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## Original article

# Influence of smoking history on the evolution of hospitalized in COVID-19 positive patients: Results from the SEMI-COVID-19 registry



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## ABSTRACT

**Introduction:** Smoking can play a key role in SARS-CoV-2 infection and in the course of the disease. Previous studies have conflicting or inconclusive results on the prevalence of smoking and the severity of the coronavirus disease (COVID-19).

**Methods:** Observational, multicenter, retrospective cohort study of 14,260 patients admitted for COVID-19 in Spanish hospitals between February and September 2020. Their clinical characteristics were recorded and the patients were classified into a smoking group (active or former smokers) or a non-smoking group (never smokers). The patients were followed up to one month after discharge. Differences between groups were analysed. A multivariate logistic regression and Kaplan Meier curves analysed the relationship between smoking and in-hospital mortality.

**Results:** The median age was 68.6 (55.8–79.1) years, with 57.7% of males. Smoking patients were older (69.9 (59.6–78.0 years)), more frequently male (80.3%) and with higher Charlson index (4 (2–6)) than non-smoking patients. Smoking patients presented a worse evolution, with a higher rate of admission to the intensive care unit (ICU) (10.4 vs. 8.1%), higher in-hospital mortality (22.5 vs. 16.4%) and readmission at one month (5.8 vs. 4.0%) than in non-smoking patients. After multivariate analysis, smoking remained associated with these events.

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◇ The complete list of members of the SEMI-COVID-19 group is listed in the Appendix.

**Conclusions:** Active or past smoking is an independent predictor of poor prognosis in patients with COVID-19. It is associated with higher ICU admissions and in-hospital mortality.

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## Influencia de la historia de tabaquismo en la evolución de la hospitalización en pacientes COVID-19 positivos: datos del registro SEMI-COVID-19

### R E S U M E N

**Introducción:** El tabaquismo puede tener un papel importante en la infección por SARS-CoV-2 y en el curso de la enfermedad. Los estudios previos muestran resultados contradictorios o no concluyentes sobre la prevalencia de fumar y la severidad en la enfermedad por coronavirus (COVID-19).

**Material y métodos:** Estudio de cohortes observacional, multicéntrico y retrospectivo de 14.260 pacientes que ingresaron por COVID-19 en hospitales españoles desde febrero a septiembre de 2020. Se registraron sus características clínicas y se clasificaron en el grupo con tabaquismo si tabaquismo activo o previo o en el grupo sin tabaquismo si nunca habían fumado. Se realizó un seguimiento hasta un mes después del alta. Se analizaron las diferencias entre grupos. La relación entre tabaquismo y mortalidad intrahospitalaria se valoró mediante una regresión logística multivariante y curvas de Kaplan Meier.

**Resultados:** La mediana de edad fue 68,6 (55,8–79,1) años, con un 57,7% de varones. El grupo con tabaquismo presentó mayor edad (69,9 (59,6–78,0 años)), predominio masculino (80,3%) y mayor índice de Charlson (4 (2–6)). La evolución fue peor en estos pacientes, con una mayor tasa de ingreso en UCI (10,4 vs 8,1%), mayor mortalidad intrahospitalaria (22,5 vs 16,4%) y reingreso al mes (5,8 vs 4,0%) que el grupo sin tabaquismo. Tras el análisis multivariante, el tabaquismo permanecía asociado a estos eventos.

**Conclusiones:** El tabaquismo de forma activa o pasada es un factor predictor independiente de mal pronóstico en los pacientes con COVID-19, estando asociada a mayor probabilidad de ingreso en UCI y a mayor mortalidad intrahospitalaria.

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**Palabras clave:**  
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## Introduction

On 11th March 2020, the World Health Organisation (WHO) declared a coronavirus pandemic (COVID-19), the aetiological agent of which was SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*). Previous studies have shown that the incidence of severe disease is higher in men, in people over 65 years of age and in those with chronic health conditions, mainly diabetes and obesity<sup>1</sup>, which leads to a longer average hospital stay and an increased risk of death<sup>2,3</sup>. Research into the factors that may influence the prognosis of the disease is essential to better understand the progression of patients and to establish strategies for their management, aiming to improve their survival.

