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Review

The Complexity in the Diagnosis and Treatment of Symptoms in Electronic Cigarette Users during the COVID-19 Pandemic

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Abstract: The issue with the overlapping clinical symptoms from an electronic cigarette (e-cigarette) or vaping product use-associated lung injury (EVALI) and coronavirus disease 2019 (COVID-19) sometimes leads to incorrect diagnosis and, consequently, wrong treatment regimen. The purpose of this review is to study the burden of vaping-associated health consequences on the diagnosis and treatment of COVID-19 in young adults and adolescents with a misconception of e-cigarettes as a safer alternative to smoking. The online reference databases, including PubMed, Google Scholar, Web of Science, Medline, and Centers for Disease Control and Prevention (CDC), were used in the literature search, as we analyzed the complexity of timely diagnosis and treatment in the current COVID-19 era with the use of e-cigarettes. This study briefly describes the dysbiosis of the oral microbiome in e-cigarette users that could potentially aggravate the COVID-19 symptoms and lead to the complexity of timely diagnosis and treatment. Additionally, the patient case reports with a history of vaping and symptoms similar to COVID-19 disease are reviewed.

Keywords: electronic cigarette; COVID-19; lung injury; coronavirus; adolescent; vaping products; addiction; overlap disease symptoms; young adult

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1. Introduction

Electronic cigarettes continue to be considered an alternate model of curbing the smoking addiction. However, there are limited data regarding their role in smoking cessation and safety when compared to conventional cigarettes [1–3]. In recent years, the use of e-cigarettes in young adults and adolescents has dramatically increased [4,5]. It has been shown that e-cigarettes not only contribute to dependency in non-smoking adolescents and young adults but also increase the chance of smoking relapse in past smokers [6–9]. Adolescents and young adults are reported to use e-cigarettes containing tetrahydrocannabinol (THC) and cannabidiol-containing compounds [10].

E-cigarettes have different types of devices that operate on battery to release aerosol for inhalation. The phenomenon of releasing the aerosol is based on the heating of the mixtures of various electronic vaping products, such as propylene glycol, flavoring, and glycerol. These products are frequently used with nicotine, tetrahydrocannabinol extract, and other addictive substances [11]. Recent studies demonstrate that the concentration of nicotine in e-cigarettes is higher when compared to the smoke from traditional cigarettes [12,13]. Electronic vaping products, such as vegetable glycerin and propylene glycol, serve as the solvent carrier for the nicotine and flavorings in e-cigarettes. The organic components from the aerosols of e-cigarettes have been suggested to be volatile and toxic in the previously published studies [14,15]. There are emerging data on the negative effect of e-cigarettes on the oral microbiome.

The continuing pandemic of coronavirus disease 2019 (COVID-19) has initiated a global health emergency with the ongoing crisis related to vaccination, therapy, and diagnosis. COVID-19 has caused infections related to the upper and lower respiratory tract

from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the severity of lung damage and/or the gradual loss of lung function due to pulmonary interstitial fibrosis [16–19]. This review deciphers the relationship between the conflict of diagnosis with the risk of vaping and the coronavirus disease health outcome. The dysbiosis of the oral microbiome in COVID-19 patients consuming e-cigarettes is discussed in this article. The diagnosis of the electronic vaping device-associated lung injury (EVALI) with the addictive substances in e-cigarettes during the COVID-19 pandemic is a challenge for treatment in these patients, and therefore, the goal of this research is to bring awareness to young adults and adolescents against the effect of e-cigarettes containing addictive substances during the COVID-19 pandemic.

2. Material and Method

Method: A detailed open literature search was conducted to capture the extensive clinical data related to e-cigarettes and COVID-19 etiology, diagnosis, and treatment. The different resources, including PubMed, Google Scholar, Web of Science, Medline, and Centers for Disease Control and Prevention (CDC), were used for the literature search. The current research was conducted using the different sets of keywords in PubMed, Google Scholar, and Web of Science, so as not to miss any relevant peer-reviewed articles. The Medline and CDC were consulted to provide the current epidemiological data related to the COVID-19 pandemic. Further, exclusion and inclusion criteria were set to filter out the articles that were not related to the vaping-related cases in COVID-19 patients. Lastly, the flow diagram was put together to take into account the total articles screened, the removal of articles based on duplicate findings, and exclusion criteria.

Keywords: There were different sets of search terms or keywords used throughout the research, so as not to exclude any relevant peer-reviewed articles. Some of the search keywords were: "Electronic cigarette, COVID-19", "EVALI, COVID-19, overlap", "Vaping, COVID-19", "Electronic cigarette, Health effect", "ENDS, COVID-19", "ENDS, microbiota".

