VpALI--Vaping-related Acute Lung Injury: A New Killer Around the Block.

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Abstract

The use of electronic cigarettes, known as vaping, has become increasingly popular over the past decade, particularly in the adolescent and young adult population, often exposing users to harmful chemicals. Vaping has been associated with a heterogeneous group of pulmonary disease. Recently, a multistate epidemic has emerged surrounding vaping-related acute lung injury, prompting the Centers for Disease Control and Prevention to list an official health advisory. In this review, we describe the current literature on the epidemiology, clinical significance, as well as recommended evaluation and treatment of vaping-related lung injury.

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Over the past decade, cigarette smoking in the United States has continued to decline. (1) There are multiple factors contributing to this descent, including the use of electronic cigarettes (ECs). Their use is known as vaping; and since their introduction to the US market in 2007, (2) ECs have been often advertised as a safe alternative to tobacco smoking and for smoking cessation. (3,4) This, at least in part, contributed to an increase in their popularity and acceptance among teenagers and young adults, (5) leading to an increase in consumers, not only in the United States but also in other countries. (6) Interestingly, their use has been associated with an increased intention to smoke cigarettes in the nonsmoking population, (7,8) with a subsequent association with cigarette smoking initiation. (9)

Approximately 3.7% of US adults are users of ECs, with the same prevalence for men and women. (10) In 2016, the Food and Drug Administration announced its final rule to regulate ECs under the Family Smoking Prevention and Tobacco Control Act. In 2017, vaping was the most common use of any tobacco-like product in adolescents, with an estimated 1.3 million new adolescents using ECs in 2018. (11) In December 2018, the US Surgeon General declared the ECs an epidemic among youth, (12) affecting more than 3.6 million US youth, with 1 of 5 high school students and 1 of 20 middle school students using EC. (13)

ANATOMY OF THE ELECTRONIC CIGARRETTE

Electronic cigarettes are battery-powered devices that allow users to inhale aerosolized liquid. The aerosol comes from the heating-process of a solution called e-liquid or vape juice that may or may not contain nicotine as well as other compounds that include propylene glycol, vegetable glycerin, flavoring agents, and additives.

These electronic devices come in different sizes and styles, ranging from those that resemble traditional cigarettes to vape pens, e-hookahs, box modes, and advanced personal vaporizers, but the structure is essentially the same: a variable-voltage battery, a heating element or heating coil that functions as an atomizer converting the e-liquid into the aerosol, a reservoir or vaporizer chamber for the e-liquid, and a mouthpiece (Figure).

The e-liquid is rapidly heated when exposed to coils made from metal alloys that can contain iron, chromium, carbon, nickel, or other metals. (14) When heating occurs, the e-liquid is exposed to high temperatures creating a suspension containing fine particles of the e-liquid--denominated aerosol; this has been inaccurately called vapor, which is the gaseous state of a substance. (15)

EFFECT OF VAPING ON THE LUNGS

Despite the perception of being less harmful than cigarettes, (16) ECs are far from being harmless. Their use is associated with adverse health consequences that not only affect the lungs but also have a negative effect on the cardiovascular system. (17) The variety of detrimental effects ranges from thermal injuries related to the malfunction of the electronic device (18) to a recent cluster of respiratory illnesses suspected to be associated with the use of ECs. (19,20)

When exposed to high temperatures, propylene glycol and vegetable glycerin decompose, generating potentially harmful carbonyl compounds such as aldehydes including acrolein, formaldehyde, and acetaldehyde. (21,22) Both the solvent and the battery output voltage significantly affect levels of carbonyl compounds found in the aerosol. These compounds have been implicated in the development of oxidative stress and release of inflammatory mediators, (23,24) increasing cardiovascular risk (25-27) and platelet function alteration, (28) airway epithelial injury, and creating disturbances in gas exchange function. (29) Furthermore, repeated exposure of the heating element to high temperatures allows emission of nanoparticles with a potential harmful effect on the respiratory system.

