

Tobacco smokers as target group for complicated coronavirus infection

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Abstract

The aim of current study was to determine, retrospectively, possible correlations between smoking and the incidence, course severity, intubation rate, and mortality (by gender and age) in patients treated for complicated coronavirus infection in the internal medicine clinic at UMHATEM "N. I. Pirogov" Sofia for the period 01.03.2020–31.12.2020. In a prospective study, the recovery period and immunogenesis in smokers and non-smokers within a one-year period after hospital discharge was investigated. The applied methods were: 1) computed tomography and blood gas analysis 2) chemiluminescent immunoassay for the qualitative determination of total IgM, IgA and IgG anti-SARS-CoV2 AB. Results showed that the part of non-smokers with a positive PCR test is significantly higher compared to the group of former and current smokers. The data obtained from the study confirmed that Covid infection is much more severe among smokers and former smokers with a higher levels of inflammatory markers noticed among the smoking group.

Keywords

complications, Covid-19, endothelial dysfunction, intubation rate, mortality, tobacco smoking

Introduction

The coronavirus infection (Covid-19) with the etiological agent SARS-CoV-2 has become a serious global health problem, the fight against which is still ongoing. The pandemic caused by the novel human beta-coronavirus strain SARS-CoV-2 has put global healthcare to a serious assessment, forcing almost all countries to respond with adequate anti-epidemic, diagnostic, treatment and prophylactic measures to multiple epidemic peaks. This fight should also be focused on the development of effective measures to optimally reduce the possibility of the emergence of new mutations that would eventually lead to the

emergence of a new strain of the Coronavirus family with significant virulence. SARS-CoV-2 is a beta-coronavirus of the Coronaviridae family. Representatives of the family usually cause respiratory complaints resembling the "common cold". Considered from the very beginning of the pandemic to the present moment, almost all countries were forced to fight adequately with several epidemic peaks in the evolution of the infection. Leading scientists from all over the world – experts in the field of medicine, and many other fields of science, continue to work diligently to find the answers to the still too many unsolved questions, necessary to find the most effective way to fight the disease caused by the virus, to limit the viral spread,

and eradicate the infection. Retrospective observations on the course of the disease in hospitalized patients have a real contribution to the collection of data on the features, characterizing the development and treatment of the infection. This information is a valuable source, able to direct the attention of the scientific community in an unexpected direction and identify a wide range of risk factors contributing to a severe course of the disease and, also, to pay attention to some bad habits and their impact on morbidity, frequency of complications, and mortality in the target groups (Anand et al. 2021).

Advanced age, cardiovascular diseases, as well as all concomitant diseases, in the pathology of which existing endothelial dysfunction, plays a major role, predispose to infection with the SARS-CoV-2 virus, and the development of "Covid-19 disease". The respiratory epithelium is the main "portal of entry" for the virus, but the endothelial cells of the pulmonary blood vessels are an equally important element in the development of lung involvement in the disease Covid-19. Endothelial cells and blood vessels are targets, but also a mechanism for the spread of the SARS-CoV-2 virus, and associated tissue changes, as well as for its dissemination to various organs in the patient's body. Therefore, prior endothelial dysfunction could make endothelial cells more sensitive to the action of the virus, leading to the more severe systemic course of Covid-19 (Tarnawski and Ahluwalia 2022).

The pathophysiological mechanism of SARS-CoV-2 virus infection is a complex process involving the interaction between "hyperinflammation", impaired lymphocyte function, endothelial dysfunction, thromboembolic complications, and fibrotic changes in the lung. These processes are not only complex and unpredictable, but show great variability among individual patients, possibly related to the heterogeneous response of the patient's immune system (van de Veerdonk et al. 2022). Infection with SARS-CoV-2 occurs through binding of the spike glycoprotein of the virus to the human angiotensin-converting enzyme-2 (ACE-2) receptor on the epithelial cell surface with the help of transmembrane serine protease 2 (TMPRSS2), ensuring viral entry in the cell (Walls et al. 2020). The ACE2 receptor is exclusively represented on the surface of epithelial cells in the nasal cavity and the lower respiratory tract, thus predetermining the epidemically significant portal of entry for viral invasion (Yan et al. 2020). After the virus enters the cells, it is recognized by specific receptors of the immune cells, which are responsible for activating the protective mechanisms of the immune system to fight the infection (complex immune response). The subsequent production of immune mediators such as cytokines and complement activation, which initially occurs to a moderate extent at the local level, is extremely important to fight infection, but overproduction of inflammatory mediators could aggravate the course of the disease in the development of the so-called "cytokine storm" (Jouan et al. 2021). A number of studies have demonstrated the importance of the IL-1 – IL-6 axis as a major signaling mechanism of the immune system,