Inclusion criteria: The research and review articles were selected and assimilated for the inclusion criteria that included articles written in English, free full text available, and dealing with ENDS or electronic cigarettes and/or EVALI and/or COVID-19, in human studies. One of the important questions that was part of the inclusion criteria was whether e-cigarettes and/or vaping could lead to the severity of the COVID-19 pathology. However, there was a lack of data, perhaps due to less focus on these studies in the current COVID-19 pandemic; therefore, this review tries to summarize the challenge in the treatment of patients who use e-cigarettes with addictive substances.

Exclusion criteria: The exclusion criteria for this review were any article published as a commentary, personal view, any social platform, health effect related to traditional cigarettes, consumption of any other form of smoking or chewing of tobacco other than electronic cigarettes, or the posters from conference presentation not published in peer-reviewed articles, national and international standards, and government reports. The impact of COVID-19 and e-cigarette users on the behavior and attitude toward vaping was also one of the exclusion criteria, as we did not study the socio-behavioral aspect of e-cigarette consumption.

Flow diagram: The search yielded 187 articles associated with this review, which were further screened by the authors for applicability and alignment with the original question posed. There was no utilization of a conflict resolution process. The free full-text articles were manually selected and reviewed for relevance. Following the review, only 85 full-text articles were found to be significant for research that included any content related to electronic cigarettes and/or COVID-19. The rationale and power of these findings were established in a qualitative assessment of the goals and outcomes of the study. The structure of the proposed review framework is provided in the flowchart in Figure 1.

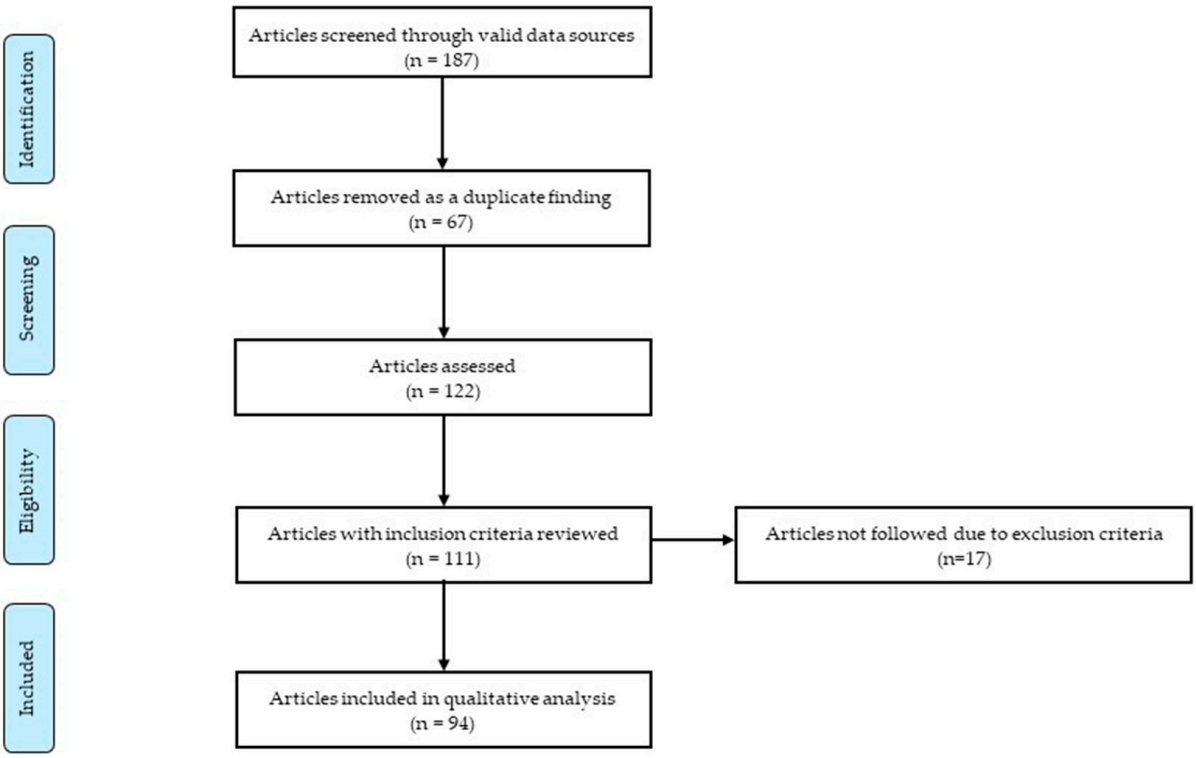

Figure 1. Flow diagram of the database search, publications identified, screened, and final full-text articles included in the review.

3. E-cigarette Components and Their Health Effects

The Center for Disease Control and Prevention (CDC) along with the Food and Drug Administration (FDA) and health departments are continuously monitoring the EVALI. CDC has reported that the different compounds in e-cigarettes, such as THC, vitamin E acetate, and various unknown chemicals, were strongly associated with the outbreak of EVALI. The CDC reported over 2807 EVALI-related hospitalizations and 68 reported deaths in 2020 in the United States.

