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# EVALI (E-Cigarette or Vaping Use-Associated Lung Injury): Pathogenesis, Etiology, AI Models, Epidemiology, 3D Bioprinting, Advanced Therapeutics, Tissue Engineering, Airways, Peyronie's and Paget's Disease

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## Abstract:

E-cigarette or Vaping Use-Associated Lung Injury (EVALI) is a new type of lung disease linked to the massive vaping and electronic cigarette use. The condition is caused by the inhalation of toxic components of the aerosol such as nicotine, tetrahydrocannabinol (THC), vitamin E acetate, flavours, and other toxic chemicals, which cause oxidative stress, immune dysregulation and acute pulmonary injury. This review provides an overview of the current knowledge of the pathogenesis, etiology, epidemiology, clinical presentation and diagnosis, imaging, and treatment of EVALI. It also identifies recent developments of artificial intelligence (AI), machine learning, deep learning, radiomics, and predictive analytics to aid in diagnosis and clinical decision-making. Moreover, a brief account of new emerging regenerative strategies like lung organoids, tissue engineering, three-dimensional (3D) bioprinting, biomaterials, and stem-cell–based therapies in relation to their use in pulmonary repair and translational medicine is provided. Issues of current challenges and clinical translation, as well as future research priorities, are also discussed. In general, the combination of AI, precision medicine and regenerative technologies holds potential for enhancing EVALI diagnosis, treatment and management in the long term, although further clinical validation is needed before it can be widely adopted..

**Keywords:** E-cigarette or Vaping Use-Associated Lung Injury (EVALI); Artificial Intelligence; Tissue Engineering; 3D Bioprinting; Precision Medicine; Lung Organoids.

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## 1. INTRODUCTION

In recent years, electronic cigarettes (e-cigarettes) and vaping products have become increasingly popular and widely used as alternatives to regular cigarette smoking, especially among adolescents and young adults[1]. While initially marketed as safer alternative methods of nicotine delivery and smoking cessation, a large body of clinical data has emerged showing that these devices can lead to a range of acute and chronic respiratory issues[2]. E-cigarette or Vaping Use-Associated Lung Injury (EVALI) emerged as an important public health issue in 2019, resulting in thousands of hospitalizations and several deaths globally. EVALI may be caused by inhaling aerosolized chemical components of e-cigarette products, such as nicotine, tetrahydrocannabinol (THC), vitamin E acetate, flavoring agents, volatile organic compounds, and heavy metals, and can cause a spectrum of lung injury from mild pneumonitis to acute respiratory distress syndrome (ARDS), which can be fatal[3].

However, recent advances in biomedical research have greatly broadened the knowledge base surrounding EVALI beyond just its clinical presentation to uncover the molecular mechanisms underlying vaping-induced lung injury. At the same time, new technologies, including artificial intelligence (AI), machine learning, radiomics, multi-omics, three-dimensional (3D) bioprinting, tissue engineering, and regenerative medicine, are revolutionizing diagnostic and treatment strategies, therapeutic development, and pulmonary regeneration[4]. They enable a range of multidisciplinary innovations that offer new opportunities for precision medicine by combining clinical, imaging, molecular, and computational data to improve diagnostic accuracy, enable precision treatment, and streamline the path from discovery to clinical application.

### 1.1 Background and Context

Electronic cigarette aerosol use has grown in widespread popularity, introducing new clinical, research, and public health questions as the long-term biological effects of e-cigarette aerosol exposure are not fully understood. Vaping aerosols have complex compositions, which may differ depending on the device design, the temperature at which it is heated, and the type of liquid used, leading to a complex mechanism of pulmonary toxicity[5]. There is increasing evidence that oxidative stress, activation of inflammatory cytokines, epithelial damage, immune system dysfunction, and impaired tissue repair all play a role in EVALI pathogenesis. Thus, there is a growing demand for extensive reviews, which combine new insights on the mechanisms of the disease with recent developments in the field of artificial intelligence, organoids and translational technologies in order to have a wider perspective of future diagnostic and therapeutic possibilities[6].

