Thieme

E-cigarette use-associated lung injury (EVALI)

Lungenschädigungen, die mit E-Zigarettennutzung einhergehen (EVALI)

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ABSTRACT

The prevalence of vaping has overtaken conventional cigarettes as the most frequent form of nicotine consumption among 15–24-year olds. There are currently a large number of both legitimate and illegitimate products and suppliers offering more than 8000 different flavors of vape on the market, whose additives are not tested, studied or regulated and whose safety and toxicity profile remains unknown. In vitro studies have demonstrated a dose-dependent decrease in the viability of normal human bronchial epithelial cells after exposure to vapor from electronic vape devices.
Short- and medium-term studies to date indicate that vapor-induced pulmonary lesions are the most serious and commonly reported side effect; such lesions include bilateral ground glass opacities in lung bases with subpleural preservation, bilateral infiltrates, pleural effusion, pneumomediastinum and nodular opacities. Cases of EVALI have been described in patients with daily exposure, as well as in users who reported having been exposed to these substances at least once a month. The most frequently inhaled substances are THC, flavored liquids of unknown content, and nicotine.
The clinical manifestations of dyspnea and cough are the most frequent respiratory symptomatology, in addition to constitutional manifestations such as fever and chills, and gastrointestinal manifestations such as vomiting, nausea, abdominal pain and diarrhea. To these can be added the presence of tachypnea, tachycardia, elevated blood pressure, hypoxia, leukocytosis with neutrophilia and elevated ESR.

ZUSAMMENFASSUNG

Das Dampfen hat die herkömmlichen Zigaretten als häufigste Form des Nikotinkonsums bei den 15- bis 24-Jährigen überholt. Derzeit gibt es auf dem Markt eine Vielzahl von legalen und illegalen Produkten und Anbietern, die mehr als 8000 verschiedene Geschmacksrichtungen anbieten, deren Zusatzstoffe nicht getestet, untersucht oder reguliert werden und deren Sicherheits- und Toxizitätsprofil unbekannt bleibt. In-vitro-Studien haben eine dosisabhängige Abnahme der Lebensfähigkeit normaler menschlicher Bronchialepithelzellen nach Exposition gegenüber Dampf aus elektronischen Verdampfungsgeräten gezeigt.
Bisherige kurz- und mittelfristige Studien deuten darauf hin, dass dampfinduzierte Lungenläsionen die schwerwiegendste und am häufigsten gemeldete Nebenwirkung sind. Zu diesen Läsionen gehören: bilaterale Mattigkeit in der Lun-

genbasis mit subpleuralem Erhalt, bilaterale Infiltrate, Pleuraerguss, Pneumomediastinum und knotige Trübungen. Fälle von EVALI wurden sowohl bei Patienten mit täglicher Exposition als auch bei Anwendern beschrieben, die angaben, diesen Substanzen mindestens einmal im Monat ausgesetzt gewesen zu sein. Die am häufigsten inhalierten Substanzen sind THC, aromatisierte Flüssigkeiten mit unbekanntem Inhalt und Nikotin.

Die klinischen Manifestationen von Dyspnoe und Husten sind die häufigsten respiratorischen Symptome, zusätzlich zu anderen konstitutionellen Manifestationen wie Fieber und Schüttelfrost und anderen gastrointestinalen Manifestationen wie Erbrechen, Übelkeit, Bauchschmerzen und Durchfall; hinzu kommt das Vorhandensein von Tachypnoe, Tachykardie, erhöhtem Blutdruck, Hypoxie, Leukozytose mit Neutrophilie und erhöhter ESR.

Introduction

In 2007 [1], the commercialization of vaping devices officially began, with a marketing promise focused on offering a healthier option than a conventional cigarette, being suitable for consumption by pregnant women, and even being "nicotine-free" because they have a high nicotine content in the form of salt rather than freebase nicotine [2, 3]. This resulted in the mass consumption of vaporizers worldwide; however, the results of studies of their short-, medium-, and long-term adverse effects were not available previous to their sale to the public [3, 4].

In August 2019, the U.S. Centers for Disease Control and Prevention (CDC) initiated an investigation into an outbreak of lung injury related to vape device use, and thereafter, an increasing number of studies have been published demonstrating the negative effects of electronic cigarettes (e-cigarette) use on lung parenchyma [3–6].

The most recent results from global youth tobacco surveys show that the prevalence of knowledge and use of e-cigarettes are highest in the European region (74.6 % and 34.5 %), and in high- and low-income countries (83.6 % and 39.4 %) in the European and American continents [7]. Consumption patterns in the German adolescent population increased from 9.2 % in 2016 to 13.4 % in 2020 [8]. While in young adults aged 18 to 25 years the prevalence of consumption in 2021 was 35.2 % [9]. It is also given evidenced that in Germany e-cigarettes with nicotine are consumed in about 41.6 % of adolescents and 56.0 % of young adults [8].

Lung injury associated with the use of e-cigarettes or vape products (EVALI) is an acute or subacute pathology that can be critical and fatal [10]. Vaping can cause a wide range of adverse health effects due to the consumption of toxic and carcinogenic substances derived from the oxidation of nitrosamine and propylene glycol, compounds used in liquids and flavorings [2, 3].

Vapor-induced pulmonary lesions are the most serious and most reported side effect [1–5, 10, 11]. However, the American Heart Association (AHA) has associated EVALI with short-term involvement of biological systems other than the lung [2, 3]. At the cardiovascular level, acroline has been associated with reduced cardiac contractility, increased blood pressure, elevated risk of arrhythmias, endothelial dysfunction, oxidative stress, and increased platelet aggregation and adhesion [2, 3]. In the central nervous system, behavioral changes, memory alterations and muscle spasms have been reported [3]. In the immune system, the consumption of e-cigarette is linked to the activation of inflammatory chains that reduce the efficacy of the defense system, leaving young patients exposed to other affectations such as influenza, covid-19, and pneumonia [3]. All these short-term effects, although less pronounced compared to cigarette smoking, represent a cost to public health, not to mention that their long-term consequences remain unknown to this day [12].