The most common organic compounds found in e-cigarettes are acrolein, aldehyde, including formaldehyde and acetaldehyde, and propylene oxide. The carcinogenicity and teratogenicity from the sources, such as heavy metals and aldehydes, add up to the toxicity of these organic compounds [20]. It was shown in several studies that vitamin E acetate and THC are the causal agents of vaping device-associated lung injury (EVALI) [21,22]. Different e-cigarette devices have a wide variety of electronic liquids that can be aerosolized; therefore, it is hard to confirm specific harmful chemicals as a source of lung injury [23].

The current model of e-cigarettes does not lessen any harmful components, and the study by Farsalinos et al. has shown the correlation of high plasma nicotine levels with the advanced technology and design of e-cigarettes when compared to the first generation of e-cigarettes [24]. Lechasseur et al. reported the increase in inflammatory infiltrates owing to heating of the additives, such as vegetable glycerin and propylene glycol. This resulted in the production of cytokines, oxidants, and inflammatory gene expression, thereby leading to lung infection [25]. Furthermore, the longitudinal analysis research by Bhatta et al. identified a 30% increase in developing lung disease in users of e-cigarettes when compared to the population who do not use e-cigarettes. Therefore, electronic vaping products, such as e-cigarettes, could be a contributing risk for the onset of respiratory diseases [26].

The study by Kasahara et al. demonstrated that the use of e-cigarettes and other electronic vaping products could alter the platelet function, thereby damaging the pulmonary structures, causing the enlargement of the alveolar airspace and the disappearance of peripheral vasculature [27]. Electronic vaping products increase the platelet-activating factor

receptor expression, thus increasing the inflammatory profile of respiratory pathogens and¬ susceptibility to pneumonia [28]. E-cigarettes or electronic nicotine delivery system products cause injury to the lungs primarily because of the compromised lung function and show signs of fever and shortness of breath. In summary, the previous studies suggest that e-cigarette vaping and the inhalation of chemicals in the aerosols could cause inflammation in the lungs, as evident by the inflammatory disorders of lung pneumonia, such as lipoid pneumonia, hypersensitivity pneumonitis, and eosinophilic pneumonia [29–31].

4. Electronic Cigarette Associated Lung Injury in the COVID-19 Pandemic

The pandemic coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibits symptoms like EVALI, which creates a problem, as it delays the diagnosis and treatment of COVID patients. EVALI, being the acute lung injury, exhibits characteristic symptoms, such as fever, cough, shortness of breath, dyspnea, vomiting, diarrhea, headache, and fatigue with a pathological diagnosis of acute fibrinous pneumonitis, diffuse alveolar damage, and pneumonia [28]. Table 1, provided as a supplemental file, shows the references with the case reports of single patients with clinical presentation, lab examination, and chest radiography. There were diagnostic challenges in differentiating the EVALI symptoms during the COVID-19 pandemic. The exclusion criteria were used to exclude the dual use of smoking and vaping and/or patients transitioning from traditional smoking use to vaping in the last year. The inclusion criteria were the associated negative COVID-19 results. Ganne et al. reported a case study of a 32-year-old female treated for COVID-19 despite testing negative for SARS-CoV-2 multiple times [32]. The symptoms and pathological diagnosis were like EVALI due to the use of e-cigarettes by the patient. This case highlighted the challenge of diagnosing rarer etiologies of respiratory distress during the COVID-19 pandemic. Pitlick et al. also reported a couple of cases of the overlap of EVALI and coronavirus disease symptoms, leading to the delay in the diagnosis of EVALI [33]. The anchoring bias due to the patients' symptoms similarity with COVID-19 symptoms was a challenge in the early diagnosis of EVALI [34]. Several case studies in male patients in the age range of 20 to 47 years have reported the e-cigarette vaping associated symptoms, including shortness of breath, chest pain, cough, fevers, myalgias, gastrointestinal symptoms, and headaches. These patients had clinical symptoms of neutrophilia, lymphopenia, leukocytosis with asymmetric bilateral patchy basilar opacities or bilateral ground-glass opacities, elevated C-reactive protein (CRP) concentration, and elevated D-dimer level. The clinical manifestations of COVID-19 patients, including fever, fatigue, cough, anorexia, myalgias, and dyspnea, are similar to the EVALI [35]. Similarly, the inflammatory markers, such as CRP, erythrocyte sedimentation rate, and procalcitonin, and coagulation markers are elevated in both EVALI and COVID-19. The diffuse hazy or consolidative opacities and ground-glass opacities are also very similar in both conditions [32]. Chatham-Stephens et al. have reported the acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) related to the vaping of e-cigarettes in over 2000 patients in 2019 [30].

