Thi-Qar Medical Journal (TQMJ):Vol.(27),No.(1),2024

Web Site: https://jmed.utq.edu Email: utjmed@utq.edu.iq

ISSN (Print):1992-9218

Smoking Prevalence among Severe and Critical Cases of COVID 19 Patients in Sulaimani/ Single Center Study

Bakhtyar Qadr Hama Khurshid, (MBCHB, FKBMS) Department of critical care medicine, Shar Teaching Hospital/ Sulaymaniyah/ Iraq
E-mail: bakhtyarqadr@gmail.com

Haval Othman Ali, (MBCHB, CABD, FIBMS) Department of Critical Care Medicine, Shar Teaching Hospital, Sulaymaniyah, Iraq
E-mail: havalothmanali@gmail.com

Abstract

Background and Objectives: Smoking is a known risk factor for various respiratory infections and diseases. However, its impact on the severity and outcomes of COVID-19 remains a subject of ongoing research. The objective is to evaluate if smoking is linked to mortality in COVID-19 patients.

Methods: A retrospective cohort study was conducted on the ICU admitted COVID-19 patients, between May, 2020 and July, 2021. Admitted patients to the hospital with positive Severe acute respiratory sendrom-2 were categorized based on smoking status. The main focus was on mortality during hospitalization. Odds ratios (OR) and 95% confidence intervals (95%CI) were presented for smoking status.

Results: Among 400 COVID-19 deaths (mean age was 61.2 ± 13.0 years), the majority was between 60-60 years (35.3%, n=141), followed by older than 70 years (27.7%, n=111) then 50-59 years (17.7%, n=71), then 40-49 years (12.3%, n=49), only 7.0% (n=28) was < 40 years. The majority was male (62.2%, n=249) rather than female (37.8%, n=151). Mean ICU stay was 9.3 ± 10.7 days. 59.5% have at least one comorbidity. The prevalence of active smoker =1.8% vs 5.3%; former smoker= 28.7% vs 22.1%; and never smoker= 69.5% vs 72.5% regarding death and discharged patients. AS has lower risk of mortality (OR= 0.36 (95%CI 0.13- 0.99; P =0.041) than NS, The AS, as well as low risk of mortality (OR=0.29 (95%CI 0.11- 0.79; P = 0.0) than FS. Indeed, the former smoker has higher risk mortality (OR was 1.25 (95%CI 0.88 - 1.78; P= 0.203) than NS.

Conclusion: The older adults, males, comorbidity are at higher mortality risk by COVID-19 infection. Active smokers have lower in-ICU mortality than former smokers and never smokers, While, the former smokers have higher risk of mortality than active smokers and never smokers.

Keywords: COVID-19; Smoking; Mortality; SARS-CoV-2.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) represents a distinct variant of coronavirus accountable for inducing COVID-19, an emerging manifestation of SARS. Within the group of coronaviruses lies a category of single-stranded RNA viruses, including strains believed to be the causative agents of Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (1). Despite sharing some similar clinical manifestations, MERS, SARS, and COVID-19 showcase varied rates of transmission (2, 3). Ever since its initial identification in China towards the end of December 2019, COVID-19 has rapidly disseminated worldwide (4).

Data until February 4, 2021, reveals a global tally of 103,448,210 COVID-19 cases, with 2,236,453 fatalities. A significant proportion of these cases have been registered in the continents of America (46,270,502) and Europe (33,534,153)(5).

An investigation originating from China revealed a greater prevalence of active smokers among critical COVID-19 cases (6). Accentuating the necessity of comprehending the link between behavior of smoking and Severe Acute Respiratory Syndrome Coronavirus 2 (1).

The primary way of viral entry into the human body involves mucosal surfaces like the nose, mouth, UTI, and occasionally the mucosa of conjunctiva (7). Exposure to tobacco smoke is recognized for instigating pulmonary and mucosal inflammation, elevation of TNF α and cytokines, augmented of epithelial cells permeability, heightened production of mucus, and compromised clearance of mucociliary (8).

Nevertheless, the intricate nature of the link between smoking and the transmissibility of SARS-CoV-2 remains a subject of investigation (9). Some studies have postulated that smoking could heighten susceptibility to COVID-19 by upregulating the expression of ACE2, the receptor utilized by Severe acute respiratory sendrom-2 for entry of cell (10). Conversely, alternate research has indicated a potential decrease in ACE2 levels among smokers, potentially mitigating this risk (11).

