

Smoking patterns and outcomes of severe sars-CoV-2 infection: a retrospective cohort study

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Abstract

The purpose of this study was to analyze the association between the number of cigarettes smoked and the length of smoking with mortality among patients who were hospitalized in the intensive care unit (ICU) due to SARS-CoV-2 infection. This retrospective cohort study was conducted at the General Hospital in Sombor (Serbia). Patients who were hospitalized because of severe SARS-CoV-2 infection between March 2021 and March 2023 were included in this study. Data were retrieved from electronic medical records, including those on smoking status, duration of smoking, and the number of cigarettes smoked per day. Of 307 patients whose medical records were analyzed, 40.7% were current smokers. Current smokers more often required treatment in the ICU, where they also had a higher mortality rate compared to current non-smokers. Longer duration of smoking was independently associated with dying of SARS-CoV-2 infection in the ICU. The Kaplan-Meier survival curve showed that hospitalized patients with SARS-CoV-2 infection who smoked had poorer survival compared to current non-smokers. According to the receiver operating characteristic curve, patients who smoked for more than 40 years had a 73.9% chance of dying from SARS-CoV-2 infection. Current smokers who smoked 22.5 cigarettes per day had a 75.4% chance of dying from SARS-CoV-2 infection in the ICU. Smokers with severe SARS-CoV-2 infection had a higher likelihood of having poor outcomes. Longer duration of smoking was an independent predictor of SARS-CoV-2 mortality. Smoking prevention and smoking cessation are of paramount importance in the prevention of SARS-CoV-2-related mortality.

Key words: COVID-19, smoking, mortality.

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Introduction

Chemicals in tobacco smoke can severely damage alveolar epithelial cells as well as vascular endothelium of lungs [1-5]. Some studies suggested that, compared to the general population, few smokers develop a typical clinical presentation of SARS-CoV-2 infection [5,6]. In fact, a large population-based study from the UK found that smoking may decrease the risk of SARS-CoV-2-related mortality [7]. However, other systematic reviews reported that smoking may be associated with poorer outcomes of SARS-CoV-2 infection [8,9]. Despite the large population samples, previous studies did not account for a wider spectrum of covariates or the length of smoking.

In efforts to better understand the association between quantity and length of smoking with SARS-CoV-2-related mortality, the use of patients' medical records provides an opportunity to analyze multiple covariates. In this way it is possible to obtain a more nuanced association between tobacco use and poor outcomes of SARS-CoV-

2 infection. In a similar vein, analysis of multiple covariates enables the identification of other relevant clinical factors of SARS-CoV-2 mortality, which could be useful in the prediction of trajectory of other respiratory infections.

The purpose of this study was to analyze the association of quantity of cigarettes smoked and length of smoking with mortality among patients who were hospitalized in the intensive care unit due to SARS-CoV-2 infection.

Materials and Methods

Setting and participants

This research is designed as a retrospective cohort study. It was conducted at the general hospital in Sombor, West Bačka district, Serbia. Patients admitted between 1 March 2021 and 1 March 2023 were included. The inclusion criteria were: having confirmed SARS-CoV-2 infection using the reverse transcription polymerase



chain reaction or antigen testing, being adult (≥ 18 years) and having severe SARS-CoV-2 infection during their hospital stay [*i.e.*, they were admitted to the intensive care unit (ICU)].

The SARS-CoV-2 infection severity assessment was based on the current protocol for treatment of COVID-19 in Serbia: the infection is classified into 4 forms, with the first indicating the mildest and the last indicating the most severe form [10]. Severe illness refers to having any of the following: oxygen saturation $< 94\%$ at room temperature at sea level; a ratio of partial arterial pressure of oxygen and fraction of inspired oxygen < 300 mm Hg; a respiratory rate exceeding 30/min, or lung infiltrates on chest imaging $> 50\%$.

All patients in this retrospective cohort study presented severe clinical picture of COVID-19. Despite the treatment of confirmed SARS-CoV-2 positive people since March 2020 in Serbia, hospital records had complete data on smoking for patients hospitalized from March 2021.