The present bibliographic research is aimed at describing the association between the use of e-cigarette and lung injury, through the characterization of the main types of substances associated with EVALI, as well as through the identification of radiological findings in tomography and the typical clinical presentation of the injury.

Antecedents and etiology

In August 2019, CDC initiated investigation of an outbreak of lung injury related to vape device use; all patients seen reported using e-cigarettes during the 3 months before the onset of respiratory symptoms [11, 13]. In February 2020, the CDC recorded more than 2800 hospitalizations and 68 deaths related to EVALI; of the reported cases, at least 15% were younger than 18 years of age [13]. Both the CDC and the Food and Drug Administration (FDA) associated 85% of the cases to nicotine and vitamin E acetate consumption, the latter being a thickening agent used especially in vape liquid containing tetrahydrocannabinol (THC) [11]. And once the main causative agent was identified, and because of the considerable decrease in hospitalizations and deaths, the CDC ceased collecting data [11].

Since the decline of EVALI hospitalizations in the United States, few studies have been conducted on the impact of e-cigarette use on its consumers [1]. Currently, research on the prevalence of EVALI in e-cigarette users in different populations around the world is essential because of the possible influence of population-specific epidemiological factors on the development of lung injury.

However, it is now known that the substances that CDC associated with lung injury are not the only ones related to endothelial dysfunction [13–15]. A recent study demonstrated that the main component of e-cigarettes, glycerol, increases neutrophil migration and fibrosis in endotoxin-induced lung injury through activation of p38 mitogen-activated protein kinase [16]. Similarly, in vitro studies have highlighted cytotoxicity, mitochondrial dysfunction, and oxidative stress induced by e-cigarette aerosols without flavoring or flavoring additives [6].

E-cigarettes produce aerosols with particle concentrations similar to or even higher than those emitted by traditional cigarettes [17], the size of these particles depends on the power of the atomizer; the higher the power, the larger the size of the particles reaching the alveoli [1, 3, 17, 18]. It has been observed that in mice exposed to e-cigarette vapor, cytokine concentrations increase in samples after bronchoalveolar lavage, mainly IL-6, MCP-1, IL-1 alpha and IL-13, leading to respiratory stress [14].

A histological study found that when buccal cells are exposed to the liquid-based component of vaporizers, marked cellular alterations occur, including apoptosis, dyskeratosis, and epithelial atrophy [14]. In vitro studies have demonstrated a dose-dependent decrease in the viability of normal human bronchial epithelial bronchial cells after exposure to vapor from electronic vape devices [14, 15]. DNA damage also appears to be dose-dependent, in addition there is a depletion of glutathione stores and an increase in cell membrane permeability [19].

Another cause of EVALI investigated is related to the heating coil of the devices, which is often made of various heavy metals, and traces of these metals have already been found in aerosol samples of vape devices [17]. As the heating coil of the devices heats and cools rapidly, trace metal molecules can reach the liquid base and subsequently be inhaled into the lung epithelium [14]. Metals found in e-cigarette aerosols include aluminum, calcium, copper, chromium, magnesium, lead, tin, and zinc [14]. Exposure to metal-containing vapors has well-established toxicity, including an association with respiratory tract infections and lung cancer [14]. In addition, e-cigarette wicks are often made of silica, the nanoparticles of which have a well-established role in respiratory dysfunction [14].

EVALI and COVID-19

EVALI-reported cases declined rapidly in January 2020, just prior to the onset of the COVID-19 pandemic in the United States [20, 21]. However, confinement led to major changes in people's lifestyle habits, including smoking and vaping increased significantly among adolescents and young adults [22, 23].

And although EVALI may have all but disappeared as a result of increased public awareness of the consequences of vaping and due to the removal of vitamin E acetate from vaping products, recent case reports of EVALI from individual institutions after SARS-CoV-2 vaccination remind clinicians that EVALI should remain in the differential diagnosis of young patients admitted with severe lung injury [20, 21].

The pathophysiology of COVID-19 and EVALI are different; on the one hand, SARS-CoV-2 relies on angiotensin-converting enzyme 2 expressed in the airway epithelium for viral entry [21]. Whereas EVALI represents a fibrotic inflammatory response following inhalation of toxic chemicals contained in vape fluids [21, 24].

During the pandemic, it was observed that COVID-19 infection is five times more likely in regular e-cigarette users and 7 times more likely in users of e-cigarettes and conventional cigarettes [21, 25–27]. This is dependent on both diffuse alveolar damage, chronic interstitial lung disease, and decreased nasal mucosal IgA response caused by EVALI that may increase susceptibility to COVID-19 infection [21, 27, 28].

Vaping compromises the immune response of patients [24]. Vaping has been associated with gene suppression (MR1, NT5E and HRAS) through down-regulation of key transcription factors [28]. Changes in innate defense proteins have also been demonstrated, with a significant increase in elastase and matrix metalloproteinase [29].

The clinical symptoms of EVALI (cough, dyspnea, fever, diarrhea, vomiting) resemble those of COVID-19 and in the context of the pandemic tended to limit diagnostic considerations [20]. Also, thoracic CT findings of EVALI and COVID-19 show significant resemblance [20, 30, 31]. EVALI typically shows bilateral and symmetric ground-glass opacities with or without consolidation predominantly in the lower lobes with subpleural preservation [20, 31–33]. Thoracic CT in COVID-19 shows similar findings, although peripheral and subpleural distribution is frequent. Subpleural preservation should be considered in EVALI rather than in COVID-19 [20, 21, 31].