One of the factors that has been studied is smoking. Smoking increases the risk of infections in general, both bacterial and viral<sup>4</sup>, and causes inflammation of the respiratory tract mucosa through the release of inflammatory mediators such as IL-8 or IL-1 $\beta$ <sup>5</sup>. In addition, SARS-CoV-2 penetrates through the mucous membranes and invades the respiratory tract, reaching the lung through receptors. One of these receptors is the angiotensin-converting enzyme 2 (ACE-2) receptor, which is most frequently expressed in alveolar macrophages and type 2 pneumocytes in the alveoli of smokers<sup>6</sup>. There appears to be a direct correlation between smoking, time of exposure to tobacco smoke and ACE-2 receptor expression. This implies that the longer smokers are exposed to tobacco smoke, the greater the number of receptors in their membranes and, therefore, the greater the risk of coronavirus lung infection<sup>7,8</sup>. In addition, binding to these receptors will control the release of ACE, which seems to play a key role in the inflammatory response of COVID-19<sup>9</sup>. Therefore, smoking may play a key role in SARS-CoV-2 infection and the course of the disease. However, previous studies have contradictory or inconclusive results in relation to the prevalence of smoking and COVID-19, they are not designed to understand the impact that tobacco causes on COVID-19, and the available data come from mainly Asian studies<sup>6,10</sup>.

The objective of this study was to analyse the possible association of smoking with higher in-hospital mortality from all causes in patients with COVID-19 in Spain.

The secondary objectives were: 1) study the progression of the disease, complications and admission to Intensive Care (ICU) during hospitalization and events at 30 days (mortality or readmission), 2) analyse the differences between active smokers and former smokers.

## Methods

### Patients

Patient data were collected from the SEMI-COVID-19 Registry, a national observational, multicentre, retrospective cohort study of 132 Spanish hospitals, presently recruiting. Inclusion criteria were age over 18, first hospital admission from February to September 2020 with a diagnosis of COVID-19, with microbiological confirmation by RT-PCR (reverse transcriptase polymerase chain reaction) of nasopharyngeal, sputum or bronchoalveolar lavage swab specimens. Patients were excluded if the variable *smoking* was not collected, if they were re-admitted or if they did not wish to participate after informed consent.

### Variables

Registry information was available in the study published by Casas-Rojo et al.<sup>12</sup>, which included the procedures and described the baseline characteristics of the patients in the registry. Some 300 variables were retrospectively collected, including epidemiological data, medical history (including smoking history), previous medications, symptoms and physical examination findings on admission, and laboratory and radiological imaging data on admission and 7 days after admission, or prior to ICU admission, as well as pharmacological treatment, ventilatory support and complications

during hospitalization and progression during the first month after discharge.

Patients were classified by smoking history into two groups: smoking group with those active smokers or former smokers and as non-smoking group with those who had never smoked.

The qSOFA index (*quick Sequential Organ Failure Assessment score*) based on respiratory rate, systolic pressure and state of consciousness, and the Charlson index according to previous comorbidities. History of myocardial infarction, angina pectoris, heart failure, and atrial fibrillation were grouped as cardiovascular disease.

Disease progression during hospitalization was considered to be the combined event of death, mechanical ventilation, and/or admission to the ICU. Regarding complications during admission, acute respiratory distress syndrome, bacterial pneumonia, sepsis/multiple organ failure/shock, heart failure, acute myocardial infarction, arrhythmias, renal failure, stroke, and venous thromboembolism were considered.

*Ethical aspects*

The study protocol was approved by the Provincial Research Ethics Committee of Malaga (Spain) following the recommendations of the Spanish Agency of Medicines and Medical Devices (AEMPS). The STROBE (*Strengthening the Reporting of Observational Studies in Epidemiology*) recommendations for the design of observational cohort studies were followed. All patients provided their informed consent. When written consent was not possible for biosafety reasons or if the patient had already been discharged, informed consent was given verbally and recorded in the medical record.

