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REVIEW ARTICLE

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A Problem To Be Solved: Vaping and EVALI in Coronavirus Days

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Abstract

Coronavirus disease 2019 (COVID-19) outbreak was declared as a global pandemic by the World Health Organization (WHO) on March 11, 2020. The disease has a high infectivity and the most common symptoms are related to respiratory system.

Electronic cigarettes (e-cigarettes), considered by many as an alternative for cigarette smoking, rapidly gained popularity in recent years. Despite a legal age requirement of 18 years for purchasing e-cigarettes, use of vaping products has been increasing particularly among younger people. These products are known to cause a special type of disease called "e-cigarette, or vaping, product use-associated lung injury" (EVALI) which may be highly fatal.

Diagnostic criteria for EVALI consists of a mixture of non-specific systemic symptoms (eg, fever, chills, and vomiting) and respiratory symptoms (eg, shortness of breath, cough, chest pain, dispnea, and hypoxia), along with detection of lung opacities and ground-glass opacities (GGOs) on imaging. Commonly, findings of EVALI reveal similarities with those of coronavirus disease 2019 (COVID-19).

In the literature, there are numerous studies indicating e-cigarette users (vapers) have impaired immune response that might increase vulnerability to COVID-19 infection and death. However, studies claiming that smoking has protective effects against COVID-19 still exist in the literature.

In this narrative review, we aimed to clarify confusions on effects of vaping on COVID-19 patients and prevent misdiagnoses of EVALI due to similarities of these diseases in many aspects.

Keywords: EVALI, vaping, smoking, COVID-19.

1 | INTRODUCTION

Since it has first emerged in Wuhan, China on December 2019, Coronavirus Disease 2019 (COVID-19) caused by the severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been investigated from many aspects such as diagnosis, clinical features, socio-economical and mental effects, treatment methods and vaccination (1) . Based on previous experience of management of Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) infections, the World Health Organization (WHO) recommends avoiding close contact with people suffering from acute respiratory infections, frequent hand-washing especially after a direct contact with ill people or their environment, and avoiding unprotected contact with farm or wild animals (2) . Since the time it turned to a pandemic, there is an ongoing debate on effects of smoking (either tobacco or electronic cigarette (e-cigarette)) on transmission and progression of the disease.

SARS-CoV-2 has been shown to bind to the angiotensin-converting enzyme 2 (ACE-2) receptors within alveolar epithelial cells, leading to elevated levels of ACE-2 and ultimately resulting in alveolar damage (3) . Based on the hypothesis that SARS-CoV-2 entry and proliferation in epithelial cells through co-expression of ACE-2 is enhanced by cellular mechanisms of nicotinic receptor activity, nicotine consumption is considered as a risk factor in COVID-19 (4) .

E-cigarettes, also known as vapes, are battery-powered devices that can heat and aerosolize liquid combinations of nicotine, tetrahydrocannabinol, cannabinoid oils, flavors, and other additives (e.g., vitamin E) for inhalation. This device is well-described in the literature as the cause of e-cigarette or vaping product use–associated lung injury (EVALI) (5) . In this narrative review, we aimed to clarify the effects of e-cigarettes which has been widely used by teenagers and young adults (6) on susceptibility, progression and severity of COVID-19.

2 | MATERIALS AND METHODS

This study was conducted entering the keywords "electronic cigarette, e-cigarette, vaping and /or EVALI" into the scientific database Pubmed© between January 19^{th} and January 21^{st}, 2021. A total of 35 articles were extracted. Those in other languages than English and with non-explanatory abstracts were excluded from the study. The publications were evaluated by two reviewers separately and discussed by all reviewers for scientific relevance.

3 | DISCUSSION

In the United States (US), approximately 3.7% of adults use e-cigarettes, and 1.8 million adolescents also vape, and this number is rising (7) .