### 1.2 Objectives of the Review

Here is a more concise version of your objectives while maintaining academic quality:

- To review the molecular mechanism and cause of EVALI.
- To review the Epidemiology, clinical manifestations, diagnosis and imaging features of EVALI.
- To assess the potential of AI in diagnosis and clinical care for EVALI.
- To talk about the developments in 3D bioprinting, tissue engineering, lung organoids and regenerative medicine.
- To investigate the current therapeutic and precision medicine strategies for EVALI.
- To establish gaps in the research, clinical challenges and future directions in the management of EVALI.

### 1.3 Importance of the Topic

Despite the greater regulation of these modern nicotine delivery systems, EVALI remains an important emerging respiratory disorder of public health and clinical importance. This fast-paced surge of vaping products and the emerging field of advanced computational and regenerative technologies underscore the need for an updated multidisciplinary review that spans between pulmonary pathology, artificial intelligence, tissue engineering, precision medicine and translational research[7]. This review integrates current data from these overlapping fields to deliver a comprehensive overview of existing knowledge and opportunities for advancing diagnosis, treatment, pulmonary regeneration, and clinical translation in EVALI patients.

## 2. PATHOGENESIS, ETIOLOGY, AI-DRIVEN DIAGNOSTICS, AND REGENERATIVE APPROACHES IN EVALI

E-cigarette or Vaping Use Associated Lung Injury (EVALI) is a multi-factorial pulmonary disease that occurs from inhaling toxic aerosolized substances produced during vaping. The disease is a complex interplay of chemical toxicants, oxidative stress, dysregulated immune responses and impaired pulmonary repair mechanisms[8]. The recent development of AI, tissue engineering, and regenerative medicine has contributed to better understanding of EVALI's pathogenesis and offered novel strategies to the field of diagnosis, disease modeling, and therapeutic interventions. The molecular mechanisms involved in the development of EVALI, new advances in AI diagnostic models, and the possibilities of regenerative technologies for repairing lung tissue are discussed[9]. The possibilities of regenerative technologies to repair damaged lung tissue and emerging AI diagnostic models are discussed[10].

### 2.1 Molecular Pathogenesis and Etiology of EVALI

EVALI starts with inhalation of a wide variety of aerosolized chemicals emitted during electronic cigarette use. Most of these aerosols contain nicotine, tetrahydrocannabinol (THC), cannabidiol (CBD), flavoring agents, volatile organic compounds, aldehydes, ultrafine particles and heavy metals like nickel, chromium and lead. The chemicals found in vaping products also vary widely in composition among different brands and between commercial and

illicit products, so there is no easy identification of a single cause[11]. Rather, there is current evidence that EVALI is a result of multiple inhaled chemical constituents of e-cigarette products acting together to cause acute inflammatory injury by disrupting the normal physiology of the lungs.

Vitamin E acetate (VEA) is the most important compound involved in EVALI, especially in vaping products that contain THC that were identified as part of the 2019 outbreak. Aerosolized vitamin E acetate affects the function of pulmonary surfactant, compromises alveolar gas exchange, and contributes to accumulation of lipid-laden macrophages, which is a pathological characteristic that has been seen in the bronchoalveolar lavage specimens obtained from affected patients[12]. Toxic aerosols also produce excessive amounts of ROS, which cause oxidative stress, mitochondrial dysfunction, injury to epithelial cells, and disruption of the alveolar-capillary barrier.

Increased production of cytokines including interleukin (IL)-6, IL-1b, IL-8 and tumor necrosis factor (TNF-a) is a component of the exaggerated inflammatory response seen in EVALI, which further contributes to the pulmonary damage[13]. These inflammatory mediators in the lung parenchyma result in diffuse alveolar damage, organizing pneumonia, pulmonary edema and impaired oxygen exchange. Histopathological findings are related to the various forms of toxic inhalational injury, such as acute fibrinous pneumonitis, diffuse alveolar haemorrhage and bronchiolitis. The knowledge of these molecular pathways allows for the development of targeted therapies and strategies for precision medicine for EVALI[14].