leading to a "hyperinflammatory" immune response (Chen et al. 2020; Giamarellos-Bourboulis et al. 2020). It has been shown on cellular level that the current coronavirus strain decreases circulating CD3+ CD8+ T-cells, which resembles sepsis-associated lymphopenia, and this phenomenon is associated with the severity of the disease and poor prognosis (Du et al. 2020). In addition to the resulting lymphocytopenia, their functional capacity, and the ability to release type II interferons are also severely reduced in patients with a severe course of Covid-19 (Bost et al. 2021; Janssen et al. 2021; Kreutmair et al. 2021).

Another essential mechanism in the development of the infection and its complications is the influence on the precise regulation of the coagulation system. Thrombosis is potentiated by hypercoagulable status, endothelial damage, and blood stasis, and exactly these factors are common in severe Covid-19 infection (van de Veerdonk et al. 2022). As a consequence, venous and arterial thromboembolic events have been reported extremely frequently: a number of studies have shown that between 21% and 69% of patients with severe disease develop thromboembolic complications during the course of the disease (Obi et al. 2021).

Although the initial "target" of the Covid 19 virus is the epithelium presented in the respiratory system, the high occurrence of vascular complications in the affected patients directs attention to the endothelial cells of the blood vessels, and their key role in the progression and deterioration of the coronavirus disease. SARS-CoV-2 causes endothelial dysfunction and increases the thrombogenic risk by two main mechanisms – by directly infecting the endothelium and compromising its antithrombotic and barrier function, and/or indirectly by inducing a local cytochrome storm, and systemic inflammatory response, which potentiate endothelial dysfunction (Tarnawski and Ahluwalia 2022). Ackerman and co-authors demonstrated the abnormalities of the pulmonary microcirculation expressed in vascular congestion and microthrombi in patients suffering from Covid-19, by objectifying using electron microscopy single-body lesions and vascular lumen, filled with cell fragments and degenerated cell organelles. This study also demonstrated an increased number of endothelial cells containing ACE2-receptors, as well as significant changes in the endothelial morphology of the lungs in autopsied patients with Covid-19 infection (Ackermann et al. 2020). Under certain pathological conditions of existing endothelial dysfunction, the ACE/Ang II axis is overactivated, leading to vasoconstriction, thrombogenesis, fibrosis, coagulopathy, and thrombophilia (Tarnawski and Ahluwalia 2022).

Endothelial cell dysfunction observed in Covid-19 has a complex pathogenesis. On the one hand, cardiovascular comorbidity in older patients with Covid-19 is associated with prior endothelial dysfunction, and ACE2 receptor deficiency. On the other hand, however, the SARS-CoV-2 virus itself could induce changes in endothelial function in different ways, for example: direct viral replication with loss of barrier function; downregulation of ACE2 receptors, and hyperactivation of the body's immune response

leading to cytokine storm and hypercoagulable state. This acute inflammatory reaction, as well as the prothrombotic response to impaired epithelial cell function, lead to deleterious effects: respiratory distress syndrome (ARDS), diffuse microvascular thrombosis and thromboembolism, life-threatening cardiovascular complications, and multiple organ failure. This endothelial dysfunction in patients who have recovered from Covid-19 could be related to the persistence of chronic inflammation and pathologically activated hypercoagulation during the course of the disease (Otifi and Adiga 2022).

In addition to concomitant diseases, some of the risk factors also play a role in the development of endothelial dysfunction, the importance of which should not be ignored and needs further evaluation. A major risk factor leading to disruption of the integral function of the vascular endothelium, and of great public importance, due to its prevalence and its effects, is smoking. Tobacco smoking is one of the largest, preventable causes of a number of diseases, increasing the morbidity and mortality of the population worldwide (Cokkinides et al. 2009). According to recent data, more than 5 million people worldwide die annually from smoking-induced diseases (Talukder et al. 2011). Cigarette smoke increases the production of free radicals and vascular superoxide, resulting in decreased nitric oxide (NO) bioactivity. Simultaneously with these pathophysiological changes, smoking increases the production of vasoconstrictor eicosanoids (Raj et al. 2001). This dysfunction is also thought to be caused by the presence of aldehydes, which are generated in large quantities in cigarette smoke. Although the effect of electronic cigarettes on health is not yet sufficiently investigated, studies demonstrate the presence of similar aldehydes in their aerosols, suggesting the same risks for vascular complications compared to conventional cigarettes (Lynch et al. 2020). Cigarette smoke is an aging accelerator (Bernhard et al. 2007).

