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A Descriptive Review of Epidemiology of COVID – 19 in Smokers

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Abstract

Coronavirus disease 2019 caused by SARS Cov 2, gains entry to bronchial epithelial cells by binding of the viral spike protein to angiotensin-converting enzyme-2 (ACE-2) receptors. We conducted a non - systematic review of databases with (English articles only), PubMed, Google Scholar using keywords like "COVID-19," "SARS-CoV-2," "novel coronavirus," smoking," "smokers," "nicotine." A total of 33 articles were reviewed. Smokers were 1.4 times more likely to have severe COVID-19 (RR=1.4 95% CI: 0.98-2.00), and 2.4 times more likely to require an ICU admission (RR= 2.4 CI: 1.43-4.04) when compared to non-smokers (n=926). Current smokers were less likely to experience an adverse outcome (OR: 0.42, 95% CI: 0.24–0.74), compared to former smokers. 22% of current smokers and 46% of former smokers had more severe complications. Current smokers had a case fatality rate of 38.5% (n=1790) and higher odds of mortality (OR= 1.25) especially males >65 years (OR=2.51). Public education about smoking cessation should be implemented along with standard guidelines to prevent disease progression.

Keywords - COVID-19, Coronavirus, Smoking, Mortality, Public Health.

Introduction

With the emergence of the COVID-19 global pandemic, the scientific community has undertaken efforts to understand the epidemiology of the disease in order to mitigate adverse outcomes and the worldwide crisis. Smoking has increased risks for many respiratory infections and may accelerate the progress of the disease in those infected. [2]

Smoking (modifiable risk factor)

upregulates ACE-2 receptor expression

decreases serine protease inhibitors

increasing susceptibility to COVID-19 infection

Fig. 1 Smoking and COVID – 19

33 Articles reviewed

Smokers:
a. 1.4 times severity (RR=1.4 95% CI: 0.98-2.00)
b. 2.4 times ICU (RR= 2.4 CI: 1.43-4.04)

Complications:
Current smokers: 22%
Former smokers: 46%

Current smokers - Case Fatality Rate: 38.5% (n=1790)

Higher mortality:
<65 y: (OR= 1.25)
>65 y: (OR=2.51)
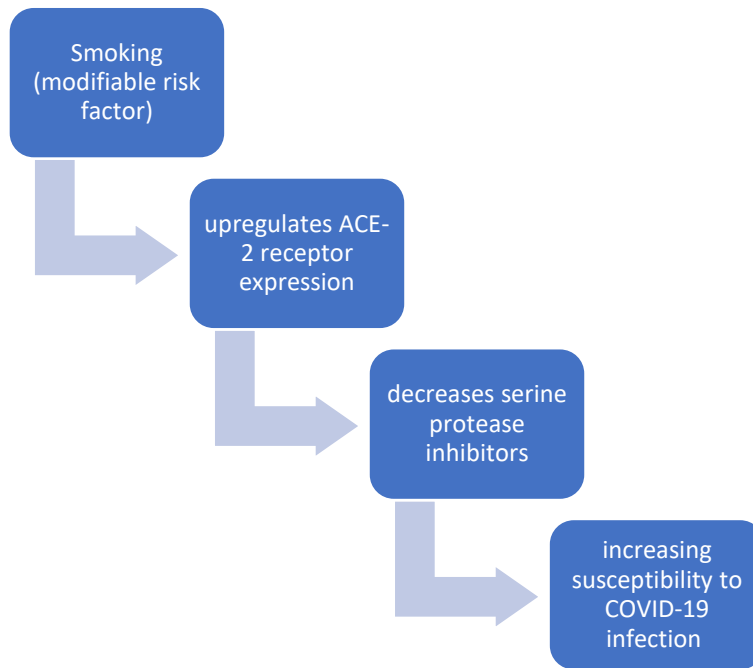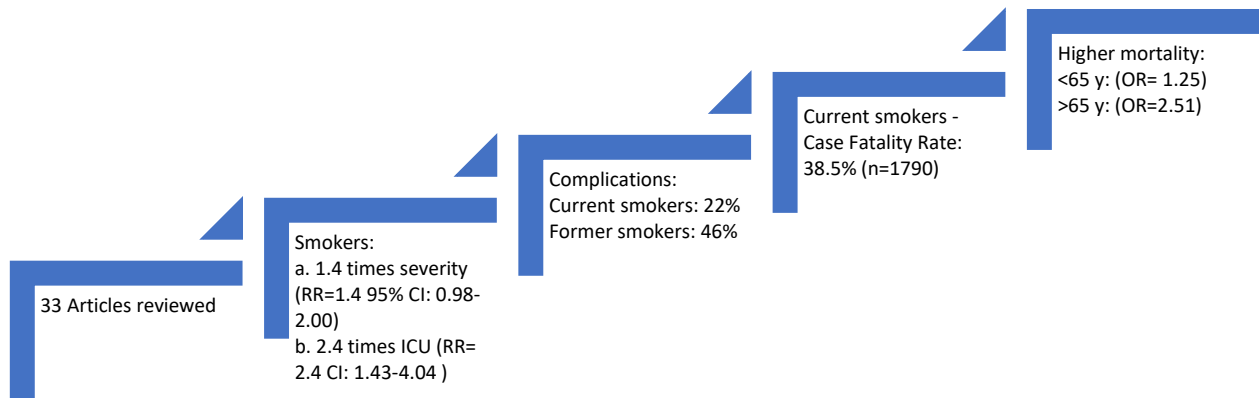
Fig 2 Results Highlights: Smoking and COVID-19

