<10 PY group), non-COPD group with 10-30 PY (10-30 PY group), non-COPD patients with 10-30 PY (10-30 PY group), and COPD group.

Data collection and definition of the outcomes

The following information was extracted from the medical records: age, sex, body mass index (BMI), smoking status, comorbidities, laboratory findings on admission, bacterial infection, and COVID-19 outcomes, such as intensive care unit admission, need for invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation, and survival. Laboratory data were collected within 48 hours of the initial visit or admission, and clinical examination was performed according to the clinical care needs of the patient. Individual clinicians determined the history of COPD by interviewing each patient. For missing core data, the first clinician correlated the data. Missing patient background data were noted as unknown. Owing to the very low incidence of extracorporeal membrane oxygenation and death in this study [18], the need for IMV was considered as the primary outcome.

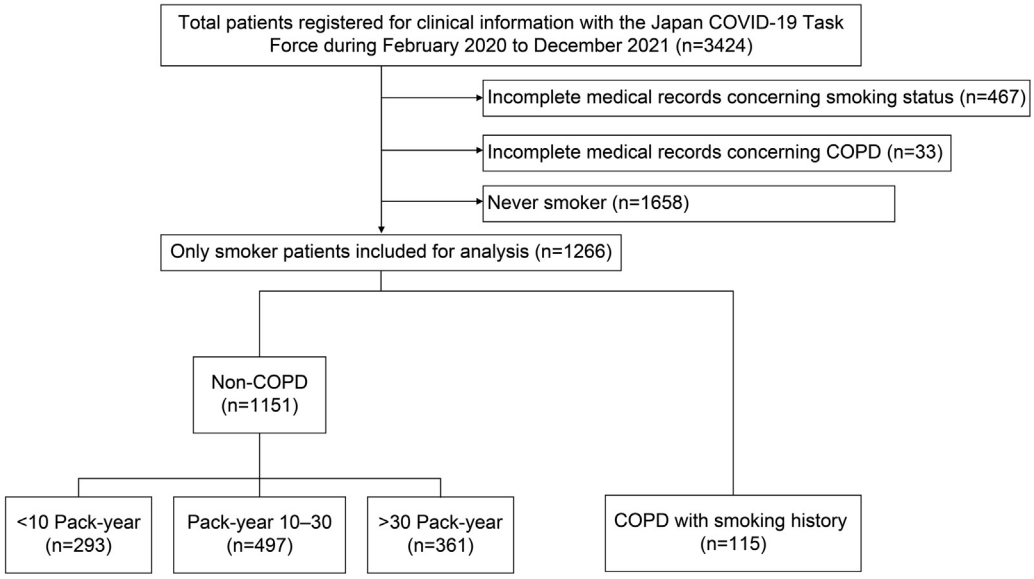

Figure 1. Population flow chart of the study cohort. A total of 3424 patients with COVID-19 were hospitalized during the study period; 500 patients with incomplete medical records and 1658 never-smokers were excluded. A total of 1266 smoking patients were included in the analysis. COPD, chronic obstructive pulmonary disease.

Statistical analysis

For the baseline characteristics, we obtained statistics using frequencies for categorical data as well as the mean and SD for continuous variables. Continuous variables are presented as means and standard deviations or medians and interquartile ranges. Data were compared among four groups: <10 PY, 10-30 PY, >30 PY, and COPD groups, using the one-way ANOVA or chi-square test, as considered appropriate. The Bonferroni test was used as a posthoc test. Comparisons between three or more groups were made using the one-way analysis of variance. To investigate the relationship between smoking history or COPD status and the need for IMV, a multivariable logistic regression analysis was performed while adjusting for COVID-19 severity factors, such as sex [4], BMI [5], hypertension, and diabetes mellitus [6], as reported previously. Age was considered a stratification factor according to previous publications. Owing to the strong correlation between smoking accumulation and age, we stratified the data by age (<65 years and ≥65 years). The adjusted odds ratio (OR) was presented with a 95% CI. A two-sided *P*-value of <0.05 was considered statistically significant. All the statistical analyses were performed using IBM SPSS® Statistics version 27.0 (IBM Corporation, Armonk, NY).