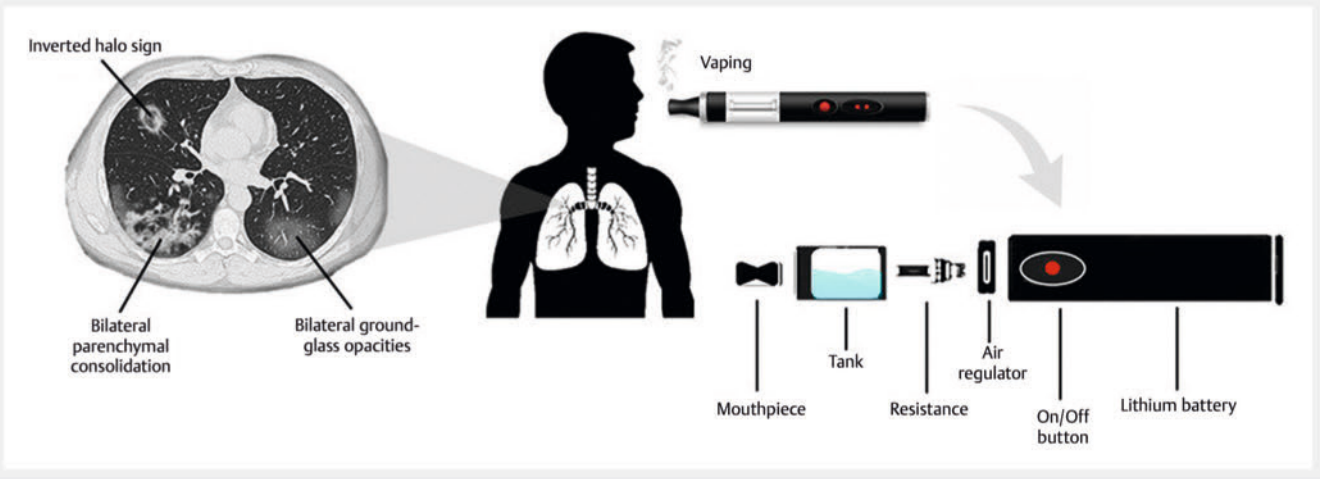
In terms of blood biometry, EVALI presents with leukocytosis, as opposed to the normal or low leukocyte count with associated lymphopenia seen in COVID-19 [20]. Rapid response to glucocorticoids is also considered a sign of EVALI in young patients with extensive pulmonary findings [20].

E-Cigarettes

Electronic cigarettes, also called vapes, vaporizers, or electronic nicotine delivery systems, are products that aerate liquid substances for inhalation [6, 10, 19, 34]. They were originally patented by a Chinese pharmacist in 2003 and introduced to the US market in 2007, and multiple iterations of this device have since been developed [3, 6].

Regardless of the design, each electronic vape device has a common operating system consisting of a lithium battery that acts as an electrical source, connected to a vaporization chamber containing the aerolizer [10, 17, 18]. The airflow produced when the user inhales through the device's mouthpiece turns on a sensor that activates the atomizer (resistance) that vaporizes the liquid substance in a small reservoir, thus supplying atomized vape liquid to the lungs [17] (▶ **Fig. 1**).

Liquid substances added to e-cigarettes contain at least three main ingredients: psychoactive agents, solvents, and flavoring compounds [10]. The most commonly used psychoactives are nicotine, THC, or both [5, 6, 18, 19, 35], and the main solvents are propylene glycol and vegetable glycerin [10]. Currently, between 8000 and 15,000 commercially available flavoring agents with uncertain toxicological profiles are described [10, 17].



▶ **Fig. 1** E-cigarette components and their effects on lung parenchyma observed in CT.

Substances used in E-Cigarette and Vape Devices

Liquids used in vaping devices contain flavorings such as diacetyl, which has previously been associated with severe bronchiolitis obliterans, known as "popcorn lung" in food industry workers [14, 15, 17]. Diacetyl is known to down-regulate the expression of cilia-related genes and decrease the total number of hair cells [14]. A recent study detected the presence of diacetyl in 39 of 51 brands of e-cigarettes tested, including in flavors such as watermelon, peach, and pomegranate [14]. Although no cases of bronchiolitis obliterans associated with e-cigarette use have been reported, given the toxicity of diacetyl inhalation, the risk is likely to exist [17, 18].

Substances used in e-cigarettes and vape devices also contain terpenes, which have been associated with pulmonary necrosis in pediatric patients [14]. The AHA has recently associated acroline, an aldehyde also commonly used in vape fluids, with cardiovascular system disorders [17, 25]. The vapor of cherry-flavored e-cigarettes contains benzaldehyde, a substance also present in the smoke of conventional cigarettes [14]. Benzaldehyde is a known respiratory irritant, which can cause airway inflammation and edema [14].

Liquid-based solvents, such as propylene glycol and glycerin, are also not exempt from toxicity, since, at high temperatures, both decompose into formaldehyde and acetaldehyde, which are also common toxicants in cigarette smoke [14, 15]. Formaldehyde has been associated with mucosal irritation, bronchitis, pneumonia, and pulmonary edema; in addition, the lipid content of vegetable glycerin may play a role in the development of exogenous lipoid pneumonia [14, 17].

