




# 3D printing in the battle against COVID-19

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## Abstract

Coronavirus disease 2019 (COVID-19) that is SARS-CoV-2, previously called 2019-nCoV, is a kind of human infectious disease caused by severe acute respiratory syndrome coronavirus. Based on the prompt increase of human infection rate, COVID-19 outbreak was distinguished as a pandemic by the World Health Organization (WHO). By 2020, COVID-19 becomes a major health problem all around the world. Due to the battle against COVID-19, there are some adversities that are encountered with. The most significant difficulty is the lack of equipment for the COVID-19 battle. Lately, there is not sufficient personal protective equipment (PPE) for hospital workers on the front lines in this terrifying time. All around the world, hospitals are overwhelmed by the volume of patients and the lack of personal protective equipment including face masks, gloves, eye protection and clothing. In addition, the lack of nasal swabs, which are necessary components, that are used for testing is another issue that is being faced. There are a small number of respirators, which are emergency devices that help patients breathe for a short period of time. To overcome the limited number of equipment available, the foremost solution can be 3D printing that allows three-dimensional renderings to be realized as physical objects with the use of a printer and that revolutionized prototyping. Low-cost desktop 3D printers allow economical 3D models and guides but have less quality approvals. 3D printing is already well integrated into the process of COVID-19 battle by manufacturing the equipment that are convenient. The goals of this review are to explore the techniques of 3D printing for the equipment that are used for COVID-19 battle and evaluate the materials that are used for manufacturing and the manufactured equipment. Lastly, the advantages and disadvantages of 3D printing are figured out.

**Keywords** COVID-19 · SARS-CoV-2 · 3D printing · Biomaterials · Tissue engineering

## 1 Introduction

SARS-CoV-2, which has affected the whole world, first appeared in a market where seafood is sold in Wuhan, China, in December 2019. As of March 11, COVID-19

disease has been declared a pandemic by the World Health Organization [1]. Many people have lost their lives in the process that has passed since the day it emerged. According to the data of the World Health Organization, 79,673,754 confirmed cases and 1,761,381 deaths (as of December 28) have occurred worldwide so far [2]. Since the disease can be transmitted from person to person, it can spread easily. The more contact, the higher the risk of contracting the disease. While the disease is highly transmitted through respiratory droplets, some studies show that the disease can be transmitted by other means [3].

Disease symptoms include lack of taste and smell, high fever, dry cough, shortness of breath, weakness, muscle and joint pain, sore throat and diarrhoea [4]. The most common of these are high fever, dry cough and malaise [5]. In the progressive course of the disease, pneumonia firstly and then multiple organ failure occur depending on the disease. Patients with severe lung damage are connected to respiratory support devices [6].

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In studies conducted on patients, it has been determined that COVID-19 disease has no effect on gender and age, and the risk of transmission of SARS-CoV-2 to people of different races, genders, and ages is equal [3].

Currently, there is no definitive treatment method for COVID-19. With the measures taken, the rate of catching the disease is tried to be prevented. For this reason, personal protective equipment (PPE) is used. Certain parts of many protection equipment used within the scope of coronavirus measures, (masks, visors), parts of ventilator devices and some of the materials used for testing purposes are produced by 3D printers [7, 8]. At the same time, 3D printing technology is promising for the treatment of organ damage caused by the disease.

3D printing is a production method in which materials such as plastic or metal are stacked in layers to obtain 3D products [9]. It is also known as additive manufacturing (AM) or rapid prototyping [10]. Until now, this method has primarily been used to create prototypes in the engineering field [9]. It has applications in a variety of industries such as aviation, automotive, construction, marine and offshore and food [10]. In addition, it is widely used in the field of health [9]. In addition to these, it is a technology that enables many new applications. Basically for each application, production speed, print resolution and materials to be used should be considered. Depending on the International Organization for Standardization (ISO)/ American Society for Testing and Materials (ASTM) 52900: 2015 standard, the process in 3D printing applications is divided into seven basic categories. These are binder jetting, directed energy deposition, material extrusion, material jetting, powder bed fusion, sheet lamination and vat photopolymerization [11]. It makes possible mass customization of products compared to traditional printers [9]. This review will cover the 3D printing applications in the battle against COVID-19, a pandemic issue.

## 2 COVID-19

### 2.1 The pathology of SARS-CoV-2

SARS-CoV-2 is an enveloped single-stranded positive-sense RNA virus from the coronavirus family, is not segmented and is between 26 and 32 kb in length [12, 13]. It has a nucleocapsid composed of genomic RNA and phosphorylated nucleoid capsid protein [13]. It comes from a common family with viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which appeared in previous years [12] (Fig. 1).