Results

Study population and baseline characteristics

A total of 1266 patients with a smoking habit were enrolled in the analysis: 293, 497, 361, and 115 patients were included in the <10 PY, 10-30 PY, >30 PY, and COPD groups, respectively. The baseline characteristics of the groups are shown in Table 1. PY positively correlated with male sex; males accounted for approximately 93.9% of the COPD cases. The median age also increased as the PY increased, with COPD being more prominent in older patients. The patients in the COPD group had a significantly lower BMI compared to those in the three non-COPD groups. The median PY of the >30 PY group was higher than that of the COPD group (50 vs 45). Considering the underlying diseases of each group, the >30 PY group had the highest percentage of hypertension, diabetes mellitus, cardiovascular disease, malignancy, and hyperuricemia among the four groups, including the COPD group.

Table 2 shows the comparison of the laboratory data and chest X-ray findings of the patients with COVID-19 between the four groups. Based on the laboratory data, as the PY and COPD incidence increased, a tendency for higher white blood cell and neutrophil counts, lower lymphocyte count, lower albumin, higher blood urea nitrogen, higher lactate dehydrogenase, higher ferritin, higher Krebs von den Lungen 6, and higher C-reactive protein was observed. Considering the chest X-rays at admission, both the rate of unilateral and bilateral ground glass opacity increased as the PY increased, with ground glass opacities being present in approximately 80% of the patients with COPD. A similar tendency was observed for bilateral infiltrating shadows. Rapid deterioration of the imaging findings within 48 hours of admission was most commonly observed in the COPD group, occurring in approximately 20% of the patients (Supplementary Table 1a); however, no significant difference was observed in the non-COPD group.

Bacterial infection and critical events among smokers

The analysis was divided into four groups (<10 PY, 10-30 PY, >30 PY, and COPD), and there were significant differences in the incidence of bacterial infections, considering post-hospitalization complications (Supplementary Figure 1b). Other complications were not significantly different between the groups owing to the sample size.

Quantitative relationship between smoking status and need for invasive mechanical ventilation

Figure 2 shows the incidence and relative risks of the need for IMV among smokers. The incidence increased with increasing PY and was highest in the COPD group (<10 PY: 7.8%, 10-30 PY: 12.3%, >30 PY: 15.2%, COPD: 26.0%; chi-square test, P <0.001). The univariate analysis demonstrated that patients in the >30 PY and COPD groups were 2.11 (95% CI: 1.26-3.52) and 4.14 (95% CI: 2.28-7.52) times more likely to require IMV, respectively, compared to those of the <10 PY group. Upon categorizing between <65 year and ≥65 year, younger patients of the 10-30 PY group showed a 2.22 times (95% CI: 1.11-4.45) risk of needing IMV compared to those of the <10 PY group, similar to the >30 PY and COPD groups.

Table 1
Baseline characteristics of non-COPD and COPD smoker patients with COVID-19, with non-COPD patients classified by pack-year.

	All (n = 1266)	Non-COPD with <10 PY[a] (n = 293)	Non-COPD with PY 10-30[a] (n = 497)	Non-COPD with >30 PY[a] (n = 361)	COPD (n = 115)	*P*-value
Sex, male (%)	1087 (85.9)	227 (77.5)	423 (85.1)	329 (91.1)	108 (93.9)	<0.001[b]
Age (mean ± SD)	57.8 ± 15.3	47 ± 16.9	54 ± 13.2	66 ± 10.9	70 ± 10.6	<0.001[c]
Body mass index (kg/m^2) (median, IQR)	24.5 (22.2-27.3)	24.4 (21.6-27.2)	25.1 (22.7-28)	24.4 (22.1-27.1)	23 (21.2-25.6)	0.001[c]
Japanese (%)	1246 (98.4)	282 (96.2)	492 (99.0)	358 (99.2)	114 (99.1)	0.009[b]
Smoking status						
Current / past (n, %)	408 (32.2) / 858 (67.8)	91 (31.1) / 202 (68.9)	172 (34.6) / 325 (65.4)	114 (31.6) / 247 (68.4)	31 (27) / 84 (73)	0.000[b]
Pack-year (median, IQR)	20 (10-40)	4 (1.5-6.1)	20 (14.5-24)	50 (40-70)	45 (36-67.5)	<0.001[c]
Comorbidities - no (%)						
Hypertension	463 (36.6)	67 (22.9)	172 (34.6)	171 (47.4)	53 (46.1)	<0.001[b]
Diabetes	291 (23)	46 (15.7)	93 (18.7)	132 (36.6)	20 (17.4)	<0.001[b]
Cardiovascular disease	142 (11.2)	17 (5.8)	49 (9.9)	63 (17.5)	13 (11.3)	<0.001[b]
Neoplasm	89 (7)	15 (5.1)	23 (4.6)	40 (11.1)	11 (9.6)	<0.001[b]
Autoimmune disease	45 (3.6)	9 (3.1)	16 (3.2)	13 (3.6)	7 (6.1)	0.465[b]
Asthma	84 (6.6)	24 (8.2)	32 (6.4)	18 (5.0)	10 (8.7)	0.296[b]
Hyperuricemia	171 (13.5)	36 (12.3)	68 (13.7)	54 (15.0)	13 (11.3)	0.686[b]
Chronic liver disease	66 (5.2)	11 (3.8)	29 (5.8)	18 (5.0)	8 (7.0)	0.502[b]
Chronic kidney disease	98 (7.7)	17 (5.8)	33 (6.6)	31 (8.6)	17 (14.8)	0.013[b]

