REVIEW ARTICLE

3D Bioprinting for Regenerating COVID-19-Mediated Irreversibly Damaged Lung Tissue

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Abstract: While the tension of COVID-19 is still increasing, patients who recovered from the infection are facing life-threatening consequences such as multiple organ failure due to the presence of angiotensin-converting enzyme 2 receptor in different organs. Among all the complications, death caused by respiratory failure is the most common because severe acute respiratory syndrome coronavirus 2 infects lung's type II epithelial, mucociliary, and goblet cells that eventually cause pneumonia and acute respiratory distress syndrome, which are responsible for the irreversible lung damage. Risk factors, such as age, comorbidities, diet, and lifestyle, are associated with disease severity. This paper reviews the potential of three-dimensional bioprinting in printing an efficient organ for replacement by evaluating the patient's condition.

Keywords: COVID-19; Irreversible heart tissue damage; Regenerative medicine; 3D bioprinting

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1. Introduction

Since the 1960s, novel coronaviruses have caused three severe acute respiratory syndromes (SARSs) outbreaks. The most recent outbreak of SARS, caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in Wuhan, China, in December 2019[1-4]. Diverse clinical variability has been observed in SARS-CoV-2 infection, from mild symptoms to acute respiratory failure requiring intensive care unit (ICU) treatment[5]. As SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) receptor, organs including the lung, heart, liver, kidney, and gastrointestinal system, where ACE2 is expressed widely, are affected most, leading to multiorgan injuries, such as acute respiratory distress syndrome (ARDS), acute myocardial injury, acute myocardial injury, acute kidney injury, and acute liver injury[6-8]. However, among all the complications, the leading cause of death in coronavirus disease 2019 (COVID-19) is respiratory failure[9]. Preferentially, SARS-CoV-2 infects the lung's type II epithelial, mucociliary, and goblet cells, and the infection leads to programmed cell death of the epithelial cells,

consequently facilitating pneumonia and ARDS that can cause irreversible lung damage in severe patients[10-14]. Worsened long-term irreversible effects on recovered COVID-19 patients correlate with lung involvement in the acute phase of infection and degree of underlying systemic inflammation[15,16].

Unfortunately, around 80% of SARS-CoV-2 patients have a different extent of lung damage and shortness of breath, indicating that recovering from the disease is not beneficial in achieving fully recovered lungs, which, however, could lead to different respiratory tract-related problems after months to years. The long-term existence of abnormal lung lesions has been proven by chest computed tomography (CT) of the recovered COVID-19 patients that showed residual lesions although the patients had been discharged from the hospital 6 months ago[17,18]. Patients with associated risk factors are mostly in danger of experiencing irreversible lung damage[19]. Moreover, severe COVID-19 patients stay in ICU for a longer period, and patients with pre-existing comorbidities are at the highest risk of getting post-COVID-19 sequelae of lung diseases, which could lead to advanced fibrosis, irrecoverable fibrosis, and lung injury. Lung transplantation would benefit the survival of severe patients; a few patients have undergone lung transplantation due to COVID-19-mediated irreversible lung damage[20,21]. However, conventional lung transplantation still has multiple limitations that can be overcome by the three-dimensional (3D) bioprinted lung.

2. Post-COVID-19 sequelae of lung diseases

Based on the previous SARS-CoV and Middle East respiratory syndrome outbreaks, it has documented that pulmonary involvement with functional and radiological impairments would persist in recovered patients after hospital discharge for months; these patients were of older age, had been in the ICU for a longer period, and had higher peak lactate dehydrogenase (LDH) levels[22-24]. Knowing the interaction between previous viral cases of pneumonia and pulmonary involvement recovery from COVID-19-mediated organ damage is a matter of concern as most of the recovered patients will make a complete recovery, whereas others will experience a sequela long after COVID-19 recovery as they were being affected with acute infection. The National Institute of Health has renamed the constellation of symptoms from "long COVID" to post-acute sequelae of COVID-19 in December 2020[25]. Numerous studies have found surprising details, for instance, COVID-19 survivors developed pulmonary embolism *de novo* and 7.1% of recovered individuals were diagnosed with pulmonary hypertension. In addition, 48.8% of survivors still have breathing difficulty and cannot perform a 6-minute walking test (6MWT) 4 months after hospital discharge. Lung ultrasound study findings indicate gradual absorption of peripherally distributed ground-glass opacities, especially in the posterior and lower lung zones, after acute COVID-19 pneumonia[26].