It is estimated that more than 7000 eliquid flavors are available in the market, (31) making these products more attractive to a young population that has the perception of being less harmful than conventional cigarettes. (32) Exposure to flavoring agents is associated with disturbances in the epithelial barrier and cellular function of the lungs, (33-35) including reduction in the ciliary beat frequency leading to diminished mucociliary clearance and impairing mitochondrial function. (36) In addition, aerosol components can alter airway cytokines as well as macrophages and neutrophil antimicrobial function while increasing the virulence of colonizing bacteria. (37)

The concentration of nicotine is variable in ECs; however, there are reports of presence of nicotine in nicotine-free products, (38,39) with an additional risk of developing nicotine addiction in nonnicotine users. Also, there are reports of mislabeling concentration of nicotine with an increment higher than 20%. (40) Moreover, e-liquids without nicotine can still trigger an inflammatory response by monocytes mediated by the production of reactive oxygen species, leading to potential tissue damage. (41)

VAPING AND CANNABIS

The relationship between cannabis and ECs is an emergent public health conundrum. In 2017, it was estimated that 3 million people 12 years or older used marijuana for the first time; this number was higher than in previous years. (42) Available data from the Centers for Disease Control and Prevention's (CDC's) National Center for Chronic Disease Prevention and Health Promotion suggested that ECs are associated not only with the use of other tobacco products but also with alcohol and other substances, such as marijuana. (45) The relationship between ECs and cannabis is not uncommon among high school students who are cannabis or EC users. (44) Overall, this may underline a misperception of the potential risks associated with its consumption. (43) Unfortunately, ECs provide an alternative gateway for cannabis use as either a dry herb or more complex cannabinoid concentrates such as butane hash oil and wax. (46)

The act of inhaling the combustion of these cannabinoid concentrates is known as dabbing. The result is a faster hallucinogen effect as a consequence of a higher concentration of tetrahydrocannabinol (THC) than that of the conventional forms of cannabis. In a study, Loflin and Earleywine (47) found an increase in tolerance and withdrawal when using this type of cannabinoid compared with the traditional inhalation of cannabis, which raises the question about a potentially more addictive effect. It is estimated that in the United States, 1 of 10 high school students ever vaped cannabis (48); however, the prevalence of ECs and cannabis remains unknown. In the adult population, justification to the combination of ECs and cannabis includes better taste, personal opinion that it is healthier, easier to conceal, lack of strong smell, convenience, and more potent hallucinogen effect. (49)

The detrimental effects of cannabis are multiple. Exposure to cannabis inhalation has a negative effect on different cellular immune mechanisms, (50,51) increasing predisposition for respiratory tract infections (52) including pulmonary aspergillosis in the susceptible population (53,55) and also enhances eosinophilic recruitment (56) with concomitant reports of eosinophilic pneumonia after recreational marijuana exposure. (57) Cannabis consumption has been associated with voice disorders, (58) pulmonary barotrauma, (39,60) cystic lung disease, (61,62) and emphysema in the young population. (63) Moreover, chronic use has a 2-fold increase in the risk of lung cancer. (64)

With the emerging acceptance of cannabis industry due to medical and recreational purposes, the boundaries have not yet been defined. Paradoxically, states where cannabis is medically legal have individuals with a higher likelihood of vaping cannabinoids. (65) Cannabidiol is a chemical found in the cannabis plant that, unlike THC, does not have psychoactive adverse effects. In the past few years, cannabidiol has been considered as a therapeutic option for different medical conditions. (66) Likewise, a combination of THC and cannabidiol is available for the treatment of spasticity and pain in more than 20 countries, although not in the United States. The use of these cannabis derivatives is controversial and still under debate, and the content area of inappropriate use is an opportunity for research (Table 1).

CLINICAL BURDEN OF VAPING

Recently, there is an increased reporting of respiratory illness cases associated with EC use; however, the pathophysiology is not clearly defined yet. The mechanism of action is hypothesized on the basis of clinical presentation and imaging findings with a lack of consensus. Several factors have been repeatedly reported such as history of tobacco smoking and recent introduction of ECs and unrevealing work-up for infectious and rheumatologic causes.

Vaping-Related Acute Lung Injury

A cluster of cases of acute lung injury related to vaping has been reported since April 2019 throughout the United States. Until August 2019, more than 120 cases in at least 15 states were identified. (67) By September 2019, more than 450 cases of vaping-related acute lung injury (VpALI) were reported to the CDC from 33 states across the nation, including 7 deaths. (68) In common, most patients were previously healthy teenagers, who developed rapid onset of symptoms, including cough and severe dyspnea, after vaping. Several patients required mechanical ventilation, some of them for several days.