One of the most significant building blocks of SARS-CoV-2 is envelope spike (S) protein. The S protein mediates the binding of the virus to the receptor, which is called angiotensin-converting enzyme 2 (ACE-2), and has the ability

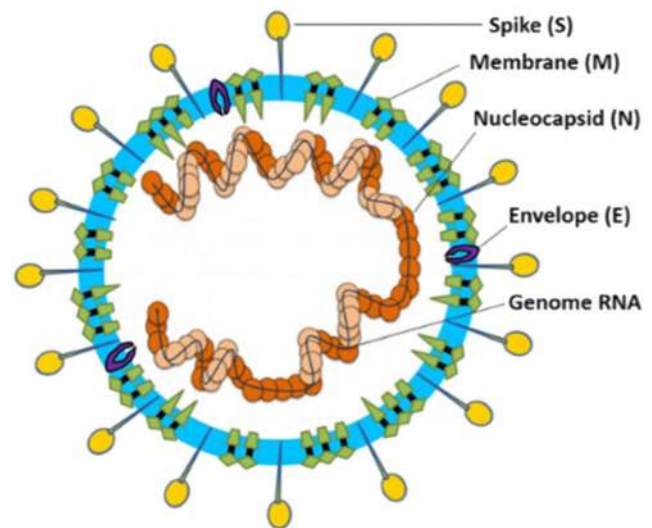


Fig. 1 Structure of coronavirus [13]

to perform membrane fusion. [4]. The areas in which this receptor is expressed are the cell entry sites for SARS-CoV-2, predominantly expressed in the pulmonary alveolar, heart, kidney and intestine [4, 14].

### 2.2 Organ damages caused by COVID-19

After the coronavirus enters the body, it can damage many organs. Although the permanence of these damages has not been proven yet, the duration of the disease varies according to the size of the damage.

Researches have indicated that coronavirus usually enters the body through respiration and causes pneumonia by damaging the lungs [6]. In the examinations performed on the lungs of patients who tested positive for COVID-19, ground-glass opacities and consolidation were detected in the lungs of some patients who underwent chest CT scans [15]. More studies are required to understand whether this condition is permanent in individuals who survive from the disease.

The liver is also affected by the disease. Abnormal levels of alanine transaminase (ALT) and aspartate transaminase (AST) have been detected in the blood of some of the patients infected with SARS-CoV-2. Detection of these enzymes at a high rate indicates that the liver has been damaged. COVID-19-induced liver damage is thought to be caused by drug-induced toxicity and systemic inflammation caused by hypoxia associated with pneumonia or cytokine storm. It is also thought that the virus can directly infect liver cells, thanks to the ACE-2 proteins found in the liver [16].

Studies about the gastrointestinal system suggested that the coronavirus could affect this system as well. The detection of SARS-CoV-2 in the stool of a sick individual by Holsue et al. suggested that the virus would also affect the gastrointestinal system [13]. Other studies have demonstrated that ACE-2 is expressed in stomach, duodenal and rectal epithelial cells. In a

study conducted in the UK, it was found that the interaction between SARS-CoV-2 and ACE-2 disrupted the function of ACE-2 and caused diarrhoea. For patients with digestive diseases or potential faecal microbiota transplant donors, the ability of the virus to be linked through the digestive system is of concern [16].

Studies on patients diagnosed with COVID-19 showed that the virus also had an effect on the cardiovascular system. Cardiovascular comorbidities were more common in individuals with severe disease. According to data from the Chinese National Health Commission, 17% of the people who got the disease had coronary heart disease. In a study conducted on 138 patients in Wuhan, China, myocardial damage was detected in 22% of the patients [17]. In a study conducted on patients in North America, Europe, and Asia, it was found that patients who died from COVID-19 had a prevalence of coronary artery disease, heart failure and cardiac arrhythmia [14]. Cardiovascular disorders caused by COVID-19 can vary depending on age, immune system function, presence of ACE-2 protein and previous cardiovascular disease [17].

Neurological problems occur in about 50% of individuals diagnosed with COVID-19. More than 300 studies conducted around the world have shown that COVID-19 patients develop mild symptoms such as headache, loss of smell and tingling. These symptoms can progress and cause severe neurological damage: paralysis, inability to speak and nervous seizures [18]. According to an article published in the journal *Brain*, patients diagnosed with COVID-19 have experienced hallucinations, paralysis and delirium. Studies were carried out on 43 patients in London. As a result of the studies, 10 patients were diagnosed with delirium, 12 patients with brain inflammation and 8 patients with nerve damage. In addition, paralysis and hallucinations were observed in some patients [19]. These damages in the brain are thought to be caused by low oxygen saturation or cytokine storm. When the autopsy of individuals who died as a result of COVID-19 in Italy was examined, viral particles were detected in the endothelial cells covering the blood vessels of the brain. This strengthened the possibility that the virus could bind directly to brain cells. Scientists have recently suspected that the virus actually causes respiratory failure and death by damaging the brain stem rather than through the lungs [18].