A number of other factors associated with smoking enhance endothelial dysfunction – stimulating the production of free radicals, increasing serum glucose, lipids and lipoproteins, as well as activating the enzyme cyclooxygenase 2 and synthesis of inflammatory mediators (Raji et al. 2001; Alfranca et al. 2006). Cigarette smoke potentiates local inflammation in the vascular wall increasing the expression of intercellular adhesion molecules, monocyte adhesion, and increase vascular permeability. Tobacco smoke cooperates with interleukin-1 β to alter beta-catenin trafficking in vascular endothelium resulting in increased permeability and induction of cyclooxygenase-2 expression *in vitro* and *in vivo* (Barbieri and Weksler 2007).

The blood serum of active smokers has the property to activate the production of free radicals in the endothelium through the activation of NADPH oxidase and subsequent induction of COX-2 expression through the p38MARK/Akt chain (Barbieri et al. 2011). The cytokines TNF- α and IL-1 β play a key role in the pathogenesis of inflammatory diseases. A number of studies have found

a relation between the risk factor smoking and a change in their expression, emphasizing the fact that even short-term exposure to cigarette smoke *in vivo* is sufficient to increase their synthesis (Castro et al. 2004; Hou et al. 2009).

The levels of these cytokines in the serum of smokers are elevated compared to non-smokers, and simultaneous inhibition of their signaling pathways prevents smoking-induced endothelial dysfunction (Barbieri et al. 2011). These cytokines predominate in the lung – mainly in epithelial cells and leukocytes. It is the action of the cigarette smoke that increases the concentration of both TNF- α (Ryder et al. 2002), and interleukin-1 β (Churg et al. 2009), found in the bronchial lavage, as well as in circulating mononuclear cells in smokers compared to non-smokers (Ryder et al. 2002). Each inflammatory process potentiates and increases vascular dysfunction induced by cigarette smoke (Barbieri and Weksler 2007). The combination of smoking and inflammation clearly leads to severe endothelial damage. The presence of previous impairment to the vascular endothelium is the basis for the pathophysiological processes characterizing the severe course and fatal complications of the Covid-19 infection (Barbieri et al. 2011). Lung-targeted overexpression of the NF- κ B member RelB inhibits cigarette smoke-induced inflammation (McMillan et al. 2011).

Oxidative stress and accelerated vascular aging are implications for cigarette smoking. (Csiszar et al. 2009). A number of studies confirm the presence of so-called low-grade systemic inflammation in smokers, as evidenced by the increased levels of CRP, fibrinogen, interleukin-6 and the increased number of leukocytes found in the body. In addition, changes also occur in a number of rheological, coagulation and endothelial functional markers such as hematocrit, blood and plasma viscosity, fibrin, D-dimer, circulatory adhesion molecules (intracellular adhesion molecule-1, selectins), tissue plasminogen activator, plasminogen activator-inhibitor type 1, in chronic smokers. Although some of these changes are reversible after smoking cessation, some inflammatory mediators (such as CRP) remain significantly elevated in ex-smokers 10 to 20 years afterward, suggesting an active inflammatory process (Yanbaeva et al. 2007).

Smoking is a major factor in the pathogenesis of a number of socially significant diseases – neoplasia, lung and cardiovascular diseases, neurological diseases, GIT diseases, etc. It is not so well-known that cigarette smoke affects the functions of the immune system, affecting both the innate and adaptive (acquired) immunity. Smoking has been shown to increase the production of a number of pro-inflammatory cytokines such as TNF- α , IL-1, IL-6, IL-8, GM-CSF and decrease the levels of anti-inflammatory cytokines such as IL-10 (Arnson et al. 2010).