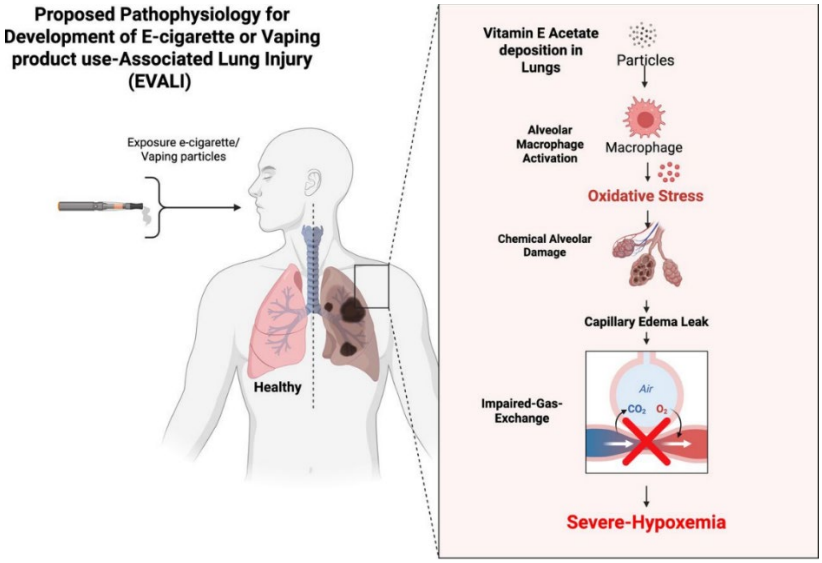


**Figure 1.** Proposed molecular pathophysiology of E-cigarette or Vaping Use-Associated Lung Injury (EVALI)

### 2.2 Artificial Intelligence Models in EVALI

AI has proven to be a useful ally in EVALI diagnosis and clinical management, when applied to complex medical data. Demographic factors, vaping history, laboratory tests, inflammatory markers and markers, pulmonary function tests, and electronic health records can all be used with machine learning algorithms to distinguish EVALI from other lung diseases that overlap in clinical presentation—such as bacterial pneumonia, viral pneumonia, COVID-19, hypersensitivity pneumonitis, and acute respiratory distress syndrome. These predictive models could help to make early diagnosis and better risk stratification in clinical practice[15].

The use of deep learning algorithms has significantly improved the interpretation of thoracic images by automatically detecting radiological characteristics linked to EVALI. Computer algorithms like the Convolutional Neural Networks (CNN) can accurately identify bilateral ground glass opacities, diffuse consolidations, septal thickening and organizing pneumonia. Moreover, radiomics allows for the extraction of quantitative imaging features such as texture, density, shape, and spatial heterogeneity, which can provide AI systems with additional data that is not necessarily intuitive in a traditional radiological assessment and is an imaging biomarker that may be useful[16].

In addition to diagnostic imaging, AI-powered predictive analytics and clinical decision support are potentially poised to revolutionize personalized management of EVALI. These systems can make continuous predictions of disease progression, estimate the likelihood of respiratory failure, guide corticosteroid therapy for patients, and optimise patient monitoring via continuous observation of longitudinal clinical data. The use of Explainable Artificial Intelligence (XAI) also enhances clinical acceptance by offering clear explanations of algorithmic predictions, thus boosting the confidence of physicians, minimizing diagnostic ambiguity, and enabling ethical deployment of AI in healthcare[17].

### 2.3 3D Bioprinting, Tissue Engineering, and Airway Regeneration

Regenerative medicine is an emerging topic of interest to treat pulmonary damage associated with EVALI. Pluripotent stem cell derived human lung organoids and patient derived lung induced pluripotent stem cells (iPSCs) recap the structural and functional features of native lung tissue. These 3-D models provide the opportunity to examine toxicity, inflammatory signaling pathways, epithelial regeneration and therapeutic responses in a physiologically relevant context induced by vaping. In the same way, airway-on-chip systems mimic the dynamic microenvironment of the respiratory tract to create more advanced disease modelling and drug screening systems[18].