An online calculator was used to define sample size (<https://www.calculator.net/>). The sample size calculation was based on the population size of the West Bačka district (approximately 180,000 people), an estimated percentage of 9% of people with SARS-CoV-2 infection who require hospital treatment [11], a confidence interval of 95%, and a 5% probability of α -error. An α -error of 0.05 indicates that one is willing to accept a 5% chance of being wrong when rejecting the hypothesis that there is no association between smoking and poorer outcomes of SARS-CoV-2 infection. Using these parameters, the minimum sample size was 126 participants.

The Ethics Committee of the general hospital of Sombor approved this retrospective study. The standard hospital admission procedure includes patients signing a consent form for all diagnostic and therapeutic procedures. On this occasion, the consent form also included the consent analyze patients' medical records for research purposes.

Data collection

All data were obtained from electronic medical records. We retrieved demographic information and presence of pre-existing chronic illnesses [hypertension, diabetes mellitus types 1 and 2, obesity, respiratory diseases (*i.e.*, having pre-existing chronic obstructive pulmonary disease-COPD, asthma, or pulmonary fibrosis), renal diseases, and malignant tumors] as well as clinical data: initial SARS-CoV-2 infection symptoms (fever, cough, fatigue, shortness of breath, and chest pain), SARS-CoV-2 vaccination status. Laboratory results upon admission were also collected from the hospital records.

Data on smoking status, duration of smoking, and the number of cigarettes smoked daily were obtained from electronic medical records, as they are part of routine patient processing. Patients provided these pieces of information upon hospital admission. Because these data were based on self-reports about current smoking, we classified the patients as "current smokers" and "current non-smokers" to minimize information bias regarding potential former smoking practices of current non-smokers.

Data analysis

Using SPSS version 17 (IBM, Armonk, NY, USA), patients were categorized based on their smoking status after the identification of multiplicative interaction ($p < 0.05$ was accepted as statistically significant). The interaction considered smoking status (yes vs. no), patients' age as well as the product term as the independent vari-

ables, when the outcome variable was patients' vital status (1-died, 0-living). The product term was statistically significant ($p < 0.01$), which provided a mathematical justification for stratification of the study cohort based on their smoking status.

The normality of distribution was evaluated using the Kolmogorov-Smirnov test. For normally distributed continuous variables, independent samples t-test was applied, otherwise the non-parametric two-sided Mann-Whitney test was used. Categorical variables were assessed using the Fisher's exact test and the Chi-square test.

The Kaplan-Meier survival curve was applied to examine survival of patients. The log-rank test was used to test the differences between smokers and non-smokers. The Cox proportional hazards model was utilized to identify factors associated with dying from SARS-CoV-2 infection. The dependent variable in this model was the vital status (1-died, 0-living). The independent variables were classified into 2 models for a more robust analysis. The first model included duration of hospital stay, vaccination status, smoking duration and quantity of cigarettes smoked per day (only in smokers), initial SARS-CoV-2 infection symptoms and presence of pre-existing chronic illnesses. The second model included laboratory data. These variables were first tested in a univariate model. Subsequently, statistically significant ($p < 0.05$) and marginally significant ($p < 0.25$) variables from the univariate analysis were included in the multivariate model. Both multivariate models were adjusted for age and gender.

The duration of smoking in years and the number of cigarettes smoked per day were analyzed using the receiver operating characteristic (ROC) curve. The area under the curve (AUC) was analyzed to better understand sensitivity and specificity.

Results

A total of 307 patients were included in the study. The majority were female (68.7%, $n=211$). The average age of patients was 64.4 ± 14.0 years. Most patients (74.6%, $n=229$) were not vaccinated. The study included 125 (40.7%) current smokers. All current smokers actively smoked tobacco at the time of developing the first symptoms of SARS-CoV-2 infection. The average duration of smoking was 27.2 ± 5.7 years. The average number of cigarettes smoked per day was 26.9 ± 14.5 .

Current smokers were more often admitted to the ICU than current non-smokers ($p < 0.001$), where they also had a higher mortality rate ($p=0.01$). Furthermore, compared to current non-smokers, current smokers more often reported chest pain ($p=0.04$) and shortness of breath ($p=0.01$) as the initial symptoms of SARS-CoV-2 infection. Current smokers were more likely to have pre-existing respiratory diseases ($p < 0.001$) and be obese ($p=0.01$) compared to current non-smokers. The only observed difference in laboratory parameters was a higher value of lactate dehydrogenase (LDH) among current non-smokers (Table 1).