Epidemiology of smoking

Smoking is a well-established risk factor for severe exacerbations or disease course in many respiratory infections, and may predispose to COVID-19 infection or worsen disease progression. With influenza and the MERS outbreak, patients who were smokers had an increased risk twice that of nonsmokers and were associated with higher mortality rates [4], so it is necessary to investigate the relation to COVID-19. Current smokers also had a higher case fatality rate of 38.5% and were 1.45 times more likely to have morbid outcomes compared to their non-smoking counterparts [4]. As a modifiable risk factor, smoking is a very crucial consideration in COVID-19, and this literature review aims to understand the risk of COVID-19 with smoking, the relation of smoking to disease progression, and explore debating information regarding nicotine and its potential protective role due to competition of nicotinic acetylcholine receptor with SARS-CoV-2 binding sites.

Pathophysiology of smoking in COVID

The disease is caused by the novel coronavirus SARS-CoV-2, which gains entry to the bronchial epithelial cells and pneumocytes by binding of the viral spike protein to ACE-2 receptors. The TMPRSS2 cleaves the ACE-2, thus promoting viral uptake by the host cells [3] [4]. We conducted a descriptive review to summarize concurrent studies and relate the impact of smoking on the severity, morbidity, and mortality of admitted COVID-19 patients. This review aims to understand the associated risk and worsening of disease in relation to smoking and explore conflicting information regarding nicotine and its potential protective role. We conducted a descriptive review to summarize concurrent studies and relate the impact of smoking on the severity, morbidity, and mortality of admitted COVID-19 patients.