A research team from France has proposed nicotine as a plausible active component responsible for the influence of smoking on the receptor of Angiotensin converting enzyme 2, potentially furnishing a defensive mechanism against SARS-CoV-2. Also, nicotine holds promise in the management of COVID-19 by mitigating detrimental inflammatory responses within the body. (12-14).

Our study was conducted to ascertain sociodemographic, clinical and pre-existing condition factors afflicted with in-hospital mortality of ICU admitted patients infected with SARS-CoV-2. As well as to identify the correlation between smoking and mortality in hospital.

Patients and Methods: This retrospective cohort study was running from May, 2020 to July, 2021 during the peak of the initial surge of the COVID-19 outbreak in Shahid Aso (COVID-19 ICU) in Sulaimani/ Iraq. The data was collected using paper medical record (PMR) and hospital databases, which are the main informative and available data till now, a diverse array of data regarding individuals tested for SARS-CoV-2 was collected. This data included details such as the timing and characteristics of test results, the types of pharmacological and non-pharmacological treatments administered, the outcomes experienced by patients, as well as any underlying health conditions and medications they were already taking).

For the present study, all patients who were admitted in Shahid Aso COVID-ICU department were enrolled; 400 deaths and 131 discharged patients. On the other hand, younger than 16 or had missing smoking status information were excluded. All patients had SARS-CoV-2 laboratory confirmed, by reverse-transcriptase polymerase chain reaction (RT-PCR) assay of nasal swab and ground grass opacity in HRCT.

Inclusion Criteria :ICU admitted COVID-19 patients who confirmed by RT-PCR assay of nasal swab s and ground grass opacity in HRCT, who aged was older than 16 years.

Exclusion Criteria: Non COVID-19 patients, younger than 16 years old and missing smoking status patients were excluded.

Statistical Analysis: The Statistical Package for the Social Sciences (SPSS) version 26 was used for analyzed our data. The values were expressed as n (%) and mean (SD) for categorical and numerical variables respectively. Chi square teste was conducted to determine the difference in the categorical data. Odds ratios (OR) with 95% CI were reported to determine the relation between status of smoker and morality of COVID-19. P-value ≤ 0.05 indicating a significant.

Ethical Endorsement: The study protocol was approved by the Kurdistan Higher Council for Medical Specialists (KHCMS), Sulaymaniyah, Iraq.

Results

Our results revealed that the mean age of COVID-19 deaths was 61.2 ± 13.0 years (10- 87 years), the majority was between 60-60 years (35.3%, n=141), followed by older than 70 years (27.7%, n=111) then 50-59 years (17.7%, n=71), then 40-49 years (12.3%, n=49), while only 7.0% (n=28) was younger than 40 years.
In respect of the gender, the majority was male (62.2%, n=249) rather than female (37.8%, n=151) as listed in Table (1).

Table (1): Demographic distribution of the COVID-19 deaths.

Patient Characteristics	Frequency (%)
Age (Mean±SD=61.2 ± 13.0) Years	
< 40	**28 (7.0 %)**
40 - 49	**49 (12.3%)**
50 - 59	**71 (17.7 %)**
60 - 69	**141 (35.3%)**
> 70	**111 (27.7 %)**
Gender	
Male	**249 (62.2%)**
Female	**151 (37.8%)**

The value of age was expressed as number (percentage)

The clinical properties of the 400 COVID-19 deaths were shown in Table (2); the mean stay of them in ICU was 9.3 ± 10.7 days (1-109 days), the ICU stay of more than half of them (51.7%, n=207) were lower than 7 days; 30.3% (n=121) were between 1-2 weeks while 18.0% (n=72) were more than 2 weeks.

Interestingly, around three- fifth of the COVID-19 deaths had at least one comorbidity including HTN (14.5%, n=58), DM (8.8%, n=35), IHD (3.3%, n=13), Asthma (1.0%, n=4) and CKD (0.3%, n=1), on the other hand, 31.8% (n=127) were associated with more than one of the above morbidities. Additionally, 40.5% (n=162) were not associated with any comorbidity.

The majority of the deaths were used NIV (86.3%, n=345), In respect of MV and O_2 the value was 8.8% (n=35) and 5.0% (n=20) respectively.