*Statistical analysis*

The results of the variables were expressed as mean (standard deviation) or median (interquartile range) according to the normal distribution criteria evaluated with the Kolmogorov Smirnov test. Continuous variables were compared using the Student *t*-test or the Mann-Whitney *U* test. Categorical variables were expressed as frequencies and percentages and were compared using the  $\chi^2$  test.

A multivariate logistic regression was used to evaluate the relationship between smoking and in-hospital mortality. The variables considered possible confounding or modifying factors were age, sex, Charlson index adjusted for age, degree of moderate-severe dependence, alcohol consumption, smoking, obesity, moderate-severe chronic renal failure, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea syndrome (OSAS), cancer and cardiovascular disease. The analysis was carried out using backward stepwise regression. In-hospital mortality in the first 100 days was also analysed using Kaplan Meier curves (with *log-rank*). Similarly, for the analysis of the influence of smoking on the secondary objectives of disease progression, complications, admission to the ICU and mortality or readmission at one month, a multivariate analysis was performed with the same variables, changing the result variable.

For the analysis of active smokers vs. former smokers, a univariate comparison was made using the  $\chi^2$  test.

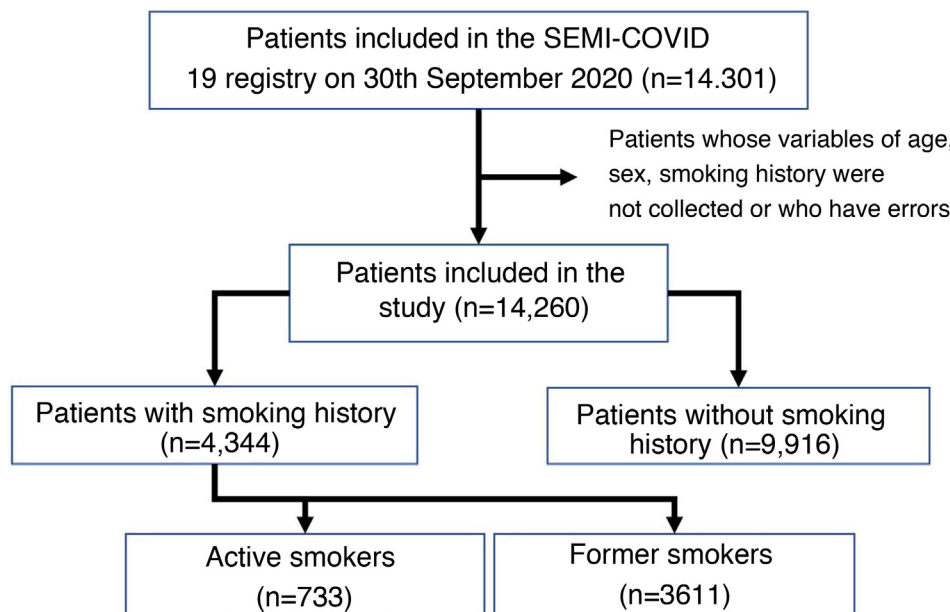
A value of  $p < 0.05$  was considered statistically significant. The SPSS version 25.0 statistical software (IBM Inc., Chicago, IL, USA) was used.

**Results**

*Baseline patient characteristics*

As of 30th September 2020, the SEMI-COVID-19 registry included 14,301 patients, of whom 14,260 met the inclusion criteria for our analysis (see Fig. 1). Characteristics are shown in Table 1, with a mean age of 68.6 (55.8–79.1), 57.7% male and a hospital stay of 9 days (5–14 days). The smoking group was significantly older, predominantly male, and had more cardiovascular risk factors and comorbidities than the non-smoking group (Table 1).