COPD, chronic obstructive pulmonary disease.
[a] Non-COPD patients were classified by pack-year.
[b] Chi-square test.
[c] One-way ANOVA test.

Table 2
Comparison of the laboratory data and chest X-ray findings of non-COPD and COPD smoker patients with COVID-19.

Laboratory data - median (IQR)	All (n=1266)	Non-COPD with <10 PY[a] (n=293)	Non- COPD with PY 10-30[a] (n=497)	Non-COPD with >30 PY[a] (n=361)	COPD (n=115)	*P*-value
White blood cell count (/μl)	5300 (4100-6800)	5200 (4100-6595)	5085 (4100-6600)	5550 (4335-7035)	5650 (3900-8200)	0.005[c]
Neutrocyte count (/μl)	3571 (2566-5090)	3427 (2374-4871)	3376 (2486-4810)	3780 (2843-5429)	3803 (2489-6120)	0.003[c]
Lymphocyte count (/μl)	950 (673-1308)	1008 (705-1384)	944 (710-1315)	920 (667-1306)	741 (492-1112)	<0.001[c]
Eosinophil count (/μl)	8.4 (0-42)	9.8 (0-51)	8.4 (0-41)	8.1 (0-40)	0 (0-36)	0.892[c]
Hemoglobin (g/dl)	14.6 (13.4-15.7)	14.8 (13.7-15.8)	14.8 (13.7-15.8)	14.4 (13-15.5)	14.1 (12.5-15.2)	<0.001[c]
Platelet count ($\times$ 10^4/μl)	18.5 (15-23.1)	19.3 (15.5-24.5)	18.4 (15.1-22.6)	18.4 (14.5–23.2)	17.5 (14.2-22.7)	0.239[c]
Albumin (g/dl)	3.8 (3.3-4.1)	4 (3.5-4.3)	3.8 (3.3-4.2)	3.6 (3.1-4)	3.5 (2.8-3.9)	<0.001[c]
Total billirubin (mg/dl)	0.6 (0.5-0.8)	0.6 (0.5-0.8)	0.6 (0.4-0.8)	0.6 (0.5-0.8)	0.6 (0.5-0.8)	0.439[c]
Alkaline phosphatase (U/l)	136 (71-209)	130 (68-202)	128 (69-205)	148 (73-218)	158 (73-228)	0.172[c]
γ-Glutamyl Transpeptidase (U/l)	50 (28-99)	46 (25-97)	53 (29-101)	50 (30-99)	46 (26-107)	0.807[c]
Aspartate aminotransferase (U/l)	34 (25-50)	31 (23-47)	35 (25-50)	38 (27-53)	34 (26-47)	0.069[c]
Alanine aminotransferase (U/l)	29 (19-49)	29 (17.3-47.8)	31 (20-52)	29 (19-50)	26 (17-38)	0.184[c]
Blood urea nitrogen (mg/dl)	14.8 (11-20)	12.9 (10.2-17.0)	14 (11-19)	16.6 (13-22)	18 (13-24)	<0.001[c]
Creatinine (mg/dl)	0.88 (0.75-1.05)	0.85 (0.73-0.98)	0.89 (0.74-1.04)	0.91 (0.79-1.1)	0.9 (0.71-1.06)	0.065[c]
Lactate dehydrogenase (U/l)	259 (202-359)	235 (189-313)	256 (200-351)	274 (215-380)	313 (222-396)	<0.001[c]
Uric acid (mg/dl)	4.8 (3.9-6.0)	4.8 (4-6)	4.8 (3.9-6)	5 (3.9-6.1)	4.8 (3.6-6.3)	0.889[c]
Ferritin (ng/ml)	486 (257-874)	384 (179-759)	505 (285-822)	517 (282-999)	562 (248-1004)	0.004[c]
Krebs von den Lungen 6 (U/ml)	260 (189-386)	220 (167-302)	246 (183-350)	318 (216-473)	358 (220-650)	<0.001[c]
D-dimer (ng/ml)	0.9 (0.6-1.5)	0.8 (0.5-1.2)	0.8 (0.5-1.3)	1 (0.6-1.9)	1.1 (0.8-2.3)	0.139[c]
C-reactive protein (mg/dl)	3.9 (1.2-8.5)	2.6 (0.4-6.5)	3.4 (1.1-8.0)	5.2 (2-10)	5.1 (2.5-9.3)	<0.001[c]
Chest X-ray findings -no (%)						
Ground glass opacity unilateral / bilateral	142 (11.2) /747 (59)	27 (9.2) / 141 (48.1)	58 (11.7) / 288 (57.9)	42 (11.6) / 240 (66.5)	15 (13.0) / 78 (67.8)	<0.001[b]
Infiltration shadow unilateral / bilateral	115 (9.1) / 282 (22.3)	24 (8.2) / 49 (16.7)	39 (7.8) / 111 (22.3)	40 (11.1) / 87 (24.1)	12 (10.4) / 35 (30.4)	0.022[b]