Smoking upregulates ACE-2 which is the target for SARS-CoV-2. However, such an effect could not have been determined in vaping. Nevertheless, pro-inflammatory cytokines and inflammasome-related genes are upregulated by both smoking and use of nicotine and flavor-containing e-cigarettes. While the chemokines upregulated in smokers are CCL20 and CXCL8, CCL5 and CCR1 are upregulated in flavor/nicotine-containing e-cigarette users. It was also reported that CXCL1, CXCL2, NOD2, and ASC genes which are implicated in inflammasomes are upregulated in both smokers and e-cigarette user. Additionally, there is a lack of evidence that vaping flavor and nicotineless e-cigarettes result in cytokine dysregulation and inflammasome activation (8) .

It is well-described in the literature that COVID-19 patients with a history of smoking tend to have more severe outcomes than non-smoking patients (9) . In another study, youth using e-cigarettes and dual-users of e-cigarettes and cigarettes are at greater risk of COVID-19 (10) .

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In the US, an association between the proportion of vapers and the number of COVID-19 infected cases and deaths suggest an increased susceptibility of vapers to COVID-19 infections and deaths (11) . This fact was also emphasized by the WHO that tobacco cigarette and waterpipe smoking contribute to increased burden of symptoms due to COVID-19 compared to non-smoking, including being admitted to intensive care, requiring mechanical ventilation, and suffering poo prognosis (12) .

E-cigarette liquid contains only nicotine, propylene glycol, and glycerine. Accordingly, most of the toxic compounds found in e-cigarette vapour are derived from the three ingredients. Carbonyl compounds are also responsible for bad health effects observed in e-cigarette consumers. Other groups of toxic compounds found in both tobacco cigarette/ waterpipe smoke and e-cigarette vapour are volatile organic compounds and inorganic compounds such as metals and carbonmonoxide (CO). All of these compounds have known toxic effects on the human body including inflammation, cancer, cardiovascular diseases and impaired cognition (13) . E-cigarettes are being presented as a safer alternative to cigarettes but its vapor affects numerous cellular processes resulting in DNA damage and cancer (14) .

When pathogenesis of damage caused by smoking and vaping was investigated, it was reported that e-cigarette aerosol with nicotine causes lung inflammation due to altered dysregulated repair response and ECM remodeling mediated by nAChR $\alpha 7$. Deletion of nAChR $\alpha 7$ may possibly protect against lung inflammation and injury by attenuating associated signaling targets for ECM remodelling. Hence, nAChR $\alpha 7$ is considered a valid target for inflammation induced by e-cigarette aerosol with nicotine in the lung (15) .

It was reported that chronic vaping impacts COVID-19 outcomes by disrupting alveolar homeostasis via its aerosol, independent of nicotine. It was also reported that this homeostasis disruption accompanied with aberrant response of lung macrophages to viral infection causes an increase in morbidity and mortality in influenza-infected mice. Lipoid pneumonia which is a life-threatening condition, may also be determined in humans with vaping habbit. E-cigarette users are under risk of bad outcomes related to COVID-19 since COVID-19 inflammation is known to progress to pneumonia resulting in pneumonia, atelectasis and alveolar collapse, hypoxemia, and consequently, loss of surfactant. The coronavirus receptor is expressed in the distal alveolar type II cells of airway epithelium. These specialized stem cells are responsible for surfactant production. Surfactant keeps alveoli open during breathing and plays an essential role to maintain normal lung function. Lung cell samples of people who died due to COVID-19 were shown to fail surfactatnt expression. Acute viral infection of AT-II cells could promote disruption of lung repair and induce acute respiratory distress syndrome (ARDS), a hallmark of novel coronavirus infection (16) .

A special type of respiratory disease caused by these products is called “e-cigarette, or vaping, product use-associated lung injury” (EVALI). The pathogenesis of EVALI has not been totally understood. Rather than a single process, it is thought to be a spectrum of illness. As a result of several pathogenic mechanisms; acute eosinophilic pneumonia, diffuse alveolar hemorrhage, lipoid pneumonia and respiratory-bronchiolitis interstitial lung disease may be observed (17) . Diagnosis of EVALI during COVID-19 is difficult since it has remarkable similarities with COVID-19 in terms of clinical, laboratory and imaging findings. It is reported that most patients with EVALI are treated as COVID-19 resulting in delays in patient care (18) . These similarities are more pronounced particularly in the setting of the COVID-19 (17) .