With regard to their symptoms (Table 2), dyspnoea was more common in patients with smoking and fever and gastrointestinal symptoms in patients without smoking. In addition, patients with smoking were admitted with an elevated qSOFA index ( $\geq 2$ ) and oxygen saturation  $< 90\%$  in a higher percentage than patients without smoking (9.9 vs. 8.5% and 33.9 vs. 31.0%,  $p < 0.01$ , respectively), while in the latter radiological lung involvement was more common. Patients with smoking also had a higher percentage of poor



**Figure 1.** Flowchart of patient inclusion.

**Table 1**  
Patient demographics and co-morbidities according to smoking history.

	Total (n = 14.260)	Non-smoking group (n = 9.916)	Smoking group (n = 4.344)	P
Age (years)	68.6 (55.8–79.1)	67.8 (53.8–79.6)	69.9 (59.6–78.0)	<0.001
Sex (male)	8.221 (57.7)	4.732 (47.7)	3.489 (80.3)	<0.001
Days of hospitalization	9 (5–14)	8 (5–13)	9 (6–15)	<0.001
Age-Adjusted Charlson Comorbidity Index	3 (1–5)	3 (1–5)	4 (2–6)	<0.001
Degree of dependency (moderate-severe)	2.179 (15.4)	1.585 (16.1)	594 (13.8)	<0.001
Alcohol use disorder	652 (4.6)	177 (1.8)	475 (11.1)	<0.001
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	2.904 (21.9)	1.864 (20.2)	1.040 (25.6)	<0.001
Hypertension	7.180 (50.4)	4.690 (47.3)	2.490 (57.4)	<0.001
Dyslipidemia	5.575 (39.1)	3.514 (35.5)	2.061 (47.5)	<0.001
Diabetes mellitus	2.764 (19.4)	1.729 (17.5)	1.035 (23.8)	<0.001
Anxiety Depression	1993 (14.0)	1.443 (14.4)	570 (13.2)	0.053
Malignant disease (solid tumour, leukaemia, lymphoma)	1.459 (10.3)	833 (8.4)	626 (14.4)	<0.001
Cardiovascular disease (myocardial infarction, angina pectoris, heart failure, atrial fibrillation)	2.691 (18.9)	1.529 (15.5)	1.162 (26.8)	<0.001
Cerebrovascular disease	93 (0.7)	62 (0.6)	31 (0.7)	0.545
COPD/chronic bronchitis	1.314 (9.2)	301 (3.0)	1.013 (23.3)	<0.001
Asthma	1.026 (7.2)	735 (7.4)	291 (6.7)	0.134
Obstructive sleep apnoea/hypopnea syndrome	862 (6.1)	401 (4.1)	461 (10.7)	<0.001
Moderate-severe kidney disease	851 (6.0)	515 (5.2)	336 (7.7)	<0.001

Data are expressed as median (25th percentile–75th percentile) for quantitative variables and as frequencies (percentages) for categorical variables.  
COPD: chronic obstructive pulmonary disease; BMI: body mass index.

prognostic laboratory parameters, with lymphopenia 42.6 vs. 37.7% and high levels of CRP (52.2 vs. 49.9%), ferritin (50.6 vs. 45.5%), D-dimer (33.9 vs. 31.3%) and LDH (33.0 vs. 29.7%),  $p < 0.01$ .

#### Patient outcomes and events

Overall, 8.8% required admission to the ICU, with a higher frequency in the smoking group (10.4% vs. 8.1%,  $p < 0.001$ ). The need for non-invasive or invasive mechanical ventilation was also higher in the smoking group (6.5 vs. 4.5% and 8.0 vs. 6.6%,  $p < 0.001$ , respectively). In addition, these also received empirical antibiotic therapy (91.0 vs. 88.6,  $p < 0.001$ ) and immunosuppressive or immunomodulatory treatments in higher percentages, such as corticosteroids in 41.0% of the smoking group vs. 33.8% of the non-smoking group,  $p < 0.001$  (Table 3).

The smoking group had more complications and mortality during admission than the non-smoking group (52.5% vs. 48.3% and 22.5% vs. 16.4%, respectively). Acute respiratory distress syndrome was the most common complication in both groups (with 28.8% moderate-severe distress in the smoking group vs. 22.2% in the non-smoking group).

Radiological worsening and disease progression also occurred more commonly in the smoking group than in the non-smoking group (42.6 vs. 36.5% and 30.2 vs. 23.0%, respectively).