Table 1. The case reports of the e-cigarette-vaping non-COVID-19 patients with clinical presentation, lab examination, and chest radiography similar to COVID-19 clinical presentation.

Reference	Age/Gender/Medical History	Clinical Presentation	Lab Examination	Chest Radiography	COVID Test- Negative Result
Rodriguez et al. [36] 10.1155/2020/8821289	23 years Male Past history of smoking marijuana in the e-cigarette three times a week. Past history of childhood asthma	Blood pressure: 135/65 mmHg Temperature: 39 °C Pulse Rate: 134 Respiratory rate: 22 Oxygen saturation at room temperature SPO_2 (RT): 96%	White blood cells: 15.3 × 10^3/µL Alanine transaminase (ALT): 69 U/L Aspartate transaminase (AST): 66 U/L Ferritin: 375.6 ng/mL C-reactive protein (CRP): 27.70 mg/dL Procalcitonin: 1.43 ng/mL.	X-ray: Bilateral interstitial infiltrates	1. Respiratory pathogen panel. 2. SARS-CoV-2 nasopharyngeal swab polymerase chain reaction (PCR) test
Hoshina. [37] 10.1002/ccr3.5016	20 years Male Past history of occasionally vaping Tetrahydrocannabinol (THC)	Dyspnea Temperature: 37.9 °C Tachycardia Tachypnea SPO_2 (RT): 93% Bibasilar crackles	Leukocytosis: 19.0 × 10^3/µL	Computed tomography (CT): Diffuse, bilateral subsegmental ground-glass opacities	SARS-CoV-2 nasopharyngeal swab PCR test
Lilley et al. [38] 10.1016/j.rmcr.2021.101465	29 years Female Past history of vaping THC daily for 5 years	Temperature: 38.9 °C Three-day history of watery, non-bloody bowel movements and non-bloody, non-bilious emesis. Tachycardia Sepsis	WBC count: 12,700 cells/mm	X-ray: Mild patchy alveolar opacities bilaterally in the basilar lung fields. Atypical pneumonitis	1. Autoimmune serologies test. 2. SARS-CoV-2 nasopharyngeal swab PCR test
Ganne et al. [32] 10.1136/bcr-2021-243885	32 years Female E-cigarette user (Five times per week) History of opioid use, generalized anxiety disorder, and latent tuberculosis	Relapsing fevers Shortness of breath Tachycardia Tachypnea Diaphoretia Anxiety Cough Myalgias Fatigue Pain with inspiration Lower abdominal pain Nausea Vomiting Headache	Decreased air movement in all lobes with scant rhonchi and wheezing Elevated CRP Elevated D-dimer Ferritin Lactate dehydrogenase	X-ray: Diffuse bilateral pulmonary infiltrates in upper and lower lungs. CT scan: Diffuse bilateral pulmonary interstitial and ground-glass opacities	1. SARS-CoV-2 nasopharyngeal swab PCR test. 2. Total antibody test
Pitlick et al. [33] 10.1016/j.mayocpiqo.2021.03.002/	34 years Male E-cigarette user with cannabis oil, polysubstance abuse. Past history of depression, anxiety, attention-deficit/hyperactivity disorder, gastroesophageal reflux disease, and hypertension	Shortness of breath Nonproductive cough Pleuritic chest pain Fevers Myalgias Abdominal pain Nausea Headaches	Leukocytosis Neutrophilia Lymphopenia Elevated CRP Elevated D-dimer	X-ray: Asymmetric bilateral patchy basilar opacities. CT scan: Diffuse, midlung-predominant, ill-defined ground-glass opacities with interlobular septal thickening	SARS-CoV-2 nasopharyngeal swab PCR test