Another organ thought to cause damage from COVID-19 is the kidney. High levels of protein in the urine and abnormal levels in blood values are among the indicators of kidney damage. Moderate or severe kidney damage has occurred in 30% of patients diagnosed with COVID-19 in China and New York. While acute kidney damage is observed in some patients, in some patients, the damage may be severe enough to require dialysis [20]. According to the data of the American Nephrology Association, 10 to 50% of patients in intensive care have kidney failure at a level that requires dialysis. Since the beginning of the pandemic in Mount Sinai,

46% of patients diagnosed with COVID-19 have been diagnosed with acute kidney disease, and many patients had no history of kidney disease [21]. SARS-CoV-2 can form clots that can impair the function of the kidney by occluding the blood vessels in the kidney. Thanks to the ACE-2 proteins found in kidney cells, it is thought that the virus can bind to these cells and damage the kidney. Concurrently, observing abnormally low oxygen levels in the blood due to pneumonia that occurs with the entry of the virus into the body can also cause kidney damage. Cytokine storm is observed as another possibility. Severe inflammation that can occur in the body due to severe cytokine influx can destroy healthy tissues in the kidney [20].

### 3 3D printing technology

The 3D printing method, known as the layered production (AM) method, is based on the principle of layered production of various materials such as powders, metal, living cells, plastic, liquids and ceramics. This method generates various and complex 3D geometries using a computer-aided design (CAD) model or computed tomography (CT) scanning [22, 23]. With the 3D printing method, it is possible to create personalized organ and scaffold models and quickly produce and print defective areas directly. In this way, 3D printing technology offers new possibilities in the field of medicine to solve donor problems and create tissue or organ models [22, 24]. Due to the low production costs of 3D printers that have fast and simple system, 3D printing method has recently gained great importance in the fields of medical equipment, implant material and cell printing [9]. The printing process includes several steps such as design, software workflow, material checks, printing, finishing, process validation and testing. First, the desired printing model is designed using a 3D CAD model. This CAD model is then converted into a file containing instructions on how the printer will create the product and sent to the printer. The most significant parameter of the designed product is the material used to create the product. It is crucial that the material used is selected according to the desired properties. The instructions are ready to be delivered to the printer as a printable software file (most commonly G-Code or AMF). After printing the product, post-processing steps and some testing can be applied to the product [25]. The main methods of 3D printing technology are shown in Table 1 below.

#### 3.1 3D printing methods

##### 3.1.1 Fused deposition modelling

In the fused deposition modelling (FDM) method, printing layers of product thermoplastic polymer filament are used.

**Table 1** A summary of main methods of 3D printing technology [23]

Methods	Materials	Application	Benefits	Drawbacks
Fused deposition modelling	Continues filaments of thermoplastic polymers Continues fibre-reinforced polymers	Rapid prototyping toys Advanced composite parts	Low cost High speed Simplicity	Weak mechanical properties Limited materials (only thermoplastics) Layer-by-layer finish
Powder bed fusion (SLS, SLM, 3DP)	Compacted fine powders Metals, alloys and limited polymers (SLS or SLM) Ceramic and polymers (3DP)	Biomedical Electronics Aerospace Lightweight structures (lattices) Heat exchangers Biomedical Large structures Buildings	Fine resolution High quality	Slow printing Expensive High porosity in the binder method (3DP)
Inkjet printing and contour crafting	A concentrated dispersion of particles in a liquid (ink or paste) Ceramic, concrete and soil		Ability to print large Quick printing	Maintaining workability Coarse resolution Lack of adhesion between layers Layer-by-layer finish
Stereolithography	A resin with photo- active monomers Hybrid polymer-ceramics	Biomedical Prototyping	Fine resolution High quality	Very limited materials Slow printing Expensive
Directed energy deposition	Metals and alloys in the form of powder or wire Ceramics and polymers	Aerospace Retrofitting Repair Cladding Biomedical	Reduced manufacturing time and cost Excellent mechanical properties Controlled microstructure Accurate composition control Excellent for repair and retrofitting	Low accuracy Low surface quality Need for a dense support structure Limitation in printing complex shapes with fine details
Laminated object manufacturing	Polymer composites Ceramics Paper Metal-filled tapes Metal rolls	Paper manufacturing Foundry industries Electronics Smart structures	Reduced tooling and manufacturing time A vast range of materials Low cost Excellent for manufacturing of larger structures	Inferior surface quality and dimensional accuracy Limitation in manufacturing of complex shapes

The filament is firstly heated until a semi-liquid state is reached at the nozzle and then extruded onto previously printed layers [23]. This method is inexpensive and easy to use and install and also has a low material cost. It can be printed by FDM printers that are using a variety of materials such as polylactic acid (PLA), ABS, TPE/TPU, soluble material, nylon and polypropylene [24].