At one-month post-discharge there were more readmissions in the smoking group, but the mortality rate was not higher.

In the subanalysis carried out to see the differences between smokers and former smokers, it was observed that the former smokers were older, with a higher percentage of men, Charlson comorbidity index and a moderate to severe degree of dependence. They also had more cardiovascular risk factors and comorbidities (although there were no differences in respiratory diseases and renal failure). Clinical symptoms and laboratory parameters were similar, as were admissions to the ICU and the need for ventilation. However, former smokers required a higher percentage of immunomodulatory and antibiotic treatment and had more complications on admission such as in-hospital mortality (23.6 vs. 17.6%,  $p < 0.001$ ), radiological worsening and disease progression, as well as readmissions (Appendix B Supplementary Tables 1–3).

A binary logistic regression was used to evaluate the factors that influenced in-hospital mortality, where the history of smoking (active or former) was an independent variable (OR 1.148 CI 95% 1.021–1.290,  $p = 0.021$ ). In addition to smoking history,

other independent variables for in-hospital mortality were age, male gender, age-adjusted Charlson comorbidity index, moderate-severe degree of dependence, obesity, and cardiovascular disease (Table 4). Smoking was also an independent variable of ICU admission and readmissions at one month, but not of disease progression, complications during admission, or death at one month (Appendix B Supplementary Tables 4–8).

Fig. 2 shows the Kaplan Meier curves for in-hospital mortality in the first 100 days. It shows how patients in the smoking group died earlier than those in the non-smoking group.

#### Discussion

This study analysed data from the SEMI-COVID-19 registry, currently the most extensive database available in Spain with patients admitted for COVID-19. The prevalence of smoking in Spain is high and the mortality attributed to its use in people over 35 years of age is also significant (12.9% of total mortality), mainly due to tumours, followed by cardiovascular and respiratory diseases<sup>11</sup>. In addition, COVID-19 also has both cardiovascular and pulmonary effects. This study assesses the association of smoking with mortality in patients with COVID-19. Smoking history was an independent predictor of in-hospital mortality. Thus, hospitalised COVID-19 patients with current or past smoking had a worse prognosis and higher mortality than those without.

In previous studies, the demographic characteristics of the patients overlapped ours, with advanced age, male prevalence, and presence of a greater number of comorbidities such as COPD or cardiovascular diseases<sup>6,9,13,14</sup>. Hospital mortality in patients with COVID-19 has been found to be increased in precisely this type of patient (over 70 years of age, male and in relation to the number of associated diseases)<sup>1–3</sup>, so it is essential to study the effect that smoking may have. At present, the impact of smoking on the progression of COVID-19 remains controversial and studies so far are scarce.

Smoking is a risk factor for acquiring other bacterial and viral infections, including MERS-CoV-2 (*Middle East Respiratory Syndrome Coronavirus*), a situation we think could be extrapolated to COVID-19<sup>6</sup>. Regardless of the effect of smoking on disease progression, the risk to which smokers are exposed for SARS-CoV-2 infection is higher than in non-smokers<sup>6,15</sup>. However, this paper has not analysed whether smokers are at higher risk of acquiring

**Table 2**  
Patients' clinical presentation, examination, and laboratory and imaging findings according to smoking history.