Preliminary data from a number of reports suggest that smokers are less susceptible to infection with the SARS-COV-2 virus. However, once infected, the risk of developing a severe infection increases. The mechanism for the lower susceptibility to infection requires further studies and research (Paleiron et al. 2021). Tobacco smoking

significantly compromises the local protective mechanisms in the lung, thus favouring the development of inflammatory changes, as well as the more severe clinical course of lung inflammation in smokers (Patanavanich and Glantz 2020). The number of ex-smokers who were hospitalized and died as a result of coronavirus infection compared to current smokers and non-smokers is significant. This effect is potentiated by the comorbidity and the advanced age in some ex-smokers (Neira et al. 2021).

Compared with patients who had never smoked, current active smokers appeared to have a reduced risk of infection with SARS-CoV-2 virus, while former smokers had a higher risk of hospitalization, more severe disease, and death. These dependencies are still subject to investigation and further studies (Simons et al. 2021).

The relation between the development of Covid-19 infection and smoking, as well as the mechanisms of their interaction, remain unknown for now. Nicotine could play a role in these processes (Oakes et al. 2018; Lan et al. 2020; Paleiron et al. 2021), as well as cigarette smoke with its fine particles and numerous chemical agents, which probably have a non-specific effect in direction of deterioration of all processes occurring in the lung, due to the viral infection (Oakes et al. 2018). The ACE-2 receptor is the specific site of entry of SARS-CoV-1 and SARS-CoV-2 viruses into the target cell, unlike MERS-CoV, in which dipeptidyl peptidase4 – DPP4 is the key "agent" (Maggi et al. 2021). In the course of MERS-CoV infection, no deterioration was observed in smokers, as well as any clinical-protective effect. That is why the hypothesis about the role of the ACE2 enzyme is widely advocated in a number of theories (Hamming et al. 2004; Yan et al. 2020), but the latest studies, in comparison with these data, even prove an increased expression of this enzyme in smokers. This would lead to an increased risk of infection in smokers, compared to non-smokers, and also in women, compared to men, because women have greater expression of ACE2 receptors. In practice, these presumptions are not confirmed (Paleiron et al. 2021). Two other older hypotheses try to explain the lower number of Covid-19 infections in smokers, but neither of them provides a satisfactory explanation for this phenomenon: one suggests an overall effect on the renin-angiotensin aldosterone system (of which ACE2 is a part), by increasing the expression of the ACE1 receptor at the expense of the ACE2 receptor (Oakes et al. 2018). The second hypothesis suggests an interaction between ACE2 and nicotinic receptors (in particular the alpha7 nicotinic receptor), which are located very close to each other on the surface of the cell membrane, and this results in spatial dysregulation in the trigger zone for the Th1 immune response (Changeux et al. 2020). Moreover, it has been suggested that nicotine and the SARS-CoV2 virus could compete for binding to nAChR acetylcholine receptors (Changeux et al. 2020; Paleiron et al. 2021).

Nicotine could be considered as a potential factor for the prevention against Covid-19 infection. Both epidemiological, clinical and *in silico* models offer evidence that Covid-19 is an acetylcholine receptor (nAChR)

disease and can be prevented and controlled by nicotine (Changeux et al. 2020). In this case, nicotine would compete sterically and allosterically with the SARS-CoV-2 virus for binding to nAChRs. Of course, the fact that nicotine is addictive, which is the core of smoking addiction, should not be overlooked (Changeux 2010).

Smoking has an extremely serious impact on human health and remains a serious threat to public health. According to some studies, however, under strict control, nicotine derivatives can be used to treat acute infection with Covid-19 (Changeux et al. 2020). Nicotine is a cholinergic agonist and pro-inflammatory cytokine inhibitor. According to some authors, smoking and nicotine reduce the amount of ACE2 receptors (the portal of entry for the SARS-CoV-2 virus), but according to other authors, ACE2-receptor representation is increased in smokers. Moreover, it is suggested that the interaction of SARS-CoV-2 with nAChR is the result of dysregulation of the nicotinic cholinergic system, which is related to the pathophysiology of Covid-19. Nicotine could restore the impaired function of the nicotinic cholinergic system and possibly reduce the cytokine storm (Korzeniowska et al. 2021). According to new information, the number of smokers hospitalized with Covid-19 is unexpectedly low, which forms a new hypothesis about individual predisposition and about different strategies to reduce the risk of infection with the SARS-CoV-2 virus, which must be confirmed in the future through large adequately designed studies (Meini et al. 2021).