In both diseases, non-productive cough, fever, chest pain, nausea, vomiting and diarrhea may be determined. Clinical suspicion comes into prominence in differentiation of EVALI and COVID-19 (14) , (19) .

Radiological findings of EVALI are known to be bilateral multifocal “ground glass opacity” (GGO) or consolidation in a symmetric pattern predominantly in the lower lung zones as in COVID-19 pneumonia (1) , (5) , (19) . Additionally, histological investigations revealed pneumonitis, bronchiolitis, and alveolar damage (20) . Other pathological findings are as follows: acute fibrinous or hypersen-

sitivity pneumonitis, diffuse alveolar haemorrhage, giant cell interstitial pneumonia, lipoid or organizing pneumonia, and accompanied bronchiolitis (14) .

Acute e-cigarette smoking increases blood pressure, causes endothelial dysfunction and increases vascular and cerebral oxidative stress responsible for the above-mentioned effects (13) . Moreover, aerosols and vapor generated by electronic substance delivery systems could participate in the dissemination of the virus in the close proximity of SARS-CoV-2 infected vapers (21) . When using an e-cigarette, one must do repetitive hand-to-mouth motion which is not recommended during the pandemic. Particularly youth consider vaping as a social activity and shring devices is a part of that activity. The risk of COVID-19 transmission increases with exhaled plume that contains aerosolised e-liquid contaminated by the user's respiratory mucous (22) . Besides inflammation-causing effect of vaping in the lung, it is very likely that vaping also supresses immune system and, thus, prolongs and intensifies lung infection (23) .

A diagnostic algorithm for EVALI was proposed. According to this algorithm, in the presence of a respiratory illness requiring hospitalization accompanying with (1) using an e-cigarette (vaping) or dabbing in the 90 days before symptom onset, (2) pulmonary infiltrate, such as opacities on plain film chest radiograph or GGO on chest CT, (3) absence of respiratory infection on initial work-up: minimum criteria include the following negative tests for SARS-CoV-2, respiratory viral polymerase chain reaction (PCR) panel, and influenza PCR or rapid test, all other clinically indicated respiratory infectious disease testing (e.g., urine antigen for Streptococcus pneumoniae and Legionella, sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, and human immunodeficiency virus–related opportunistic respiratory infections if appropriate), (4) no evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process). In patients with EVALI, a higher concentration of serum C-reactive protein (CRP) was determined, however, its diagnostic value is low since CRP may elevate in numerous infections (24) .

Comparison of EVALI and COVID-19 in terms of signs and symptoms, pathogenesis, clinical properties and radiological findings is summarized in the table.

Higher susceptibility to COVID-19 in e-cigarette users may be linked to increased expression of ACE2 in the lungs. This fact could partially contribute to the severity of COVID-19 prognosis (7).

E-cigarette users are not only under risk of higher exposure rate to COVID-19 and COVID-19-related health risks related to e-cigarette aerosol, but also financial burden and stress related to addiction, (25) . It was reported in a study that over 20% of the users tried to quit smoking to reduce risk of harm from COVID-19 during the pandemic (26) . However, trade of these products is contiunuing both in vape shops and online platforms, threatening underage youth, particularly. Even though they have difficulties to obtain these products from shops due to restrictions, any significant difference in difference in quitting or reduced use between underage youth and young adults could not be determined (27) . Staying at home with parents, difficulties in accessing the products and the belief that e-cigarettes may weaken lungs may cause a decrease in vaping (28) . In a study, it was reported that most patients believed that smoking and vaping increased their vulnerability to COVID-19, half reported increased interest in quitting, but others reported increasing smoking and vaping during the COVID-19 pandemic (29) .