	Total (n = 14.260)	Non-smoking group (n = 9.916)	Smoking group (n = 4.344)	P
<i>Clinical presentation</i>				
Fever	12.008 (84.4)	8.398 (84.9)	3.610 (83.2)	0.009
Cough	1.0471 (73.5)	7.262 (73.3)	3.209 (73.9)	0.423
Odynophagia	1.400 (9.9)	981 (9.9)	419 (9.7)	0.667
Dyspnoea	8.223 (57.8)	5.615 (56.7)	2.608 (60.1)	<0.001
Diarrhoea	3.467 (24.4)	2.482 (25.1)	985 (22.7)	0.003
Nausea	1.769 (12.5)	1.324 (13.5)	445 (10.3)	<0.001
Vomiting	1.134 (8.0)	859 (8.7)	275 (6.3)	<0.001
Abdominal pain	950 (6.7)	695 (7.0)	255 (5.9)	0.013
<i>Physical examination and laboratory and imaging findings</i>				
qSOFA $\geq 2$	1.218 (9.0)	804 (8.5)	414 (9.9)	0.008
Oxygen saturation (pulse oximetry) (<90%) or oxygen therapy	4.403 (32.9)	2.897 (31.0)	1.506 (32.9)	<0.001
Pulmonary infiltrates	12.348 (87.2)	8.628 (87.6)	3.720 (86.2)	0.017
Total lymphocytes ( $\times 10^6/L$ )	940 (690–1.300)	971 (700–1.300)	975 (640–1270)	<0.001
Total lymphocytes $<800 \times 10^6/L$	5.557 (39.2)	3.717 (37.7)	1.840 (42.6)	<0.001
LDH (U/L)	321 (247–433)	320 (247–426)	327 (246–447)	0.011
LDH > 400 U/L	3.841 (30.7)	2.573 (29.7)	1.268 (33.0)	<0.001
CRP (mg/L)	61 (20–128)	59 (20–125)	65 (21–137)	0.001
CRP > 60 mg/L	6.824 (50.0)	4.650 (49.0)	2.174 (52.2)	0.001
Serum ferritin (mcg/L)	612 (287–1.232)	583 (279–1.193.5)	671 (307–1.302)	<0.001
Serum ferritin > 650mcg/L	2.809 (47.1)	1.869 (45.5)	950 (50.6)	<0.001
D-dimer (ng/mL)	662 (371–1241)	640 (363–1220)	700 (400–1.290)	<0.001
D-dimer > 1.000 ng/mL	3.661 (32.1)	2.497 (31.3)	1.164 (33.9)	0.007

Data are expressed as median (25th percentile–75th percentile) for continuous variables and as frequencies (percentages) for categorical variables.

CRP: C-reactive protein; LDH: lactate dehydrogenase; qSOFA: *quick Sequential Organ Failure Assessment* score.



**Table 3**  
Disease progression and events 30 days after discharge according to smoking history.

	Total (n = 14.260)	Non-smoking group (n = 9.916)	Smoking group (n = 4.344)	P
ICU admission	1.251 (8.8)	801 (8.1)	450 (10.4)	<0.001
Invasive mechanical ventilation	999 (7.0)	650 (6.6)	349 (8.0)	0.001
Non-invasive mechanical ventilation	734 (5.1)	450 (4.5)	284 (6.5)	<0.001
Immunomodulatory treatment	5.433 (43.2)	3.574 (41.0)	1.859 (48.1)	<0.001
Systemic corticosteroids	5.117 (36.0)	3.341 (33.8)	1.776 (41.0)	<0.001
Tocilizumab	1.301 (9.1)	871 (8.8)	430 (9.9)	0.032
Antibiotic treatment	12.721 (89.3)	8.776 (88.6)	3.945 (91.0)	<0.001
Complications during admission	6.620 (46.4)	4.341 (43.8)	2.279 (52.5)	<0.001
<i>Acute respiratory distress syndrome</i>				
No	9.501 (66.8)	6.827 (69.0)	2.674 (61.7)	<0.001
Mild	1.289 (9.1)	877 (8.9)	412 (9.5)	
Moderate	1.106 (7.8)	718 (7.3)	388 (9.0)	
Severe	2.336 (16.4)	1.477 (14.9)	859 (19.8)	
Bacterial pneumonia	1.558 (10.9)	986 (9.9)	572 (13.2)	<0.001
Sepsis	871 (6.1)	550 (5.5)	321 (7.4)	<0.001
Venous thromboembolism	335 (2.4)	211 (2.1)	124 (2.9)	0.008
In-hospital mortality	2.609 (18.3)	1.631 (16.4)	978 (22.5)	<0.001
radiological worsening	4.277 (38.4)	2.788 (36.5)	1.489 (42.6)	<0.001
Disease progression	3.595 (25.2)	2.285 (23.0)	1.310 (30.2)	<0.001
<i>Events 30 days after discharge</i>				
Readmission at 30 days	526 (4.5)	332 (4.0)	194 (5.8)	<0.001
Mortality at 30 days	158 (1.4)	106 (1.3)	52 (1.5)	0.262