Recent developments in 3D bioprinting have made it possible to create biomimetic lung tissues made of living pulmonary cells and various extracellular matrix components, hydrogels, collagen, and gelatin methacrylate. Such man-made models offer standardized substrates to study airway injury, test new drugs and explore airway remodeling after toxic air inhalation[19]. Scopal properties also promote cellular attachment, proliferation, differentiation, and ECM remodeling, which provides an ideal environment for pulmonary tissue regeneration and function restoration, using biomaterial-based scaffolds[20].

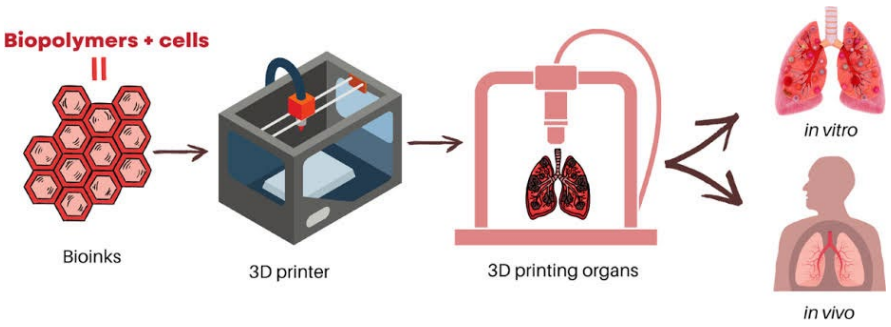


**Figure 2.** Schematic representation of three-dimensional (3D) bioprinting for lung tissue engineering and regenerative medicine

The potential of stem-cell–based regenerative therapies is significant, including the use of mesenchymal stem cells (MSCs), which have shown anti-inflammatory, immunomodulatory, and tissue-repairing effects. The extracellular vesicles and exosomes produced by MSCs could be used to reduce the damage and injury caused by cytokines, promote regeneration of epithelial cells, help to repair alveolar integrity, and speed up recovery after severe lung inflammation[21]. In the future, further AI-driven advances in tissue engineering, patient-specific organoids, sophisticated biomaterials, and precision regenerative medicine could create a new multidisciplinary approach to personalized treatment of EVALI, but more clinical testing is needed before this can be clinically used.

## 3. CLINICAL, EPIDEMIOLOGICAL, AND THERAPEUTIC ADVANCES IN EVALI

EVALI is now an emerging public health problem due to the growing use of electronic cigarettes globally, especially by adolescents and young adults. Despite the advances in knowledge regarding its epidemiology, presentation, and treatment, there are still many challenges in establishing the standardized diagnostic criteria and evidence-based treatment strategies. Emerging research in precision medicine, nanotechnology, and translational research are opening new avenues in therapeutic approaches and patient care[22]. The epidemiology, clinical features, diagnostic evaluation and advance of therapeutic options for EVALI are briefly summarized.

### 3.1 Epidemiology, Risk Factors, and Clinical Manifestations

The 2019 EVALI outbreak brought attention to the broad range of health risks from electronic cigarette and vaping products. Epidemiological investigations showed that most people experiencing the effects of vaping were teens and young adults who reported frequent vaping, often through informal or illegal sources, particularly those containing THC. While cases have receded due to greater public awareness and regulatory measures, vaping-associated lung injury remains a public health problem and is reported sporadically throughout the world[23]. Factors known to impact disease susceptibility include demographic factors, frequency of vaping, duration of exposure, pre-existing respiratory disease, and concurrent smoking habits.

There are multiple potential risk factors for EVALI, such as exposure to vitamin E acetate, flavoring chemicals, volatile organic compounds, heavy metals, and the aerosolization process itself to produce ultrafine particulate matter. Pulmonary toxicity could be even more serious for people who suffer from asthma, chronic obstructive pulmonary disease, weakened immune system, or frequent use of high-temperature vaping devices. Dual use of traditional and electronic cigarettes, lengthened vaping sessions and the use of unregulated vaping cartridges further increase the risk of developing serious respiratory problems.

Clinically, EVALI has a wide range of respiratory and systemic symptoms. Cough, dyspnea, chest pain, fever, chills, fatigue, nausea, vomiting, abdominal pain, and weight loss are common symptoms among patients and may mimic infectious pneumonia or ARDS. Illness can be mild with respiratory symptoms or more rapidly progressive, leading to hypoxemic respiratory failure, and requiring intensive care support. The clinical manifestations have many similarities with other pulmonary diseases and careful clinical assessment is still required to ensure that an appropriate diagnosis and treatment can be given in time[24].