Notably, only 5.3% (n=21) were used vasoactive drugs, while 94.8% (n=379) were not used such medications. Out of the COVID-19 deaths,80.5% (n=322) were used Enoxaparin while 19.5% (n=78) were used heparin vial.

Except 3 patients (0.8%), all of the deaths (99.2%, n=397) were received a steroid as therapy.

The plasma was used for 37.9% (n=9) of them, on the other hand, the plasma for the others were not administrated.

Table (2): Clinical properties of COVID-19 deaths.

Clinical Characteristics	Frequency (%)
ICU Stay (Mean±SD=9.3 ± 10.7) Day	
<7 Days	**207 (51.7 %)**
7- 14 Days	**121 (30.3 %)**
>14 Days	**72 (18.0 %)**
Comorbidity	
No	**162 (40.5 %)**
HTN	**58 (14.5 %)**
DM	**35 (8.8 %)**
IHD	**13 (3.3 %)**
Asthma	**4 (1.0 %)**
CKD	**1 (0.3 %)**
More Than One Above	**127 (31.8 %)**
Respiratory Support	
NIV	**345 (86.3 %)**
MV	**35 (8.8 %)**
O_2	**20 (5.0 %)**
Needing Vasoactive Drugs	
No	**379 (94.8 %)**
Yes	**21 (5.2 %)**
Coagulation Profile	
Enoxaparin	**322 (80.5 %)**
Heparin	**78 (19.5 %)**
Received Steroid	
No	**3 (0.8 %)**
Yes	**397 (99.2 %)**
Received Plasma	
No	**252 (63.0 %)**
Yes	**148 (37.9 %)**

The value of age was expressed as number (percentage); DM: Diabetes millets; HTN: Hypertension; IHD: Ischemic heart disease; CKD: Chronic Kidney disease; O2: Oxygen; NIV: Non-invasive ventilation; MV: Mechanical Ventilation.

Our result revealed that among 400 deaths, only 1.8% (n=7) were active smoker; 28.7% (n=115) were former smoker, while 69.5% (n=278) was never smoked, these results were very surprisingly when compared to the 131 discharged COVID-19 patients, especially in the prevalence of active smoker, it was 5.3. % (n=7), the

former smoker was 22.1% (n=29), the never smoker was 72.5% (n=95). Statistically there was a significant invers relation between smoking status and mortality rate in the COVID-19. As shown in Table (3).

Table (3). Association between smoking status and in ICU COVID-19 admitted patients' mortality

Smoking Status	Admitted To ICU With COVID-19 (N = 531)	Discharge From COVID- 19 (N= 131)	Death From COVID- 19 (N= 400)	P- Value
Active Smoker	14 (2.6 %)	7 (5.3 %)	7 (1.8 %)	0.038 *
Former Smoker	144 (27.1 %)	29 (22.1 %)	115 (28.7 %)	
Never Smoker	373 (70.2 %)	95 (72.5 %)	278 (69.5 %)	

The value of age was expressed as number (percentage); n: Number; %: Percentage; *: Significant difference. The data was analyzed using Chi- Square test.

Notably, The OR = 0.36 (95%CI 0.13- 0.99; P =0.041) for AS vs. NS, his results perhaps indicate the AS are low risk of mortality than NS. Also, our findings have demonstrated that active smoker has lower risk of mortality in comparison to the FS, OR =0.29 (95%CI 0.11- 0.79; P = 0.01). Indeed, the former smoker has higher risk of in ICU COVID-19 mortality than non-smoker (never smoker); the OR= 1.25 (95%CI 0.88 - 1.78; P= 0.203) for FS vs. NS. As shown in Table (4).

Table (4). Association between smoking status and mortality in ICU COVID-19 patients

Smoking Status	OR	CI (99% CI)	P- Value
Active Smoker Vs Never Smoker	0.99	0.13 - 0.99	0.044
Active Smoker Vs Former Smoker	0.29	0.11 – 0.79	0.010
Former Smoker Never Smoker	1.25	0.88 – 1.78	0.203

%: Percentage; CI: Confidence of interval; OR: Odds ratio.