Table 1. *Cont.*

Reference	Age/Gender/Medical History	Clinical Presentation	Lab Examination	Chest Radiography	COVID Test- Negative Result
Pitlick et al. [33] 10.1016/j.mayocpiqo.2021.03.002/	47 years Male History of vaping with cannabis oil several times daily in the weeks before admission	Fever Nonproductive cough Myalgias Malaise Nausea Diarrhea	Leukocytosis Lymphopenia Elevated CRP Elevated platelets Elevated D-dimer	X-ray: Bilateral patchy airspace opacities. CT scan: Extensive bilateral ground-glass opacities in a predominantly central distribution with associated interlobular septal thickening	1. SARS-CoV-2 nasopharyngeal swab PCR test. 2. Respiratory pathogen panel
Pitlick et al. [33] 10.1016/j.mayocpiqo.2021.03.002/	20 years Male History of vaping tetrahydrocannabinol products	Shortness of breath Nonproductive cough Nausea Temperature: 38.4 °C Tachycardia (heart rate:110 beats/min)	Mild leukocytosis Lymphopenia Elevated CRP Elevated D-dimer	CT scan: Diffuse bilateral ground-glass opacities with a peripheral predominance	SARS-CoV-2 nasopharyngeal swab PCR test
Adhikari et al. [39] 10.7759/cureus.13541	23 years Male Vaping history of 8 years, immunocompetent	Fever Shortness of breath Tachypnea Nausea Diarrhea	Leukocytosis Lymphopenia Elevated procalcitonin Elevated erythrocyte sedimentation rate (ESR) Elevated CRP	X-ray: Bilateral pneumonia CT scan: Bilateral lung infiltrates	
Hassoun et al. [40] 10.1016/j.jemermed.2020.12.005	19 years Female Vaping tetrahydrocannabinol (THC)	Abdominal pain Vomiting Diarrhea Fevers Shortness of breath Vomiting Transient oxygen desaturation: 92% Tachycardia Tachypnea Diffuse abdominal tenderness	Ketonuria Elevated WBC count Neutrophilia Elevated CRP Elevated ESR Elevated D-dimer Elevated fibrinogen	X-ray: Mild left perihilar opacity. CT scan: Bilateral ground-glass opacities, with consolidation in the left lower lobe	1. Autoimmune serologies test. 2. SARS-CoV-2 nasopharyngeal swab PCR test
Hassoun et al. [40] 10.1016/j.jemermed.2020.12.005	19 years Male History of vaping nicotine and THC oils	Nausea Lightheadedness Anorexia Mild sore throat Cough Fever	Elevated WBC Elevated ESR Elevated CRP	CT scan: Bilateral ground-glass opacities with reticulation and interlobular septal thickening, most prominently at the right lower lobe and left lingula	1. SARS-CoV-2 nasopharyngeal swab PCR test 2. Group A streptococcus test was positive
Hassoun et al. [40] 10.1016/j.jemermed.2020.12.005	21 years Male	Febrile Tachycardia Tachypnea Hypoxic	Slightly elevated WBC Markedly elevated CRP Elevated ESR Elevated fibrinogen	CT scan: Bilateral subtle scattered ground-glass opacities. CT scan: Possible airway inflammation	1. Autoimmune serologies test. 2. SARS-CoV-2 nasopharyngeal swab PCR test

Table 1. *Cont.*

Reference	Age/Gender/Medical History	Clinical Presentation	Lab Examination	Chest Radiography	COVID Test- Negative Result
Kichloo et al. [41] 10.1177/2324709620972243	31 years Male Binge smoking disposable E-cigarette pods Vaping nicotine, tetrahydrocannabinol and cannabidiol Medical history of Crohn's disease	Fever Fatigue Dry cough Dyspnea Tachycardia SpO2 (RT): 86%	Elevated serum ACE Elevated lactate dehydrogenase (LDH)	X-ray: Faint bilateral pulmonary interstitial opacities. CT scan: Diffuse ground-glass opacities	SARS-CoV-2 nasopharyngeal swab PCR test
Patel et al. [42]10.7759/cureus.10302	26 years Female History of daily marijuana vaping use	Idiopathic chronic abdominal pain Diarrhea Cough Acute onset nausea Vomiting Abdominal pain Afebrile SPO_2 (RT): 99% Tachycardia	Anion gap metabolic acidosis Elevated lactate Mild hyponatremia Leukocytosis Lymphopenia	CT scan: Ground glass opacities in bilateral lung bases	SARS-CoV-2 nasopharyngeal swab PCR test
Ansari-Gilani et al. [43] 10.1016/j.hrtlng.2020.06.008	37 years Male History of marijuana vape use	Fever Cough Shortness of breath SPO_2 (RT): 92%		CT scan: Extensive ground-glass opacities in both lungs with slight lower lung predominance	SARS-CoV-2 nasopharyngeal swab PCR test
Galo et al. [44] 10.1016/j.rmcr.2020.101154	36 years Male History of vaping THC-containing e-cigarette, irritable bowel syndrome and major depressive disorder	Worsening dyspnea on exertion Shortness of breath Cough Myalgias Fever Desaturation Hypoxemic SPO_2 (RT): 86%	Elevated CRP: 269 mg/L. Bronchoscopy lavage indicated clusters of small foamy macrophage with intracellular lipid droplets	X-ray: Indeterminate infiltrate lungs, X-ray: Bilateral peripheral and basilar ground-glass opacities with mediastinal adenopathy	

5. Disease Pathology in E-Cigarettes and COVID-19

The popularity of e-cigarettes in recent years has led to some serious health concerns. COVID-19 has been known to affect patients with comorbidities or the susceptible older population. However, the youth and adolescents consuming e-cigarettes are five times more likely to be susceptible to COVID-19 [29].