### 3.2 Imaging, Diagnosis, and Emerging Diagnostic Technologies

The diagnosis of EVALI is often difficult because there are no specific laboratory tests or imaging findings. Diagnosis is made based on recent vaping history, typical clinical features, excluding infective causes, laboratory investigations, bronchoalveolar lavage when indicated and characteristic radiological findings. The presence of lipid-laden macrophages, leukocytosis, hypoxemia and elevated inflammatory markers can aid in diagnosis and should be taken into context with the patient's clinical history.

Thoracic imaging is a crucial role in the evaluation of the disease. The chest radiograph is often bilateral pulmonary infiltrates, and high-resolution computed tomography (HRCT) shows bilateral ground-glass opacities, diffuse consolidations, interlobular septal thickening, organizing pneumonia, and diffuse alveolar damage. Imaging results match the inflammatory process, and help the clinician track disease course and response[25]. There is a significant overlap with viral pneumonia, hypersensitivity pneumonitis, diffuse alveolar haemorrhage and acute eosinophilic pneumonia and diagnosis is essential.

The field of pulmonary imaging has experienced significant improvements in the accuracy and advancements of artificial intelligence analysis and diagnosis. Deep learning algorithms and radiomics as well as machine learning models can detect subtle imaging biomarkers, quantify disease burden, differentiate EVALI from other pulmonary diseases and predict clinical outcomes. The combination of imaging with the laboratory biomarkers, pulmonary function testing and electronic health records allows for the creation of AI-driven clinical decision support which would support early detection, personalized risk stratification and precision care for patients with vaping-associated lung injury.

### 3.3 Advanced Therapeutics and Future Translational Perspectives

Treatment for EVALI currently is supportive, supplemental oxygen therapy, cessation of vaping product use, and systemic use and/or IV administration of corticosterone to help control

excessive pulmonary inflammation. In moderate-to-severe disease, corticosteroids are the mainstay of treatment as they decrease the production of inflammatory cytokines, enhance pulmonary function, and speed clinical recovery[26]. For patients who are critically ill, other supportive treatments such as mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and intensive care management may be needed. Although a corticosteroid therapy has been shown to be effective in many patients, there is an ongoing search for treatment protocols and the best doses.

In addition to traditional management, there are a number of emerging therapeutic options currently being explored to enhance long term pulmonary recovery. In more severe disease states with cytokine-induced lung injury there may be additional benefits derived from immunomodulatory therapies directed against inflammatory signal pathways. To achieve targeted delivery of drugs to the pulmonary tissue, while reducing or eliminating toxicity on the systemic level, the use of nanomedicine \based drug delivery systems is being considered. Precision medicine strategies that combine genomics, transcriptomics, inflammatory biomarkers, and AI can help target potential therapeutic strategies in individual patients and optimize personalized therapy plans. In addition, regenerative technologies such as mesenchymal stem-cell therapy, extracellular vesicles, tissue engineering, and three-dimensional bioprinting could encourage the healing of damaged alveolar tissue and promote normal lung function[27].

However, there are still issues that need to be addressed to enable these novel therapies to be more widely and routinely applied in routine clinical practice. Further clinical trials with a large multicenter design are required to prove the safety and efficacy of precision therapeutics, regenerative medicine, and AI-driven treatment algorithms. Further studies regarding the validation of biomarkers, standardization of diagnostic criteria, use of explainable AI, and personalized treatment pathways to integrate clinical, radiological, molecular and pathological data are also required. These multi-disciplinary strategies should help enhance patient care and enable the widespread adoption of experimental technologies into clinical practice.