Different follow-up studies have demonstrated significant results indicating various long-term complications in a recovered study population, whereas some have reported lung recovery in patients over time. A follow-up study lasting for 8 months, including 40 COVID-19 patients discharged from the hospitals, out of which 25 individuals had severe clinical outcomes while staying in hospital, illustrates the long-term impact of severe COVID-19. Severe patients still have physical and/or psychological symptoms, a higher rate of abnormal diffusing capacity of the lung for carbon dioxide (DLCO), small airway dysfunction, and resistance in the peripheral airways. The analysis demonstrates that severe patients requiring longer oxygen treatment and with increased CT scores are at higher risk of abnormal DLCO, indicating long-term irreversible lung injury[27]. Similarly, in another follow-up study, after 1 year of hospital discharge, patients experienced severe COVID-19 outcomes and had irreversible fibrotic interstitial lung abnormalities[28].

On the other hand, Chen *et al*. observed gradual improvement of around 47% of discharged COVID-19 patients with the help of CT score in a 1-year follow-up study, whereas elderly patients have shown the risk of long-term complications because of unsatisfactory recovery since hospital discharge. Elderly patients who have been given steroids are also at risk of long-term irreversible complications, whereas most studies have observed recovery of patients from lung injury[29-31]. Post-infectious pulmonary fibrosis is another common finding in critically ill COVID-19 patients diagnosed with chest X-ray, presence of hypoxia, or 6MWT[32]. Recalde-Zamacona *et al*. analyzed 10 critical COVID-19 patients with at least one comorbidity, and the histopathological findings match with other studies where numerous features have been observed, including diffuse alveolar damage, type II pneumocyte hyperplasia, hypertrophy, and reactive atypia. Moreover, they detected small pulmonary artery thrombosis, diffuse peripheral ground-glass opacities, and air bronchogram[33-35]. According to another 6-month follow-up study, more than half of the recovered patients had at least one common sequela, and nearly 60% had more than 1 symptom.

Another unusual complication observed recently in recovered COVID-19 patients is lung cavitation. A case report by Angirish and Parmar demonstrates lung cavitation in a 51-year-old recovered patient by CT re-examination while the patient was negative for SARS-CoV-2, bronchoscopy, tuberculosis, and fungal

infection[36]. Numerous case reports have already been published mentioning that lung cavity due to COVID-19 pneumonia as pneumonia weakens the patients' immunity, and secondary infection can occur during this period. However, a great concern has also been shown toward the elevation of lung cavity size, which can damage the lung. Unfortunately, patients with pre-existing lung disease or risk factors, which could lead to worse prognosis, are more prone to cavitation[37-43].

Pulmonary fibrosis is another major threat to COVID-19. According to research, around 40% of COVID-19 patients develop ARDS, and 20% have severe ARDS that influence the development of pulmonary fibrosis. Besides, cytokine storm and abnormal coagulopathy are the potential factors underlying the development of pulmonary fibrosis. Although pulmonary fibrosis is found to recover in most patients, patients with risk factors of severe complications might develop the irreversible form of pulmonary fibrosis[44-49]. Persistent post-COVID-19 pulmonary fibrosis can develop permanent pulmonary architectural distortion and irreversible pulmonary dysfunction in elderly individuals and heavy cigarette smokers during follow-up compared to the mild COVID-19 patients[50,51]. A comparison in pulmonary function between the control subjects and the COVID-19 survivors revealed decrease in total lung capacity (TLC), TLC %PRED, forced vital capacity, forced expiratory volume in the first second (FEV1), FEV1/FEV, and DLCO, along with a higher percentage of the restrictive lung in the post-COVID-19 group[52].