### 3.1.2 Binder jetting

In this rapid and additive manufacturing method, a liquid binder is selectively deposited to coalesce the powder particles. In binder jetting process, a lot of materials including sands, polymers, metals, hybrid and ceramics can print. Moreover, the binder jetting process is fast, simple, inexpensive and capable of printing large products [26].

### 3.1.3 Directed energy deposition

Directed energy deposition (DED) method is mainly used in the production of high-performance super alloys [23]. This method is used for printing polymers, ceramics, metals and metal-based hybrids [26].

### 3.1.4 Material jetting

In material jetting, the material is selected and deposited drop by drop. This process is based on the dispensing of photosensitive material droplets by a printhead, building a part layered manufacturing using the ultraviolet (UV) light. A multi-material print is available with materials such as biologicals, polymers, composites, hybrids and ceramics [26].

### 3.1.5 Powder bed additive manufacturing (PBF)

This 3D printing process examples are selective laser sintering (SLS), electron beam melting (BM) and selective heat sintering (SHS) printing techniques. In this method, the material powder is melted using an electron beam or laser. Various materials are used such as metals, hybrids, ceramics, polymers and composites [26].

### 3.1.6 Sheet lamination technology

In this method, sheets of material are bonded together to produce a portion of a product. Ultrasound additive manufacturing (UAM) and laminated object manufacturing (LOM) are examples of this process [26].

### 3.1.7 Vat polymerization process

Vat polymerization technique is generally based on the principle of using a light, ultraviolet (UV) or laser to the curing of

photopolymers. The examples of this process are digital light processing (DLP) and stereolithography (SLA). A high-quality product with good details is possible by the photopolymerization method [26].

### 3.1.8 Inkjet printing and contour crafting

According to digital instructions, inkjet printing technique uses electromagnetic, piezoelectric or thermal technology to depositing droplets of “ink” onto a substrate. Heated printhead generates air bubbles that collapse, generating pressure pulses to ejecting drops from nozzles [27]. This method, which is efficient and fast, creates flexible complex structures [23].

### 3.1.9 Other methods

3D printing also has methods such as high-resolution 3D printing, 3D printing using reversible addition-fragmentation chain transfer (RAFT) photopolymerization and 4D printing. In this 3D printing method that works with high-energy ultraviolet (UV) light, liquid resins are transformed into solid objects with high speed and high resolution. This method provides many advantages such as lower cost, high biocompatibility and deeper penetration [28]. The alternative method is the photoredox-catalysed RAFT polymerization method using different reagents. RAFT polymerization is activated by a photoredox catalyst through a light-induced transfer of electron or energy between the RAFT agent and the catalyst [29]. 4D printing is also the creation of three-dimensional structures that have the ability to adopt different shapes when exposed to various environmental stimuli with smart materials. This method offers numerous advantages such as low cost, short time period, flexibility, versatility and low margin of error [30]. In 4D bio-printing method, after living cellular structures are printed, cells can continue to develop and form structures similar to natural tissue [29]. Although there are certain limits to these methods, they could create new opportunities of producing 3D printed materials with vivid characters, but more systematic studies are needed.

## 3.2 3D printing technology applications in manufacturing

3D printing is frequently used in many areas such as aerospace industry, construction, architecture, building, medicine, electricity, automotive industry, food, textile, fashion industry, healthcare and medical industry. In the healthcare and medical industry, 3D printing technology has several advantages:

- With 3D printing technology, the natural structure of the skin is produced at a lower cost.

- By printing drugs with 3D printing technology, drug efficiency can be increased; size reduction, required dosage and accurate control of drugs are provided.
- With 3D printing, the function of organs and tissues can be improved, replaced or maintained.
- 3D printing technology focuses on producing, improving or preserving the function of the bone or cartilage as a result of damage from trauma or disease.
- Organ failure that is caused by accidents, illness and birth defects can also be printed by 3D printing technology.
- 3D printing technologies can create controllable models of cancer tissues and have the potential to accelerate great cancer research [26].