Discussion

The current cohort research indicated that the majority was between 60-60 years (35.3%, n=141), followed by older than 70 years (27.7%, n=111) then 50-59 years (17.7%, n=71), then 40-49 years (12.3%, n=49), while only 7.0% (n=28) was younger than 40 years; meaning that the prevalence of the mortality in ICU COVID-19 higher in older adults compared to younger ages. A narrative review by Gkoufa et al., 2021 conducted old that the ages of COVID- 19 patients in comparison to

their younger counterparts, exhibited a higher prevalence of additional health issues and experienced a range of outcomes, although mortality rates were notably elevated, individuals had comorbidity and experienced various, though high, death rates (15). Earlier studies have already shown the correlation between age and mortality in the critically ill COVID-19 patients (16).

Among the COVID-19 deaths, the majority was male (62.2%) rather than female (37.8%). In the conclusion of the study of Nguyen et al., 2021 in a comprehensive analysis involving 308,010 adults hospitalized with COVID-19 in US academic centers revealed that males exhibit a greater likelihood of requiring respiratory intubation, experiencing prolonged hospital stays, and facing higher mortality rates compared to females. This trend persists even when accounting for factors such as age, race/ethnicity, payment methods, and comorbidities (17). Also, our result was in line with the study by Meijs, et al., 2022, which hypothesize that better COVID-19 intensive care unit survival in females, independent of age, disease severity, comorbidities, and treatment (18).

Our data revealed that around three- fifth of the COVID-19 deaths had at least one comorbidity including HTN (14.5%, n=58), DM (8.8%, n=35), IHD (3.3%, n=13), Asthma (1.0%, n=4) and CKD (0.3%, n=1), on the other hand, 31.8% (n=127) were associated with more than one of the above morbidities. In agreement with our study was a prospective cohort study performed by Prats-Uribe et al., 2021, in UK, It has been recorded that, based on data from Hospital Episodes Statistics (HES), several chronic condition and other disease in the previous believed to be linked with morbidity and mortality of COVID-19 include HTN, DM, IHD, various cardiac disease such as cardiac failure, chronic lower respiratory diseases (such as asthma or COPD), and renal impairment (19).

The impact of smoking on death from COVID-19 is uncertain and debated (20). Systematic reviews found link between smoking status (Former Smoker and Current Smoker) and bad COVID-19 outcomes, but were hindered by small samples, similar populations, incomplete smoking status data (21).

In this prospective cohort, the current smokers were associated with a lower risk of severe COVID-19 outcomes, The prevalence of active smoker in the COVID-19 deaths was only 1.8%, which was three times lower than the prevalence in the discharged COVID-19 patients which estimated 5.3%. The prevalence of former smoker was 28.7% in COVID-19 deaths, which was higher than the prevalence of FS in COVID-19 discharged patients (22.1%).

Interestingly, The OR of in-ICU COVID-19 mortality was 0.36 (95%CI 0.13 - 0.99; P =0.041) for AS vs. NS. Our results perhaps indicate the AS are low risk of mortality than NS. This is may be due to Active smoking leads to an augmentation in the quantity of goblet cells and a reduction in ciliated cells, consequently leading to the replacement of typical epithelium with metaplasia of mucosa (22). Hence, It is conceivable that the reduction in ciliary cells and the heightened mucus secretion by goblet cells among active smokers may confer a protective against COVID-19 infection complications in current smokers (21). Par. In agreement with our study a study was

conducted by Razjouyan et al., 2022, in his retrospective cohort study performed among US Veterans, documented that OR was 0.81 (95%CI 0.65 - 1.01; P = 0.065) for CS vs. NS (20)

At the early of COVID-19 pandemic, smoking was recognized as a risk factor for more severe outcomes of COVID-19, a logical inference considering smoking is linked to a heightened occurrence of many respiratory infections. (23). Over time, this view was reversed, numerous additional investigations carried out at the onset of the pandemic documented a decreased occurrence of active smokers among individuals with COVID-19 in comparison to the broader populace. Furthermore, a substantial population-centric study executed in the United Kingdom revealed that smoking exhibited an association with decreased probabilities of mortality from COVID-19 following adjustments for various prognostic indicators (24).