3. Risk factors of COVID-19 associated with fatal disease courses

Specification of the risk factors along with disease immunopathology related to severe outcomes in COVID-19 patients is advantageous for physicians in identifying the high-risk patients who require immediate treatment to prevent disease progression and adverse outcomes[53]. Risk factors include demographic factors such as age[19,54-56], diet and lifestyle habits[57,58], underlying diseases and complications[59,60], and laboratory indications[61,62]. These aspects can influence disease severity, progression to critical stage, and long-term complications.[63,64].

Although SARS-CoV-2 infects young, middle-aged, and older individuals, the dramatic elevation of disease severity has been observed in older adults as activation of the acquired immune system is delayed in older people, thereby facilitating viral replication and stimulating increased production of pro-inflammatory response[9,65-71]. While observing the hospital inpatients, Wang *et al*. found that patients requiring ICU admission (n = 36) are of older age (median age, 66 years) and have pre-existing comorbidities, including hypertension, diabetes, cardiovascular disease, and cerebrovascular disease[56]. Similarly, Zhang *et al*. reported disease severity in older adults (median age, 64 years) with pre-existing comorbidities[72]. A study containing 548 COVID-19 patients revealed that the risk factors of severe and long-term complications include elder age (surprisingly, males of elder age), underlying hypertension, underlying cardiac injury, hyperglycemia, and high LDH level, which is associated with sudden death[73]. Interestingly, two comprehensive meta-analyses indicate the positive correlation between smoking habit and disease progression in patients with critical illness of COVID-19.

Moreover, males over 65 years with advanced hypertension, diabetes, cardiovascular disease, and respiratory diseases are at higher risk of having long-term irreversible complications, a 6-time higher chance of getting hospitalized, and a 12-time higher chance of death than healthy individuals[71,74-76]. Cao *et al*. and other researchers found that higher disease susceptibility occurred in males as a remarkable number of ICU patients were male compared to the non-ICU patients (89.5% vs. 46.9%)[70,75,77,78]. Unexpectedly, obesity is another leading risk factor that causes poor outcomes in COVID-19-induced lung injury because of the high prevalence of undiagnosed obstructive sleep apnea[79]. Analysis of a cohort containing COVID-19 patients admitted into ICU demonstrates the relation between higher body mass index and intensive care requirements independent of age and comorbidities, such as diabetes and hypertension, which is a matter of concern[80]. Among all the comorbidities, Ebinger *et al*. found a strong correlation between pre-existing diabetes and concerning outcomes in COVID-19 patients as lymphocyte counts, amount of red blood cells, and hemoglobin level were comparatively lower in diabetic patients[58,81]. The increased blood glucose level caused impaired innate immunity in diabetic patients. Thus, cytokines' glycosylation disrupts cytokine function dependent on type I helper T lymphocytes[82].

In addition, higher expression of ACE2 in the lungs and other tissues of type 2 diabetes mellitus patients is associated with chronic inflammation, insulin resistance, and endothelial cell activation that, in turn, aggravate alveolar-capillary barrier functionality[83,84]. A cohort of 54 COVID-19 patients demonstrates the threat of hypertension toward the severe outcomes of COVID-19, such as ARDS, that is surprisingly independent of age[85]. Moreover, based on the baseline characteristics of 1591 ICU patients, the risk of hypertension with COVID-19-induced long-term complications and mortality by affecting lung function and disrupting oxygen delivery as 49% of patients had pre-existing hypertension[70,82]. Thus, COVID-19-mediated cardiovascular deaths correlate with poor blood pressure control. Moreover, downregulated

ACE2/angiotensin-(1-7) and upregulated ACE/angiotensin II have a greater impact on increasing the risk of severity of COVID-19 patients with comorbidities[86].