Comparison between current, ex-smokers, non-smokers

Jackson, S.E., et al. study with 53 002 adults in the UK showed the following values: While comparing with non-smokers (0.26% (95% CI 0.21% to 0.33%)), the prevalence among current smokers with confirmed COVID-19 was higher (0.56% (0.41% to 0.75%)) but not in the ex-smokers (0.19% (0.13% to 0.28%)). They found that the associations before (current: OR=2.14 (1.49–3.08); ex-smokers: OR=0.73 (0.47–1.14)) and after (current: OR=1.79 (1.22–2.62); ex-smokers: OR=0.85 (0.54–1.33)) were similar after adjustment. For current smokers, this was moderated by socio-economic position, with higher rates only seen in those without post-16 qualifications (OR=3.53 (2.04–6.10)). After including suspected cases, prevalence was higher among current smokers (11.2% (10.6% to 11.9%), OR=1.11 (1.03–1.20)) and ex-smokers (10.9% (10.4% to 11.5%), OR=1.07 (1.01–1.15)) than never smokers (10.2% (9.9% to 10.6%)), but remained higher only among ex-smokers after adjustment (OR=1.21 (1.13–1.29)). Current and ex-smokers had higher odds than never smokers of reporting significant stress about becoming seriously ill from COVID-19 (current: OR=1.34 (1.27–1.43); ex-smokers: OR=1.22 (1.16–1.28)). Adherence to recommendations to prevent spread of COVID-19 was high (96.3% (96.1% to 96.4%)), but lower among current than never smokers (OR=0.70 (0.62–0.78)) [33]

Farsalinos, K., et al. Study showed the following values: "Among 6515 patients, the pooled prevalence of current smoking was 6.8% [95% confidence interval (CI): 4.8–9.1%]. The gender-adjusted POR was

0.20 (95% CI: 0.16–0.25, *p* < 0.001), and the gender and age-adjusted POR was 0.24 (95% CI: 0.19–0.30, *p* < 0.001). Current smokers were more likely to have an adverse outcome compared with non-current smokers [odds ratio (OR): 1.53, 95%CI: 1.06–2.20, *p* = 0.022] but less likely compared with former smokers (OR: 0.42, 95% CI: 0.27–0.74, *p* = 0.003). When pre-publications were added (*n* = 10,631), the gender-adjusted POR was 0.27 (95% CI: 0.19–0.38, *p* < 0.001) and the gender and age-adjusted POR was 0.34 (95% CI: 0.24–0.48, *p* < 0.001).-[34]

Umnuayponrlert, A., et al. study showed the following values: "A total of 1248 studies were retrieved and reviewed. A total of 40 studies were finally included for meta-analysis. Both current smoking and former smoking significantly increase the risk of disease severity (OR=1.58; 95% CI: 1.16–2.15, p=0.004; and OR=2.48; 95% CI: 1.64–3.77, p<0.001; respectively) with moderate appearance of heterogeneity. Similarly, current smoking and former smoking also significantly increase the risk of death (OR=1.35; 95% CI: 1.12–1.62, p=0.002; and OR=2.58; 95% CI: 2.15–3.09, p<0.001; respectively) with moderate appearance of heterogeneity. There was no evidence of publication bias, which was tested by the funnel plot, Begg's test and Egger's test." -[35]

Smoking, FEV1, and COPD association in respiratory diseases

Chronic Obstructive pulmonary disease is characterized by structural and functional changes in the lungs that is caused by long term inhalation of substances. COPD involves persistent inflammation and airway remodeling that leads to airway obstruction mediated by cytokines and other inflammatory mediators. Cigarette smoke has several toxic particles and chemical substances that leads to persistent chronic inflammation and airway damage that persists even after smoking cessation.[36] Many markers of oxidative stress and reactive oxygen species have been implicated in the pathogenesis of COPD like lipid and hydrogen peroxides that are increased in the respiratory tract and blood of COPD patients. Healthy lungs have antioxidants that act as a defense and maintain the balance between oxidants and antioxidants. Disruption of balance causes increased airway inflammation, increased airway mucus production and inactivation of antiproteases. [37]Cigarette smoke induced mitochondria autophagy that initiates necroptosis .Necroptosis is a new mechanism of cell death that causes more inflammatory damage unexplained by apoptosis. This also contributes to the complex mechanism of cigarette smoke induced COPD damage [38] while SARS COV can affect individuals of any age, this is mostly associated with people over age >55 and with significant comorbidities like COPD [39]

COPD should be diagnosed by a board certified physician or a decrease in FEV1 < 70% according to the spirometry guidelines [40] smoking and COPD both are associated with increased expression of ACE 2 receptors which is supposed to be the entry mechanism of COVID 19.St.Pauls hospital conducted a cohort study in patients with chronic nodules have undergone bronchoscopy followed by cough and lymphadenopathy.