Vitamin E acetate is a thickening agent used especially in THC-containing vape liquid, and is the substance identified by the CDC as responsible for the 2019 EVALI outbreak [10] in the United States. However, the use of this substance in liquid manufacturing is not well regulated, in addition to recent research not holding it responsible as the sole substance causing acute lung injury and other systemic damage [10, 18]. Analysis of fluid cartridge remnants has more closely linked vitamin E acetate to EVALI, as that substance has been found in bronchoalveolar lavage fluid samples [5, 19, 35, 36]. The pathophysiological mechanism linking vitamin E acetate to lung injury may derive from its ability to be absorbed by lung tissue, leading to its accumulation and interference with surfactant [35].

In addition to the damage produced by the harmful compounds derived from the thermal decomposition of vitamin E acetate, this compound is also incorporated into the natural phospholipids that compose the surfactant, increasing its permeability and decreasing its function, which increases the surface tension of the alveoli, in addition to the possibility of provoking an inflammatory cascade in the lung tissue [14]. So far, the amount of exposure necessary to cause EVALI is unclear [35]. On the other hand, researchers do not exclude the possibility of an alternative etiology or multiple agents involved so far unknown [5, 35, 36].

EVALI

EVALI is the syndrome associated with acute lung injury secondary to the use of electronic vaping devices [3–6, 10, 17–19, 35, 37]. It is characterized by an acute pulmonary inflammatory process resulting in alveolar collapse and severe impairment of gas exchange secondary to alveolar-capillary membrane damage due to disruption of pulmonary endothelial and epithelial barriers by exposure to toxic vapor particles from vaping fluids [38]. Such exposure leads to increased permeability, excessive fluid transudation, recruitment of neutrophils and monocytes into the alveoli, and release of proinflammatory cytokines [19].

The clinical presentation of EVALI encompasses a syndrome of respiratory, gastrointestinal, and constitutional symptoms [37, 39, 40–44]. Many patients with EVALI may present with pneumonia-like symptoms with severe sepsis, in addition to being dehydrated from severe gastrointestinal fluid losses and insensible losses secondary to fever [35].

Anna Tzortzi, et al., [45], in their systematic review study on lung injury associated with vaping, revealed that, out of a total

of 133 publications and 238 individuals analyzed, the most frequent diagnosis in e-cigarette users was EVALI (26%), in addition to other related diagnoses such as EVALI and secondary pneumothorax (2%) and EVALI associated with asthma (2%).

The most frequently used substances in the vapor of e-cigarette liquids in patients with confirmed EVALI are: THC in most cases, followed by nicotine, simultaneous use of THC and nicotine, unspecified liquids or liquids of unknown origin, vitamin E acetate, and CBD consumption independently or associated with one or more of the above substances [6, 19, 37, 39–43, 45].

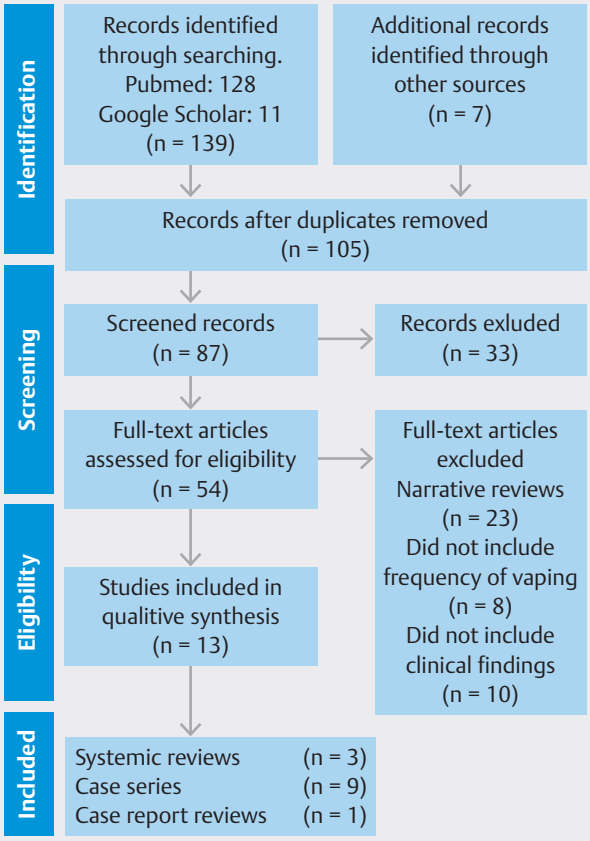
Similarly, the frequency of consumption of these compounds has a direct influence on the development of the disease; thus, in most records of patients with EVALI who declared the type of substances they consumed, there is a record of daily consumption [19, 39, 41, 43]; however, cases of EVALI have also been documented in patients who reported inhaling these compounds once or several times a month, for a period of less than a year [19, 39, 43, 44].

Regarding radiological findings, 94% of patients have abnormalities on chest radiography, these abnormalities include nonspecific bilateral opacities or infiltrates [17]. The most common radiological findings in CT (▶ **Fig. 1**) found in several investigations have been bilateral diffuse and basilar ground-glass opacities with subpleural preservation [15, 17–19, 37, 39, 43–48], in addition to interlobular septal thickening, bilateral parenchymal consolidation, bilateral pleural effusions, pneumomediastinum, mediastinal/hilar lymphadenopathy, pulmonary edema, emphysema, multiple nodules, fibrosis, pulmonary emboli and inverted halo sign [6, 19, 39, 42–45, 47, 48].

Respiratory clinical manifestations are the most frequent [34, 41], followed by constitutional and gastrointestinal symptoms [6, 34, 37, 39, 41–44, 47]. The most frequent respiratory manifestations are dyspnea and cough [6, 19, 34, 37–44, 47, 48], also: chest pain, bilateral diffuse crackles, bilateral wheezing, rhonchi, use of accessory musculature and hemoptysis [16, 19, 37, 39, 42–45, 47, 48]. Constitutional symptoms are: chills, fatigue, fever, weight loss, headache, myalgia, diaphoresis [35, 37, 42, 43]. Gastrointestinal signs are: nausea, vomiting, diarrhea and abdominal pain [37, 39, 42–45, 47].