The mechanism of acute lung injury is not yet well understood, and an isolated model has not been identified. Lung biopsies from 17 patients with VpALI revealed nonspecific injury, suspected to be an airway-centered chemical pneumonitis. Histopathological findings include acute fibrinous pneumonitis, diffuse alveolar damage, organizing pneumonia, interstitial edema, and intraalveolar fibrin accumulation. Despite these different patterns, foamy macrophages and pneumocyte vacuolization were found in all cases. (69) Additionally, the CDC released a recent communication reporting presence of vitamin E acetate in the bronchoalveolar lavage (BAL) samples from patients who developed VpALI. (70) The uncertainty of an exact process of lung injury provides areas of future research (Table 2).

Signs and Symptoms

Hypoxemia is a constant, and respiratory symptoms usually include nonproductive cough and shortness of breath; however, initial constitutional symptoms were also mentioned. (71,72) Interestingly, cases related to the inhalation of cannabis have been reported with overall similar factors and findings. In contrast to traditional vaping cases, hemoptysis was more frequently reported in cannabis users. (73-73) The diagnosis ranges from hypersensitivity pneumonitis, (76,77) eosinophilic pneumonia, (78,79) diffuse alveolar hemorrhage, (80) lipoid pneumonia, (81,82) organizing pneumonia, (75,83) respiratory bronchiolitis-associated interstitial lung disease (84) to acute lung injury and ARDS. In addition, pneumomediastinum, pleural effusion, and pneumothorax have been reported. (72) The findings of highresolution computed tomography are often ground-glass opacities and interlobular septal thickening reflecting emulating crazy paving, although pulmonary nodules have been reported. (84) Laboratory findings include leukocytosis; however, acute phase reactants and other markers of inflammation are not frequently requested. Usually, coverage of broad-spectrum antibiotics is provided, suggesting a concomitant infectious process.

Assessment

Early recognition of these cases is critical. A thorough initial assessment needs to include a detailed social history. The Centers for Disease Control and Prevention recommends screening all patients for EC use. If the patient reports use within the past 90 days, they also recommend targeted questioning regarding devise and type of liquid used, location of purchase, and inquiring whether the product or device has been shared with others. Thorough questioning should be completed to evaluate for alternative diagnoses such as rheumatologic, infectious, or neoplastic disease. When there is a high index of suspicion for VpALI, a rigorous assessment of vaping cannabinoids or other illegal substances is warranted. Removal of the offending agent should be a priority, and counseling on quitting is fundamental. Close monitoring including hospitalization is justified. The initial approach varies depending on the degree of respiratory compromise. Some cases required observation only after removal of the offending agent and oxygen supplementation; nevertheless, patients with a higher severity of illness required mechanical ventilation support and even extracorporeal membrane oxygenation (77,85) because of progression to ARDS. (86) Timely interventions can prevent further deterioration and directly influence prognosis.

Management and Treatment

Coverage with broad-spectrum antibiotics is encouraged with sequential de-escalation if no evidence of respiratory tract or systemic infection is found. Direct airway examination should be performed if the patient is hemo-dynamically stable and airway is secure. If there is a suspicion for inhalation injury, direct airway examination can be performed with fiber-optic bronchoscopy using the Abbreviated Injury Score (63) as a tool to predict gas exchange impairment, morbidity, and mortality. (87,88) Bronchoalveolar lavage can provide valuable information on the etiology and mechanism of lung injury. L Evidence of lymphocytic, neutrophilic, or eosinophilic cellular patterns can lead to an appropriate diagnosis of the lung injury type. The presence of Oil Red O--positive macrophages is suggestive of lipoid pneumonia. (81,82) Systemic steroids have been used in several instances judged to be appropriate by the prescribing clinician. At this moment, it is unclear whether steroids are beneficial.

Mechanical ventilation with lung protective strategies is often required, especially when there is progression to ARDS. The potential of mechanical ventilation to produce harm needs to be reduced because the pathophysiology of lung injury induced by ECs remains to be completely understood. It is imperative to monitor ventilator-induced lung injury, especially when clinical deterioration justifies more aggressive measurements. Overdistension of the alveoli from either high positive end-expiratory pressure (PEEP) or high tidal volumes can lead to volutrauma, and simultaneously an excessive airway pressure can result in pneumothorax. Likewise, oxygen should be titrated to a minimal arterial oxygen tension of 65 mm Hg to reduce the risk of oxygen toxicity.