Factors associated with mortality among current smokers

In the univariate Cox regression, factors associated with dying from SARS-CoV-2 among current smokers were a longer hospital stay ($p=0.01$), longer duration of smoking ($p=0.03$), having shortness of breath ($p < 0.01$), and chest pain ($p=0.01$) as the initial symptoms, having pre-existing hypertension ($p=0.03$), respiratory diseases ($p < 0.01$), and obesity ($p < 0.01$), as well as a higher LDH ($p < 0.01$) (Supplementary Table 1).



Table 1. Characteristics of the study cohort according to smoking status.

Variable	Smokers, n=125 n (%)	Non-smokers, n=182 n (%)	p
Age (mean±sd)	65.2±14.2	63.9±13.8	0.40
Gender			
Men	43 (14.0)	53 (17.3)	0.32
Women	82 (26.7)	129 (42.0)	
Admitted to ICU	63 (20.5)	23 (7.5)	<0.01
Died in the ICU	35 (11.4)	11 (3.6)	<0.01
SARS-CoV-2 vaccination	27 (8.8)	51 (16.6)	0.20
Duration of smoking in years	27.2±5.7	n/a	n/a
Cigarettes smoked daily	26.9±14.5	n/a	n/a
Duration of hospital stay	19.2±5.5	14.5±5.3	0.04
Initial symptoms of SARS-CoV-2 infection			
Fever	108 (35.2)	148 (48.25)	0.24
Cough	100 (32.6)	138 (59.3)	0.39
Fatigue	62 (20.2)	80 (26.1)	0.30
Shortness of breath	82 (26.7)	80 (26.1)	<0.01
Chest pain	14 (4.6)	19 (6.2)	0.03
Chronic illnesses			
Hypertension	56 (18.2)	54 (17.6)	<0.01
Diabetes mellitus	32 (10.4)	42 (13.7)	0.61
Insulin dependent diabetes	19 (6.2)	16 (5.2)	0.08
Oral antidiabetics	15 (4.9)	26 (5.5)	0.56
Obesity	14 (4.6)	7 (2.3)	0.01
Malignant tumors	5 (1.6)	4 (1.3)	0.35
Respiratory diseases	13 (4.2)	2 (0.7)	<0.01
Chronic kidney disease	17 (5.5)	15 (4.9)	0.13
Laboratory characteristics			
Red blood cells	4.1 (3.4-4.6)	3.9 (3.3-4.5)	0.28
Hemoglobin	127.0 (114.0-137.0)	123.0 (110.0-134.0)	0.16
White blood cells	7.0 (4.2-9.0)	7.0 (4.3-9.1)	0.72
Lymphocytes	1.4 (0.9-1.9)	1.4 (1.01-1.9)	0.83
Neutrophils	5.1 (3.4-6.6)	4.9 (3.4-6.6)	0.83
D-dimer	0.6 (0.4-0.9)	0.6 (0.42-1.0)	0.51
Prothrombin time	12.9 (12.2-13.6)	13.1 (12.2-13.8)	0.53
International normalized ratio	1.1 (1.0-1.1)	1.0 (1.0-1.1)	0.49
Glycemia	7.5 (4.6-9.9)	7.1 (4.9-9.6)	0.92
Creatinine	125.0 (91.0-150.0)	126.0 (88.7-163.2)	0.76
Urea	2.1 (1.0-2.1)	2.4 (1.1-3.7)	0.21
Albumin	34.0 (31.0-36.0)	33.0 (31.0-36.0)	0.81
Procalcitonin	0.9 (0.5-1.5)	2.6 (0.8-3.6)	0.07
Lactate dehydrogenase	291.0 (237.0-364.0)	387.0 (224-468.0)	0.04
C-reactive protein	64.8 (33.7-85.9)	69.7 (39.4-93.8)	0.36
Ferritin	609.9 (374.0-796.5)	804.3 (296.0-1234.0)	0.75
Alanine aminotransferase	61.0 (39.0-79.5)	62.5 (40.7-81.0)	0.50
Aspartate aminotransferase	62.0 (32.0-89.0)	59.0 (30.7-81.2)	0.21
Gamma glutamyl-transferase	58.5 (40.2-80.7)	56.0 (37.0-79.25)	0.61
Creatine kinase	226.5 (137.0-322.0)	245.0 (115.8-364.6)	0.73

ICU, intensive care unit; sd, standard deviation; n/a, not applicable.



