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Smoking and COVID-19 in ICU Patients

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ABSTRACT

Background: Case studies revealed an astonishingly low number of current among patients suffering from symptomatic COVID-19 compared to general population, leading to the conclusion that smoking/nicotine uptake might have a preventive effect. **Objective:** This study aims to show the relation between smoking habits, present and past, and severity and outcome in COVID-19 patients hospitalized in the ICU of the University Hospital in Pristina. **Methods:** This paper reports the results of possible association between smoking habits and severity and outcome of COVID-19. Data on smoking habits, present and past, among 73 patients with severe COVID-19 hospitalized at ICU are analysed and presented. **Results:** Smokers (active and ex-smokers) in total were 16 (21.9%) cases ($P < 0.0001$); active smokers were 5 (6.8%) cases ($P < 0.0001$), ex-smokers 11 (15.1%) cases ($P < 0.0001$), and non-smokers were 57 (78.1%) of the cases. From 16 cases (21.92%) identified as active smoker and ex-smoker, 8 of them ended with death, and other 8 cases survived; while 40 cases (54.79%) from the non-smoker group died, while 17 cases (23.29%) from this group survived (95% CI: 0.2881 to 1.5430, $P = 0.3792$). Out of 5 (6.85%) cases of active smokers, 3 (4.11%) of them ended with death (95% CI: 0.1692 to 2.6846, $P = 0.855$); while from 11 (15.07%) of ex-smokers, 5 (6.85%) died (95% CI: 0.1995 to 1.6412, $P = 0.3561$). OR for death among smoker group of cases (active and ex-smokers) was 0.4250 (95% CI: 0.1370 to 1.3189, $P = 0.1386$); for active smokers 0.2550 (95% CI: 0.0547 to 1.1892, $p = 0.0820$), and 0.3542 (95% CI: 0.0950 to 1.3199, $P = 0.1220$) for ex-smokers. Data on the influence of smoking on incidence and severity of COVID-19 ICU cases are conflicting. **Conclusion:** A protective effect of smoking in COVID-19 should not be inferred.

Keywords: COVID-19, smoking, outcome, ICU.

1. BACKGROUND

The risk factors for contracting symptomatic COVID-19 are not fully understood, age and certain health conditions are considered to be detrimental in this respect. Case studies revealed an astonishing low number of current smokers among patients suffering from symptomatic COVID-19 compared to the general population, leading to the conclusion that smoking/nicotine uptake might have a preventive effect (1).

This relationship between smoking and COVID-19 is complex. Studies found an increased expression of the angiotensin-converting enzyme (ACE-2) in smokers, the entrance gate of the coronavirus into human cells (1).

Smoking, active, passive and third-hand exposure, is known to increase the occurrence of respiratory illnesses (2), infectious and non-infectious, acute and chronic (3), the last ones listed as comorbidities which favours the development of severe COVID-19.

The WHO presented worrying statistics that lung-related deaths due to smoking, including second-hand smoke, totalled 3.3 million in 2017 and included 1.5 million people dying from chronic respiratory diseases and 1.2 million deaths from tracheal, bronchial and lung cancer (3).

Many studies strongly support a significant association between history of smoking and severe COVID-19 progression, in-hospital outcomes and death (4-11).

But there are studies which conclude the opposite; suggesting that active smokers are underrepresented among patients with COVID-19 (12-14), showing a much lower percentage of hospitalised current smokers than expected (15), or claiming even adverse impact of smoking on disease severity and mortality of hospitalized COVID-19 patients (16).

These studies suspect that nicotine could contribute to an amelioration of the cytokine storm and the severe related inflammatory response through

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the $\alpha_7\text{nAChR}$ -mediated cholinergic anti-inflammatory pathway during a patient's aggravation (16).

All the studies on this matter, does not recommend cigarette smoking to prevent evolution into severe or critical forms of COVID-19, since the many and multifaceted unhealthy effects of cigarette smoking are well established (17), suggesting additional prospective and collaborative efforts to clarify the complex the complex relationship between smoking and COVID-19 (17,18).

It is estimated that some 20% of the 1.8 million Kosovo population are smokers (20).

2. OBJECTIVE

This study aims to show the relation between smoking habits, present and past, and severity and outcome in COVID-19 patients hospitalized in the ICU of the University Hospital in Pristina.

3. PATIENTS AND METHODS

This is analytical observational study. 73 patients hospitalized at ICU for COVID-19 were selected at random from a list of medical record numbers corresponding to patients with a confirmed diagnosis of COVID-19. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab.

Data, including those on smoking, present and past, of COVID-19 patients hospitalized in the ICU were collected according to a questionnaire designed for this study.

Ethical approval was not required.

SPSS Statistics version 23 was used for statistical analysis.