Assessment of the pulmonary mechanics needs to be mandatory. Important tools such as driving pressure, esophageal balloon, and stress index can give us critical information on the patient's needs. The management should be personalized and tailored to each patient's physiology. The prone position needs to be implemented when indicated with no delay as well as neuromuscular blockade. Fluid restriction and adequate nutrition are crucial. Furthermore, health care providers have to be attentive to superimposed complications such as ventilator-associated pneumonia. Extracorporeal membrane oxygenation may be necessary depending on the severity of illness. (77,83) Finally, a multidisciplinary approach is vital to improve chances of intensive care unit survival. Implementing strategies such as ABCDEF bundle (90) and coordinating multidisciplinary care should be the cornerstone of management (Table 3).

Social and Geographical Spread

Patients who were willing to speak to media outlets reported that they had bought their vaping products from a "friend of a friend," cheaper on the streets, and not from dispensaries. (98) Some of them also identified that the color of the vaping substance did not look correct compared to previous use. Even though the largest cluster of cases started in the borders between southeastern Wisconsin and northeast Illinois, the actual products used were not traced or linked to a common source. In a recent largest case series, Layden et al (72) reported 53 cases of VpALI. Cases were divided on the basis of outbreak definitions as confirmed cases and probable cases. The concomitant use of nicotine, THC, and cannabidiol products was mentioned, THC being the most commonly reported in this cohort. More than half required intensive care unit level of care, and one-third were supported with mechanical ventilation. Some patients underwent bronchoscopy, and BAL exhibited lipidladen macrophages with Oil Red O stain, with similar reports in Utah and North Carolina. (99,100) When biopsy was attempted, the pathology report revealed nonspecific inflammation, diffuse alveolar damage, and granulomatous pneumonitis.

FUTURE DIRECTIONS

There is a paucity of studies related to the detrimental effects of vaping. Currently, there are trials developed to better understand the effects of cannabis vaping (Vaping THC From Electronic Cigarettes [V-PAX]; ClinicalTrials.gov Identifier: NCT02955329), but to this day, there is no scientific data that provide a safety profile for these products that can guide consumers. Nevertheless, studies need to focus on identifying unknown risk factors, delineating severity of illness, understanding the mechanisms of VpALI, and proposing strategies to ameliorate lung injury. The rapidly growing scope and scale of this outbreak of VpALI is a public health emergency of paramount importance. The current health crisis has also reminded the public health community that we need to develop an understanding of the long-term risks of vaping long before we repeat the mistakes of past generations when more than 50 years lapsed before we began to recognize the long-term risks of tobacco smoking.

Along with this, the education and participation of the community are imperative. Major stakeholders across local communities need to assemble to provide important insight into negative consequences of vaping and work together to implement effective interventions to prevent the progression of this epidemic. The lack of awareness of its serious adverse health effects needs to be confronted by instructing the new generations about the potential for life-threatening outcomes. In addition, we need more strict measures, restrictive policies, and regulatory taxes. The availability of these products to children through Internet and retail stores is alarming and is an indication that effective policies should be used by local, county, and state governments as well as implementation of national regulation by the Food and Drug Administration.

In addition, further research is needed to understand the mechanism of action of acute lung injury, role in pregnancy, and long-term effects.

CONCLUSION

Exposure to EC aerosol can be fatally harmful. Health care providers should encourage discontinuation, and regulatory policies are needed to protect vulnerable groups and individuals promoting population-based interventions. There is a potential risk for addiction, and an association with previous use of illicit drugs has been reported. Regarding using ECs for smoking cessation, it should be analyzed more deeply because there are different compounds in EC aerosols that can have adverse health effects, which, in contrast to tobacco smoke, can cause acute and life-threatening lung injury.

Vaping should be considered as a risk for acute lung injury, and health care providers need to be familiar with this new modality of illicit drug consumption. Health care providers need to be aware and prepare to identify and treat these cases. Reporting of new cases of lung injury related to the use of ECs to the CDC should be encouraged to generate a formal definition and provide a more standardized approach and treatment.

Finally, careful investigation is urgently needed to understand the cluster of cases of acute lung injury; however, this may be just the tip of the iceberg.

ARTICLE HIGHLIGHTS

* Vaping-related acute lung injury incidence is increasing. Regulatory measures, community education, and familiarization with diagnosis and treatment are imperative to face this public emergency.

* The consumption of electronic cigarette products carries potential risks of addiction, initiation of tobacco use in the nonsmoker population, and use of illicit drugs. Detrimental effects of different electronic cigarette compounds can occur, not only limited to the respiratory system.

