Smoking amidst the COVID-19 Pandemic - the invisible threat?

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Smokers at greater risk of severe COVID-19 illness?

A curious observation during the ongoing pandemic is the remarkably low proportion of smokers amongst hospitalized COVID-19 patients. Data from China suggests smokers account for only 6.5% of such patients despite a high smoking rate (26.6 %) in the general population.[1,2] Similarly, the Center for Disease Control and Prevention (CDC) found only 1.3% of 7,162 Covid-positive hospitalized Americans were smokers against a national smoking prevalence of 14%.[3] Could nicotine have a protective effect against COVID-19, or are these disproportionately low figures due to varying definitions and inaccurate reporting of smoking status amidst an emerging and overwhelming epidemic? Patients might be too sick or fearful to provide an honest or coherent report of tobacco use. Doctors may be too busy to take a detailed history. Smoking is more prevalent among lower socioeconomic classes where affordable access to hospital care might be an issue.

A study by Guan Wei-Jie et al from the original epicenter (Wuhan, China) of 1,099 Covid-positive patients suggests smokers were overrepresented in the subgroup with severe illness. Their composite primary outcome of intensive care unit (ICU) admission, mechanical ventilation or death occurred in 17 /137 (12.4%) of current smokers whilst only 44/927 (4.7%) of non-smokers developed severe disease.[4] Smokers were 2.4x more likely to require ICU admission, ventilation or die. (RR=2.4, 95%CI: 1.43-4.04). Similarly, Liu W et al identified smoking as an independent risk factor for disease progression on multivariate logistic analysis in a study of 78 COVID-19-induced pneumonia patients. Smokers were 14x more likely to die from Covid-19.[5] (OR14.285; 95% CI: 1.577-25.000; P=0.018). Farsalinos et al however conducted a pooled (six studies) meta analysis of 1,701 hospitalized COVID-19 patients and concluded that 'actively' smoking was not a risk factor for hospitalization.[6]

SARS-CoV-2, Smoking and the ACE-2 receptor

The critical cellular entry point for the SARS-CoV-2 coronavirus is the angiotensin converting enzyme II (ACE-2) receptor located in the respiratory epithelium, type II alveolar pneumocytes, small intestine, kidneys and endothelium. The defining crown-like appearance of coronaviruses is attributed to a large type 1 transmembrane spike (S) glycoprotein which has two distinct functional domains; S1 and S2. The ACE-2 receptor-binding site is located at S1 and is responsible for initial virion entry. The S2 domain facilitates fusion between the host cell and virus, a prerequisite for cellular infiltration.[7] The S proteins are enzymatically modified and cleaved to expose the fusion site for cellular adhesion by furin, a protein convertase which is highly expressed in the lungs.[8,9] In 2003, researchers identified the ACE-2 receptor as the entry route and binding site for the S protein of the SARS-coronarvirus (SARS-CoV).[10] Recent studies have demonstrated that the modified S protein of the SARS-CoV-2 (COVID-19) has a higher affinity (10-20 fold increase) for the ACE-2 receptor than SARS-CoV.[11,12]

Researchers from China recently reported increased ACE-2 gene expression in type II pneumocytes where viral replication and transmission is highly expressed.[13] Brake SJ et al reported elevated ACE-2 levels in the resected pulmonary tissue of smokers but found none in non-smokers.[14] A contemporary study by Leung JM et al involved transcriptomic RNA sequencing of cytologic bronchoscopic brushings in 42 patients. They found significantly increased ACE-2 expression in the respiratory epithelial cells of smokers compared to non-smokers, after adjusting for age and gender.[15] They noted similar findings with ACE-2 protein (antigen) expression in resected lung between smokers and non-smokers. ACE-2 expression significantly correlated inversely with lung function (predicted FEV1). Their work was reaffirmed with two separate patient cohorts totalling 449 patients. Additionally Leung found that the levels of ACE-2 gene expression in former smokers was in-between that of never and current smokers. Historical analyses however have described the opposite; that nicotine and smoking downregulates ACE-2 expression.[16,17] Farsalinos et al hypothesize that nicotine may paradoxically protect against cholinergic mediated Covid-induced acute inflammatory lung injury.[6]

Clinical bottom line

There is conflicting evidence on the effects of smoking on ACE-2. Contemporary studies suggest smoking increases expression and upregulation of pulmonary ACE-2 receptors. As ACE-2 is the critical host viral entry point and given the high affinity of the SARS-CoV-2 coronavirus for the ACE-2 receptor, it is plausible that smokers have a greater risk of severe COVID-19 infection due to the higher viral load. Smokers however are more likely than non-smokers to have co-morbid risk factors that could themselves portend a worse outcome.

It remains uncertain whether smokers have a higher risk of contracting SARS-CoV-2 in the first place given the disproportionately low incidence documented in hospitalized COVID-19 patients. This could be due to unreliable data on

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smoking status and confounded by other factors. Cohorts of hospitalized patients may not resemble the true COVID-19 prevalence amongst smokers in general, given the lack of community testing in the vast majority of asymptomatic cases. Amongst patients already hospitalized, smokers carry higher odds of severe COVID-19 illness and worse outcomes from retrospective observational studies which have inherent limitations.

There is no evidence to suggest that Asians harbour any unique or different genetic ACE-2 polymorphisms from other populations to account for its' increased expression.[18] Until an efficacious vaccine is widely available, there is potential to develop drugs that modulate the ACE-2 receptor through conformational changes to prevent virus interaction and inhibit the helicase and protease sites of ACE-2 which are essential for viral replication. Simple inhibition of ACE-2 is problematic as it has a crucial regulatory role in the renin-angiotensinogen pathway.

Implications for Malaysia

The World Health Organization (WHO) has identified smoking as a specific risk factor for COVID-19.[19] Despite various anti-smoking measures, prevalence here remains high with approximately five million current smokers; highest amongst adult males at 43%.[20]

The illicit cigarette trade here is rampant. An estimated six of every ten cigarettes (62.5%) sold in Malaysia last year evaded taxes.[21] Increasing the minimum price of cigarettes will be counter productive and further fuel contraband sales if there is no ban of cigarette transshipment. Customs and border controls must be more vigilant and meticulous to curb this illicit practice and simultaneously reduce influx of new cases and strains of the COVID-19 virus. The nationwide smoking ban at eateries must be diligently monitored and strictly enforced once the movement-controlled order (MCO) is lifted. Any proposal to fund designated public smoking areas must be resisted as it will normalise smoking and runs counter to the goal of creating a smoke-free culture. In 2005, Malaysia ratified the WHO Framework Convention on Tobacco Control which advocates against this due to a lack of credible evidence for their safety and effectiveness.[22]

Passive-smoking Spread

The threat of passive smoking-induced spread of COVID-19 is real. A recent Hong Kong study suggests that infectivity is highest just before symptoms appear when viral shedding is maximal.[23] The deep exhaled puff from an infected but asymptomatic smoker may exacerbate community viral spread through aerosolisation and possibly airborne transmission. The markedly reduced levels of ACE-2 expression in former smokers highlights the value of smoking cessation. Health authorities should promote and prioritise smoking cessation alongside fastidious handwashing, wearing of facemasks and social distancing to mitigate the spread of COVID-19. Quitting smoking during these anxious times is admittedly difficult. If MCO restrictions are prolonged, behavioural support for smoking cessation can be delivered remotely. There is evidence that automated mobile phone SMS interventions increase smoking cessation rates.[24]

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