COPD, chronic obstructive pulmonary disease.
[a] Non-COPD patients were classified by pack-year.
[b] Chi-square test.
[c] One-way ANOVA test.

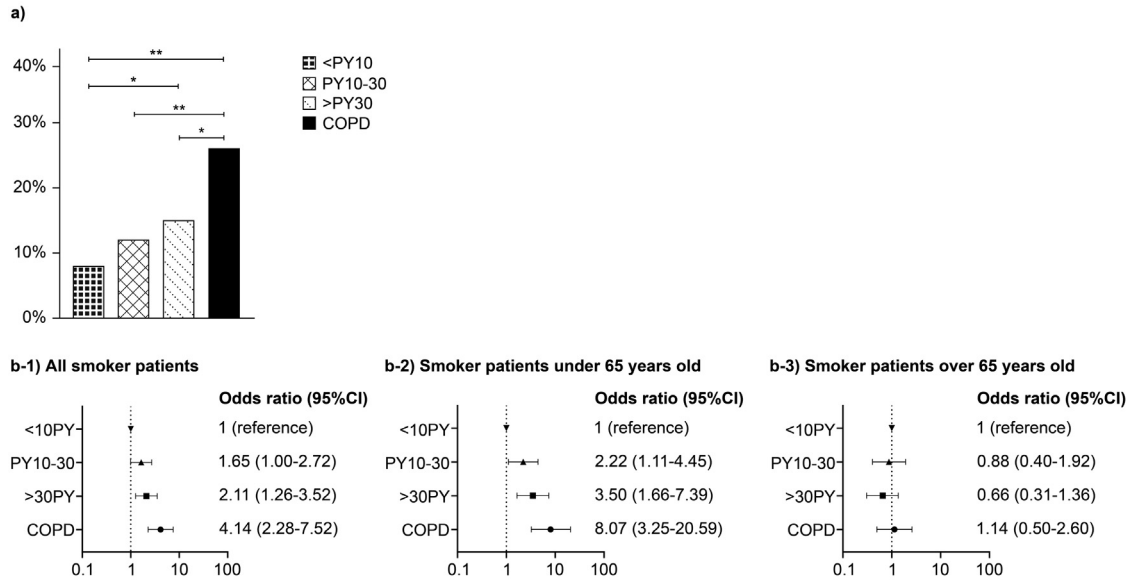

Figure 2. (a) Incidence of bacterial infection among non-COPD patients classified by PY and COPD patients. (b) Incidence of intensive care unit admission, requirement of invasive mechanical ventilation, extracorporeal membrane oxygenation, and death among smokers. One-way analysis of variance with Bonferroni test: $^{**}P$ <0.001, $^{*}P$ <0.05. COPD, chronic obstructive pulmonary disease; PY, pack-year.

