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COVID-19: tobacco smoking and other risk factors in the elderly

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COVID-19 is a pandemic viral infection which poses a particular threat to middle-aged and older adults. We review the evidence of important risk factors for elderly individuals, namely gender, age, tobacco smoking, chronic diseases (i.e., chronic lung disease, immune-impaired status, high blood pressure, diabetes and cardiovascular disease). We discuss benefits of tobacco cessation in elderly patients with chronic diseases, which may lower the risk of poorer COVID-19 outcomes.

Key words: COVID-19, risk factor, tobacco smoking, chronic diseases, aged

INTRODUCTION

The pandemic from the new SARS-CoV-2 coronavirus which, since about 1 year, is bringing Italy and the entire planet to its knees from a health, economic and psychosocial point of view. After almost one year of this pandemic, to date (November 13, 2020), in Italy, against 1,107,303 total cases of infected, 44,139 deaths are recorded. Equally merciless, as reported by the World Health Organization (WHO) (Health Emergency Dashboard, November 12, 2020 at 10.13.am), are the global numbers of the world with 52.177.708 confirmed cases since the beginning of the pandemic and 1.286.063 of deaths [1]. SARS-CoV-2, labelled by the WHO, as an agent of the COVID-19 disease, has largely spared a group typically considered biologically vulnerable such as children but poses a particular threat to middle-aged and older adults, especially men [2].

GENDER AND AGE AS RISK FACTORS

Since the beginning of the pandemic, the Chinese Center for Disease Control and Prevention [3] has published the largest analysis of coronavirus cases. Although men and women were infected in almost equal numbers, the researchers found that the mortality rate among men versus women, obtained from patient medical records, was twice as high as 2.8 *vs* 1.7 respectively. This disparity between men and women has been seen in the past in previous viral epidemics. Men have been disproportionately affected during episodes of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), caused by coronavirus. More women than men were infected with SARS in Hong Kong in 2003,

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but the death rate among men was 50% higher, according to a study published by Choi et al. [4]. The same phenomenon occurred for MERS with a mortality rate for infected males of 32% compared to 26% of women [5]. For both of these diseases, tobacco smoking was an independent risk factor. Even during the 1918 flu epidemic, the so-called "Spanish flu", mortality among young adult males was higher than among peers.
The factors causing this gender disparity are of a different nature, but scientists tend to be sure of one thing: "When it comes to opposing an immune response to an infection, males are the weaker sex." Why? Numerous factors could work against men with viral respiratory infections, including the current epidemic, including some biological and other factors rooted in their lifestyle. Sexual dimorphism in immunity has been well studied and described in both branches of immunity, innate and adaptive [6].
Experiments in which mice were exposed to the SARS coronavirus revealed that males were more susceptible to infections than females, a disparity that increased with age, including in mortality from bronchopneumonia. Oestrogen may play a protective role on infections. Therefore, this increased immune reactivity in women helps to develop effective resistance to infections; women are less susceptible to viral infections, but, on the other hand, they can develop a predisposition to autoimmunity due to hyper-immune responses [7,8].
The study by Guan et al. [9] of 1099 patients with COVID-19 from 552 hospitals in 30 provinces of China found that 58% were men.
Galbadage et al. [10] highlighted some risk factors that cause specific populations to be disproportionately susceptible to SARS-CoV-2 infection. The risk factors currently known to be able to cause serious COVID-19 outcomes include, among others, advanced age (65 years and over). Yang et al. found in a study of critically ill patients, men were more prevalent (67%) than women [11]. According to Higham et al. clinical outcomes, including mortality, in COVID-19 were worse in males, older individuals, and patients with diabetes, cardiovascular disease, and obesity. This information has been used to guide "shielding" strategies during the COVID-19 pandemic, identifying high-risk subgroups who should stay home, away from the social contact that allows viral transmission [12]. Borghesi et al. studied the level of severity of the radiographic image in 783 COVID-19 patients in Italy, with particular reference to age. Males aged > 50 years or older and females aged 80 years or older had the highest risk of developing severe lung disease [13]. Moderbacher et al. studied the specific antigen immunity to SARS-CoV-2 in acute COVID-19 and the associations with the age and severity of the disease. They remarked that the coordination of SARS-CoV-2 specific antigen responses was impaired in subjects ≥ 65 years of age. The scarcity of naïve T cells was also associated with advanced age and negative disease outcomes. A minimal explanation is, according to the authors, that coordinated responses of CD4 + T cells, CD8 T cells and antibody are protective, but uncoordinated responses frequently fail to control the disease, with a relationship between older age and altered immune responses to SARS-CoV-2 [14].