There was an increased association between COPD and smoking with ACE 2 expression. There was an inverse relationship between ACE 2 expression and FEV% suggesting a dose dependent response. According to Cornell and BCCA cohorts there was an increased ACE 2 expression in smokers and nonsmokers. [41]

Nicotine and COPD

There are increased implications related to nicotinic receptor anticholinergic system and ACE 2 inhibitors that they increase the ACE 2 receptor expression in bronchial epithelial cells.[42] Nicotine up-regulates ACE-2 through alpha7 nAChRs which are present in neuronal and non-neuronal cells [43] But the nAChR relationship is still controversial and needs to be explored. Epithelial cell expression of CHRNA7 which encodes Alpha 7-nicotinic Acetylcholine receptor is correlated with increased gene expression of ACE .There was a positive pearson correlation between ACE expression and nAchR. There is an increased expression of CHRNA7 expression in COPD patients and current smokers indicating a positive progression of the disease. It was also inversely correlated with FEV1 percentage in COPD patients [44]

Mortality/ Morbidity

According to Salah, H.M., T. Sharma, and J. Mehta's Meta-Analysis, which included ten studies with a total of 11,189 patients, mortality was found to be 29.4% among smokers in comparison to 17.0% in non-smokers. RR was found to be 2.07 (95% CI: 1.59, 2.69). But mortality risk in current and former smokers was found to have no difference (RR: 1.03; 95% CI: 0.75, 1.40) based on analysis in four studies with 532 patients- [45]. This analysis shows, in patients with COVID-19 smoking is associated with significantly higher risk of mortality.

Nicotine as a protective agent

Efficient viral invasion and replication can generate an aggressive hyper inflammatory immune response with release of large number of proinflammatory cytokines which is clinically known as cytokine storm[46]. It is characterized by overwhelming systemic inflammation, hyperferritinemia, dysfunction of hemodynamics and multiorgan dysfunction which can lead to death[47]. This cytokine storm is one of the common causes of death in COVID19. Therapeutic management of Cytokine storm can reduce mortality and morbidity in COVID19. One of the mechanisms by which body tackles proinflammatory signals is through nicotinic Acetylcholinergic System (NAS). Generally, NAS inhibits proinflammatory cytokine production by inhibiting NF-KB pathways[48]. Alexandris et al. showed protective effect of nicotine in COVID19 by simulating cholinergic anti-inflammatory pathways [49]. According to their study, nicotine prevents with SARS-CoV-2 S1 protein to bind with nAch Recpetors for their entry. Further, Nicotine prevents proinflammatory effects of virus through NAS anti-inflammatory pathways.

Methodology

Search method and strategy

An extensive literature review was conducted of databases PubMed, Google Scholar, Cochrane using keywords like "COVID-19," "SARS-CoV-2," "novel coronavirus," smoking," "smokers," "nicotine." from December 2019 through 30th October 2020. English articles related to the epidemiology of COVID-19 in adult smokers, including systematic reviews, meta-analysis, prospective and retrospective cohort studies, cross-sectional studies, case series, and case reports based on the relevance of titles and abstracts to the topic were included. The search was comprehensive with cross-checking of reference

lists from the articles retrieved. In doing so, we had 33 articles for the final review. Our review included studies from various countries from across the globe. Referencing was done according to guidelines using EndNote.

Ethical approval and funding

This study did not require ethical approval as data was obtained from already available databases, and patients were not directly involved. No funding was obtained for this review.

Results

Our search results lead to 54 studies and after removing duplicates. We also performed the manual search to look for related articles. 33 studies were included in the final analysis.

Smokers were 1.4 times more likely to have severe COVID-19 (RR=1.4 95% CI: 0.98-2.00), and 2.4 times more likely to require an ICU admission (RR= 2.4 CI: 1.43-4.04) when compared to non-smokers (n=926). Smoking enhances the activity of ACE 2 receptor and TMPRSS2 inhibitor and hence helps in the facilitation of viral entry and activation.