## 4 Materials

### 4.1 Materials used in 3D printing for COVID-19

Considering personalized medicine, which is an upcoming major area, 3D printing is the perfect technology. A wide variety of biomaterials such as polymeric biomaterials, hydrogel, ceramic-based and composite have been used and developed as inks for creating 3D structures with a wide range of size and stiffness [31]. There are plentiful printable materials with great specifications for using in external applications, but biomaterials must have specific features for being implantable. Printable biomaterials must be biocompatible, have suitable mechanical properties, have acceptable degradation kinetics and demonstrate tissue biomimicry, and also their degradation by-products must be safe for the physiological conditions and interactions with the body. In addition, FDA approval is another major factor for the biomaterial used in 3D printing [32, 33].

In the battle against COVID-19, there are three approaches: preventing the virus from entering the cell, preventing the virus proliferation in the cell and preventing the body's overreaction to the virus. Studies continue based on these approaches all around the world, but as is known, organ damage from COVID-19 may occur. Tissue engineering can be used to treat organ damage caused by COVID-19, but the applications of 3D printing in the field of tissue engineering are limited because of the biomaterials that are used in this technology. Despite the existence of limitations, there are a variety of materials such as protein-derived biomaterials like albumin, fibronectin, collagen, hyaluronic acid and this kind of materials that also provide an appropriate environment for cell growth [34]. Proteins, natural polymers, are used widely because of their beneficial characteristics like biodegradability, biocompatibility, and abundant availability [35]. Polymeric materials have important advantages such as low cost, high availability, effortlessness in design and synthesis and unique mechanical properties for organ scaffold synthesis and support, but there polymers that provide biocompatibility are not enough [36]. PLA, PVA and

ABS can be given as examples. Synthetic and natural polymer combinations are also used for scaffold designing in tissue engineering for organ damage [36].

SARS-CoV-2 infection can be divided into three levels. In stage 1, there is an asymptomatic incubation period, while stage 2 and 3 are non-severe and severe symptomatic periods, respectively [37]. Therefore, when the immune response of the host is insufficient, devastation of the affected tissue will occur, especially organs like the kidney and intestine where ACE-2 expression is high. As a result of this destruction, the damaged cells stimulate the initiation of inflammation in the lungs. The key to life-threatening respiratory disorders at the severe stage is lung inflammation, so the focus at this point should be about pushing down inflammation and managing symptoms [38]. 3D printing can be used for producing simple design, proper, inexpensive, structured and tailored drug delivery systems for this purpose. HPMC, poly(acrylic acid), cellulose acetate, and polyvinyl alcohol (PVA) are the examples of the materials used in 3D for drug delivery systems [39].

Although there are plenty of studies that determine the treatment of COVID-19, another significant point about this issue is preventing the spread of infection. In accordance with this purpose, the lack of equipment is a significant limitation in the battle against COVID-19. Consequently, there is an increasing demand for medical devices, visualization aids and personal protective equipment (PPE) such as gloves, face masks and face shields, respirators and their filters, which are used by hospital staff. For the manufacturing of PPEs like face mask, polylactic acid (PLA) polymer can be used [40]. In addition, arthroplasty helmets are redesigned to use as a PPE in a study by using silicone [41]. Lastly, 3D printing can also be used for the fabrication of temporary emergency dwellings to isolate people under quarantine [42].

### 4.2 Which types of equipment that are printed by 3D for COVID-19

Since the COVID-19 is a pandemic issue, to detect SARS-CoV-2 infection during early stages, the nasopharyngeal (NP) swab is an urgent equipment to collect nasal epithelial mucosa for testing. Currently, the demand for the nasopharyngeal swabs is unpredictably increasing, and with the help of 3D printing, immediate mass production for new swabs can be made [43].

Medical face shields have been become a trendy PPE to fabricate especially for healthcare workers. Face/eye protection demands more attention for the issues associated with severe infectious agents since the face is the most commonly exposed part of the body. Although wearing a surgical face mask might ensure protection from a distance between healthcare workers and patients who are diagnosed with COVID-19, additional PPE would be a necessity. 3D printing is sufficient to overcome the high demand for PPE. Because of this reason, different concept designs for face shield products are produced by additive

manufacturing. In the additive manufacturing process for face shields, biodegradable thermoplastic polymer/poly(lactic acid (PLA)-based material is used [44].

Currently, there are two types of focus in PPE, which are barrier PPE and filtering PPE. Since COVID-19 outbreak happened so quickly, the whole world needs both types immediately. Production methods that allow rapid shift manufacturing to PPE and related supplies can be used; however, the supply chain system is not prepared completely. Since 3D printing entails limited or no modification for a replacement from one product to making another, it is an elegant technology to do this. In the homemade 3D-printed face mask models with an integrated filter medium, 3D component ensures an airtight atmosphere between the airway of the user and the filter material [45].