* Symptomatology can be unspecific initially; thus, clinicians need to conduct exhaustive investigation into potential exposure during the initial assessment, keeping a high index of suspicion for vaping-related acute lung injury, especially in populations at risk.

Abbreviations and Acronyms: ARDS = acute respiratory distress syndrome; CDC = Centers for Disease Control and Prevention; EC = electronic cigarette; THC = tetrahydrocannabinol; VpALI = vaping-related acute lung injury

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Caption: FIGURE. Schema of electronic cigarette.

TABLE 1. Health-Related Effects of Electronic Cigarettes Pulmonary effects Heat--and solvent-related carcinogenic compounds Respiratory epithelial injury Reduced mucociliary clearance Increased risk of respiratory tract infections Vaping-related acute lung injury (see Table 3) Increased airway reactivity Cardiovascular effects Increased oxidative stress and inflammation Increased platelet aggregation Increased odds of myocardial infarction Thermal injury Psychosocial effects Nicotine addiction Increased cannabis tolerance and withdrawal Increased use of other tobacco products, alcohol, and illicit drugs

TABLE 2. Electronic Cigarette Associated Pulmonary Syndromes Inhalation injury Exogenous lipoid pneumonia Hypersensitivity pneumonitis Acute eosinophilic pneumonia Diffuse alveolar hemorrhage Pneumothorax/pneumomediastinum Acute respiratory distress syndrome Respiratory bronchiolitis-interstitial lung disease Bronchiolitis obliterans Acute fibrinous pneumonitis Organizing pneumonia Granulomatous pneumonitis