4. RESULTS

Of the 73 patients included in the study, 51 (69.9%) were male, and 22 (30.1%) females. The average age of patients was 60.53 years (min 20–max 86, SD 12.67).

Most of the patients treated in the ICU, 71 (97.3%) had comorbidities. Most of them have had more than one comorbidity. Thus, 28 cases (38.4%) had 2 different comorbidities, 24 cases (32.9%) had 3 comorbidities at once, 9 cases (12.3%) had 4 comorbidities, 8 cases (11.0%) had 1 comorbidity, and 2 cases (2.7) had 5 comorbidities. The most common comorbid condition was obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) in 40 cases (54.8%) and diabetes mellitus (40 cases, 54.8%), followed hypertension (38 cases, 52%), cardiovascular and cerebrovascular diseases (23 cases, 31.5%), chronic respiratory diseases (21 cases, 28.8%), chronic kidney disease (11 cases, 15.0%) and atrial fibrillation (11 cases, 15.0%).

Most of the patients admitted to the ICU had laboratory biological data. 70 (95.9%) had data on leukocytes (mean $14.1 \times 10^9/\text{L}$, SD 5.73, min 2.6 max 29.0) and platelets (mean $239.9 \times 10^9/\text{L}$, SD 90.06, min 26 max 419) and 71 (97.3%) had data on CRP (mean 94.2 mg/dL, SD 42.2, min 1 max 224). All ICU cases had a positive SARS-CoV-2 RT-PCR test.

| | ICU cases with COVID-19, n = 73 |
|---|---------------------------------|
| Age, years [min-max] | 60.53 (20–86) |
| Male, n (%) | 51 (69.9%) |
| Main comorbidities | n (%) |
| Obesity (body mass index $\geq 30 \text{ kg/m}^2$) | 40 (54.8) |
| Diabetes mellitus | 40 (54.8) |
| Hypertension | 38 (52) |
| Cardio-vascular and cerebro-vascular diseases | 23 (31.5) |
| Chronic respiratory diseases | 21 (28.8) |
| Chronic renal failure | 11 (15) |
| Atrial fibrillation | 11 (15) |
| Comorbidities / case | n (%) |
| 5 Comorbidities | 2 (2.7) |
| 4 Comorbidities | 9 (12.3) |
| 3 Comorbidities | 24 (32.9) |
| 2 Comorbidities | 28 (38.4) |
| 1 Comorbidity | 8 (11) |
| Biological data | Mean (n) |
| Leukocyte count | 14.1x10 ⁹ /L |
| Platelets | 239x10 ⁹ /L |
| C-reactive protein | 94.2 mg/dL |
| Outcome | n (%) |
| Survived | 25 (34.2) |
| Died | 48 (65.8) |

Table 1. Main characteristics of 73 ICU COVID-19 patients

All cases (100%) in the ICU were performed radiological examinations of the lungs (x ray and/or CT/MRI of the lungs), and 65 (89.0%) of them had pneumonia.

The length of the treatment on ICU was on average 9.4 days (SD 10.68, min 1 max 34). Most of the cases, 45 (61.6%), were hospitalised for ≤ 3 days.

The length of the treatment for cases ended with death was 11.13 days (SD 12.04, min 1 max 34), while for the survived group this time period was 6.08 (SD 6.39, min 1 max 24). Cases ended with death had more comorbidities (mean 2.83, SD 0.930, min 1 max 5) than the cases which survived (mean 1.84, SD 0.893, min 0 max 3). 48 (65.8%) of the cases ended with death, and 25 (34.2%) survived.

Main data of 73 ICU COVID-19 cases are presented in Table 1. Smokers (active and ex-smokers) in total were 16 (21.9%) cases (95% CI: 40.9862% to 67.4405%, $P < 0.0001$); active smokers were 5 (6.8%) cases (95% CI: 57.7803% to 80.1400, $P < 0.0001$), ex-smokers 11 (15.1%) cases (95% CI: 48.3542% to 73.2353%, $P < 0.0001$), and non-smokers were 57 (78.1%) of the cases.

The proportion of the active and ex-smokers in the studied group of ICU cases is in proportion with the smoker group in general population (95% CI: -6.0485% to 12.6580%, Chi-squared = 0.165, $P = 0.6849$).