Conducted studies prove that patients with respiratory diseases, in the etiology of which smoking plays an important role, have an increased risk of developing a severe Covid-19 infection. Patients who smoke and have comorbidities are at increased risk for infection with Covid-19, and have a worse prognosis both for the course of the viral infection and for complications of their comorbidities (Haddad et al. 2021). Serum neutrophils, NLR and ferritin levels, which are widely used to predict the course of Covid-19, are found to be elevated in current and ex-smokers. These results support the proposition that the prediction of increased susceptibility to SARS-CoV-2 infection is aggravated by smoking (Kargin 2021)

Smoking deteriorates the lung's immune defense and impairs the upper respiratory tract, thus increasing the risk of infection and more severe infectious diseases. That is why smoking is an independent risk factor for the progression of Covid-19 and for increased mortality. These effects appear to be more pronounced in young patients. Smoking prevention and cessation should remain a major goal for society, physicians, and health care in general, especially during the Covid-19 pandemic (Patanavanich and Glantz 2021). Patients with a history of smoking are particularly vulnerable to a severe form of Corona virus infection. The threat of adverse outcome in smokers is significant, due to impaired endothelial function, and all the pathophysiological processes resulting from this phenomenon. In addition to the fact that the hypothetical protective role of nicotine in coronavirus disease remains

unproven, it is practically evident that nicotine does not reduce the severity of the infection in smokers. In the absence of targeted therapy, prevention and strategies to reduce morbidity and mortality in former smokers and current smokers are of utmost importance (Reddy et al. 2021)

Active smoking and a history of previous long-term smoking are definitely factors associated with the risk of a severe form of coronavirus infection (Gülşen et al. 2020). There are analytical studies supporting a causal relationship between smoking and severe clinical presentation of Covid-19 infection (Clift et al. 2022).

The discussion of these actual problems in parallel with the analysis of the results of the present study aims to establish whether there is a causal relation between smoking and infection with the SARS-CoV-2 virus as well as between the course of the disease in complicated coronavirus infection, for the patients treated at the Internal Medicine Clinic at UMHATEM "N. I. Pirogov", Sofia, for the period 01.03.2020 - 31.12.2020.

Materials and methods

The study included 2,073 patients out of a total of 2,090 patients diagnosed and treated in the internal medicine clinic for complicated coronavirus infection, in the period from 01.03.2020 - 31.12.2020. 17 patients under the age of 18 were excluded. The studied patients were over 18 years of age with main complication "viral pneumonia", and a positive result for the presence of the SARS-CoV2 causative agent using the diagnostic method RT-PCR from nasopharyngeal swab and mandatory serum RT PCR. The group includes 895 women and 1178 men. Only patients with more than 5 pack-years (PY) (≥ 20 cigarettes smoked per day) were included in the group of smokers. All patients at hospitalization had moderate to severe pneumonia. Defined as moderately severe pneumonia, according to the CT-score, is whenever 25% to 50% of the lung parenchyma is involved. Defined as severe pneumonia by the CT-score involves more than 50% of the lung parenchyma.

The monitoring of pulmonary changes was carried out based on diagnostic imaging by computed tomography and assessment of gas exchange by blood gas analysis.

Immunogenesis was monitored by determining Anti-SARS-CoV2 AB. The measurements were performed based on a chemiluminescent immunoassay with Micro Well technology. The test is "semi-quantitative" and is designed for the qualitative determination of total IgM, IgA and IgG anti-SARS-CoV2 AB. In the present study, Total anti-SARS-CoV2 AB and IgG anti-SARS-CoV2 AB were monitored in each included patient.

Results and discussion

For the indicated period, there was a total of 2,073 patients who were diagnosed and treated for complicated coronavirus pneumonia at the Internal Medicine Clinic. Viremia

was demonstrated in each of the patients. The study group included 895 women and 1178 men. Only patients with more than 5 pack-year (PY) (with more than 20 cigarettes smoked per day) were included in the group of smokers.

Our study consists of two stages – retrospective and prospective:

1) Retrospective:

- To determine the frequency of smokers by gender and age among the group of patients treated in the internal medicine clinic during the fixed period.
- To determine the severity of the course of disease in smokers and compare it with the severity in patients from the non-smoking group.
- To determine the frequency of intubated patients in the smoking group and compare it with the frequency of intubated patients in the non-smoking group.
- To determine the mortality in the smoking group and compare it with the mortality in the non-smoking group.