Laboratory findings may help illustrate the risk factors of extreme disease outcomes. Decreased lymphocyte and eosinophil counts, C-reactive protein, procalcitonin, and D-dimer concentrations are more noticeable in severe COVID-19 patients than in non-severe patients. These are some of the potential risk factors used to indicate disease progression[9,55,71,72,77]. Moreover, estimating serious outcomes in COVID-19 patients are possible through the neutrophil-to-lymphocyte ratio, neutrophil-to-$CD8^+$ T cell ratio, platelet-to-lymphocyte ratio, and N terminal pro B type natriuretic peptide[61,87-90]. Additionally, a biopsy study observed less amount of peripheral CD4 and CD8 T cells cause lymphopenia in COVID-19.[91]. Changes in serum D-dimer levels indicate the crosslink between the elevated D-dimer concentration and the dramatic risk of thromboembolism, long-term complications, and COVID-19-mediated mortality[5,87,92].

4. Different 3D bioprinting techniques

3D bioprinting is an alternative to conventional prototyping methods that utilize computer-aided designs to develop new products, including cells, biomaterials, or even living tissue. Bioprinting technology can be divided into three distinct categories, such as material jetting, material extrusion, and vat polymerization (**Figure 1**)[93].

4.1. Material jetting

Material jetting can be used to build different materials on a pre-defined platform by jetting droplets. Different types of material jetting are available now.

4.1.1. Inkjet-based bioprinting

Different cells or biomaterials can be deposited as droplets through various dispensing forces. The heating reservoirs or piezoelectric actuators apply heat to create gasification while generating and printing bubbles. On the other hand, piezoelectric actuators give rise to pressure pulses to print cells in a pre-determined place. Although inkjet-based bioprinting is faster, there is a high chance of cell damage and lysis during the printing because of high temperature and pressure. In addition, the droplets are not uniform in all the places[94].

4.1.2. Laser-assisted bioprinting

During laser-assisted bioprinting, a laser gets illuminated on the donor ribbon layer so that the energy gets absorbed and a high-pressure bubble gets created. The bubble influences the bioink to be deposited in the pre-determined place as a droplet. This high laser energy is responsible for cell damage and is one of the major disadvantages of this technology[94].

4.1.3. Acoustic droplet ejection bioprinting

In acoustic droplet ejection bioprinters, heat, pressure, voltage, or shear stress are not applied. Rather, the bioinks are influenced to produce droplets through acoustic waves. However, slight disturbance while printing can cause uncontrolled droplet ejection[95].

4.1.4. Microvalve bioprinting

Pneumatic pressure is given to operate the microvalve for droplet generation. After applying the voltage pulse, a magnetic field is generated that pulls the plunger upwards, and the back pressure causes bioink ejection. Depending on the pressure, this technique can be either continuous or not. Compared to other bioprinting techniques, the microvalve bioprinting technique generates identical droplets. In addition, cells printed through this technique retain their functionality and proliferation capability, and their genotype and phenotype are preserved, making this technique favorable for printing numerous types of cells[95].

4.2. Material extrusion-based bioprinting

Mechanical or pneumatic system is being utilized in this technique to disperse bioink through a micro-nozzle for creating two-dimensional or 3D structures. This technology has multiple advantages, including the ability to deliver different types of cells and materials and to disperse highly viscous bioinks containing a high number of cells, pellets, and tissue spheroids. Compared to other techniques, the cell viability in this technique is above 90%, and the fabrication time is short. That is why, the technique is advantageous to all[95].

4.3. Vat polymerization-based bioprinting

Vat polymerization-based bioprinting has better resolution and accuracy than other bioprinting technologies, making this technology attractive for fabricating complex extracellular matrices[93]. Different types of vat polymerization-based bioprinting are described in the following:

4.3.1. Stereolithography

Stereolithography utilizes a laser or digital light projector to crosslink the bioinks photolytically in a single printing plane. The advantages of this technique include high resolution, short printing time, and high cell viability[95].