The mean age of the active smoker group was 65.2 years (SD 13.44, min 48 max 80), ex-smoker group 54.73 years (SD 12.24, min 34 max 68), and non-smokers 61.24 years (SD 12.55, min 20 max 83). There is no significant difference between the mean age of active smokers and non-smokers (95% CI: -15.7260 to 7.8060, $P = 0.5034$) as

| | ICU cases with COVID-19 n = 73 |
|----------------------------------|--------------------------------|
| Smoking status | n (%) |
| Active smokers | 5 (6.8) |
| Ex-smokers | 11 (15.1) |
| Non-smokers | 57 (78.1) |
| Age | years |
| Active smokers | 65.24 |
| Ex-smokers | 54.73 |
| Non-smokers | 61.24 |
| Pneumonia | n (%) |
| Active smokers | 5 (100) |
| Ex-smokers | 11 (100) |
| Non-smokers | 49 (75.38) |
| Comorbidities/case | mean |
| Active smokers | 3.20 |
| Ex-smokers | 2.18 |
| Non-smokers | 2.49 |
| Length of treatment | days |
| Active smokers | 8.4 |
| Ex-smokers | 7.91 |
| Non-smokers | 9.77 |
| Outcome/deaths | n (%) |
| Active smokers | 3 (4.11) |
| Ex-smokers | 5(6.85) |
| Smokers (active plus ex-smokers) | 8 (10.96) |
| Non-smokers | 40 (54.79) |

Table 2. Data on smoking influence on COVID-19

well as between ex-smokers and non-smokers (95% CI: -5.1797 to 18.1997, $P=0.2697$).

All of the active smoker group (5 cases, 100%) and all of the ex-smoker group (11 cases, 100%) had pneumonia, while from 57 cases of non-smoker group, 49 (75.38%) had pneumonia (95% CI: 3.1239% to 37.1652%, Chi square = 4.810, $p=0.0283$). No significant difference was observed in smoker group (active and ex-smokers) (95% CI: 3.1239% to 37.1652%, Chi-squared=4.810, $P=0.0283$); active smokers (95% CI: -19.8209% to 37.1652%, Chi-squared=1.565, $P=0.2109$); ex-smokers (95% CI: -2.8970% to 37.1652%), Chi-squared=3.362, $P=0.0667$) and non-smoker group.

The number of comorbidities on smoker group was 3.20 comorbidities/case (SD 1.30, min 2 max 5), on ex-smoker group was 2.18 comorbidities/case (SD 1.25, min 0 max 4), and 2.49 comorbidities/case (SD 0.947, min 0 max 5) on non-smoker group. No significance difference was observed between active smoker group and non-smoker group and (95% CI: -1.6192 to 0.1992, $P=0.1235$), and ex-smoker group and non-smoker group (95% CI: -0.3467 to 0.9667, $P=0.3494$).

The length of treatment on ICU for the active smokers was 8.40 days (SD 14.35, min 1 max 34), for ex-smokers 7.91 days (SD 4.7, min 3 max 12), and for non smokers 9.77 (SD 11.28, min 1 max 34). There is no significant difference between active smoker group and non-smoker group (95% CI: -10.2256 to 12.9656, $P=0.8140$) as well as between ex-smoker group and non-smoker group (95% CI: -5.8964 to 9.6164, $P=0.6337$).

From 16 cases (21.92%) identified as active smoker and ex-smoker, 8 (10.96%) of them ended with death (10.96), and other 8 cases survived; while 40 cases (54.79%) from the non-smoker group died, while 17 cases (23.29%) from this group survived (95% CI: 0.2881 to 1.5430, $P=0.3792$). Out of 5 (6.85%) cases of active smokers, 3 (4.11%) of them ended with death (95% CI: 0.1692 to 2.6846, $P=0.855$); while from 11 (15.07%) of ex-smokers, 5 (6.85%) died (95% CI: 0.1995 to 1.6412, $P=0.3561$).

OR for death among smoker group of cases (active and ex-smokers) was 0.4250 (95% CI: 0.1370 to 1.3189, z statistic 1.481, $P=0.1386$); for active smokers 0.2550 (95% CI: 0.0547 to 1.1892, z statistic 1.739, $p=0.0820$), and 0.3542 (95% CI: 0.0950 to 1.3199, z statistic 1.564, $P=0.1220$) for ex-smokers.

Data on smoking and outcome of COVID-19 cases are presented in Table 2.

5. DISCUSSION

Our study didn't find significant difference between the mean age of active smokers and non-smokers (95% CI: -15.7260 to 7.8060, $P=0.5034$) as well as between ex-smokers and non-smokers (95% CI: -5.1797 to 18.1997, $P=0.2697$); study didn't find significant difference on the pneumonia presence among studied groups (95% CI: 3.1239% to 37.1652%, Chi square = 4.810, $p=0.0283$), length of treatment at the ICU (active smokers, 95% CI: -10.2256 to 12.9656, $P=0.8140$; ex-smokers, 95% CI: -5.8964 to 9.6164, $P=0.6337$; active and ex-smokers, 95% CI: -1.6192 to 0.1992, $P=0.1235$; non-smokers, 95% CI: -0.3467 to 0.9667, $P=0.3494$). These finding are in correlation with most of review studies on this topic (3-5,10,13,15,16).