2) Prospective:

- To track the recovery period in smokers and compare it with the same in non-smokers within a one-year period after hospital discharge.
- To track immunogenesis in smoking patients and to compare it with non-smoking patients within a one-year period after hospital discharge

According to their smoking experience, the studied patients were divided into three age groups, and for each age group the frequency of active smokers, non-smokers and former smokers was determined. The first group included 576 patients between the ages of 18 and 49, 1300 patients between the ages of 50 and 79 are included in the second group, and above 80 years were 197 patients (Table 1.).

The Fig. 1. reflects the distribution of men and women according to their smoking status as follows: smokers, non-smokers and former smokers. It is noteworthy that, in general, the part of non-smokers with a positive PCR test is significantly higher compared to the group of former and current smokers. This difference is extreme between the non-smokers and smokers. The number of non-smokers with positive nasopharyngeal and serum PCR tests is ten times more than the number of smokers. This applies to both men and women.

The distribution of men and women in other age groups is illustrated on Fig. 2. (between 50 and 79 years) and on Fig. 3., (over 80 years).

In these two age groups, the same correlation is preserved as in the first age group.

Another important thing, analyzed in this study, is the severity of disease progression in smokers and patients who had never smoked. Unsatisfactory results of non-invasive ventilation methods – persistent hypoxemia, respiratory distress, and the need for intubation and mechanical

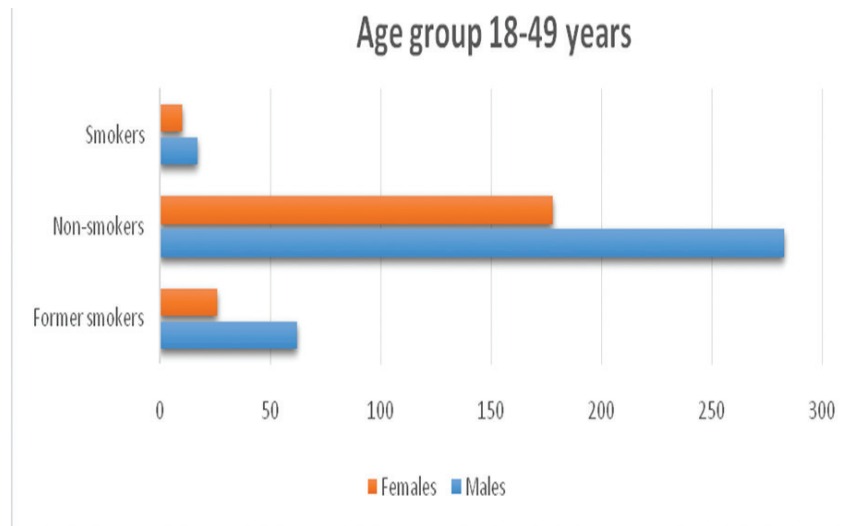


Figure 1. Distribution of men and women in age group 18–49 years, according to their smoking status.

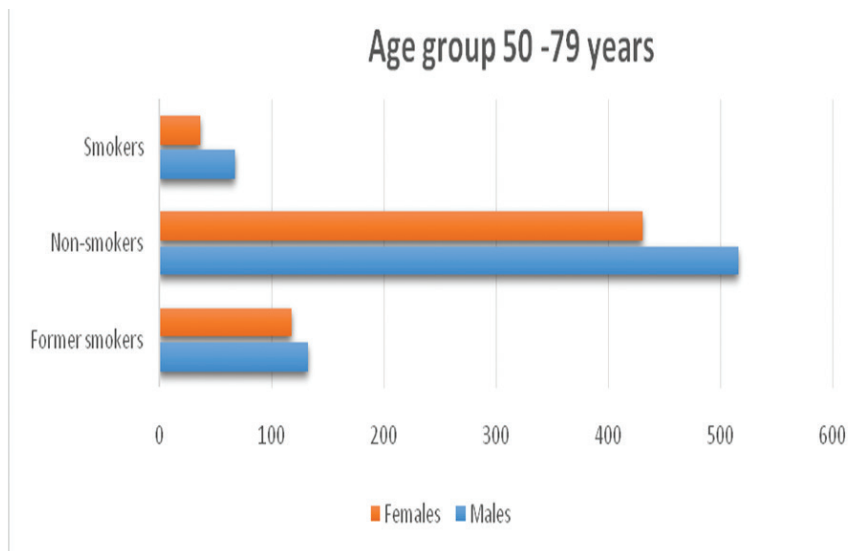


Figure 2. Distribution of men and women in age group 50–79 years, according to their smoking status.