TOBACCO SMOKING AS A RISK FACTOR

Even using the most pessimistic projections possible, deaths from COVID-19 are well below the burden of deaths from tobacco use. Moreover, COVID-19 is more fatal among the older population suffering from multiple concomitant diseases, while half of tobacco deaths occur in people aged 30-69. Furthermore, the most relevant conditions that predispose to negative outcomes of COVID-19 (for example, cardiovascular, neoplastic and respiratory diseases) are mainly due to tobacco smoke [15]. Behaviours and lifestyles, and especially cigarette smoking, differ by gender, especially in some societies, and can affect health status and play a role in different responses to infections. These can affect the onset of some chronic diseases such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD), lung cancer and heart disease. Chinese men have higher rates of type 2 diabetes [16] and hypertension [17] than women, as well as COPD rates are nearly double in Chinese men compared to women, while 70% of lung cancer cases is observed in men compared to Chinese women [18]. All of these pathologies have increased the risk of complications following coronavirus infection. The link that unites these diseases, largely smoke-related, is undoubtedly tobacco smoke.
China has the largest smoking population in the world with 316 million people, representing nearly one third of all smokers on the planet. They make up about 40% of the world's tobacco consumption with an average of 22 cigarettes per day. Given the small number of female smokers (1.8%), the clear prevalence of male smokers (47.6%) should be noted. This tobacco epidemic, beyond the new coronavirus, translates into a massacre that each year reaches one million deaths in China, for the most part among the male population, with an impressive upward trend that could reach 2 million deaths in 2030, exceeding 3 million by 2050, if the current smoking trend persists, transforming this trend into a "growing epidemic of premature death" [19].
In Italy, the majority of adults (18-69 years old) do not smoke (57%) or have stopped smoking (18%), but one out of four Italians is a current smoker (25%). Cigarette

smoking is more frequent among the most disadvantaged socio-economic classes (i.e., less educated and/or with greater economic difficulties) and in men. Average daily consumption is around 12 cigarettes, however nearly a quarter of smokers consume more than one pack per day [20].

Chronic smokers often have a range of comorbidities, including chronic bronchitis, emphysema, cardiovascular disease, hypertension, diabetes, and impaired immune function [21] which can in turn affect the prognosis of COVID-19. These pathologies increase the risk of complications following COVID-19 infection, due to the depressive action that tobacco smoke exerts on the mechanical system of mucociliary clearance, on the bronchopulmonary immune system and on the likely greater virulence exerted by tar, with consequent acute bronchopulmonary inflammation due to bacteria [22], mycobacteria [23] and probably also from viruses. One of the first articles on COVID-19, relating to 1,099 Chinese cases of COVID-19 disease, was published by Guan et al. on the NEJM [24]. This gave the opportunity to Gorini and al. to make *ex novo* statistical analysis elaborations [25] by taking the absolute numbers from the tables and calculating the percentages, with interesting results. 32% of patients with a history of smoking (smokers and former smokers) had severe COVID-19 pneumonia at the time of hospitalisation, compared with 15% of non-smokers. In addition, 16% of patients with a history of smoking were subsequently admitted to intensive care or died, compared with 5% of non-smokers.

Salah et al conducted a meta-analysis of recent reports of the mortality risk from COVID-19 in smokers. The Authors analysed ten studies with a total of 11,189 patients. Mortality among smokers was 29.4% compared to 17.0% among non-smokers. RR was 2.07 (95% CI: 1.59, 2.69). Instead, based on the analysis of four studies (532 patients), there was no significant difference in mortality risk between current and former smokers (RR: 1.03; 95% CI: 0.75, 1.40). Current or past smoking is associated with higher mortality in COVID-19 patients [26].

The ACE2 receptors present in various cells of different systems, including in the bronchopulmonary and cardiovascular systems, represent the gateway of SARS-CoV-2 into cells. Various studies have shown that ACE2 receptors are expressed to a greater extent in smokers and COPD patients than in non-smokers and healthy subjects [27]. In common with other corona-viruses, SARS-CoV-2 uses angiotensin converting enzyme2 (ACE2) as a receptor for cell attachment (mediated by S1 binding subunit and S2 membrane fusion subunit, proteins contained at the level of the spike.). Mutations in the SARS-CoV-2 spike protein are thought to allow for greater affinity for binding to ACE2, thereby increasing this virus's ability to gain cellular access.