Evidence suggests that smoking impacts the ACE-2 receptors utilized by the virus for cellular entry; however, there is conflicting data regarding whether it increases or decreases the expression of this receptor. While the decrease in expression could be perceived as a potential protective mechanism against infection, an increase may offer protection against the onset of severe lung pathology. An investigation on SARS-CoV revealed a reduction in ACE2 expression, which was directly associated with the progression of severe lung disease (14). Another noteworthy mechanism involves nitric oxide (NO), which is among the numerous chemicals present in cigarette smoke and is also pertinent to nicotine. Smokers exposed to elevated levels of NO through inhaling smoke and also experience endogenously released NO following nicotine uptake in the brain. NO also exhibits antiviral properties (25).

The findings of this study have demonstrated that the active smoker has lower risk of mortality compared to the FS; OR was 0.29 (95%CI 0.11 - 0.79; P = 0.01). A study performed by Farsalinos et al., 2020, in their systematic review of the literature hypothesis that active smoker was less likely to have an adverse outcome compared with former smokers (OR: 0.42, 95% CI: 0.27 - 0.74, P=.003). (26)

The current study indicates that the former smoker has higher risk of in ICU COVID- 19 mortality than non-smoker; the OR was 1.25 (95%CI 0.88 - 1.78; P= 0.203) for FS vs. NS. Razjouyan et al., 2022 revealed that, the OR was 1.36 (95%CI 1.2 - 1.55; p < 0.001) compared to NS (20). In their analysis of a retrospective cohort of in-hospital patients, they discovered that the likelihood of in-hospital mortality among patients who were former smokers and infected with SARS-CoV-2 is greater than that of both never smokers and active smokers. (20). In their cohort study in England, Gao et al., 2022, documented that former smoker were at higher risk of severe COVID-19: HRs: 1.07 (1.03 to 1.11) for hospitalization, 1.17 (1.04 - 1.31) for ICU admission, and 1.17 (1.10 - 1.24) for death (23).

Therefore, we must objectively evaluate both the well-documented adverse effects of cigarette smoking and the potentially significant scientific findings emerging from various countries

worldwide, indicating that active smokers may exhibit a degree of 'protection' against severe SARS-CoV-2 complications, such as interstitial pneumonia and ARDS. (27).

Conclusions

Our analyses of this in-ICU cohort of single COVID-ICU center showed that older adults, males, hypertension with IHD, individuals with renal impairment, as well as those diagnosed with diabetes mellitus along with associated complications, face an elevated susceptibility to mortality linked with the novel coronavirus disease. Active smokers have lower in-ICU mortality due to COVID-19 than former smokers as well from as never smokers, on the contrary the former smokers have higher risk of COVID-19 mortality than both current smokers and never smokers.

References

1. Zhang H, Ma S, Han T, Qu G, Cheng C, Uy JP, et al. Association of smoking history with severe and critical outcomes in COVID-19 patients: a systemic review and meta-analysis. European journal of integrative medicine. 2021;43. doi. 10.1016/j.eujim.2021.101313.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England journal of medicine. 2020;382(8). doi. 10.1056/NEJMoa2001017.
3. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? International journal of epidemiology. 2020;49(3). doi. 10.1093/ije/dyaa033.
4. Organization WH. World Health Organization (WHO) Director-General's Opening Remarks at the Media Briefing on COVID-19. 2020.
5. Wang C, Wang Z, Wang G, Lau JY-N, Zhang K, Li W. COVID-19 in early 2021: current status and looking forward. Signal transduction and targeted therapy. 2021;6(1). doi. 10.1038/s41392-021-00527-1.
6. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18). doi. 10.1056/NEJMoa2002032.
7. Yadav V, Rajput M, Diwakar R, Kumar R. An Overview on Transmission of Diseases in Special Reference to COVID-19 and Potential Targets to Control this Pandemic. J Adv Microbiol Res. 2020;4. doi. 10.24966/AMR-694X/100015.
8. Strzelak A, Ratajczak A, Adamiec A, Feleszko W. Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: a mechanistic review. International journal of environmental research and public health. 2018;15(5). doi. 10.3390/ijerph15051033.
9. Prinelli F, Bianchi F, Drago G, Ruggieri S, Sojic A, Jesuthasan N, et al. Association between smoking and SARS-CoV-2 infection: cross-sectional study of the EPICOVID19 internet-based survey. JMIR public health and surveillance. 2021;7(4). doi. 10.2196/27091.
10. Wang J, Luo Q, Chen R, Chen T, Li J. Susceptibility analysis of COVID-19 in smokers based on ACE2. 2020. doi. 10.20944/preprints202003.0078.v1.
11. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2018;315(5). doi. 10.1152/ajpregu.00099.2018.