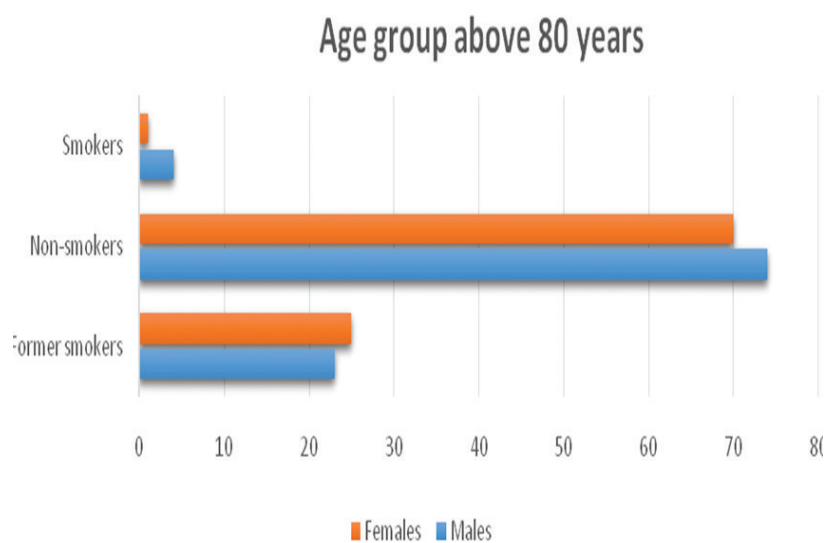


Figure 3. Distribution of men and women in age group over 80 years, according to their smoking status.

Table 1. Distribution of men and women in age groups, according to their smoking status.

	Males	Females	Total	Males	Females	Total	Males	Females	Total
	18 - 49 years			50 - 79 years			Above 80 years		
Smokers	17	10	27	67	36	103	4	1	5
Former smokers	62	26	88	132	118	250	23	25	48
Former smokers + smokers	79	36	115	199	154	353	27	26	53
Non-smokers	283	178	461	516	431	947	74	70	144
Total	362	214	576	715	585	1300	101	96	197

Table 2. Intubation rate in males and females from the group of smokers, former smokers and non-smokers (Table 2).

	Males	Females	Total	Intubated		Non-intubated	
				% from total in group	% from total intubated	% from total in group	% from total non-intubated
Former smokers	217	169	386	121	31.35	265	68.65
Smokers	88	47	135	78	57.78	57	42.22
Former smokers + smokers	305	216	521	199	38.20	322	61.80
Non-smokers	873	679	1552	133	8.57	1419	91.43
Total	1178	895	2073	332	16.02	1741	83.98

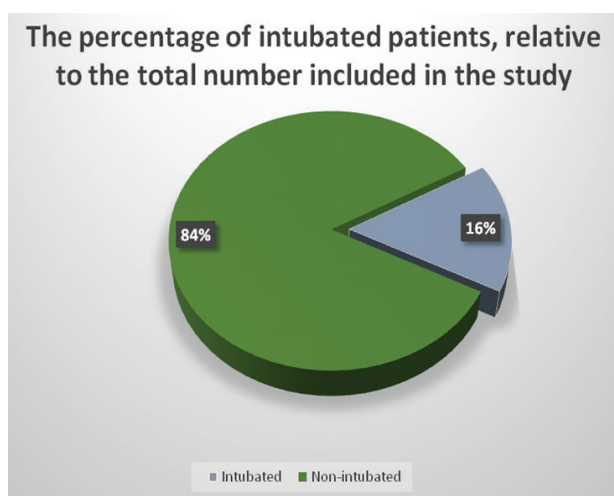
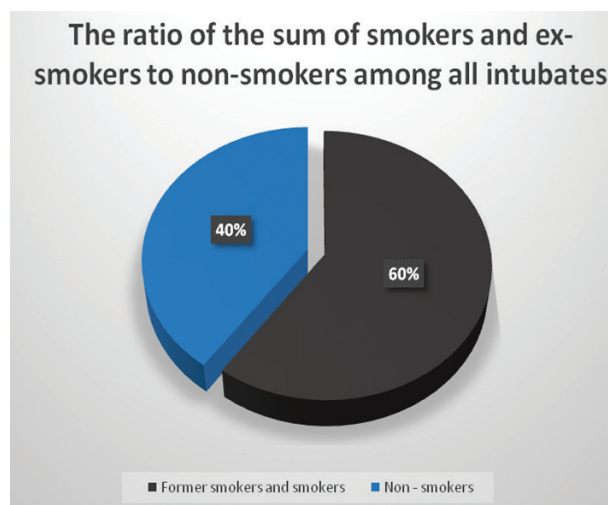
ventilation are considered as indicators of severe course of coronavirus pneumonia. To this purpose, the intubation rate in patients from the group of smokers and former smokers was determined and compared with the rate of intubation in the group of non-smokers (Table 2).