Over the course of the disease, nicotine eventually leads to a cytokine storm by the release of IL-6, TNF-α, IFN-γ, IL-2, IL-7, IP-10, MCP-3 or GM-CSF and other inflammatory mediators. The reduction in serine protease inhibition can lead to the cleavage of the S1/S2 site by furin and thereby enhance the cell to cell transmission.

Current smokers were less likely to experience an adverse outcome (OR: 0.42, 95% CI: 0.24–0.74), compared to former smokers. 22% of current smokers and 46% of former smokers had more severe complications compared to nonsmokers with COVID-19 infection. Current smokers had a case fatality rate of 38.5% (n=1790). They had higher odds of mortality compared to nonsmokers (OR= 1.25), especially males >65 years (OR=2.51). Tobacco smoke upregulates inflammatory cytokines like TNF-α, IL-1**β**, and neutrophils by activating NF-k. This leads to increased epithelial cell permeability, mucus production, and impaired mucociliary clearance.

The pro-inflammatory action of tobacco smoke impairs the basal laminar cells and causes endothelial dysfunction of the BBB and blood vessels, which leads to neurological, cerebrovascular, and thrombotic complications. (8) 7.63% (95%CI 3.83%-12.43%) has been related to smoking in hospitalized patients with COVID-19. (9)Nicotine reduces the macrophage response and thereby increases the risk of tuberculosis by 2 times and   legionella, pneumococcal and mycoplasma infection by 3-5 times. There have been studies showing association of FEV1 with increased ACE gene expression.

Higher mortality in smokers has been seen as compared to non-smokers [1·25 (95% CI 1·12–1·40) i(10)n=3027,male: OR = 1.76, 95% CI (1.41, 2.18), P < 0.00001 age over 65 years old: current smoking: OR =2.51, 95% CI(1.39, 3.32), P = 0.0006].(11)Permeability of BBB alteration and modification of Na+ K+ 2Cl- cotransporter causes neurological complications in smokers. In 214 patients in a study, of the smokers studies, 36.5% showed neurological symptoms and 18.7% were admitted in ICU. (12)

Discussion

Our analysis clearly demonstrates smoking as a risk factor for severe COVID19 infection. Myriads of pathophysiological processes like pulmonary epithelial cell permeability, mucus production, and impaired mucociliary clearance due to increased inflammatory cytokine production are well linked to nicotine smoking [13]. This kind of predisposition could be one of many other reasons that smokers (active) are highly susceptible severe form of COVID19 infection (Fig. 1,2, 3, 4, 5).

As the COVID-19 pandemic still continues to be a major health threat in the world today, any strategies that could reduce the rate of infection or help in flattening the curve of the virus transmission should be adopted without any delay. Hence, with the evidence provided by our study that smoking tobacco increases the risk of COVID19 infection, we should consider smoking cessation as an essential step to reduce COVID19 infection.