All these variables as well as the marginally significant ones (age, vaccination status, number of cigarettes smoked daily, pre-existing insulin-dependent diabetes and chronic kidney disease, red blood cell count, hemoglobin, urea, creatinine, and alanine transaminase levels) entered the multivariate model. This model showed that a longer hospital stay ($p=0.03$), longer duration of

smoking ($p=0.04$), having shortness of breath ($p<0.01$) as the initial symptom of SARS-CoV-2 infection ($p<0.01$), having pre-existing respiratory diseases ($p<0.01$), and obesity ($p<0.01$), and higher levels of LDH ($p<0.01$) and urea ($p=0.04$) were associated with dying from SARS-CoV-2 in the ICU among current smokers (Table 2).

Table 2. Factors associated with SARS-CoV-2-related mortality in smokers and non-smokers.

Model 1	Smokers			Non-smokers		
	HR	95% CI	p	HR	95% CI	p
Age	1.01	0.98-1.09	0.14	1.06	1.00-1.09	0.04
Gender	1.03	0.91-1.04	0.09	1.65	0.89-1.98	0.29
Duration of hospital stay	1.22	1.14-1.45	0.02	1.32	1.32-1.42	<0.01
SARS-CoV-2 vaccination	0.82	0.51-1.29	0.91	1.03	1.02-1.05	0.09
Duration of smoking	1.09	1.01-1.02	0.04	n/a	n/a	n/a
Cigarettes smoked daily	1.18	0.98-1.31	0.08	n/a	n/a	n/a
Fever						
Cough						
Fatigue						
Shortness of breath	1.21	1.01-1.23	<0.01			
Chest pain	1.45	0.98-1.92	0.06	1.36	0.83-1.45	0.36
Hypertension	1.54	0.74-1.82	0.12			
Insulin dependent diabetes	1.64	0.26-1.94	0.91	1.02	0.81-1.03	0.25
Oral antidiabetics						
Obesity	1.65	1.01-2.85	<0.01			
Malignant tumors						
Respiratory diseases	1.54	1.12-1.98	<0.01			
Chronic kidney disease	1.61	0.96-2.97	0.08			
Model 2	Multivariate estimates			Multivariate estimates		
	HR	95% CI	p	HR	95% CI	p
Age	1.01	0.99-1.11	0.13	1.02	1.00-1.05	0.02
Gender	1.02	0.98-1.04	0.12	1.35	0.87-1.77	0.13
Red blood cells	0.87	0.66-1.15	0.32			
Hemoglobin	0.99	0.97-1.00	0.20			
White blood cells						
Lymphocytes						
Neutrophils						
D-dimer				1.82	1.06-2.64	0.01
Prothrombin time						
International normalized ratio						
Glycemia						
Creatinine						
Urea	1.87	1.68-2.12	0.04			
Albumin	0.45	0.21-1.21	0.45	0.84	0.54-0.64	0.04
Procalcitonin						
Lactate dehydrogenase	1.09	1.01-1.12	<0.01			
C-reactive protein				1.02	0.87-1.04	0.09
Ferritin						
Alanine aminotransferase	1.03	0.74-1.02	0.91			
Aspartate aminotransferase				1.23	0.97-1.45	0.35
Gamma glutamyl-transferase						
Creatine kinase						

HR, hazard ratio; CI, confidence interval; n/a, not applicable.



Factors associated with mortality among current non-smokers

In the univariate Cox regression, factors associated with mortality in current non-smokers were a longer hospital stay ($p < 0.01$), being older ($p = 0.04$), as well as having low albumin levels ($p = 0.04$) and high D-dimer levels ($p < 0.001$) (*Supplementary Table 1*).