12. Piao W-H, Campagnolo D, Dayao C, Lukas RJ, Wu J, Shi F-D. Nicotine and inflammatory neurological disorders. Acta Pharmacologica Sinica. 2009;30(6). doi. 10.1038/aps.2009.67.
13. Besaratinia A. COVID-19: a pandemic converged with global tobacco epidemic and widespread vaping—state of the evidence. Carcinogenesis. 2021;42(8). doi. 10.1093/carcin/bgab061.
14. Norden MJ, Avery DH, Norden JG, Haynor DR. National smoking rates correlate inversely with COVID-19 mortality. MedRxiv. 2020. doi. 10.1101/2020.06.12.20129825.
15. Gkoufa A, Maneta E, Ntoumas GN, Georgakopoulou VE, Mantelou A, Kokkoris S, et al. Elderly adults with COVID-19 admitted to intensive care unit: A narrative review. World Journal of Critical Care Medicine. 2021;10(5). doi. 0.5492/wjccm.v10.i5.278.
16. Le Borgne P, Dellenbach Q, Alame K, Noizet M, Gottwalles Y, Chouihed T, et al. The impact of age on in-hospital mortality in critically Ill COVID-19 patients: A retrospective and multicenter study. Diagnostics. 2022;12(3). doi. 10.3390/diagnostics12030666.
17. Nguyen NT, Chinn J, De Ferrante M, Kirby KA, Hohmann SF, Amin A. Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. PloS one. 2021;16(7). doi. 10.1371/journal.pone.0254066.
18. Meijs DA, van Bussel BC, Stessel B, Mehagnoul-Schipper J, Hana A, Scheeren CI, et al. Better COVID-19 Intensive Care Unit survival in females, independent of age, disease severity, comorbidities, and treatment. Scientific reports. 2022;12(1). doi. 10.1038/s41598-021-04531-x.
19. Prats-Uribe A, Xie J, Prieto-Alhambra D, Petersen I. Smoking and COVID-19 infection and related mortality: a prospective cohort analysis of UK biobank data. Clinical Epidemiology. 2021. doi. 10.2147/CLEP.S300597. eCollection 2021.
20. Razjouyan J, Helmer DA, Lynch KE, Hanania NA, Klotman PE, Sharafkhaneh A, et al. Smoking status and factors associated with COVID-19 in-hospital mortality among US veterans. Nicotine and Tobacco Research. 2022;24(5). doi. 10.1093/ntr/ntab223.
21. Neira DP, Watts A, Seashore J, Polychronopoulou E, Kuo Y-F, Sharma G. Smoking and risk of COVID-19 hospitalization. Respiratory medicine. 2021;182. doi. 10.1016/j.rmed.2021.106414.
22. Martinez FJ, Han MK, Allinson JP, Barr RG, Boucher RC, Calverley PM, et al. At the root: defining and halting progression of early chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2018;197(12). doi. 10.1164/rccm.201710-2028PP.
23. Gao M, Aveyard P, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, et al. Association between smoking, e-cigarette use and severe COVID-19: a cohort study. International Journal of Epidemiology. 2022;51(4). doi. 10.1093/ije/dyac028.
24. Clift AK, Von Ende A, San Tan P, Sallis HM, Lindson N, Coupland CA, et al. Smoking and COVID-19 outcomes: an observational and Mendelian randomisation study using the UK Biobank cohort. Thorax. 2022;77(1).
25. Vleeming W, Rambali B, Opperhuizen A. The role of nitric oxide in cigarette smoking and nicotine addiction. Nicotine & tobacco research. 2002;4(3). doi. 10.1080/14622200210142724.
26. Farsalinos K, Barbouni A, Poulas K, Polosa R, Caponnetto P, Niaura R. Current smoking, former smoking, and adverse outcome among hospitalized COVID-19 patients: a systematic review and meta-analysis. Therapeutic advances in chronic disease. 2020;11. doi. 10.1177/2040622320935765.
27. Rossato M, Di Vincenzo A. Cigarette smoking and COVID-19. Pulmonology. 2021;27(3). doi. 10.1016/j.pulmoe.2020.12.013.