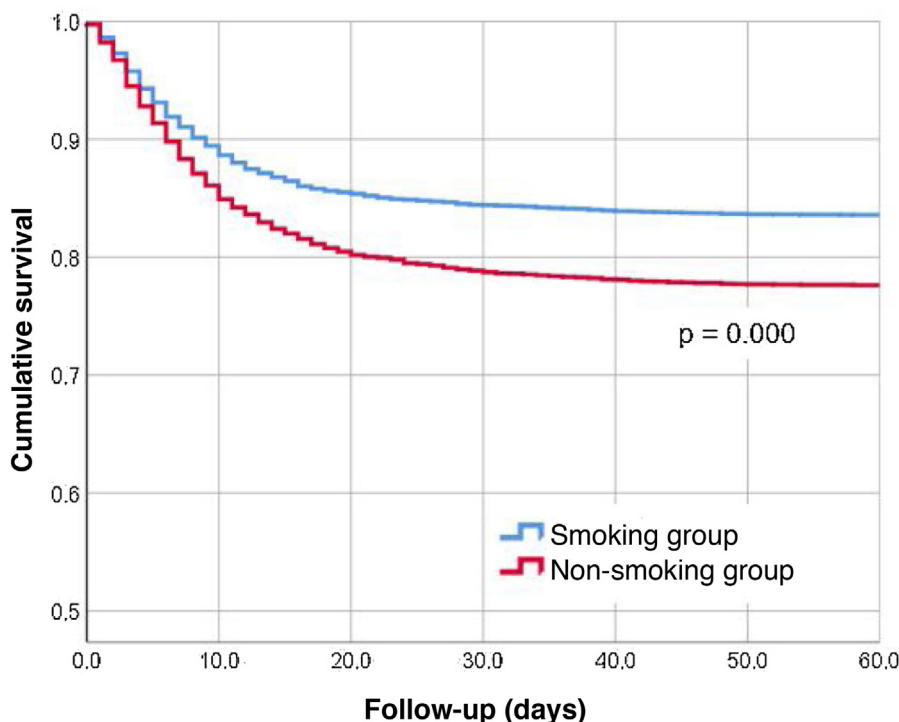
Data are expressed as frequencies (percentages).

ICU: intensive care unit. Disease progression (ICU admission, non-invasive/invasive mechanical ventilation and/or in-hospital death).

**Table 4**  
Binary logistic regression of in-hospital mortality from any cause.

Independent variables	Coefficients	P	OR	95% CI	P
Age (years)	0.058	0.003	1.059	1.053–1.065	<0.001
Sex (male)	0.532	0.059	1.702	1.516–1.911	<0.001
Age-Adjusted Charlson Comorbidity Index	0.137	0.013	1.147	1.117–1.177	<0.001
Degree of dependency (moderate-severe)	0.497	0.066	1.644	1.446–1.869	<0.001
Smoking	0.138	0.059	1.148	1.021–1.290	0.021
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	0.267	0.061	1.305	1.157–1.472	<0.001
Cardiovascular disease (myocardial infarction, angina pectoris, heart failure, atrial fibrillation)	0.183	0.060	1.200	1.066–1.351	0.002
Constant	-6.849	0.198	0.001		<0.001

BMI: body mass index.



**Figure 2.** Kaplan Meier curves for patient in-hospital mortality according to smoking.

the infection, only if the progression is different once they have been infected.

Pathophysiologically, cigarette smoke elicits an inflammatory response through activation of nuclear factor  $\kappa$ B, activated B-cell light chain enhancer, tumour necrosis factor- $\alpha$ , IL-1 $\beta$  and neutrophils<sup>9</sup>. It is known that patients with SARS-CoV-2 infection have elevated levels of inflammatory cytokines, so the sum of both would contribute to increased severity in COVID-19<sup>14</sup>. Previous meta-analyses have shown that being or having been a smoker increased the likelihood of severe disease progression<sup>6,9,16</sup>. The number of smokers has been found to be disproportionately higher among serious COVID-19 patients than among non-serious patients<sup>13,15–17</sup>. These results are similar to ours, where tobacco-exposed patients were admitted with a higher qSOFA and had acute respiratory distress syndrome more often and more severely, as well as a greater need for non-invasive mechanical ventilation or orotracheal intubation than non-exposed patients.