Authors conclude that smoking cessation can drastically reduce risk of virus exposure by decreasing the hand to mouth action. Additionally, smoking cessation decreases the pathological proinflammatory impact of nicotine in pulmonary vasculature that helps viral entry though the respiratory tract.
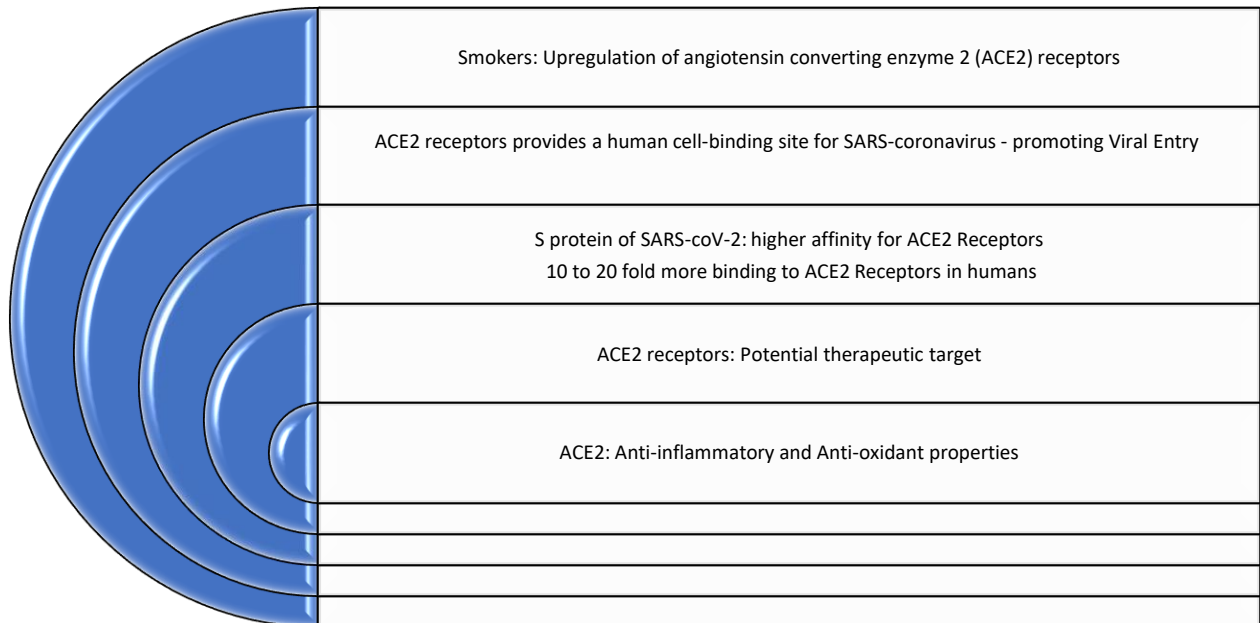

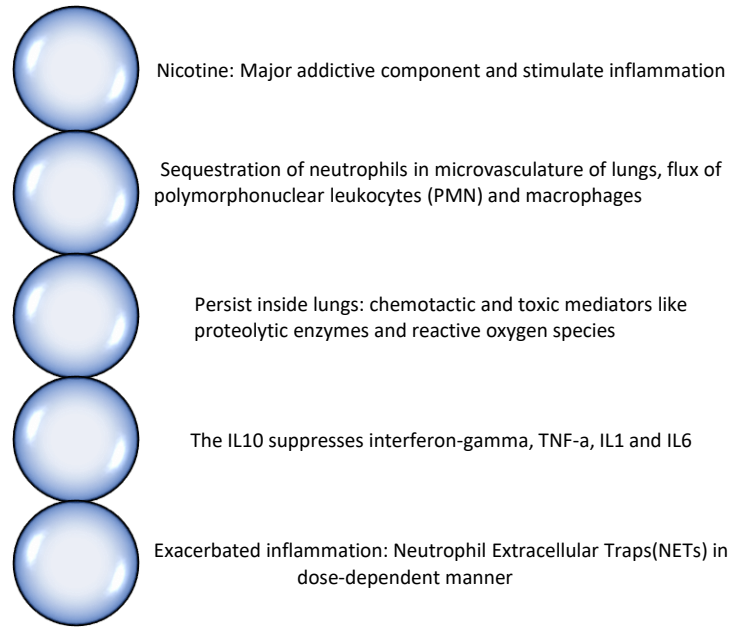Fig: 3 Receptors common in smoking and COVID – 19 (Ref. 14 - 17)

Nicotine: Major addictive component and stimulate inflammation

Sequestration of neutrophils in microvasculature of lungs, flux of polymorphonuclear leukocytes (PMN) and macrophages

Persist inside lungs: chemotactic and toxic mediators like proteolytic enzymes and reactive oxygen species

The IL10 suppresses interferon-gamma, TNF-a, IL1 and IL6

Exacerbated inflammation: Neutrophil Extracellular Traps(NETs) in dose-dependent manner

Fig: 4 Tobacco smoke as an inflammatory agent (Ref. 18 – 25)