We found that the proportion of active and ex-smokers is in correlation with the smoker group in general population (95% CI: -6.0485% to 12.6580%, Chi-squared = 0.165, $P=0.6849$). This finding is not in correlation with several studies included in the Wenzel EC report (1), which revealed an astonishing low number of current smokers among COVID-19 patients, or the work of Tsigaris (2), which found negative association between smoking prevalence and COVID-19 occurrence at the population level in 38 European countries.

Statistically significant negative correlation between smoking in general (active and ex-smoking) (95% CI: 40.9862% to 67.4405%, $P<0.0001$), as well as active (95% CI: 57.7803% to 80.1400, $P<0.0001$) or ex-smoking (95% CI: 48.3542% to 73.2353%, $P<0.0001$) and the severity of disease, defined as ICU cases, was found in our study.

This is not supported by the studies of Grundy et al. (4) and Reddy et al (5), which found an association between smoking and COVID-19 severity, and increased risk of severe and/or critical COVID-19 for current smokers. Our study is in contrast also with the study of Gülsen et al. (6), Alghamadi et al. (7), Vardavas et al. (8), or Kashyap et al. (9), who came to the conclusion that active smoking and history of smoking are clearly associated with severe COVID-19; that patients with any smoking history are vulnerable to severe COVID-19; that smoking is most likely associated with negative progression

and averse outcomes of COVID-19; or that epidemiological meta-analyses findings suggest that active smoking is significantly linked with the risk of more severity of COVID-19.

When it came to the death rates of COVID-19 ICU cases, our study finds that there is no statistically significant difference between the death rate in smoker group (active and ex-smokers), and the rate of death in the non-smoking group (95% CI: 0.2881 to 1.5430, $P=0.3792$). The same is also when death rates of active (95% CI: 0.1692 to 2.6846, $P=0.855$) and ex-smokers (95% CI: 0.1995 to 1.6412, $P=0.3561$), are compared.

Our study showed decrease in odds for death in smoking exposed groups. OR for death among smoker group of cases (active and ex-smokers) was 0.4250 (95% CI: 0.1370 to 1.3189, z statistic 1.481, $P=0.1386$); for active smokers 0.2550 (95% CI: 0.0547 to 1.1892, z statistic 1.739, $p=0.0820$), and 0.3542 (95% CI: 0.0950 to 1.3199, z statistic 1.564, $P=0.1220$) for ex-smokers.

Contrary to finding in our study, Alghamdi et al. (7), found worse in-hospital outcome in COVID-19 patients; while Alqahtani et al. (10), comparing former and newer smokers, found that current smokers were at greater risk of severe complications and higher mortality rate. N van Zyl-Smit R, et al. (11), reported a review in which the increased risk for severe disease and need for mechanical ventilation and death for current smokers and COVID-19.

However, our finding is similar to some other studies, which found lower prevalence of smokers among hospitalised patients with COVID-19, when compared to general population (13).

Even some studies, which earlier didn't demonstrate significant association between active smoking and COVID-19 severity (14), after adjustment of multiple additional covariates, the same study found that smoking was with a reduced risk for COVID-19 mortality (13). Another review study indicated that a smoking habit lowers the likelihood of being hospitalised by COVID-19 (15), while a study by Karanasos et al. (16) concluded a possible adverse impact of smoking on disease severity and mortality, which was found in our study too.

Despite our findings, we do support the standings of many other studies, that smoking cannot be recommended to prevent evolution into severe or critical forms of COVID-19 (17), that the cigarette smoking is detrimental for the lungs in several ways (18), and that non-significant P values in the evaluated and the results of the meta-analyses do not necessarily rule out the association between the use of tobacco products and COVID-19 severity (19).

The authors are aware of the limitations of the study, like the small number of samples included in the study, or the substantial but unexplored influence of the passive smoking, in countries and societies, like our, where restrictions on smoking are not respected.

6. CONCLUSION

Data on the influence of smoking on incidence and severity of COVID-19 ICU cases are conflicting. A pro-

tective effect of smoking in COVID-19 should not be inferred.

- **Institutional Review Board Statement:** Ethical review and approval were waived for this study. According to the National Code on Clinical trials, this is a proper observational retrospective study for which ethical approval is not required.
- **Informed Consent Statement:** Patient consent was waived due to the study's retrospective nature; all procedures performed were part of routine care.
- **Author's contributions:** IT, NB conceived the original idea. IT designed, supervised and provided a critical reading of the manuscript. NB, LM and HF made data analyses and the figures. All the authors made the final approval of the article for publication.
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