Table 3
Results of the multivariate analysis on smoking status and need for invasive mechanical ventilation divided by age (over and under 65).

	Adjusted for sex[a]		Adjusted for sex and BMI[a]		Adjusted for sex, BMI, hypertension and diabetes[a]	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Smoker patients under 65 years old						
<10 PY	1 (ref)		1 (ref)		1 (ref)	
10-30 PY	2.13 (1.06-4.27)	0.034	1.81 (0.89-3.68)	0.104	1.73 (0.84-3.54)	0.134
>30 PY	3.25 (1.54-6.89)	0.002	2.98 (1.40-6.37)	0.005	2.38 (1.10-5.15)	0.027
COPD	7.30 (2.92-18.59)	<0.001	8.97 (3.50-22.96)	<0.001	7.94 (2.99-20.74)	<0.001
Smoker patients over 65 years old						
<10 PY	1 (ref)		1 (ref)		1 (ref)	
10-30 PY	0.86 (0.40-1.89)	0.712	0.82 (0.36-1.86)	0.636	0.92 (0.39-2.17)	0.855
>30 PY	0.61 (0.29-1.29)	0.198	0.61 (0.28-1.33)	0.211	0.59 (0.26-1.33)	0.202
COPD	1.07 (0.47-2.46)	0.868	1.04 (0.99-2.24)	0.936	1.20 (0.48-2.99)	0.696

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; PY, pack-year.
[a] Forced entry method.

Table 3 shows the results of the multivariate analysis of the need for IMV study outcome. Among patients <65 years, the risk of requiring IMV was 2.13, 3.25, and 7.30 times higher for the 10-30 PY, >30 PY, and COPD groups, respectively, after adjusting for sex. In addition, after adjusting for sex, BMI, hypertension, and diabetes, the risk of needing IMV remained 2.38 and 7.94 times higher in the >30 PY and COPD groups, respectively. Supplementary Table 1 shows the baseline characteristics of smokers ≥65 years and <65 years. Patients with COPD were also subdivided according to PY, and a similar trend was observed with non-COPD patients (Supplementary Table 2).

Discussion

This study demonstrated that in non-COPD patients, smoking intensity was significantly associated with the risk of severe COVID-19 disease, specifically, the risk of requiring IMV. Moreover, the presence of COPD was associated with an even greater risk than smoking intensity. To our knowledge, this is the first study to compare the impact of COPD status and quantitative smoking index on COVID-19 outcomes. Several studies have reported on the association between smoking and fatality attributed to COVID-19. Tortolero *et al.* [11] reported that after adjusting for age, the association between smoking and fatality remained statistically significant (OR 1.73, 95% CI: 1.34-2.22, P <0.001), and after adjusting for age, sex, race, and the number of comorbidities, the risk of mortality among patients with a history of smoking was 1.54 times greater compared to that of never-smokers [11]. Our data in this study showed that smokers had 1.032 times higher risk of needing IMV; however, a significant difference in mortality was not observed.

The impact of smoking intensity on COVID-19 was quantitatively evaluated using the number of PY. Only one study demonstrated that the accumulation of PY results in severe COVID-19 disease [17]. Similar to their study, our results showed that as the cigarette consumption dose increased from <10 PY to 10-30 PY and >30 PY, the median age and underlying diseases of the patients tended to increase, which was considered the reason for the observed quantity-response relationship.

An analysis of the comorbidities in patients with COVID-19 across China demonstrated COPD to be a risk factor for intensive care unit admission, IMV, or death (OR: 2.68, 95% CI: 1.42-5.05, *P*-value = 0.002), even after adjusting for age and smoking [2]; however, it focused on the COPD group with the worst outcomes, rather than the group with the highest smoking exposure i.e., the >30 PY group. It is predicted that in addition to the direct associa-

tion between smoking and COVID-19 severity, COPD features, such as structural destruction of the lungs, could also contribute to the disease severity [19].