**Table 1.** Comparative Overview of EVALI Pathology, AI Applications, Therapeutic Strategies, Regenerative Approaches, and Future Translational Perspectives

| Component | Key Features | Clinical Significance |
|---|---|---|
| Pathology | Vitamin E acetate, oxidative stress, cytokine-mediated inflammation, lipid-laden macrophages | Mechanisms underlying pulmonary injury |
| AI Applications | Machine learning, deep learning CT analysis, radiomics, predictive analytics | Early diagnosis, risk prediction, clinical decision support |
| Therapeutics | Corticosteroids, supportive care, immunomodulators, oxygen therapy | Current standard management |

| | | |
|---|---|---|
| Regenerative Medicine | Lung organoids, 3D bioprinting, biomaterials, stem-cell therapy | Future pulmonary tissue repair |
| Precision Medicine | Multi-omics, AI-guided treatment, personalized therapeutics | Individualized disease management |
| Future Translation | Biomarker-guided diagnosis, explainable AI, clinical validation | Accelerating clinical implementation |

## 4. CLINICAL TRANSLATION AND FUTURE IMPLEMENTATION

A key challenge for research in EVALI is continuing to translate scientific discoveries into real-life clinical applications[28]. Despite significant advances in elucidation of disease mechanism and in the development of sophisticated diagnostic technologies, there are a number of obstacles to their widespread clinical use. New advances in AI, multi-omics, regenerative medicine, and precision healthcare will greatly improve the diagnosis, monitoring, and management of EVALI. This section will first address the current state of clinical translation, as well as examine new technological breakthroughs, and highlight the regulatory, safety, and implementation hurdles that need to be overcome to achieve broad adoption.

### 4.1 Human-Based Evidence and Clinical Translation

Observational studies, case reports, multilevel registries, retrospective analysis and public health data surveillance after the 2019 outbreak are the main sources of current knowledge on EVALI. The investigations have contributed significantly to the disease presentations, imaging features, pathological findings, and therapeutic effects of vaping products, as well as their association with acute lung injury[29]. The lack of large prospective clinical trials and harmonized diagnostic criteria, however, still restricts the quality of evidence in the evidence-based approach to the management of the disease.

The use of human-based experimental models has become more and more relevant to link the gap between laboratory studies and clinical application. Lung organoids that have been extracted from patients, precision-cut lung slices, bronchoalveolar lavage specimens, and airway-on-chip platforms are physiologically relevant systems used to study pulmonary toxicity, inflammatory mechanisms and therapeutic responses, which do not necessarily depend on animals. These platforms provide a chance to characterize patient disease and to develop personalized therapeutic approaches, while enhancing the translational impact of the preclinical work[30].

It will be necessary in the future for patients to obtain clinical translation from the collaboration of several different disciplines including pulmonology, radiology, pathology, biomedical engineering, computational science, and regulatory agencies. For the establishment of safe, effective and repeatable protocols for the treatment of patients, as well as for the validation of new diagnostic technologies, the establishment of standardized clinical databases, multicenter collaborations, and prospective clinical trials are critical. Building human-centered evidence

will help to speed the use of novel diagnostics and therapeutics in routine clinical care. Increasing human-centered evidence will facilitate the adoption of novel diagnostics and therapeutics into routine clinical care.

### 4.2 Emerging Technologies

The future of E-cigarette or Vaping Use Associated Lung Injury (EVALI) research is rapidly changing, with new technologies providing opportunities for early diagnoses, better monitoring of the disease, and more individualized therapeutic approaches. The combination of AI, multi-omics technologies, digital health platforms, regenerative medicine, and tissue engineering is opening new avenues to enhance the understanding of disease mechanisms and patient management. Many of the innovations are still early in the clinical application process, but they have great potential to make precision medicine more precise, faster to develop new treatments and more readily available in the clinic.