Frequently altered vital signs are temperature ≥ 38° C [19, 37, 39, 40, 43, 44, 47], tachypnea > 20 rpm, tachycardia > 100 bpm, blood pressure > 120/80 mmHg, O_2 saturation < 95% [37, 43, 44, 47]. Laboratory examination parameters usually include leukocytes > 11,000 cells/mm^3 with neutrophils > 60%, ESR > 30 mm/h, CRP > 10 mg/L, procalcitonin > 0.07 ng/ml, LDH > 280 U/L, Pro BNP > 125 pg/mL [19, 37, 40, 43, 44]; in addition, respiratory alkalosis with pH ≥ 7.45 and $PaCO_2$ < 35 mmHg [19]. Creatinine elevation is infrequent, but may occur due to prerenal causes such as hypovolemia due to dehydration [41].

Lukasz Antoniewicz, et al., [49], in their randomized, double-blind, crossover study, found that inhalation of e-cigarette aerosols for 30 minutes, both with and without nicotine, increases the fraction of exhaled nitric oxide and decreases vital capacity, suggesting immediate effects of non-nicotine chemicals on lung function and inflammation. E-cigarettes with nicotine cause an increase in airflow resistance 30 min after exposure, indicating obstruction of the conducting airways. The fraction of exhaled nitric oxide increased at 2 hours, and vital capacity continued to decrease after 2 hours.



▶ **Fig. 2** Flowchart of the process of identification and selection of literature.

Chaumont Martin, et al., [38], in their randomized, double-blind, three-period crossover study in 30 regular e-cigarette users, observed that forced expiratory flow (FEF-25%) was higher after 15 days of e-cigarette use (5 days with nicotine, followed by 5 days without nicotine and, finally, 5 days without vaping). All other parameters of lung function and diffusion capacities were not modified in any of the 3 sessions. In addition, short-term cessation of vaping in regular users was observed to increase anti-inflammatory protein CC16 and FEF-25%, suggesting a slight improvement in lung health.

The ▶ **Table 1** describes the association of lung injury and e-cigarette use as a function of vape fluid components, frequency of vaping, and radiological and clinical findings. For the information selection process, the literature reviewed was hierarchized through processes of by identification, selection, eligibility, and inclusion of the literature, as described in the following flow diagram (▶ **Fig. 2**).

▶ **Table 1** Association of lung injury and use of e-cigarettes and vape devices.

Author/ Year/ Country	Title	No. of studies or participants	Substances used and frequency of vaping in patients with EVALI	Associated radiological findings (CT)	Clinical presentation of patients
Marrocco A., et al., 2022; EE.UU [19]	"E-cigarette vaping associated acute lung injury (EVALI): state of Science and future research needs"	186 studies (161 medical reports, 85 case reports, 85 clinical cases, 59 case series, 17 epidemiological reports, 25 review articles)	CBD: 2 % (225/11 ,244) THC: 34 % (3823/11,244) Nicotine: 17 % (1911/11,244) CBD and THC: 8 % (900/11,244) CBD and Nicotine: 4 % (450/11,244) THC and Nicotine: 25 % (2811/11,244) CBD, THC and Nicotine: 10 % (1124/11,244) Daily: 53 % (1445/2727) 2–3 times/week: 25 % (691/2727) Few times a month: 6 % (164/2727) 1 time/month or less: 16 % (427/2727)	▪ Bilateral ground-glass opacities (115 studies) ▪ Bilateral parenchymal consolidation (46 studies) ▪ Bilateral pleural effusions (25 studies) ▪ Bilateral pulmonary interstitial infiltrates (34 studies) ▪ Interlobular septal thickening (47 studies) ▪ Fibrotic features (14 studies) ▪ Pneumomediastinum (18 studies) ▪ Pulmonary emboli (3 studies) ▪ Mediastinal/hilar lymphadenopathy (18 studies) ▪ Inverted halo sign (2 studies)	**Respiratory:** ▪ Bilateral diffuse crackles (29 studies) ▪ Bilateral wheezing (16 studies) ▪ Roncus, use of accessory musculature, decreased breath sounds in both lung bases (21 studies) **Vital signs:** ▪ SaO_2 < 95 % on room air or with oxygen supplementation (78 studies) ▪ Fever ≥ 38° C (50 studies) ▪ Tachypnea > 20 rpm (66 studies) ▪ Tachycardia > 100 bpm (61 studies) ▪ Blood pressure > 120/80 mmHg (20 studies) ▪ **Laboratory:** ▪ Leukocytes > 11,000 cells/mm^3 with neutrophils > 60 % (87 studies) ▪ Inflammatory markers (ESR: > 30 mm/h, CRP: > 10 mg/L, procalcitonin > 0.07 ng/mL, LDH > 280 U/L, NT-proBNP > 125 pg/mL) (64 studies) ▪ Respiratory alkalosis with pH ≥ 7.45 and PCO_2 < 35 mmHg (20 studies)
Kligerman S, et al., 2021; EE.UU [39]	"CT Findings and Patterns of Electronic Cigarette or Vaping Product Use-Associated Lung Injury (EVALI)"	160 patients (79.4 % men, 20.6 % women) Mean age: 28.2 ± 11.2 (15–68) years old	THC: 48.1 % (68/160) Nicotine: 9.4 % (15/160) THC and Nicotine: 42.5 % (77/160) Daily: 57.5 % (92/160) Multiple times a week: 13.8 % (22/160) 1 time/week or less: 4.4 % (7/160) Data not available: 24.4 % (39/160)	▪ Ground-glass opacities in lower lobes, with subpleural opacity (78.1 %), lobar (58.4%), or peribronchovascular preservation (40 %) ▪ Septal thickening (50.6 %) ▪ Lymphadenopathy (63.1 %) ▪ Centrolobulillary nodules (36.3 %) ▪ Thickening of the alveolar wall (11.9 %) ▪ Emphysema (7.5 %) ▪ Bronchiolar dilatation (5.6 %) ▪ Pulmonary hemorrhage (3.8 %) ▪ Pneumomediastinum (3.7 %) ▪ Inverted halo sign (3.1 %) ▪ Pneumothorax (0.6 %)	**Respiratory:** ▪ Dyspnea (81.9 %) ▪ Cough (35 %) ▪ Hemoptysis (7.5 %) **Gastrointestinal:** ▪ Nausea/vomiting (47.5 %) ▪ Diarrhea (20.6 %) **Vital signs:** ▪ Fever ≥38° C (63.4 %)