Aging is one of the most significant confounders of COVID-19 [3], and the number of PY is directly affected by age. Therefore, we analyzed the impact of smoking on COVID-19 in younger and older adults and set the age threshold at 65 years [20]. The smoking intensity was more strongly associated with COVID-19 severity in younger patients than in older patients. This could be attributed to smoking having a weaker influence on the critical illness of older adults owing to their many underlying diseases. Matsushita *et al.* [15] reported a higher risk of severe disease in former smokers than in current smokers owing to the greater number of underlying diseases attributed to smoking.

Smoking is an important risk factor for both viral and bacterial respiratory infections [9], and bacterial infections are more common in patients with COPD [21]. Patients with COPD also develop bacterial infections secondary to viral infections, such as influenza [22]. In the present study, bacterial infection was 1.36 times (95% CI: 1.07-1.73) more frequent in smokers than in never-smokers, and 2.49 times (95% CI: 1.58-3.91) more frequent in patients with COPD. Thus, in COVID-19, as well as in other viral infections such as influenza, smoking increased the rate of secondary bacterial infections, and this rate further increased with the accumulation of smoking. Furthermore, the incidence of bacterial infections also increased with increasing PY and was the highest in patients with COPD.

This study had certain limitations. First, heated cigarettes have accounted for 20-30% of smoking in Japan in recent years [23]. However, this database did not have detailed data regarding the use of heated cigarettes. Second, the presence of COPD in this study was based on the patients' self-completed questionnaire, which could have been underestimated owing to the absence of pulmonary function tests. Pulmonary function testing is difficult in the acute phase of COVID-19 because of the risk of spreading infection to the surroundings [24]. Moreover, many studies on COVID-19 have reported that COPD contributes to the severity of COVID-19 based on self-audit COPD diagnoses [25].

The underestimation of COPD in the population is a problem; however, our study demonstrated that smoking dose and COPD remain risk factors for severe COVID-19 disease, even after considering an underestimation. Indeed, the incidence of COPD has been reported to correlate with smoking index [26], and it is possible that COPD will be more prevalent among patients with high smoking intensity, especially among those with PY >30. However, we recognize that the COPD group has showed a significant impact on outcomes compared to the non-COPD group, which possibly includes patients with undiagnosed COPD. Therefore, COPD remains as an important risk factor for severe COVID-19, although we may be underestimating it. Third, detailed findings on computed tomography and a comparison of the relationship between emphysema, airway thickness, and COVID-19 disease severity were not evaluated.

In conclusion, our results showed that smoking intensity was additively associated with COVID-19 outcomes, and COPD affected disease severity more than smoking accumulation, especially in patients aged <65 years. Thus, healthcare providers should obtain a detailed smoking history, including PY, from patients diagnosed with COVID-19. Patients with COPD or >30 PY should also be monitored closely for disease severity, especially those younger than 65 years.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Ethical approval

This study was approved by the ethics committee of the Keio University School of Medicine (20200061) and affiliated institutes.

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Author contributions

Conceptualization: M.W., K.M., S.C., H.N., T.A., H.K., M.I., N.H., and K.F. Data curation: M.W., H.T., H.L., A.M., S.O., K.N., M.W., and T.K. Formal analysis: M.W., K.M., S.C. Methodology: M.W., S.C., and H.N. Supervision: S.C., N.H., T.A., H.K, M.I., N.H., N.H., T.U., S.U., T.I., K.A., F.S., T.Y., Y.N., Y.M., Y.S., K.M., Y.O., R.K., Y.K., A.K., S.I., S.M., S.O., T.K., and K.F. Visualization: S.C., H.N., and T.A. Writing—original draft: W.M., K.M., T.A., S.C., and H.N. Writing—reviewing and editing: W.M., K.M., T.A., S.C., N.H., H.K, M.I., N.H., N.H., T.U., S.U., T.I., K.A., F.S., T.Y., Y.N., Y.M., Y.S., K.M., Y.O., R.K., Y.K., A.K., S.I., S.M., S.O., T.K., and K.F.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.12.019.

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