- **Artificial Intelligence (AI):** AI has emerged with great promise to enhance the diagnosis and management of EVALI by combining clinical history, imaging characteristics, laboratory indicators, pulmonary function tests, and electronic health records. By leveraging machine learning and deep learning algorithms, early disease detection, automated image interpretation, risk stratification, and personalized therapeutic decision-making are enabled, leading to improved diagnostic accuracy and clinical efficiency.
- **Multi-Omics Technologies:** Combining genomics, transcriptomics, proteomics, metabolomics and lipidomics allow us to gain a comprehensive picture of the molecular mechanisms involved in EVALI. These high dimensional data are used to find disease-specific biomarkers, inflammatory pathways, and therapeutic targets. Combined with AI, multi-omics can be used to make a more precise diagnosis and provide a treatment strategy that is tailored to the specific patient[31].
- **Digital Twin Technology:** Digital patient models, called digital twins, which are virtual representations of an individual based on clinical, imaging and molecular data and reflecting the physiological and pathological properties of the patient. These computational models are able to simulate disease development, predict therapeutic response, evaluate treatment efficacy and optimize clinical management for individualized therapy prior to clinical interventions.
- **Lung Organoids and Airway-on-Chip Systems:** Human lung organoids and airway-on-chip systems are advanced experimental models that can be used to study vaping-induced injury to the lungs. The technologies closely replicate the human respiratory microenvironment, enabling disease pathogenesis to be studied, drug efficacy to be tested, inflammatory mechanisms to be explored, and advancing translational research, whilst minimizing reliance on the traditional animal models.
- **Precision Medicine and Regenerative Technologies:** Precision medicine brings together clinical data and molecular profiling, imaging biomarkers and AI-based

analytics to provide tailored treatment in patient-specific manner. Beyond this, tissue engineering, three-dimensional (3D) bioprinting, innovative biomaterials, and stem-cell–based regenerative therapies are promising strategies for damaged pulmonary tissue repair, airway regeneration, and improved long-term pulmonary outcomes in patients with EVALI.

### 4.3 Safety, Challenges, and Regulatory Considerations

AI diagnostic and regenerative medicine still had some issues of safety and implementation which need to be addressed before they can be integrated into day-to-day healthcare. AI models need to be trained on diverse, high-quality, and large clinical datasets to work across various populations. These factors can introduce a lack of clinical reliability and may impact patient safety due to incomplete datasets, algorithmic bias, lack of external validation or limited interpretability. Likewise, an extensive study of durability of therapeutic effects, immunogenicity and biological safety is needed prior to widespread clinical use of regenerative therapies.

An additional important aspect of successful clinical translation is regulatory oversight. The use of AI clinical decision support systems, digital health platforms, regenerative biomaterials, and stem-cell therapies must meet stringent regulatory requirements for safety and efficacy, manufacturing quality, and ethical considerations. To be approved by the regulatory bodies and to ensure clinician confidence in these new technologies, it is critical they be transparent in the way they are developed, explainable, standardized in reporting and robustly clinically validated. Global regulatory framework harmonization will further support the use of AI-powered innovations in healthcare.

The successful implementation of precision healthcare for EVALI will require collaboration and interaction across multiple disciplines between clinicians, biomedical researchers, engineers, data scientists, regulators, and public health agencies. To translate from research to clinical practice, standardized diagnostic criteria, multicenter clinical trials, AI integration with precision medicine, and international clinical practice guidelines are needed. Ongoing investment in technological innovation, clinical validation and regulatory harmonization will be essential in making advanced diagnostic and therapeutic strategies available to patients who will trust, be able to access and benefit from them as part of every day care.

**Table 2.** Summary of Recent Studies on EVALI, Lung Regeneration, and AI-Driven Therapeutic Advances

| Author(s) & Year | Study Focus | Key Findings | Translational Contribution |
|---|---|---|---|
| Smith et al. (2021)[32] | EVALI pathology | Identified diffuse alveolar damage, organizing pneumonia, and lipid-laden | Improved pathological understanding and diagnostic evaluation of EVALI. |

| | | | |
|---|---|---|---|
| | | macrophages as key pathological features. | |
| Standiford & Ward (2016)[33] | Acute lung injury therapies | Reviewed anti-inflammatory and pulmonary repair strategies for ALI/ARDS. | Supports therapeutic approaches applicable to severe EVALI. |
| Tituana et al. (2024)[34] | Clinical review of EVALI | Summarized epidemiology, pathogenesis, diagnosis, and management of EVALI. | Provides updated evidence for clinical diagnosis and treatment. |
| Torkashvand et al. (2024)[35] | Lung tissue engineering | Demonstrated regenerative potential of exosome-loaded bioscaffolds for lung repair. | Highlights tissue engineering as a future strategy for EVALI recovery. |
| Wang et al. (2025)[36] | AI in pulmonary therapeutics | Reviewed AI applications in target discovery and drug development for lung diseases. | Supports AI-driven precision medicine and therapeutic development for EVALI. |