According to WHO, one in six COVID-19 patients is suffering from difficulty breathing. By this reason, ventilator that supplies sufficient oxygen into the patient's lungs and that removes the carbon dioxide support may be required. A promising development about 3D-printed ventilators has taken place in Spain. Although it cannot be described as a ventilator but an emergency unit, it can be beneficial for patients who are suffering from breathing difficulty, but cannot be for the serious cases [46] (Fig. 2).

## 5 The role of 3D printing and its applications in COVID-19

During the COVID-19 outbreak, more than 100 different 3D printable PPE designs have been developed [47]. This systematic review is written by benefiting different Internet libraries. These libraries were ScienceDirect, PubMed, Google Scholar, and Google News. The words “3D print”, “COVID-19” and “materials” were used during searches for the studies examined in this section. The search year range in all libraries is set to cover November 2019 and beyond, the date of the first appearance of the disease. Moreover, 195 results were found in ScienceDirect and 119 results in PubMed. Furthermore, 7530 results were found in Google Scholar, but there are repeated results in these results. The article is selected by the usage of the 3D printing method and whether the printed material was used in the fight against COVID-19. Articles that do not comply with these terms were not included in the review. Related researches are described in detail below in subheadings.

### 5.1 Personal protective equipment

Minimizing the transmission of the virus from person to person depends on the effective use of personal protective equipment such as face and respirator masks, air-purifying respirators and face shields [7].

Medical staffs are working with great pressure increasing day by day since the alarming increase in the number of COVID-19 cases, not to mention virus mutations. One of the most important issues is the required number of medical equipment stock such as ventilators or face shields is inadequate because of the high demand and general disruptions to the global supply chain [48]. Protection of healthcare workers is a significant issue, especially during the treatment of COVID-19 patients, since their risk of being exposed to disease is too high. Healthcare workers are obliged to wear a mask with high filtering properties and a face shield while working. For this subject, efforts have been started to produce new ones instead of personal protective equipment that are inadequate (Table 2). To provide more technical notes, there is an article reporting the entire digital workflow of Charlotte and Dave connectors to breathing devices [59]. The *NIH 3D Print Exchange* portal, where various protection equipment are also designed, models to be 3D printed can be discovered and created, which were launched by the National Institute of Health [8].

#### 5.1.1 Face masks

Face masks are one of the leading personal protective equipment. Masks that are named as surgical masks cover the nose and mouth, but do not fit the face properly and are loose. A face mask that provides a one-sided protection also ensures to prevent outcoming body fluid and to hold germs. Yet, respirators fit perfectly and do not leak, and their filter retention rate is very high. Respirators without valves provide double-sided protection, since they filter the incoming and outgoing air. However, ventilators provide one-sided protection, although they facilitate breathing of air and reduce moisture accumulation. In addition, there are 3 types of respirator masks: disposable, half face and full face. Various studies have been carried out to provide high protection and to increase the comfort of usage [55] (Figs. 3 and 4).

The 3D-printed mask designed by Tomas et al. consists of 3 reusable parts, which are mask base, filter grill and filter insert [49]. As PLA does not harm in contact with the skin, these components are obtained by using polylactic acid (PLA). In addition to harmlessness, PLA is inexpensive and easy to print and does not require high temperatures to be shaped. Ultimaker S3 printer was used to print the mask parts. Mask straps are produced by using phlebotomy straps, which can be reused or disposed of. The disposable filter is placed between filter grill and filter insert. As a filter, nano-sized Cummins filters with the ability to filter over 95% are used [49, 50].

The aim of the project designed by Kvattho is to produce a mask with a reusable and replaceable HEPA filter with 3D printing technique to enhance its user and environmental