The Center for Disease Control and Prevention (CDC) has reported 70,641,725 cases of COVID-19 around the world so far, with 864,203 reported deaths [45]. COVID-19 cases and deaths are on the increase around the world with a new variant. The SARS-CoV-2 viral spiked envelope, S2 domain, binds to the ACE-2 receptor on the lung epithelium. ACE-2 is a COVID-19 receptor, whereby the SARS-CoV-2 virus has a high affinity to the lung epithelium ACE-2 receptor [43,44]. Smokers and patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis are known to have upregulated ACE-2 expression [35,46]. E-cigarettes could contribute to the upregulation of ACE-2 owing to the high content of nicotine, thereby aggravating the COVID-19 complications [47,48]. The nicotinic acetylcholine receptors (nAChRs) in the central nervous system activate acetylcholine neurotransmitter signaling pathways [49,50]. Nicotine aerosol inhalation through e-cigarettes acting as an nAChR agonist potentially initiates the ACE-2 receptor pathway, thus inducing lung inflammation, dysregulated repair, and ECM remodeling. Thus, e-cigarette vapers, like traditional cigarette smokers, are highly susceptible to COVID-19, as they have upregulated or activated ACE-2 expression.

Previous findings suggest that the renin–angiotensin system, an endocrine sub-system, plays an important role in respiratory disease and inflammation [51]. The angiotensin-converting enzyme 2 (ACE-2) receptor in the host cell binds to the spike (S) protein of the SARS-CoV-2 virus, whereby the virus delivers its nucleocapsid to the host cell for replication [52]. Smokers are at a higher risk of developing COVID-19 disease owing to the enhanced expression of ACE-2 in the airway epithelium and ciliated airway epithelial cells, mediated by α7-subtype nicotinic receptors (α7-nAChR) [53]. There are limited data regarding the relationship between vaping and induction of the lung and airway ACE-2 expression. Some research studies have shown that vaping causes EVALI, thus influencing the epidemiology of transmissibility, morbidity, and mortality in COVID-19 [22].

Another mechanism of action explained by the researchers is that TMPRSS2 protease, which is important in the virus's entry into the host cells, could be altered by ACE-2 in vapers [54]. TMPRSS2, a cellular serine protease, is highly expressed in the nasal ciliated and goblet cells. SARS-S engages ACE-2 as the entry receptor and uses TMPRSS2 for S protein priming to facilitate the viral entry into the host target cells and viral spread in the infected host [55,56].

E-cigarette vaping induces oxidative stress and the inflammatory response, thus leading to complications in the COVID-19-related symptoms. The use of e-cigarettes could further lead to compromised barriers causing the impairment of mucociliary clearance, enhancement in the mucosal permeability, peribronchial inflammation, and fibrosis.

Recent in vivo and in vitro studies have also shown that the aerosol from e-cigarettes increases oxidative stress, inflammation, and DNA damage to the oral tissues [20,21]. Naidu et al. have shown experimentally in animals that e-cigarette vapors led to an increase in airway inflammation, impairment in lung function, and upregulation of the ACE-2 expression in the lungs [57]. This study also emphasized the augmented ACE-2 enzyme expression in animal models owing to the presence of nicotine in the vapor. The relationship between the presence of nicotine and augmentation of ACE-2 expression was found to be the activated nicotinic acetylcholine receptors (nAChR). The α7 subtype of nAChR is expressed in the lung resident cells, including bronchial epithelial cells, alveolar epithelial cells (type 2), and lung fibroblasts [58]. Thus, nicotine, through α7-nAChR, is required for the downstream signaling of phospho-Akt and phospho-Erk, which is in turn required for the nicotine-dependent ACE-2 expression in human primary airway epithelial cells [59]. Additionally, nicotine could aid in the entry of SARS-CoV-2 into the lung cells [60].

A study by Masso-Silva et al. on experimental animals revealed that e-cigarette aerosols led to changes in the lung gene expression and neutrophil activation. This was also observed with the intake of vaping mint, as the ACE-2 expression increased in animal models [61].