Exposure to cigarette smoke increases the expression of the *ACE2* gene in mice. In primary bronchial epithelial cells, nicotine-dependent activation of the $\alpha 7$ subtype of nicotine acetylcholine receptors ($\alpha 7$-nAChR) has been shown to increase the expression of the *ACE2* gene. The levels of CHRNA7 (the gene that encodes $\alpha 7$-nAChR) in bronchial epithelium are higher in current smokers and levels are positively correlated with ACE2 expression ($r = 0.54$ $p = 2.31 \times 10\text{-}8$) and negatively correlated with forced expiratory volume in 1 s (FEV_1)% predicted ($r = -0.37$ $p = 2.83 \times 10\text{-}4$) in COPD patients [28]. According to Cai, published studies on the biology of viral infection and clinical management of the disease have shown that differences in the prevalence and severity of COVID-19 are associated with sex, and that tobacco smoking is correlated with higher ACE2 expression, the SARS-CoV-2 severe acute respiratory syndrome receptor, which could be another risk factor [29]. Zhao et al. using single-cell sequencing, found that ACE2 expression was more predominant among Asian men than women and patients of other ethnicities, which may explain the higher prevalence of COVID-19 in this subgroup of patients [30]. Therefore, for all these reasons, smoking cessation could reduce the risks associated with SARS-CoV-2 infections [31]. The study by Guan et al. [24] of 1099 patients with COVID-19 from 552 hospitals in 30 provinces of China found that 58% were men. Sexual predisposition according to Cai could be associated with the much higher prevalence of tobacco smoking of men than women in China (288 million men *versus* 12.6 million women were smokers in 2018). Noteworthy is Cai's study which found that ACE2 expression was not different between Asians and Caucasians, men and women or subgroups aged over or under 60 years, but significantly higher among current smokers of Asian ethnicity compared to Asians. Non-Smoking [32]. Hopkinson et al. conducted a study on the risk of COVID-19 in 2.4 million people, with an average age of 43.6 and 15.1 years, 63% females, with an overall prevalence of current tobacco use of 11%. 834,437 participants reported feeling unwell and indicated at least one of 19 COVID-19 related symptoms (35%). Current smokers were more likely to develop symptoms suggesting a diagnosis of COVID-19; classic symptoms adjusted OR [95% CI] 1.14 (1.10-1.18). > 5 symptoms 1.29 (1.26-1.31), > 10 symptoms 1.50 [95% CI] (1.42-1.58). Smoking was associated with reduced ACE2 expression in adipose tissue. These findings were consistent with smokers' increased risk of COVID-19. The authors concluded that the data combined with evidence of a worse outcome in hospitalised smokers with that condition, support the contention that smoking increases individual risk for COVID-19 [33].

CHRONIC DISEASES AS RISK FACTORS FOR COVID-19

According to Galbadage et al., Many recent studies have highlighted certain risk factors that cause specific populations to be disproportionately susceptible to SARS-CoV-2 infection. Risk factors currently known to cause serious COVI-19 outcomes include: advanced age (65 years and older), chronic lung disease, immune-impaired status, and other comorbidities such as high blood pressure, diabetes and/or cardiovascular disease [10]. Higham et al. reviewed the scientific literature and clinical data to investigate the effects of COPD on the course of COVID-19. Specifically, if there are mechanisms by which COPD patients are more susceptible to SARS-CoV-2 infection, if inhaled corticosteroids (ICS) offer protection against COVID-19, and what are the clinical outcomes of COVID- 19 in COPD patients. According to the Authors, COPD patients may be more susceptible to SARS-CoV-2 infection due to changes in ACE2 expression. Cigarette smoking appears to be a major risk factor, while preliminary evidence suggests that obesity may play a role. It can also increase the susceptibility to vascular abnormalities being involved. COPD patients with more frequent exacerbations suffer from worse clinical outcomes, including worsening lung function and mortality. Viral infections are common causes of COPD exacerbations, with secondary bacterial infections commonly occurring.

Several randomized clinical trials have shown that ICS reduce exacerbation rates when used as part of a combination treatment with a long-acting β-agonist (LABA) or a LABA plus a long-acting muscarinic antagonist. 'action. This ICS advantage appears to be greater in patients with higher blood eosinophil counts, with little or no benefit in patients with lower counts. ICS treatment can cause side effects, including osteoporosis, diabetes, and especially pneumonia. Because of these potential risks, ICS should be used in a personalized way using the risk of exacerbation and counts eosinophils in the blood to identify individuals who are most likely to benefit from them.