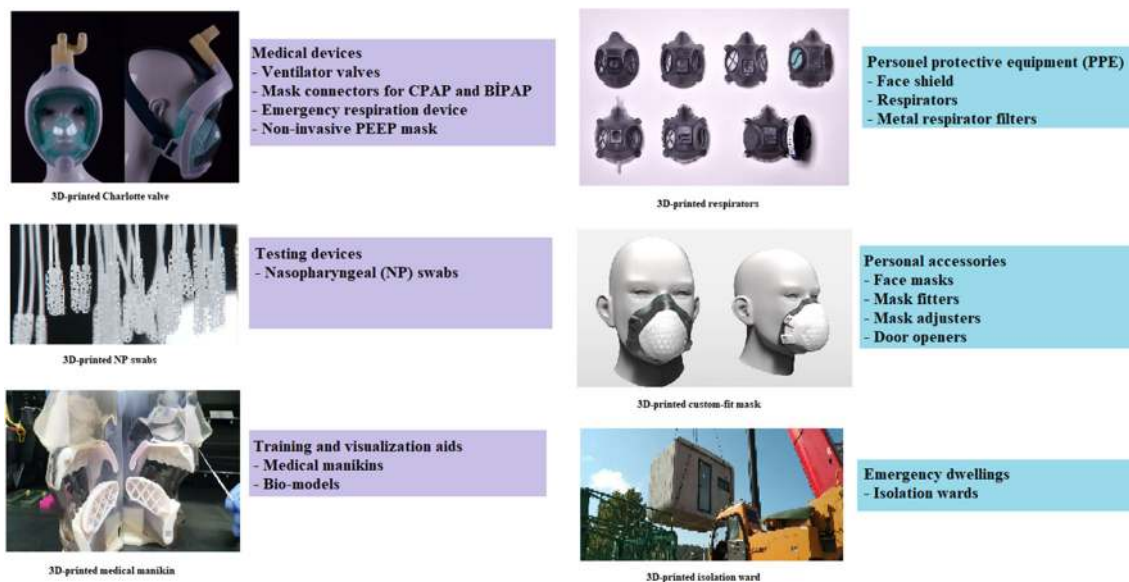


Fig. 2 Equipment that are printed by 3D for COVID-19 [40]

protection. In this study, the PLA filament was preferred for the mask to be more compatible with each individual. It also has good sealing and high efficiency. This mask is highly advantageous since the plastic part of the mask can be reshaped using both microwave and hot water to ensure a better fit on the user’s face [52, 53].

In the Lowell Makes’ mask 3D-printed design, a design that filters can be put into the masks, mask straps

are flexible and adjustable, and PLA and polyethylene terephthalate glycol (PETG) are ideal for printing these types of masks [53, 54].

Another significant system, powered air-purifying respirator (PAPR), is a system that provides filtered air, containing filters with a filtration rate of 95% or higher. Thus, it provides superior protection. Erickson et al. developed a helmet modification system with 3D printing. For this purpose, a new

Table 2 Personal protective equipment produced by 3D printing

Personal protective equipment (PPE)				
Producer	Materials	Purposes	Method	References
Face mask				
Thomas et al.	PLA	Customized mask production	FDM	[48]
Kvatthro	PLA	Customized mask production	FDM/microwave	[49, 50]
Lowell Makes	PLA/PETG	Flexible and adjustable strap	FDM	[50, 51]
Erickson et al.	N/A	Converting Flyte helmets to PPE	FDM	[52]
Swennen et al.	PLA	To produce a perfect fit mask with 3D face scanning	FDM	[53]
Agarwal et al.	PLA	Comfortable breathing and preventing the formation of fog in glasses	FDM	[54]
Copper 3D mask	PLA/copper	To produce antibacterial copper nanoparticle masks	N/A	[55]
Face shields				
Tino et al.	PLA	Producing suitable face shields	FDM	[56]
Mueller et al.	PLA/PETG	Obtaining more durable face shields	FDM	[57]
Auxiliary accessories				
Manero and friends	PLA	To facilitate the use of masks	FDM	[58]



**Fig. 3** Respirator types: **a** disposable, **b** half face, and **c** full face [55]



manifold design that is placed on the fan and creates a sealed air that goes to the filter was produced. The manifold design is 3D printed using durable materials. A 2-port optimized design for an adequate approach was formed to enable the production of 3D-printed designs and the most ideal manifold. Thus, the Stryker Flyte helmet has been modified to create a design that will filter the air entering the helmet in the best way [41].

In addition, face masks printed by 3D printers can be custom-made by using face scanning programs. The image obtained with the face scanning program was designed with the 3D modelling program and masks were produced in these dimensions. This mask has two reusable parts (3D face mask and filter membrane support) and two non-reusable parts (head fixing tape and filter membrane). In this project, the custom-made face mask is produced with the additive production of two reusable components, and the disinfection of these components can be provided with antimicrobial solutions. For the filter membrane, which is one of the non-reusable components, blown polypropylene and Velcro tape were used as the head fixing band [60].

Agarwal et al., on the other hand, determined the problems of masks’ inability to provide proper air circulation, the formation of vapour in the glasses, the inability to prevent the passage of particles adequately and the masks to be disposable and carried out studies to solve these problems. For this

purpose, using the 3D method, the mask was produced by using PLA, which is a more durable and biodegradable material than surgical masks. In addition, the mask is lightweight and allows comfortable breathing due to its valves, which prevent vapour formation in glasses. At the same time, this mask can be shaped according to the facial anatomy of the user [56].