▶ **Table 1** (Continuation)

Author/ Year/ Country	Title	No. of studies or participants	Substances used and frequency of vaping in patients with EVALI	Associated radiological findings (CT)	Clinical presentation of patients
Sreedharan S, et al., 2021; EE.UU [48]	"Radiological findings of e-cigarette or vaping product use associated lung injury"	30 studies with 184 patients (76.6 % men, 23.4 % women) Mean age: 24.5 years old	THC: 65.17 % (112/172) Nicotine: 62.21 % (107/172) CBD: 9.50 % (16/172) Cannabis: 2.25 % (4/172) –	▪ Bilateral infiltrates (36.9 %) ▪ Bilateral ground-glass opacities (33.3 %) ▪ Subpleural opacification (17.3 %) ▪ Pleural effusions (14.83 %) ▪ Centrolobular nodularity (7.7 %) ▪ Mediastinal lymphadenopathy (7.1 %) ▪ Thickening of the alveolar wall (4.2 %) ▪ Pneumothorax (5.9 %) ▪ Pneumomediastinum: (3 %) ▪ Bronchiectasis (1.8 %)	–
Blagev D, et al., 2019; EE.UU [44]	"Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping"	60 patients (80 % men, 20 % women) Mean age: 27 (22–36) years old	Nicotine: 67 % (40/60) Nicotine only: 17 % (10/60) THC: 78 % (47/60) THC only: 30 % (18/60) THC and Nicotine: 48 % (29/60) CBD: 5 % (4/60) <1 year: 43 % (10/23) 1- <2 years: 17 % (4/23) 2 - <3 years: 26 % (6/23) ≥3 years: 13 % (3/23)	▪ Bilateral ground-glass opacities in lung bases (90 %) ▪ Bronchial wall thickening (16.7 %)	**Respiratory:** ▪ Dyspnea (85 %) ▪ Cough (78 %) ▪ Hemoptysis (12 %) Constitutional: ▪ Chills (48 %) ▪ Fatigue (48 %) **Vital signs:** ▪ Fever ≥ 38° C (57 %) ▪ Tachycardia > 100 bpm (83 %) ▪ Tachypnea > 20 rpm: (72 %) ▪ SaO_2 < 88% (52 %) **Gastrointestinal:** ▪ Nausea (75 %) ▪ Vomiting (72 %) ▪ Abdominal pain (47 %) **Laboratory:** ▪ Leukocytosis > 11,000 cells/ mm^3 (77 %) ▪ ESR > 30 mm/h (100 %)
Layden J, et al., 2020; EE.UU [37]	"Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin – Final report"	98 patients (79 % male 21 % female) Mean age: 21 (15–53) years old	Nicotine: 73 % (59/81) Nicotine only: 11 % (9/81) THC: 89 % (72/81) THC only: 27 % (22/81) Nicotine and THC: 60 % (49/81) CBD: 9 % (7/78) –	▪ Bilateral infiltrates in middle and lower lobes (100 %)	**Respiratory:** ▪ Dyspnea (85 %) ▪ Cough (85 %) ▪ Hemoptysis (8 %) **Gastrointestinal:** ▪ Nausea (66 %) ▪ Vomiting (61 %) ▪ Abdominal pain (34 %) **Constitutional:** ▪ Chills (60 %) ▪ Fatigue (47 %) **Vital signs:** ▪ Fever ≥ 38° C (33 %) ▪ Tachypnea > 20 rpm: (43 %) ▪ Tachycardia > 100 bpm: (63 %) ▪ SaO_2 < 88 % (25 %) **Laboratory:** ▪ Leukocytosis > 11,000 cells/ mm^3 (83 %) ▪ Neutrophils > 80 % (91 %) ▪ ESR > 30 mm/h (90 %)

▶ **Table 1** (Continuation)