However, the e-cigarette industry appears to have taken advantage of the COVID-19 pandemic to aggressively market its products. Pandemic related discounts, asserting health claims and assuring consumers that e-cigarette products will not transmit COVID-19 may be given as examples to these marketing strategies. This method attracts young people and and encourage them to use e-cigarette. In fact, potential harmful effects of e-cigarettes and their use in smoking cessation are not literally discussed. There is also a lack of a screening tool to determine

how common e-cigarettes are among young people (30). Social media posts in various platforms (particularly Twitter) reveal that e-cigarette users had more concerns about the COVID-19 pan-demic (31) . These paltforms may be useful in dis-couraging smoking and vaping if used correctly (32) . The main target of vaping product marketing is Pathogenesis, Clinical Properties and Radiological Findings younger population and youth access to these prod-ucts should be reduced (33) .

4 | Conclusion

There is an ongoing debate on effects of smoking and vaping on COVID-19 transmission, progression and outcomes. Although there are studies in the literature claiming smoking does not apparently seem to be signicantly associated with enhanced risk of pro-gressing towards severe disease in COVID-19 (34) , numerous studies claim the opposite. Moreover, due to anti-inflammatory effects of nicotine, it was stated that smoking might be protective in COVID-19. Theoretically, blunted immune system smokers may have protective effects against cytokine storm seen in COVID-19.

Additionally, increased nitric oxide in the respiratory tract of the smokers may inhibit replication of SARS-CoV-2 and its entry into cells. However, similar to other respiratory infec-tions, smoking may cause susceptibility to infec-tion and worsen prognosis in COVID-19 (35) . Our review revealed that smoking and vaping may cause transmission of SARS-CoV-2 among young population. Similatiries in signs and symptoms and radiological findings of EVALI and COVID-19 may cause misdiagnosis. Additionally, both are associ-ated with bad outcomes in COVID-19. Vapers take advantage of easy trading policy of social media. Uncontrolled advertisements and marketing in social media results in a rapid spread of these products.

TABLE 1: Comparison of EVALI and COVID-19 in terms ofSigns and Symptoms, Pathogenesis, Clinical Properties and Radiological Findings

	EVALI	COVID-19
Signs and Symptoms	Non-productive cough, fever, chest pain, nausea, vomiting and diarrhea.	Mild, influenza-like symptoms; fever, cough and expectoration, diarrhea.
Pathogenesis	Upregulation of pro-inflammatory cytokines and inflammasome-related genes. Acute eosinophilic pneumonia, diffuse alveolar hemorrhage, lipoid pneumonia and respiratory-bronchiolitis interstitial lung disease may be observed CCL5 and CCR1 are upregulated in flavor/nicotine-containing e-cigarette users. CXCL1, CXCL2, NOD2, and ASC genes which are implicated in inflammasomes are upregulated. Causes lung inflammation due to altered dysregulated repair response and ECM remodeling disrupting alveolar homeostasis Affects numerous cellular processes resulting in DNA damage and cancer.	Receptor of coronavirus is ACE2. In normal lung tissue, ACE2 is mainly expressed by type I and type II alveolar epithelial cells. Majotity of alveolar cells express ACE2.
Clinical Properties	Acute eosinophilic pneumonia, diffuse alveolar hemorrhage, lipoid pneumonia and respiratory-bronchiolitis interstitial lung disease.	Interstitial pneumonia, ARDS.
Radiological Findings	Bilateral multifocal GGOs or consolidation in a symmetric pattern predominantly in the lower lung zones.	Single or multiple patchy ground glass shadows accompanied by a septal thickening. Bilateral and peripheral GGO in the superior segments of both lower, peripheral lobes. Patchy consolidation and GGOs observed in chest CT may be distributed along the bronchial bundles or subpleural regions in both lungs. Crazy-paving pattern, consolidation and residual parenchymal bands may be observed.

ACE 2: Angiotensin-converting enzyme 2, ECM: Extrcellular matrix, GGO: Ground-glass opacity, CT: Computed tomography, ARDS: Acute respira-tory distress syndrome

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