Another study by Sivaraman et al. has shown an increase in pulmonary inflammation and infection, resulting in mortalities in mice pre-exposed to the vaped electronic liquid upon infection with the murine-tropic coronavirus MHV-A59 [62]. There could be a potential role for vaping-related Ca^{2+} mobilization in inflammation, as observed by the dysregulation of cytokine activation. Therefore, these animal vapers could have an increased susceptibility to SARS-CoV-2 viral infection with a higher risk of developing COVID-19 [62]. However, the mechanism for non-nicotine-containing e-cigarette vapor induction in ACE-2 expression in the lungs is not well defined in humans. There is an urgent research need to understand the role of α7-nAChR in the increased predisposition and SARS-CoV-2 virulence, where the enhancement of small airway ACE-2 expression may be relevant to vaping using nicotine-based e-cigarettes [47]. E-cigarettes have been shown to augment the phenotype, virulence, and inflammatory profile of the Streptococcus pneumoniae pathogen, which may increase bacterial persistence and inflammatory potential [63]. An increase in the platelet-activating factor receptor led to the pneumococcal adherence to vaping, thereby leading to the increased risk of pneumonia [64,65]. McAlinden et al. observed that the pathological biomarkers, such as chemokines IL-8/CXCL8, extracellular matrix proteins, and mitochondrial dysfunction markers, were increased in the cells exposed to e-cigarettes. The research group also found that, with the increase in the use of these devices, there was an increase in oxidative stress, inflammation, infections, and airway remodeling in the lungs [47]. Wang et al. have shown that acute exposure with or without the presence of nicotine in e-cigarettes could result in the inflammation and extracellular matrix (ECM) remodeling/dysregulated repair [66]. The flavoring additive in e-cigarettes has been shown to cause lung inflammation, oxidative stress, and dysregulated repair [67]. A recent study by Merianos et al. has reported that the use of e-cigarettes and cannabis concomitantly is a risk factor for COVID-19-related outcomes [68]. Figure 2 indicates the comparison of the clinical presentation, laboratory findings, imaging, and histopathology results of the EVALI and COVID-19 cases. As can be seen in Figure 2, there are a few differences in the characteristic symptoms of EVALI and COVID-19, but there are some overlapping characteristics that EVALI and COVID-19 share, which trigger the complexity in timely diagnosis and treatment in the current COVID-19 era with the use of e-cigarettes. Many of the respiratory, constitutional, and gastrointestinal symptoms are similar to the EVALI and COVID-19 symptoms, as can be seen in Figure 2 [69,70].

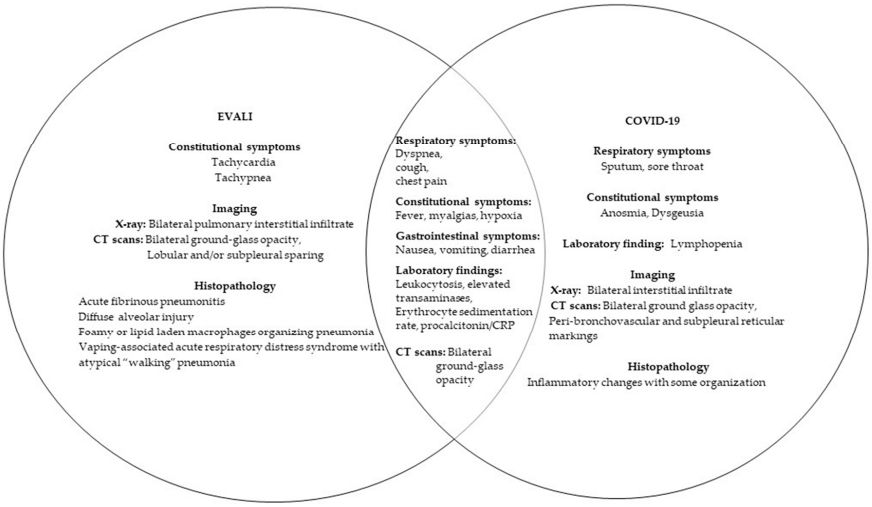

Figure 2. The Respiratory features of vaping product use-associated lung injury (EVALI) and COVID-19 during the COVID-19 pandemic.