Author/ Year/ Country	Title	No. of studies or participants	Substances used and frequency of vaping in patients with EVALI	Associated radiological findings (CT)	Clinical presentation of patients
Zou R, et al., 2020; EEUU [40]	"Clinical Characterización of E-Cigarette, or Vaping, Product Use-Associated Lung Injury in 36 Patients in Pittsburgh, Pennsylvania"	36 patients (78 % male, 22 % female) Mean age: 21 (19–30.5) years old	THC 88 % (32/36) Data not available: 12 % (4/36) –	Bilateral opacities in ground glass 97 % (28/29)	**Vital signs:** ▪ Fever: 38.1 (37.2–38.7) °C ▪ SaO_2: 94 (90–98) % **Laboratory:** ▪ Leukocytosis: 13.5 (11.4–17.5) cells/mm^3 ▪ Neutrophils 89 (81.2–93) cells/mm^3
Adkins S, et al., 2020; EE.UU [41]	"Demographics, Substance Use Behaviors, and Clinical Characteristics of adolescents with e-Cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI) in the United States in 2019"	2155 patients 360 adolescent patients (13–17) years old 859 young adult patients (18–24) years of age 936 adult patients (25–49) years old	Nicotine and THC: (83.2 %) 1793/2155 Daily: (64.36 %) 1387/2155	Bilateral opacities in ground glass (100 %)	**Respiratory:** 71 % **Gastrointestinal:** 67.4 % **Constitutional:** 70.67 % **Gastrointestinal or constitutional, but not respiratory:** 68.54 %
Artunduaga M, et al., 2020; EE.UU [42]	"Pediatric Chest Radiographic and CT Findings of Electronic Cigarette or Vaping Product Use – associated Lung Injury (EVALI)"	14 patients (50 % male, 50 % female) Mean age: 16 (13–18) years old.	Nicotine: 7.14 % (1/14) THC: 64.29 % (9/14) Nicotine and THC: 28.57 % (4/14) –	▪ Bilateral opacities in ground glass (100 %) ▪ Consolidations (64 %) ▪ Interlobular septal thickening (14 %) ▪ Subpleural preservation (79 %) ▪ Inverted halo sign (36 %)	**Respiratory:** Dyspnea: 14.86 % Cough: 86 % Increased work of breathing: 43 % **Gastrointestinal:** Vomiting: 86 % Nausea: 71 % Diarrhea: 14.64 % Abdominal pain: 43 % **Constitutional:** Fever: 14.86 % Weight loss: 14.43 % Fatigue: 14.43 % Chills: 14.21 %
Chatham K, et al., 2019; EE.UU [34]	"Characteristics of Hospitalized and Nonhospitalized Patients in a Nationwide Outbreak of E-cigarette, or Vaping, Products Use-Associated Lung Injury"	1905 patients (68 % male, 32 % female) Mean age: 24 (13–78) years old.	Nicotine: 61 % (723/1184) Nicotine only: 13 % (150/1184) THC: 83 % (984/1184) THC only: 35% (411/1184) Nicotine and THC: 48 % (573/1184) None: 4 % (50/1184) –	Bilateral opacities in ground glass 100% (28/28) not hospitalized	**Respiratory:** 85 % (47/55) **Gastrointestinal:** 57 % (27/47) **Constitutional:** 76 % (51/54) **(Non-hospitalized)**

▶ **Table 1** (Continuation)

Author/ Year/ Country	Title	No. of studies or participants	Substances used and frequency of vaping in patients with EVALI	Associated radiological findings (CT)	Clinical presentation of patients
Heinzerling A, et al., 2020: EE.UU [43]	"Severe Lung Injury Associated With Use of e-Cigarette, or Vaping, Products-California, 2019"	160 patients (62 % men, 38 % women) Mean age: 27 years (14–70) years old	THC: 83 % (71/86) Nicotine: 56 % (47/86) CBD: 48 % (40/86) Vitamin E or Vitamin E Acetate and THC: 84 % (20/24) ≥ 1 time daily 73 % (63/86) ≥ 5 times daily 35 % (30/86)	▪ Bilateral infiltrations or opacities (94 %) 100/106 ▪ Bilateral opacities in ground glass (49 %) 52/106 ▪ Pulmonary edema (12 %) 13/106 ▪ Subpleural effusion: (7 %) 7/106	**Respiratory:** ▪ Cough: 84 % (89/106) ▪ Dyspnea: 82 % (87/106) ▪ Hemoptysis: 9 % (9/106) **Gastrointestinal:** ▪ Nausea: 61 % (65/106) ▪ Vomiting: 56 % (59/106) ▪ Abdominal pain: 31 % (33/106) ▪ Diarrhea: 34 % (36/106) **Constitutional:** ▪ Chills: 76 % (80/106) ▪ Myalgia: 23 % (24/106) ▪ Headache: 26 % (27/106) ▪ Weight loss: 18 % (80/106) ▪ Diaphoresis: 16 % (80/106) **Vital signs:** ▪ Temperature ≥ 38° C: 39 % (41/106) ▪ Heart rate >90 bpm: 89 % (94/106) ▪ Respiratory rate 20 rpm: 65 % (69/106) ▪ SaO_2 < 93 %: 69 % (73/106) **Laboratory:** ▪ Leukocytosis > 12,000 cells/mm^3: 81 % (86/106) ▪ Neutrophils > 80%: 81% (86/106) ▪ ESR > 30 mm/h: 95 % (35/37)
Jonas A, Raj R. 2020; EE.UU [6]	"Vaping-Related Acute Parenchymal Lung Injury"	169 studies	THC: 80 % (160/200) Nicotine: 60 % (120/200) CBD: 7 % (14/200) –	▪ Bilateral opacities in ground glass (80 %) 160/200 ▪ Bilateral infiltrates: (24 %) 48/200 ▪ Pleural effusion: (9 %) 18/200 ▪ Pneumomediastinum: (5 %) 10/200	**Respiratory:** 95 % (190/200) ▪ Dyspnea: 81 % (162/200) ▪ Cough: 75 % (150/200) ▪ Hemoptysis: 9 % (18/200) **Gastrointestinal:** 73 % (146/200) **Constitutional:** 87 % (174/200)
Kalininskiy A, et al., 2019; EE.UU [47]	"E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach"	12 patients (58% men and 42 % women) Mean age: 27 (21–35) years old	THC 92 % (11/12) Nicotine: 58 % (11/12) Nicotine only 8 % (1/12) CBD: 8 % (1/12) –	▪ Subpleural opacification (64 %) 7/12 ▪ Bilateral ground-glass opacification: (100 %) 12/12 ▪ Pleural effusions: (9 %) 1/12 ▪ Fibrotic features (reticulation, bronchiectasis, honeycombing): (18 %) 2/12 ▪ Mediastinal lymphadenopathy: (27 %) 3/12	**Respiratory** ▪ Dyspnea: 91 % (10/11) ▪ Cough: 82 % (9/11) ▪ Pleuritic pain: 55 % (6/11) ▪ Hemoptysis: 9 % (1/11) Constitutional symptoms: ▪ Malaise: 75 % (9/12) ▪ Diaphoresis: 42 % (5/12) ▪ Chills: 25 % (3/12) ▪ Myalgias: 17 % (2/12) **Gastrointestinal symptoms:** ▪ Vomiting: 91 % (10/11) ▪ Nausea: 64 % (7/11) ▪ Abdominal pain: 27 % (3/11) ▪ Diarrhea: 27 % (3/11) **Vital signs:** ▪ Temperature ≥ 38° C: 75 % (9/12) ▪ Heart rate >100 bpm: 67% (8/12) ▪ Respiratory rate 20 rpm: 25 % (3/12) ▪ SaO_2 < 94%: 75 % (9/12)