In disagreement with our findings, some investigators suggest a protective effect of smoking and nicotine on COVID-19, based on epidemiological studies where age and associated comorbidities have not been considered<sup>10</sup>. Even so, we must bear in mind that the cumulative risk of smoking to an individual's health outweighs the theoretical benefits<sup>14</sup>. Though data on the association between smoking and COVID-19 are confusing, the available scientific evidence suggests that smoking is associated with greater disease severity and mortality in these patients<sup>15,17</sup>.

In general, studies do not differentiate between current and former smokers. Smoking cessation improves lung function; however, this benefit is reduced among smokers who have been exposed for a long time due to accumulated lung injury over a prolonged period of time. Ex-smokers had a higher Charlson score and required more aggressive therapies than active smokers according to the sub-analysis. This could be due to a longer tobacco exposure, which has not been collected, which prevents a complete understanding of the impact of smoking on COVID-19 and has been identified as a limitation in most of the studies conducted<sup>13</sup>. Recently, two studies have assessed the cumulative effect of smoking, by pack-year and exposure time, suggesting cumulative exposure as an independent risk factor for hospital admission and death from SARS-CoV-2. The increase in cumulative smoking was associated with a higher number of admissions and deaths. This effect was greater in ex-smokers than in active smokers, in relation to older age and comorbidities<sup>18,19</sup>.

Just as the relationship between smoking and COVID-19 is unclear, so is the relationship between COPD and COVID-19. Zhao et al.<sup>13</sup> conducted a meta-analysis showing that the risk of severity during COVID-19 is four times higher in COPD patients than in non-COPD patients. A two-fold increased risk was also found in patients with active smoking. It appears that COPD patients are not at increased risk of SARS-CoV-2 infection but do have an increased mortality from COVID-19 compared to non-COPD patients (38.3% vs. 19.2%,  $p < 0.001$ ). The prognosis during admission is even worse in COPD patients with associated comorbidities (hypertension, chronic kidney disease, cerebrovascular disease, etc.) than in COPD without comorbidities<sup>20</sup>.

Strengths of this study include the fact that the data come from a large registry with different hospital care levels, which makes their extrapolation to other populations easier. Previously, most of the published studies have been in Asian populations<sup>1,7,13,17</sup>. In addition, patients have been included at different chronological points in time and data have been obtained from medical records prepared by physicians.

In relation to limitations, this is a retrospective study in which we do not have an adequate smoking history: active/passive smoking, degree of exposure (packs/year), it does not discriminate between smoking devices (conventional cigarette, electronic

cigarette, hookahs. . .) and neither the degree of exposure nor the time of smoking cessation was considered.

The inclusion of hospitalised patients makes it impossible to assess the risk of developing infection or requiring hospitalization. In addition, the design of the SEMI-COVID-19 registry generates the usual biases of observational studies (selection biases). The patients included have followed the hospital treatment and management protocol individualised to each health area, which may have been modified during the chronological development of the pandemic.

We are facing an unprecedented situation, with many areas of uncertainty, including the natural history of the disease. A prospective study with adequate data collection on smoking history would be useful in order to draw rigorous conclusions.

Given that our data suggest that patients exposed to tobacco have an unfavourable disease course with increased mortality and admission to the ICU, we believe smoking should be understood as a risk factor for poor outcome. Therefore, an adequate assessment of smoking history on admission could help us to design the management strategy for hospitalised patients.

## Conclusions

Smoking, active or past, is an independent predictor of poor prognosis in patients with COVID-19, as it is associated with an increased likelihood of ICU admission and in-hospital mortality.

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## Conflict of interests

The authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

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