The presented diagrams demonstrate as follows: 1) the percentage of intubated patients to the total number included in the study (Fig. 4.); 2) the ratio of the percentage of smokers + former smokers to non-smokers among all intubated patients (Fig. 5.); 3) the rate of intubation among smokers and former smokers (Fig. 6.).

The results of our study correspond with most of the results of the world statistics and confirm the theory that Covid infection is much more severe among smokers and former smokers. The most likely reason for this fact is the occurring endothelial dysfunction with different clinical manifestations, including concomitant lung and cardiovascular diseases, a consequence of long-term smoking.

The condition of the patients was followed by a standard package of examinations on the first, sixth month and after one year from the day of their hospital discharge. These follow-up tests include computed tomography, laboratory blood tests – Full blood count (FBC), biochemistry, coagulation, inflammatory markers, blood gas analysis and anti-SARS-CoV-2 antibody level. Higher levels of inflammatory markers were noticed as a trend among the smoking group. Resorption and reversal of inflammatory changes in the lung parenchyma, assessed by computed tomography follow-up in the target period, were also delayed.

Immunogenesis was monitored by determining Anti-SARS-CoV2 AB antibodies. The measurements were performed based on a chemiluminescent immunoassay with Micro Well technology. The test is “semi-quantitative” and is designed for the qualitative determination of total IgM, Ig A and IgG anti-SARS-CoV2 AB. In the present study, anti-SARS-CoV2-total AB and anti-SARS-CoV2-IgG AB

**Figure 4.** Distribution of intubated and non-intubated patients among the total number of patients treated.**Figure 5.** Distribution of smokers + former smokers and non-smokers among all intubated patients.

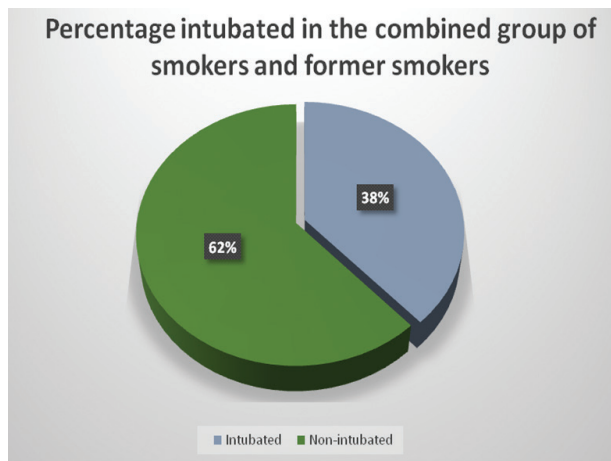


Figure 6. Distribution of intubated and non-intubated patients among the smokers + former smokers groups.

were tracked in each enrolled patient. No difference was observed regarding the presence or absence of antibodies among those who recovered from the infection. All our patients had anti-SARS-CoV-2 AB. The amount of IgG antibodies slightly decreases, while the amount of Ig Total

sensitively (often times) increases within the one-year period during which the patients were followed.

Conclusions

Advanced age, cardiovascular diseases, as well as all concomitant diseases, in the pathology of which endothelial dysfunction plays a major role, predispose to a more severe course of the Covid-19 infection. One of the socially significant bad habits that directly affects the health status and mortality of people, having a direct role in the development of endothelial dysfunction, is smoking. The fact that smoking potentiates serious complications in the course of coronavirus pneumonia is undeniable. This is also confirmed by our observations for the specified period. These results prove the need for comprehensive study and monitoring of pandemic processes and the impact of lifestyle and risk factors on the course of Covid-19. The phenomenon remains unclear – why non-smokers are more susceptible to infection (contagion) with the SARS-CoV-2 virus and is there a possibility that the answer to this question will open new doors for the prevention of Covid-19?!

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Supplementary material 1

Graphical abstract

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