4.3.2. Digital light processing

Digital micromirror device is utilized in digital light processing to crosslink photocurable bioinks for

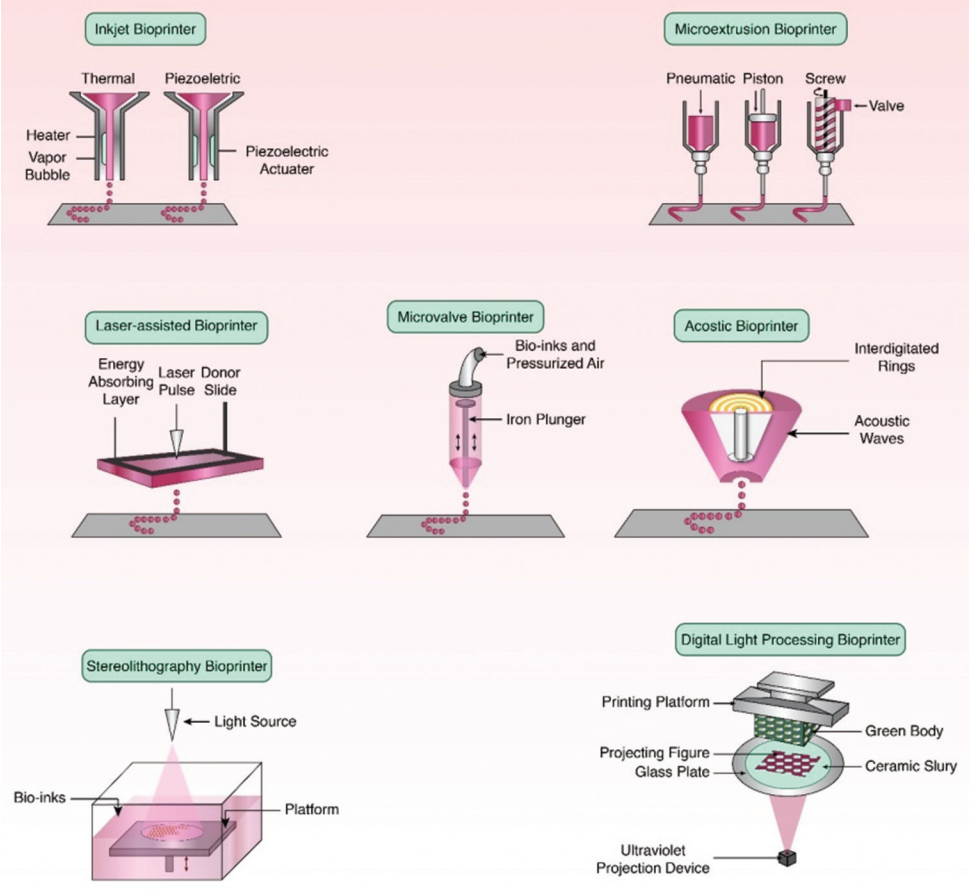

Figure 1. Different techniques of 3D bioprinting.

immediate crosslinking. Depending on the layer thickness, the building time can be potentially reduced. Moreover, the required energy input can be controlled by modifying light source and exposure time[93].

5. Application of 3D bioprinted lung to treat irreversible lung damage

3D bioprinting is a biofabrication method that utilizes computer-aided design for depositing various cells or tissues in a pre-decided location. It is intelligent enough to create complex geometric parts at a faster pace, which other technologies may not be able to catch up with. Moreover, a high degree of fidelity can be maintained. Quick redesign and repair of the printed construct are also possible with the help of 3D bioprinting as it utilizes computer software[96]. This technology can control the structure of the cell biomaterial architecture and help maintain and mature the tissue construct by providing the required physicochemical and biological environment. Selection of the perfect bioink is necessary to fabricate a 3D structure that mimics the actual tissue or organ, and multiple biomaterials can be mixed based on the mechanical properties and requirements[94]. Selection of potential bioinks, perfect bioprinting technique, and maintenance of microenvironment for promoting tissue morphogenesis will lead to the generation of a construct with all the required functionalities[97]. Total lung construct requires different living tissues and other components to be functional, and 3D bioprinting can deposit all the components, including cells, growth factors, and matrix material. That is difficult for other methods because of the complexity of human body[96].

