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More Than Meets the Eye: The Similarities Between Coronavirus Disease 2019 and Smoking

To The Editor: Research shows that cigarette smoking upregulates angiotensin-converting enzyme 2, the receptor by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains entry to the host resulting in coronavirus disease 2019 (COVID-19), in the lungs and, therefore, potentially leads to increased morbidity.[1] However, the virus and smoking share far more similarities than meet the eye (Table).

As part of a tobacco treatment campaign implemented at the beginning of the pandemic at McDonald Army Health Center, we performed a literature search and found that SARS-CoV-2 and smoking both contribute to myocarditis, thrombosis, immune impairment, and increased inflammation. SARS-CoV-2 leads to an increase in nuclear factor kappaB, tumor necrosis factor α, and lymphocyte dysregulation. Smoking leads to an increased neutrophil count and can cause neutrophil to lymphocyte ratio elevation. Together, this can contribute to the development and worsening of outcomes in patients with acute respiratory distress syndrome.[2]

Fibrin deposition in pulmonary vasculature, which is increased in both COVID-19 and smoking, is thought to contribute to the development of acute respiratory distress syndrome. Tissue factor, which initiates the extrinsic coagulation cascade, is highly expressed by alveolar macrophages and epithelial cells. Inflammatory cytokines and regulators, including tumor necrosis factor α and nuclear factor kappaB, upregulate tissue factor expression, leading to fibrin deposition, further inflammation, and microvascular permeability in the lungs.[3] Both SARS-CoV-2 and smoking upregulate this cytokine release and lead to an increased risk of coagulopathy.[4,5]

The upregulation of angiotensin-converting enzyme 2 in smokers may predispose this population to an increased risk of SARS-CoV-2 infection. The host cell transmembrane protease, serine 2 (TMPSRSS2), which primes the SARS-CoV-2 S protein for entry, may also be upregulated in smokers,[6] which would further increase the odds of viral infectivity.

From a cardiovascular perspective, N-terminal pro—brain natriuretic peptide, lactate dehydrogenase, and ferritin have been shown to be predictors of poor outcomes and cardiac tissue damage in those with COVID-19.[7] Smoking has been shown to cause elevations in all these parameters, potentially contributing to the detrimental impact of SARS-CoV-2 on the myocardium.[8-10]

Although the lungs are a gateway to the body for both tobacco smoke and SARS-CoV-2, they each exhibit harmful systemic effects throughout the body. Our goal is to bring awareness to the similar and potentially synergistic ways in which smoking and SARS-

TABLE. Similarities Between COVID-19 and Smoking

Characteristic	COVID-19	Smoking
Viral entry	Primed for entry by TMPRSS2 Enters through ACE2	↑ TMPRSS2 ↑ ACE2
Cardiovascular	↑ NT-proBNP ↑ LDH ↑ Ferritin ↑ Risk of developing myocarditis	↑ NT-proBNP ↑ LDH ↑ Ferritin ↑ Risk of developing or worsening myocarditis
Coagulation	Prothrombotic state ↑ Fibrin deposition	Prothrombotic state ↑ Fibrin deposition
Inflammation	↑ NF-κB ↑ TNF-α ↓ Lymphocytes ↑ IL-2R ↑ IL-6	↑ NF-κB ↑ TNF-α ↑ Neutrophils ↑ IL-1β

ACE2 = angiotensin-converting enzyme 2; COVID-19 = coronavirus disease 2019; IL = interleukin; LDH = lactate dehydrogenase; NF-κB = nuclear factor kappaB; NT-proBNP = N-terminal pro—brain natriuretic peptide; TMPRSS2 = transmembrane protease, serine 2; TNF-α = tumor necrosis factor α.

CoV-2 cause harm to guide research and work toward a better understanding of both conditions.

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Repeated Testing in SARS-CoV-2 Infection

To the Editor: In a recently published article in the journal, Challener et al[1] showed that 2.0% of participants (ie, 22 of 1113) tested positive within 1 week of the first negative nasopharyngeal swab for identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This evidence persuaded the authors to conclude that repeating an identical test in a low-prevalence environment is unlikely to generate added clinical value. However, some important considerations would lead us to disagree with this conclusion.

The fact that the SARS-CoV-2 identification is directly related to the number of subsequent nasopharyngeal swabs collected is now widely acknowledged. Zhang et al[2] found that 99% diagnostic sensitivity could be achieved after the fourth consecutive specimen collection. This suboptimal accuracy is attributable to a vast number of preanalytical and analytical issues, which have been comprehensively reviewed elsewhere.[3] Besides these technical aspects, our perception is that a 2% rate of false-negative results on initial testing is not a negligible value and is not reassuring even (or especially) in a low-prevalence environment.

The underdiagnosis or delayed diagnosis of SARS-CoV-2 infection has been highlighted as an important reason for rapid spread of infection in the community. It has now been clearly established that the viral load of asymptomatic patients, which represent most SARS-CoV-2 infections in low-prevalence areas, is almost identical to that of symptomatic patients.[4] This would imply that underdiagnosing these asymptomatic individuals would lead to a substantial risk of contagion and generation of new local outbreaks, especially in a low-prevalence scenario, where a perception of scarce virus circulation may have attenuated the degree of vigilance (ie, social distancing, use of face masks, quarantine, and so forth). From this perspective, a recent analysis by Li et al[5] highlighted that asymptomatic cases may have been responsible for nearly 80% of SARS-CoV-2 contagions to date, thus further emphasizing the need for timely identification and immediate isolation of positive cases to prevent further spread of the virus. Notably, with an estimated basic reproduction number (ie, R0) of 3.3 for SARS-CoV-2, even a single presymptomatic infected individual may rapidly contribute to infect nearly 270 people within 5 days, which is the typical incubation time of SARS-CoV-2 infection.[6] Moreover, although we agree that collection of alternative specimens (eg, bronchoalvage fluid or sputum) may potentially yield higher diagnostic accuracy, it must also be acknowledged that this approach is impractical, or even unfeasible, as a screening strategy for outpatients, especially when these are asymptomatic, presymptomatic, or mildly to moderately symptomatic.

Unlike what has been concluded by Challener and colleagues, we believe that short-interval repeated collection and testing of nasopharyngeal swabs in individuals with high baseline clinical and environmental risk of being infected by SARS-CoV-2 (eg, those with a high likelihood