These variables along with the marginally significant ones (gender, vaccination status, fever, chest pain, insulin-dependent diabetes, C-reactive protein and aspartate aminotransferase levels) entered the multivariate model. This model showed that longer hospital stays ($p = 0.03$), being older ($p = 0.04$), not having fever ($p = 0.04$), as well as high D-dimer levels ($p = 0.02$) and low albumin levels ($p = 0.04$) were associated with dying from SARS-CoV-2 in the ICU among current non-smokers (Table 2).

Receiver operating characteristic curve analysis

Given that duration of smoking was predictive of dying from SARS-CoV-2, we analyzed this variable in more detail using the ROC curve (Table 3). The AUC was > 0.7 suggesting that duration

of smoking was able to discriminate current smokers who had more likely died in the ICU. Specifically, current smokers who smoked for more than 40 years had a 73.9% chance of dying from SARS-CoV-2 infection compared to those patients who smoked for a shorter period of time (Figure 1A). Similarly, the number of cigarettes smoked daily showed a discriminative power ($AUC > 0.7$) in predicting the ICU mortality. Specifically, current smokers who smoked more than 22.5 cigarettes per day had a 75.4% chance of dying from SARS-CoV-2 infection in the ICU compared to people who smoked fewer cigarettes per day (Figure 1B).

Comparative survival based on smoking status

Since we observed that smoking might have contributed to mortality in the ICU in our study cohort, we analyzed the Kaplan-Meier curve to estimate survival of patients relative to smoking (Figure 2). The Kaplan-Meier survival curve showed a statistically significant difference in mortality between current smokers and current non-smokers (Log-rank test $p < 0.001$). This means that hospitalized patients with SARS-CoV-2 infection who were current smokers had poorer survival compared to current non-smokers.

Table 3. Parameters on the receiver operating characteristic curve analysis.

Variable	Mortality as an outcome variable		
	Area under the curve	Standard error	p
Duration of smoking in years	0.70	0.06	< 0.01
Cigarettes smoked daily	.71	.05	< 0.01
	Cut-off	Sensitivity	Specificity
Duration of smoking in years	40 years	73.9%	69.7%
Cigarettes smoked daily	22.5 per day	75.4%	73.9%

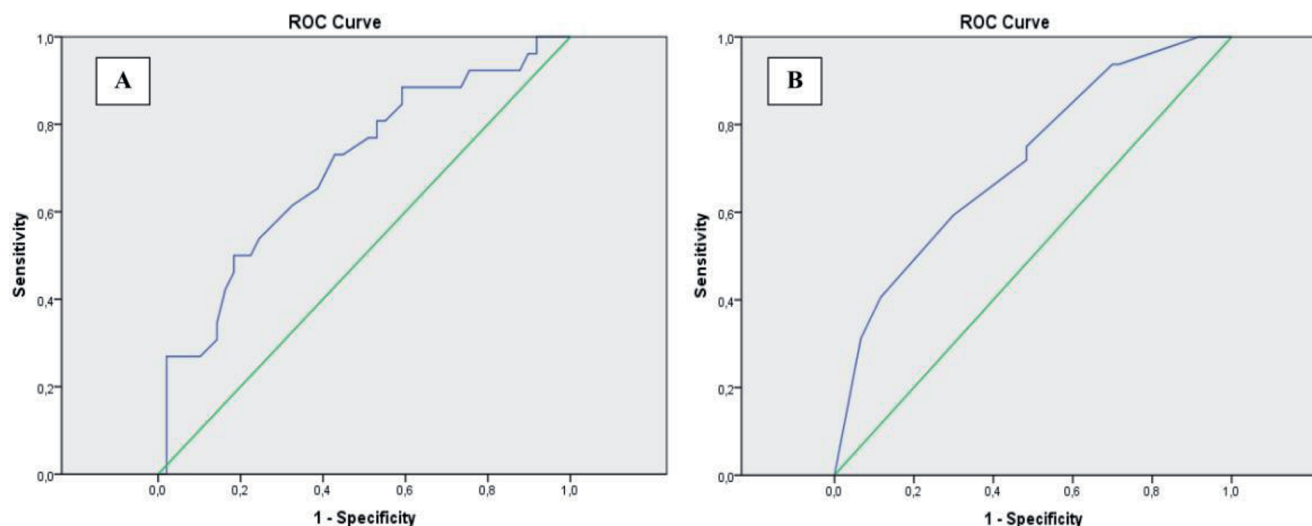


Figure 1. Receiver operating characteristic curve analysis to differentiate COVID-19 patients (A) who died in the intensive care unit (ICU) based on according to the years of the smoking trail and (B) who died in the ICU based on the number of cigarettes consumed per day. ROC, receiver operating characteristic.