Bioinks preparation, selection of appropriate bioprinting technique, and bioprinting procedure are the major steps of this stage, and among these three, preparation of bioinks and bioprinting technique selection are the most crucial steps because the bioinks and the chosen technique could influence the effectiveness of the printed construct. Preparation of bioinks is governed by multiple factors, such as suitable cell source, perfect scaffold materials, and proper additives (growth factors, chemicals, and microcarriers)[97]. Moreover, selecting a perfect bioprinting technique is necessary to increase cell viability as cell viability depends on factors such as duration of the whole printing procedure and cells' sensitivity. Thus, to secure the required number of cells, a bioprinting technique requiring lesser time to

complete the printing procedure and supply all the required components to the cells (culture media) must be chosen[98]. Post-bioprinting is the third stage that includes all the post-processing steps to make a mature and fully functional bioprinting construct for *in vivo* usage[97].

3D bioprinting has the capability of influencing stem cell differentiation throughout the printing procedure, and this technique is capable of replicating supple and tough textures *de novo* along with the precise control over different cellular compositions, structural complexity, distribution, and effective printing with accurate features that are reproducible and repeatable[97-100].

Recently, human alveolar lung model has been successfully fabricated *in vitro* through 3D bioprinting technique (microvalve bioprinting). The lung model had collagen matrix as well as alveolar lung epithelial, endothelial, and fibroblast cells. This printed construct maintained high cell viability, proliferation, and survivability. However, optimization of the cell printing parameters was not easy. Thus, more investigations are warranted to optimize the fabrication of 3D bioprinted organ that can be transplanted into human[101].

Grigoryan *et al*. have created an air sac with a detailed internal structure including blood vessels and airways, enabling air pump, and oxygen delivery to the surrounding environment. Moreover, the lung analog could withstand the inhalation and exhalation pressure. Interestingly, the whole printing procedure took a few minutes, which is superior over the conventional technique. Primary stem cells of mice were taken for printing to treat the chronic liver damage of the mice and the printed construct's details were inspected. The survival of liver cells in the mice indicates that the bioprinted blood vessels can deliver nutrients to the surrounding cells[102,103]. 3D-bioprinted construct requires scaffolds with controllable microstructures for the survival and growth of the printed cells following transplantation *in vivo*. The porous scaffolds promote the diffusion of nutrients and oxygen, improve the mechanical stability of the implant, and stimulate the formation of new organizations. Rapid prototyping with computer-aided design helps control the internal structure of the scaffold characterized by all the required features[96].

Risk factors, including age, pre-existing comorbidities, and critical laboratory findings, are associated with long-term irreversible lung damage. The severity determines whether the damage is reversible or not[19]. Moreover, some patients have already undergone lung transplantation due to COVID-19-mediated sudden and irreversible lung damage accompanied by numerous challenges[20,104]. Unfortunately, the number of COVID-19 recovered patients requiring a lung transplant will dramatically increase in the long run, leading to a shortage of donors. However, having a donor would not be an effective solution because of the high chance of mismatch. Another concern is antibody-mediated graft rejection, which is life threatening to the host[104,105].

3D bioprinting is becoming a promising tool for reconstructing organs by utilizing specific issues and structures from patients for different purposes[106]. A 3D-bioprinted lung that mimics the natural lung has been constructed and transplanted into a New Zealand rabbit model. Kim *et al*. demonstrated an efficient method for creating a 3D-printed trachea with a functional, cartilaginous, and epithelialized airway to improve host survivability[107].