6. E-Cigarettes, Microbiome, and COVID-19

The microbiota in different organ systems, including the oral cavity, gut, and lungs, is related to the host's immune tolerance of the viruses and the severity of the viral infection [71,72]. Any alteration in the microbiota species and metabolites may alter the course of respiratory viral infections, thus affecting the function of the lungs [73]. The reduced microbiome diversity, significant change in the microbiome in the nasopharyngeal and upper respiratory tract, high dysbiosis, and complications in the lungs are associated with a loss of microbial genes and metabolic pathways and have been reported in the hospitalized COVID-19 patients [74–79]. E-cigarette vaping compromises airway microbiota and its antiviral responses. There are recent studies that show that the liquids in e-cigarettes can negatively affect the oral microbiome by creating dysbiosis of microbial communities in the mouth. This can trigger an inflammatory response in the host. Earlier studies suggested that flavorings in e-cigarettes could impair the innate immune response in the lungs [80,81]. Furthermore, in vitro studies by Clapp et al. and Gerloff et al. have shown that e-liquids could impair the innate immune response in the lungs [74,78]. There are currently over 7700 different commercially available flavorings [82]. The prolonged inhalation of some flavorings, classified as generally recognized as safe (GRAS) for oral consumption by the United States FDA, could cause irreversible lung disease. The diacetyl, 2,3-pentanedione and acetoin are the two main causative agents that have been studied [83,84]. The data from the in vivo studies further elicit the suppression of macrophage function by the e-liquid flavorings, including aromatic aldehydes, vanillin, and cinnamaldehyde [81]. In the animal model, an increase in cytokine production and inflammation lung injury have been observed with the use of e-cigarettes [71,72]. The COVID-19 virus also propagates with the innate immune response, and the disease is clinically manifested with predictive cytokine and chemokines innate response. Pushalkar et al. and others have reported the abundance of several bacterial taxa, including *Veillonella*, *Haemophilus*, *Fusobacteria*, and *Actinomyces,* in e-cigarette smokers when compared to non-smokers or conventional cigarette users [85]. The elevated level of all these and other bacterial taxa was reported in COVID-19 patients [86,87]. The usage of e-cigarettes leads to oral inflammation and increased secretion of cytokines, which indicates the dysbiosis of specific bacteria. The levels of interleukin IL-6 and IL-1β were reported to be elevated in e-cigarette users [85]. The exposure to aerosol in e-cigarettes triggers the release of cytokines and antimicrobial peptides following inflammation that can alter the oral microbiome [88]. E-cigarettes can modulate approximately 284 genes that can change the metabolic pathways and protein functions. SARS-CoV-1 infects the lung epithelial cells and immune cells to trigger the elevation of Th2 cytokines, causing a strong immune response [89,90]. The elevated levels of serum pro-inflammatory cytokines, such as interleukin-6 and interleukin-10, are a hallmark of COVID-19 infection [91]. The chronic inflammation or baseline activation of the immune system due to EVALI could significantly influence the COVID-19 severity and course of disease progression. The high level of circulating pro-inflammatory cytokines alters the gut microbiota and compromises the intestinal integrity, thereby leading to exacerbation of the illness [92]. COVID-19 patients using e-cigarettes might have an increased effect on the dysbiosis of the oral, gut, and lung microbiome, thus affecting the function of the lungs. There is a need for research studies with relevant case reports on COVID-19 patients with a history of vaping and the extent of dysbiosis of the microbiome in the respiratory system. The data from these studies could further shed light on any correlation between e-cigarettes and COVID-19 cumulative role in the dysbiosis of the microbiome.

7. Conclusions

Current research studies on the different components of e-cigarettes show that they can create a health hazard and potentially contribute to an enhanced COVID-19 infection, thereby posing a health threat specifically to the youth and adolescents, with increasing reports of vaping addiction. In this review, we discussed the severe health effect of the different components of e-cigarettes that may or may not be considered safe for use. For

example, the flavoring in e-cigarettes could impair the innate immune response. Vitamin E acetate and tetrahydrocannabinol are the causal agents of EVALI [21,93]. Some other flavorings, although classified as GRAS, could potentially cause irreversible lung damage by impairing the innate immune response. E-cigarette usage could impair the innate immune response while compromising the airway microbiota. Further, vaping could result in the release of cytokines and antimicrobial peptides through the exposure to aerosol, which could potentially lead to the alteration in the oral microbiome of e-cigarette users.

Unlike COVID-19, EVALI is not caused by any virus. It is a result of the toxicity of different components in e-cigarettes, as discussed in this article. Teens and young adults often consider e-cigarettes less harmful, and as a result, their use has significantly increased over the course of the past decade, unfortunately leading to the increase in the cases of EVALI that make the diagnosis and treatment complicated, specifically during the COVID-19 pandemic [80,94,95]. Patients with EVALI typically have a nonspecific presentation that is characterized by respiratory, constitutional, and gastrointestinal symptoms, which overlap with the COVID-19 disease symptoms. There is growing evidence to show the concomitant use of e-cigarettes with cannabis is a risk factor of complexity in the COVID-19 pandemic. There is an ongoing need for research focusing on the components of e-cigarettes that are continuously being modified with new designs, flavors, and additives. The issue with the overlapping clinical symptoms from e-cigarette or vaping product use-associated lung injury (EVALI) and COVID-19 sometimes leads to incorrect diagnosis and, consequently, wrong treatment regimen. If a patient tests negative for COVID-19, then the symptoms are considered for EVALI testing in a patient using e-cigarettes. Even if a patient tests negative for COVID-19, it is time consuming to obtain a thorough history of a patient consuming e-cigarettes, which oftentimes contain harmful addictive substances. The optimal treatment for EVALI remains unclear, and antibiotics and glucocorticoids with unknown efficacy are prescribed to patients for the treatment of community-acquired pneumonia and clinical symptoms. Therefore, the treatment of patients with or without a COVID-19 infection consuming e-cigarettes adds to the complexity of timely diagnosis and treatment.

The current research sheds light on the overlapping symptoms of vaping and COVID-19 disease, which is a challenge in the timely diagnosis and treatment. With the ongoing mutations in the SARS-CoV-2 virus and failure to obtain substance use patient history, there is a need for further research to manage vaping cessation plans.

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