COPD patients, as well as current smokers, are consistently reported to have worse outcomes after COVID-19 infection. Several large patient cohorts reported an association between coexisting COPD and worse clinical outcomes among COVID-19 patients in hospitals, and a meta-analysis reported an 88% increased risk of ICU admission or death among those with Coexisting COPD (RR 1.88, 95% CI 1.4-2.4). Furthermore, the risk of developing severe complications was 45% higher among current smokers (RR 1.45, 95% CI 1.03-2.04), arguing against a protective effect of current smoking against COVID-19 [34]. Similar results were reported in an Italian study by Bartoletti et al. involving 1044 hospitalized patients; COPD patients had a significantly increased risk of severe respiratory failure (RR 1.17, 95% CI 1.09-1.27) [35]. According to Viana et al., typical symptoms of COVID-19 disease are fever, dyspnoea, which progresses to pneumonia and ultimately death. Nausea and diarrhoea are equally frequent, suggesting viral infection or transmission via the gastrointestinal system. Abnormal functions of ACE2 receptors are associated with worse outcomes such as more severe COVID-19 disease and higher mortality levels in patients with pre-existing age-related comorbidities, indicating dysbiosis of the intestinal microbiota as a possible role [36]. Messner et al. published a review on smoking and cardiovascular disease. Smoking is one of the most important avoidable risk factors for the early development of atherosclerosis. Vascular dysfunction induced by smoking began with a reduced bioavailability of nitric oxide (NO) and subsequently with an increased expression of molecular adhesion and consequent endothelial dysfunction. A smoke-induced increase in platelet and macrophage adhesion causes the development of a pro-coagulant and inflammatory environment. Following trans-endothelial migration and activation, macrophages take on lipoproteins that arise from oxidative modifications and differentiate into foam cells. In addition to direct physical damage to endothelial cells, tobacco smoke induces tissue remodelling and pro-thrombotic processes together with the activation of inflammatory signals, which globally contribute to the alterations of the atherogenic vascular walls. Therefore, the authors conclude, smoking cessation is the most effective measure to reduce the damage that has already occurred and prevent adverse cardiovascular outcomes [37]. Gong et al. evaluated an analysis on the correlation between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia.

Among the 100 patients included in the analysis, 34 patients belonged to the mild group, 34 were serious and 32 were critical. The mean age was 57.02 years and 59% of the patients were male. Age of the mild group (mean ± SD: 45.29 ± 13.08 years) was significantly different from that of severe patients (mean ± SD: 60.41 ± 9.80 years) or critically ill patients (mean ± SD: 65.88 ± 13.61 years). No significant differences were found between severe and critically ill patients. To better detect critical illness, the receiver operating characteristic analyzes (ROC) age curve (AUC = 0.755, p = 0.000) was administered and listed. The best age cut-off point was 67.5 years with a specificity of 88.2% and a sensitivity of 59.4%. This study also found IL-6 and IL-10 levels were associated with the severity of COVID-19 pneumonia. IL2R levels, ferroprotein levels, PCT levels,