## 5. DISCUSSION

As e-cigarette use has grown in prevalence, E-cigarette or Vaping Use-Associated Lung Injury (EVALI) has emerged as a novel, complex respiratory illness of great clinical interest with varied and complicated pathological mechanisms[37]. This review brings together the latest information regarding molecular pathogenesis, epidemiology, artificial intelligence (AI)-based diagnostics, regenerative medicine, tissue engineering, and translational advances of EVALI. All the available evidence to date shows that multidisciplinary programmes involving clinical medicine, computational technologies and regenerative sciences are opening up new possibilities for earlier diagnosis and better therapeutic interventions and for patient management tailored to individual needs[38].

### 5.1 Interpretation and Analysis of Findings

The evidence in this review suggests that EVALI is a multifactorial inflammatory lung disease, driven by toxic vaping products, oxidative stress, immune dysfunction, and pulmonary damage. Vitamin E acetate is the most conclusively linked causative agent, and inflammatory cytokines and oxidative stress play a major role in disease progression. In parallel, the incorporation of AI into medical imaging has improved diagnostic precision, while the development of innovative lung organoids, tissue engineering, and 3D bioprinting has provided novel platforms for disease modeling and pulmonary repair[39]. At the same time, new technologies such as AI based on medical imaging advances have boosted diagnostic accuracy, and novel technologies for pulmonary repair (including organoids, tissue engineering and 3D bioprinting) have provided novel platforms for disease modeling and pulmonary repair. The

findings highlight the need to combine the advances of biology, clinical care and technology for effective management of EVALI[40].

### 5.2 Implications and Significance

The utilization of AI, precision medicine, regenerative medicine and advanced imaging technologies have significant implications for the diagnosis and treatment of EVALI. AI-driven clinical decision support systems can help identify disease at an early stage and risk stratification, and a multi-omics and precision medicine strategy can enable personalized therapeutic interventions. In addition, tissue engineering, biomaterials, and stem-cell–based regenerative approaches may play a role in the recovery of pulmonary function after severe lung injury. Together, these advances pave the way for a shift to individualized evidence-based care of vaping-associated pulmonary disease.

### 5.3 Research Gaps and Limitations

However, there are still significant research gaps to be addressed. The majority of the evidence available is based on observational studies, case reports, and retrospect studies; and less evidence comes from the few prospective clinical trials that validate emerging diagnostic and therapeutic technologies. There is a lack of standardized diagnostic criteria, validated biomarkers, long-term studies, and external validation of AI algorithms. Likewise, regenerative medicine strategies, tissue-engineered constructs, and precision therapeutics will need to undergo additional clinical studies to demonstrate the long-term safety, efficacy, and translational potential of these strategies before widespread clinical use.

### 5.4 Future Research Directions

Larger, multicenter clinical trials incorporating AI, multi-omics, advanced imaging, and precision medicine to enhance early diagnosis and personalized management of EVALI are warranted. Further advances in the development of explainable AI, digital twins, lung organoids, airway-on-chip and 3D bioprinting technology will further advance disease modelling and therapeutic development. Furthermore, international standardization, research collaborations and regulation will play a key role in speeding up the clinical translation of innovative diagnostic and regenerative strategies while enhancing long-term patient outcomes.

## 6. CONCLUSION

E-cigarette or Vaping Use-Associated Lung Injury (EVALI) is a novel condition of the lungs that results from the interaction of toxic components of vaping devices, oxidative stress, immune dysfunction, and lung inflammation. Advances in artificial intelligence, radiomics, precision medicine, tissue engineering, 3D bioprinting, and regenerative medicine have enriched knowledge, diagnosis, and management of EVALI and facilitated more personalized medicine. These technologies will be broadly adopted before further clinical validation, the development of standardized diagnostic protocols, the development of biomarkers, and regulatory harmonization are achieved. Multidisciplinary studies are needed to turn these

innovations into safe, effective strategies that can be utilized to diagnose, treat, and manage EVALI long-term.

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