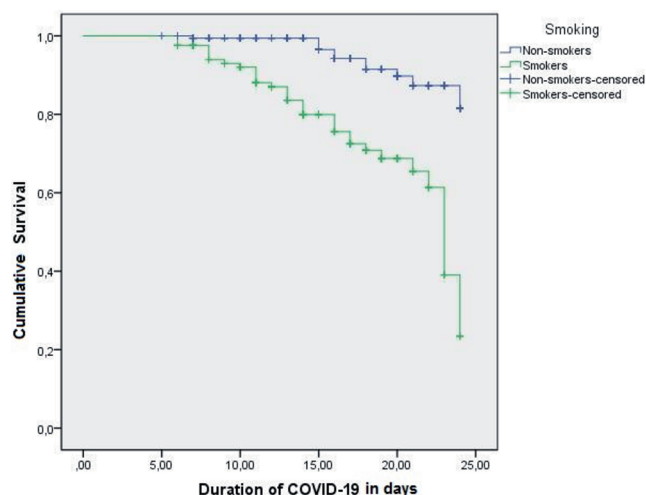


Figure 2. Comparative survival of smokers and non-smokers (log rank test for difference $p < 0.001$).

Discussion

The results of this study suggest that longer smoking duration is associated with mortality from SARS-CoV-2 infection in hospitalized patients. Moreover, survival of current smokers with SARS-CoV-2 infection was shorter compared to current non-smokers. These findings are in line with previous results across cultures and health care systems, such as Bangladesh and the US [12,13], indicating universal detrimental effects of smoking on SARS-CoV-2-related survival. This is especially relevant for populations with a high prevalence of smokers such as Serbia, where 37.9% of men and 31.6% of women smoke [14].

Understanding the underlying mechanisms of smoking in the development and progression of COVID-19 is of paramount importance. Chemicals in tobacco smoke irritate the epithelial membrane causing chronic inflammation of the alveoli. This inflammation can lead to the accumulation of fibrin and the formation of micro thrombi, which decrease gas exchange and promote oxidative stress over decades of active smoking [6,15]. At the same time, ciliary function becomes impaired, which results in mucus hypersecretion and delayed clearance [16]. This creates a microenvironment conducive to microbe colonization [17]. Nicotine also boosts the expression of angiotensin-converting enzyme (ACE) in lungs, while the receptor of its homolog enzyme ACE2 acts as a portal of entry of several coronaviruses, including SARS-CoV-2 [2,3]. Therefore, the interaction between nicotine and SARS-CoV-2 could influence the type of symptoms and the severity of clinical presentation of SARS-CoV-2 infection [4]. Further, tobacco smoke has been linked to genetic mutations, including the loss of heterozygosity and microsatellite instability, which disrupt the integrity of the alveolar-capillary barrier through mitophagy, oxidative stress and cellular damage [18]. These sub-cellular changes increase the susceptibility to severe outcomes of SARS-CoV-2 infection [19].

Smoking can impair the immune response by decreasing the CD4+T cell count. It has been observed that smoke lowers the production of interleukin (IL)-22, while it stimulates the secretion of catecholamine, which results in immune suppression [20,21].

Chronic cigarette smoking has detrimental effects on immune function *via* the hypothalamic-pituitary-adrenal (HPA) axis activation [22]. Nicotine rapidly crosses the blood-brain barrier, and in the central nervous system it increases cerebral glucose uptake, and stimulates adrenocorticotropic hormone, norepinephrine, and epinephrine release [22]. This HPA axis activation also has immunosuppressive effects [22]. Moreover, smokers have elevated expression of IL-6, tumor necrosis factor- α , and other proinflammatory agents, which contribute to severe immune responses and lung inflammation [20,21]. Because the primary complication of COVID-19 is the acute respiratory distress syndrome, whose underlying pathophysiological mechanism is the cytokine storm, tobacco smoking could, therefore, facilitate the onset of severe clinical forms of SARS-CoV-2 infection.