and EC counts were also related to disease severity. IL-6 > 100 pg/mL could represent the emergence of an "inflammatory storm" [38]. Chen et al conducted a study to evaluate the cardiovascular damage of patients with COVID-19 and determine the correlation of natriuretic type B pro-B (NT-proBNP) and cardiac troponin-I (cTnI) with COVID-19 severity and the impact of concomitant cardiovascular disease the severity of COVID-19 was also assessed. A cross-sectional study of 150 consecutive COVID-19 patients was designed in Wuhan's Tongji Hospital fever clinic from January 19 to February 13, 2020, including 126 mild cases and 24 ICU cases. Both univariate and multivariate logistic regression was used to analyze correlation of past medical history including hypertension, diabetes, and coronary heart disease (CHD), as well as serum NT-proBNP and cTnI levels to disease severity of COVID-19 patients. Patients' age, hypersensitive C-reactive protein (hs-CRP), and serum creatinine levels were higher in ICU than in mild cases (all $p < 0.05$). Male prevalence, elevated NT-proBNP and cTnI levels, hypertension and coronary heart disease were significantly higher in critical cases in treated patients than in mild cases (all $p < 0.05$). Univariate logistic regression analysis showed that age, males, elevated NT-proBNP, elevated cTnI, elevated hs-CRP, elevated serum creatinine, hypertension, and CHD were significantly correlated with critical disease status (all $p < 0.05$). Multivariate logistic regression analysis showed that elevated cTnI (OR = 26.909 with 95% CI 4.086-177.226, $p = 0.001$) and CHD (OR = 16.609 with 95% CI 2.288-120.577 with $p = 0.005$) were the independent risk of critical illness state. The Authors concluded that COVID-19 can significantly affect cardiac function and lead to myocardial injury. Past medical history of CHD and increased cTnI level are 2 independent determinants of the clinical status of the disease in COVID-19 patients [39]. Yang et al. evaluated with a unique retrospective and observational study in Wuhan, China, some risk factors for mortality among COVID-19 patients admitted to hospital from January to March 2020, who had a combination of arterial hypertension, coronary heart disease or diabetes. Patients with COVID-19 nucleic acid positivity and combination with hypertension, coronary heart disease and diabetes were considered. They collected clinical data and laboratory test results of suitable patients to assess related risk factors for mortality. In the study, 94 enrolled COVID-19 patients were divided into the deceased group (13 cases) and the survivors group (81 cases), the mean age was 66.7 years. Compared to the survival group, the deceased group had a faster baseline heart rate (03.2 beats/min *vs* 88.4 beats/min, $p = 0.004$), shortness of breath (29.0 breaths/min *vs* 20,0 breaths/min, $p < 0.001$), higher neutrophil count (9.2 × 109/L *vs* 3.8 × 109/L, $p < 0.001$), lower lymphocyte count (0.5 × 109/L *vs* 1.1 × 109/L, $p < 0.001$), creatine kinase MB (CK -MB, 3.2 µg/L *vs* 0.8 µg/L, $P < 0.001$), high sensitivity cardiac troponin (hs- cTn, 217.2 ng / L *vs* 4.9 ng / L, $p < 0.001$), N-terminal pro brain natriuretic peptide (NT-proBNP; 945.0 µg/L *vs* 154.0 µg/L, $p < 0.001$), inflammatory factor ferritin (770.2 µg/L *vs* 622.8 µg/L, $p = 0.050$), interleukin-2 receptor (IL-2R, 1586.0 U/mL *vs* 694.0 U/mL, $p < 0.001$), interleukin-6 (IL-6, 82.3 ng/L *vs* 13.0 ng/L, $p < 0.001$), interleukin-10 (IL-10,9.8 ng/L *vs* 5.0 ng/L, $p < 0.001$) were higher than that I of the group of survivors. Univariate logistic regression analysis showed that the risk factors for death were advanced age, low oxygen saturation, low lymphocyte count, myocardial damage, abnormal increase in IL 2R, IL-6 and IL-10. Multivariate regression showed that older age (OR = 1.11, 95% CI = 1.03-1.19, $p = 0.026$), low oxygen saturation (OR = 0.85, 95% CI = 0.72-0.99, $p = 0.041$) and abnormal increase in IL-10 (9.1 ng/L, OR = 101.93, 95% CI = 4.74-2190.71, $p = 0.003$) were independent risk factors for COVID-19 patients combined with hypertension, coronary heart disease, or diabetes. The authors therefore concluded that in COVID-19 patients combined with hypertension, coronary heart disease or diabetes, the risk factors for adverse outcome were advanced age, low oxygen saturation, low lymphocyte count, myocardial damage and abnormal increase in IL- 2R, IL-6 and IL -10. Age, low oxygen saturation and the abnormal increase in IL-10 were independent risk factors [40].

Pinto et al. investigated the risk factor of type 2 diabetes mellitus (T2DM) for the severity of COVID-19 with a meta-analysis. The meta-analysis included a total of 1592 patients, 138 with a previous diagnosis of diabetes and 1454 without diabetes. Among those with diabetes, 59 (42.75%) developed severe COVID-19 compared with 256 (17.60%) of non-T2DM patients, with an odds ratio of 3.53 (95% confidence interval 1, 48 to 8.39; I2 64%; p for heterogeneity = 0.011). According to the authors, diabetes mellitus appears to be an important age-independent risk factor for COVID-19 severity. Further studies may point out the mechanisms by which diabetes can affect the prognosis of COVID-19 and how improved glycaemic control could affect the course of the disease [41].

THE BENEFITS OF SMOKING CESSATION

Elderly smoking patients with chronic illnesses who have quit smoking for 15 years had a comparable risk of non-smokers of having chronic illness, according to a 2002 Pensioner Health (HRS) study of 12,652 subjects aged 50-60 and 8125 subjects aged 60 to 70 years.

Instead, in the current smokers of these two groups there was a constant negative dose response from illness and tobacco smoke [42]. The harmful effects of smoking can last for years, but stopping smoking causes an improvement in lung function [43], a progressive normalization of the respiratory epithelial architecture [21], a decrease in hyperplasia [44], an overall reduction disease burden [45] and a down-regulation of ACE2 levels [46].

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For this kind of survey no specific ethical considerations are needed The research was conducted analysing ethically correct data, in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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