Regulatory considerations for customizable tissue-engineered constructs are important for the approval of the 3D-bioprinted construct. Bioresin selection is a challenge as there are no approved bioresins. Moreover, there is no effective way to determine the printed construct's toxicity and biocompatibility, making the whole procedure harder to complete. The absence of threshold process parameter limit and well-defined processing steps puts a constraint on process reproducibility. Thus, a reconsideration of all essential components is a prerequisite for simplifying the 3D bioprinting process and increasing its application[93].

6. Evaluation techniques of irreversible lung damage

Recovered COVID-19 patients who have associated risk factors before the infection are vulnerable to irreversible lung injury, which necessitates a new lung for survival. Before planning for replacement, accurate evaluation of the existing lung is compulsory.

The easiest evaluation can be carried out with a portable chest X-ray, which can determine infected or damaged area in the patient's lung and help with further decision-making[108]. A very common evaluation technique is 6MWT, which is utilized during the follow-up studies on recovered COVID-19 patients to estimate the extent of lung damage and the probability of irreversible lung damage[109]. A pulmonary function test can potentially evaluate lung conditions and determine further treatment for individual patients[110,111]. A comprehensive CT examination will be advantageous in evaluating any contiguous or overlapping thin section in the chest. The presence of cysts, emphysema, mosaic attenuation, persistent air trapping, and acute or chronic pulmonary thromboembolic disease can also be determined with the help of CT. Numerous features can be used to guide the transplantation decision, including interlobular septal thickening, abnormal ground-glass opacity, and/or DLCO[112]. Moreover, any sequential change in lung volumes and pulmonary opacity can be observed through quantitative CT, and the disease progression can be determined by correlating lung fibrosis with

physiological impairment[113-115]. In addition, there are few semi-quantitative methods available that can be utilized to evaluate the condition of the lung, such as a calculation method using software that automatically sketches volume, a calculation method for evaluating the degree of involvement according to four lobes or six zones of the lung, and pulmonary inflammation index[116].

Artificial intelligence-assisted chest high-resolution CT is another technique used to evaluate the extent and the degree of lung inflammation. Moreover, the degree of pulmonary fibrosis can be utilized in determining the long-term effect of pulmonary fibrosis[117].

An automatic biochemical analyzer can analyze irreversible lung damage by determining the concentration of KL-6 in patients' serum. Individuals with pulmonary fibrosis have a higher level of KL-6 compared to healthy individuals, and the optimal threshold for COVID-19-mediated irreversible fibrosis is 674 U/ml, with a sensitivity of 0.824 and specificity of 0.838. Comparing the standard level with the level in patients with irreversible fibrosis can help determine the condition before deciding on further treatment[118,119].

7. Conclusion

Receptor specificity of SARS-CoV-2 leads to multiple organ dysfunction. Respiratory failure causes the highest number of deaths and irreversible lung damage. Post-COVID-19 sequelae of lung diseases have been observed in 80% of the infected individuals despite complete eradication of the virus. Complications, including pulmonary embolism, pulmonary hypertension, breathing difficulty, and post-infectious pulmonary fibrosis, have been observed during the follow-up studies in the recovered COVID-19 patients. Surprisingly, the research found that more than half of the recovered patients experienced at least one sequela, whereas 60% experienced more than 1 symptom. Post-COVID-19 sequelae of lung diseases are associated with several risk factors, such as age, diet and lifestyle habits, comorbidities, long-term ICU admission, and D-dimer concentration. This irreversible lung damage can cause sudden death and raise other serious concerns. To avoid these issues, 3D bioprinting can be utilized to print patient-specific lung, which is capable of working perfectly in the host, thereby saving the lives of individuals with irreversible lung damage.

Conflict of interest

The authors declare no conflicts of interest regarding the publication of the manuscript.

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