Symptoms: Hyposmia, Headache, Dizziness, Weakness and Altered level of consciousness

Encephalitis, Demyelination, Ischemic injury and Neuropathy

Smoking and Vaping: disruption in the integrity of the blood brain barrier

Interact with neuronal and glial ACE2 receptors and start a viral proliferation cycle - Neuronal Damage

Decrease neuronal glucose utilization - increased risk for ischemic brain injury and stroke

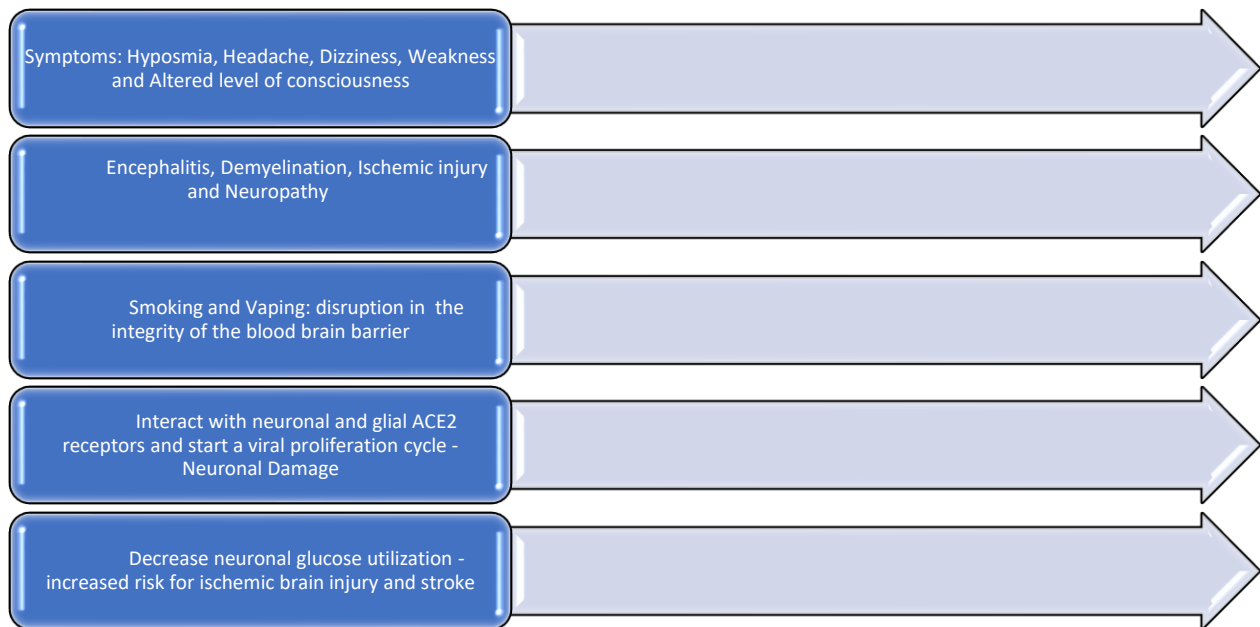Fig. 5 Neurological risks (Ref. 26 – 32)

Conclusion

Smoking is associated with worse outcomes and mortality in COVID-19.Smoking is found to be one of the high risk factors related to severity and complications of COVID-19. Nicotine accumulated by smoking impairs lung function, and hence makes lung susceptible to severe respiratory infections. There is a need for further studies to gather evidence on the effects of second-hand smoke on the effects of

SARS-CoV-2 infection. But, it can be well assumed that smokers may have a serious risk of succumbing to SARS-CoV-2 infection. Abstinence or cessation of smoking helps to recover ciliary clearance of the airway and immune function as early as 30 days. Thus, smoking cessation awareness campaigns are strongly recommended as part of public health measures to curb the global impact of COVID-19. Public education about smoking cessation should be implemented along with standard guidelines to prevent disease progression in this susceptible population.

Conflict of Interest

There is no conflict of interest from all authors.

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