TABLE 3. Reported Cases of Vaping-Related Acute Lung Injury No. of patients Year Age, sex Comorbidities Exposure 1 2012 42, F Asthma, Vaping rheumatoid 7 mo arthritis, HTN 1 2014 20, M None Vaping 3 d 1 2015 19, M Marijuana Dabbing use 6 d 1 2015 43, M HTN, former Vaping smoker 3 d 1 2015 60, M Cigar Vaping 1 smoking unknown time 1 2015 31, F Active Vaping smoking 3 mo 1 2016 27, M Active Vaping smoker 7 mo 1 2016 19, M Marijuana Dabbing use 6 d 1 2016 20, M None Vaping 6 mo 1 2017 54, M None Vaping cannabis for years 1 2017 33, M Active smoker, Vaping mixed germ 3 mo cell tumor treated with bleomycin 1 2017 46, M Former smoker Vaping 3 mo 1 2017 56, F Liver Vaping transplant, 1 mo active smoker 1 2018 33, M Diabetes Vaping mellitus, 2 mo seizures 1 2018 40, F Active smoker Vaping 1 mo 1 2018 18, F Mild asthma Vaping 2-3 wk 1 2018 16, F Obesity, Vaping anxiety, recently active smoker 1 2018 34, F Former smoker, Vaping thrombo- 3y cytopenia, anemia, GERD 1 2018 16, M Asthma Vaping 2 wk ago 1 2019 18, F Active smoker, Dabbing marijuana 3 Y 1 2019 18, F None Vaping 2 mo No. of Clinical Chest patients presentation imaging findings 1 Dyspnea, Crazy paving productive cough and subjective fever 1 Cough, dyspnea, Bilateral facial flushing ground-glass opacities 1 Dyspnea, cough, Bilateral pleuritic chest infiltrates, pain, trace pneumomedia- hemoptysis stinum 1 Dyspnea Consolidation pleuritic and pleural chest pain effusions on the chest radiograph 1 Weakness, Bilateral 1 chills, cough ground-glass opacities 1 Progressive Crazy paving dyspnea, cough 1 Dyspnea, cough, Pulmonary fever, nodules hemoptysis 1 Dyspnea, Bilateral pleuritic chest infiltrates pain, trace with areas of hemoptysis consolidation 1 Dyspnea, fever Bilateral infiltrates, interlobular septal thickening 1 Dyspnea, Bilateral hemoptysis centrilobular nodular pattern 1 Minimal dyspnea Poorly differentiated pulmonary nodules with fluffy infiltrates 1 Night sweats, Bilateral fever, weight ground-glass loss opacities, traction bronchiectasis 1 Nonproductive Crazy paving cough 1 Dyspnea, Diffuse hemoptysis ground-glass, bilateral patchy consolidations 1 Dyspnea, Bilateral chest pain ground-glass opacities 1 Dyspnea, Dependent pleuritic opacities, chest pain, small pleural cough effusions, interlobular septal thickening 1 Dyspnea, Bilateral headache, ground-glass lower back opacities pain 1 Dyspnea, Diffuse cough, ground-glass, hemoptysis interlobular septal thickening, subpleural cyst 1 Cough, Bilateral fatigue, ground-glass dyspnea infiltrates and consolidation 1 Dyspnea, Bilateral productive patchy cough, nausea, infiltrates headache 1 Dyspnea, Bilateral pleuritic patchy chest pain, infiltrate and nonproductive nodules cough, fever No. of Bronchoalveolar patients lavage Diagnosis Steroids 1 48% neutrophils Lipoid 8% lymphocytes pneumonia 43% monocytes 1% eosinophils ORO-PM 1 17% macrophages Acute eosi- Yes 74% eosinophils nophilic pneumonia 1 Nonspecific ARDS Yes alveolitis, <10% eosinophils 1 Not performed Pneumonia -- 1 Not performed Inhalation -- pneumonitis 1 Reactive ARDS, lipoid Yes pneumocytes, pneumonia ORO-PM 1 Nondiagnostic Bronchiolitis Yes obliterans organizing pneumonia (biopsy) 1 23% lymphocytes Inhalation Yes 8% eosinophils pneumonitis 1 60% eosinophils Acute Yes 20% lymphocytes eosinophilic 15% macrophages pneumonia 5% neutrophils 1 61% neutrophils Inhalation -- 8% lymphocytes pneumonitis 2% eosinophils Organizing CD4/CD8 ratio 0.46 pneumonia (biopsy) 1 Nondiagnostic Respiratory -- bronchiolitis interstitial lung disease (biopsy) 1 18% macrophages Acute alveo- Yes 57% neutrophils litis with 18% eosinophils intralveolar CD4/CD8 ratio 0.6 fibrosis ORO-PM (biopsy) 1 90% macrophages ALI by -- 5% neutrophils inhalation 5% lymphocytes 1 3000 RBCs Diffuse Yes 800 WBCs alveolar 42% neutrophils hemorrhage 36% lymphocytes 21% macrophages 1 Nondiagnostic Organizing Yes pneumonia (biopsy) 1 26% neutrophils ARDS, Yes 25% mononuclear hyper- 22% eosinophils sensitivity 14% monocytes 13% pneumonitis 1 Macrophage ARDS Yes predominant 1 18% lymphocytes Lipoid Yes 2% neutrophils pneumonia 64% macrophages (biopsy) 2% eosinophils 1 15% eosinophils ARDS, acute Yes 52% neutrophils eosinophilic 33% lymphocytes pneumonia 1 Not performed ALI by Yes inhalation 1 26% eosinophils Acute Yes eosinophilic pneumonia No. of Reference, patients Outcome year 1 Clinical McCauley improvement et al, (82) 2003 1 Clinical Thota and improvement Latham, (78) 2014 1 Clinical Stahlmann improvement et

al, (71) 2015 1 Clinical Moore et improvement al, (91) 2015 1 Clinical Atkins and 1 improvement Drescher, (76) 2015 1 Clinical Modi et improvement al, (81) 2015 1 Clinical Mantilla et improvement al, (92) 2016 1 Clinical McMahon et improvement al, (73) 2016 1 Clinical Kamada et improvement al, (93) 2016 1 He et al, (75) 1 Radiographic Flower et improvement al, (84) 2017 1 Clinical Koh et improvement al, (71) 2017 1 Clinical Sturek and improvement Malik (94) 2017 1 Clinical Agustin et improvement al, (80) 2018 1 Clinical Khan et improvement al, (83) 2018 1 Clinical Sommerfeld et improvement al, (95) 2018 1 Unknown Attis et al. (77) 2018 1 Clinical Viswam et improvement al, (96) 2018 1 Clinical Aokage et improvement al, (85) 2018 1 Clinical Anderson improvement and Zechar, (97) 2019 1 Clinical Arter et improvement al, (79) 2019 ALI = acute lung injury; ARDS = acute respiratory distress syndrome; F = female; GERD = gastric esophageal reflux disease: HTN = hypertension; M = male; ORO-PM = Oil Red O--positive macrophage; RBC = red blood cell; WBC = white blood cell.

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