In this study, smoking more than 22 cigarettes per day showed a high level of sensitivity when distinguishing individuals with severe SARS-CoV-2 infection who might have poor prognosis. Jiang *et al.* reported that male smokers, who smoke more than 25 cigarettes per day, are 2.5 times more likely to develop pneumonia compared to non-smokers [23]. Another research from Spain found that the risk of pneumonia increases 3.9 times in smokers who smoke more than 20 cigarettes per day [24]. Nuorti *et al.* observed that smoking was the strongest independent risk factor for the development of an invasive pneumococcal disease, where pneumonia in smokers was 4.1 times more likely than that in non-smokers [25]. In fact, exposure to secondhand smoke may increase the risk of pneumonia as well [26].

On the other hand, smoking cessation has been associated with the reduction in pneumonia risk [25]. People who quit smoking more than 4 years prior had a significantly lower risk of pneumonia compared to those who quit smoking less than 1 year prior [27]. It seems that 5 years after quitting smoking the risk of pneumonia among former smokers decreases to a level similar to that of non-smokers [24]. Bearing in mind these empirical data, smoking prevention and smoking cessation may play a crucial role in prevention of poor outcomes of SARS-CoV-2 infection.

The results of this study showed that people who smoked for more than 40 years were at a higher risk of dying when hospitalized with SARS-CoV-2 infection. Xu *et al.* reported that smoking more than 20 pack-years independently increases the risk of developing influenza in hospitalized patients with COPD [28]. Smoking over 20 pack-years and initiation of smoking before the age of 16 years were factors contributing to developing tuberculosis in Turkey [29]. Therefore, previous empirical evidence highlights that cumulative effect of long-term smoking may increase the risk of complications of respiratory diseases and systemic infections. For this reason, efforts to limit and quit smoking could subsequently lessen the burden of health care interventions and hospitalization.

The limitations of this study should be discussed. Because we used the existing hospital records, we were unable to retrieve data about former smoking practices and classify the patients into current smokers, former smokers and never smokers. As a result, the influence of former smoking remains unexplored. This study was conducted in a single hospital, which might limit the generalizability of the findings to broader populations. The majority of patients in this study were women, which stands in contrast with the previous notion that men are more likely to be hospitalized with SARS-CoV-2 infection [30-32]. However, this gender composition of the study sample reflected the demographics of the hospitalized patients during the study period at our hospital. In addition, the retrospective nature of the study might have introduced information bias, especially with regards to initial symptoms of SARS-CoV-2 infection and



smoking patterns because they were self-reported. The retrospective study design cannot entirely provide inference on causality, so the data might not fully capture the complex interplay between smoking and other coexisting factors. Furthermore, the study relied on the accuracy and completeness of medical records, and the possibility of misclassified data cannot be completely ruled out.

Conclusions

In conclusion, longer duration of smoking was identified as an independent risk factor for SARS-CoV-2-related mortality. Current smokers also had shorter survival compared to current non-smokers. Cumulative effects of smoking after more than 4 decades of being a smoker have a high level of sensitivity in predicting poor outcomes of SARS-CoV-2 infection. Smoking prevention and smoking cessation is of paramount importance in prevention of poor outcomes of SARS-CoV-2 infection. These strategies should be prioritized in the post-COVID-19 period, so that the epidemic of respiratory infections in the future has a lower impact of population mortality.

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Online supplementary material:

Supplementary Table 1. Results of the Cox proportional hazard model: univariate associations with mortality in smokers and non-smokers.

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Informed consent: data were retrospectively analyzed from hospital records. Patients provided informed consent for treatment and use of their data for research when hospitalized.

Patient consent for publication: upon hospital admission, patients signed consent for all diagnostic and therapeutic procedures and agreed to have their medical records analyzed and published in scientific journals.

Availability of data and materials: the dataset which was the base of this study is available on a reasonable request to the corresponding author.

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