▶ **Table 1** (Continuation)

Author/ Year/ Country	Title	No. of studies or participants	Substances used and frequency of vaping in patients with EVALI	Associated radiological findings (CT)	Clinical presentation of patients
Tzortzi A, et al., 2020; EE.UU [45]	"A Systematic Literature Review of E-Cigarette-Related Illness and Injury: Just for the Respirologist"	133 studies with 238 patients (69 % men and 31 % women)	CBD or THC: 36 % (86/238) CBD or THC and Nicotine: 10 % (24/238) CBD or THC and Unknown Liquid: 10 % (24/238) Nicotine: 3 % (8/238) Unknown or Unspecified Liquid: 40 % (96/238)	▪ Bilateral opacities in ground glass (38 %) 18/52 ▪ Bilateral opacities in ground glass and consolidation (12 %) 6/52 ▪ Opacities (10 %) 5/52 ▪ Multiple nodules (6 %) 4/52 ▪ Bilateral ground-glass opacities plus multiple nodules (6 %) 4/52 ▪ Other (28 %) 15/52	**Respiratory:** ▪ Dyspnea: 83 % ▪ Cough: 59 % ▪ Dyspnea and cough: 53 % ▪ Chest pain: 22 % ▪ Hemoptysis: 9 % ▪ Respiratory arrest: 5 % **Vital signs:** ▪ Fever: 40 % **Gastrointestinal:** 26 %

CT: computed tomography. THC: tetrahydrocannabinol. CBD: Cannabidiol. SaO_2: oxygen saturation. ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein. NT-proBNP: N- terminal pro-B-type natriuretic peptide. LDH: lactate dehydrogenase. PCO_2: partial pressure of carbon dioxide. pH: potential of hydrogen

Treatment

Remembering that the best long-term treatment is smoking cessation, patients with a confirmed diagnosis of EVALI who are evaluated for respiratory, gastrointestinal or constitutional symptoms may be indicated for outpatient treatment, as long as they have a normal oxygen saturation ≥ 95 %, do not present respiratory distress, do not have comorbidities that could compromise pulmonary reserve, have social support systems that ensure follow-up within 24–48 hours of initial assessment, have reliable access to health care, and can seek medical attention promptly if respiratory symptoms worsen [50, 51]. If the patient fails to comply with any of these requirements, hospital admission should be made [52].

In terms of medical treatment, EVALI should be considered a diagnosis of exclusion, so empirical treatment with corticosteroids, antibiotics and antivirals is warranted in patients with severe pulmonary and extrapulmonary manifestations [50].

Corticosteroids produce a slowing of the inflammatory response [37, 53]. It has been observed that treatment with oral prednisone at doses of 40 to 60 mg causes an improvement in respiratory symptoms 48 hours after administration [53, 54].

Early antibiotic treatment for community-acquired pneumonia should be in accordance with guidelines established by each region, and should be considered due to overlapping signs and symptoms of these conditions [50]. During the influenza season, influenza should be considered in all patients with suspected EVALI, and antivirals should also be considered in accordance with guidelines established by each region [52].

Hospitalized patients should be documented as clinically stable for 24–48 hours prior to discharge [50]. After discharge they should have a follow-up visit within 48 hours [51]. Follow-up evaluation should include: clinical assessment, ensuring compliance with medication regimens such as tapering corticosteroids if these were prescribed at discharge, reinforcing the importance of abstinence from use of e-cigarettes or vape products, and connecting patients to necessary social, mental health, and substance use disorder resources [50].

Long-term pulmonary follow-up should generally be performed in the 2–4 weeks after discharge following completion of corticosteroid tapering to assess pulmonary function and resolution of radiographic findings [52]. Additional follow-up testing should be performed 1–2 months after discharge and may include: spirometry, pulmonary diffusing capacity for carbon monoxide and a chest X-ray or chest CT scan [50].

Conclusion

In conclusion, EVALI is characterized by an acute inflammatory pulmonary process secondary to damage to the alveolar-capillary membrane, which causes the collapse of the alveoli and a serious alteration of gas exchange. This inflammation is a response directly proportional to the exposure of the pulmonary endothelium both to the toxicity of the substances contained in the liquids of electronic cigarettes and to the frequency and time of exposure to them. In light of the documentation of cases of lung injury associated with the use of e-cigarettes or vaping, the use of these devices should not be recommended as a smoking cessation tool; abstinence from all vaping devices is the best way to prevent primary and recurrent secondary lung injury.

Conflict of interest

The authors declare that they have no conflict of interest.

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