Copper 3D mask has been developed since there are deficiencies in the design of surgical masks and the existing surgical masks do not create a complete barrier against microbes. Copper 3D mask is produced by printing a flat piece from PLA filament and is biocompatible. Copper nanocomposite was loaded to gain antimicrobial properties and can be recycled, which is considered its positive speciality. This mask can inactivate viruses like SARS virus and H1N1 and has an antibacterial effect against many bacteria [51].

In addition, although the filters of reusable 3D-printed masks can be changed, the parts outside the filter also need to be disinfected [61]. For this reason, selection of a suitable disinfecting product is an important issue to produce reusable 3D-printed masks. A variety of disinfection products can be used, from alcohol to quaternary ammonium compounds. However, the product to be used should be selected in accordance with the mask material and printing technique to prevent any damage for the material.

**Fig. 4** Respirator types: **a** with valve and **b** without valve [55]



### 5.1.2 Face shields

Protective face shields are simple devices that completely protect the face, including eyes, nose and mouth. Face shields consist of a cap that can be printed with 3D printers and a transparent layer attached to this cap. Considering its plain design, it is accessible to print with 3D devices. In addition, due to PPE limitation during the pandemic process, Prusa Research and some companies shared their face visor designs to be printed with a 3D printer for free [57].

Tino et al. used PLA filaments in their 3D printing design. Velcro strips, adhesive foam and transparent film are required to complete the shields. To make a face shield, it must first be digitally designed. Then, printer and filament settings such as nozzle diameter, height, horizontal and vertical position and material type and density are formed, and the title is printed. Finally, using the necessary materials, the transparent plate is mounted on the printed hood [58].

In addition, synthetic polymers such as polycarbonate, polyester and polyvinyl chloride are often used in making face shields due to their transparent, lightweight and easy-to-print characteristics with 3D printers [62].

PLA and polyethylene terephthalate glycol (PETG) were used in the face shield studies with 3D printers by Mueller et al. PLA is thermoplastic and known to be environmentally friendly due to the resources it produced and can be easily shaped. It can be printed at temperatures between 190 °C and 220 °C. However, it is not resistant to temperature, not mechanically strong, and not food safe and bacteria can easily reproduce during the process. PETG is more resistant to temperature and outdoor weather conditions and is a food-safe polymer. Considering these properties, PETG is used instead of PLA for face shields. Nonetheless, it must be sterilized before using [63].

During the process of printing face shields, the printing convenience and printing time of the polymer used should be considered. Moreover, with only a face shield as a protection, an individual is inadequately protected against the virus, so it is insufficient without at least a face mask.

### 5.2 Auxiliary accessories

Manero and his friends have made accessories that facilitate the use of masks using 3D devices [64]. These accessories are ear savers or mask extenders that increase mask wearing comfort. Polylactic thermoplastic was used for the mask extender and was printed with a 3D desktop-type font. These accessories can be made of many different materials and production can be carried out quickly due to their easy design. Mueller and his colleagues also worked on surgical mask straps [63]. Since accessories are easy to print and design, there are many computer-aided designs (CADs) that can be printed quickly with 3D devices (Fig. 5).

## 5.3 Diagnostic tools

### 5.3.1 Swabs

Millions of people around the world have been diagnosed with COVID-19. The diagnosis for SARS-CoV-2 consists of three stages: sample collection, nucleic acid extraction and reverse transcriptase PCR (RT-PCR) [65]. The World Health Organization (WHO) and the U.S. Center for Disease Control and Prevention (CDC) recommend nasopharyngeal (NP) swabs as the most ideal diagnostic example for COVID-19 [66]. Nasopharyngeal specimens are collected with NP swabs that are FDA Class 1 medical devices, 15 cm long and 2–3 mm in diameter, designed to collect secretion from the nasopharynx [43]. The head part of the rod is called the herd and consists of filaments or tubers that provide the collection. The swab is placed in the nasopharynx and poured several times to collect material. After this process, it is placed in a bottle, and the head part is separated from the breaking point on the rod. The bottle is sealed and sent for testing [43, 66].

The increasing number of diagnosed people steadily and the need for more tests to distinguish the diseased ones increase the need of NP swabs. Although swab manufacture was tried to increase to meet the need, adequate production could not be achieved during the pandemic period with existing production methods. The inadequate production encouraged researchers and engineers to develop effective methods that can allow them to manufacture convenient and abundant swabs (Fig. 6). As a result of these studies, many researchers have stated that swabs can be produced in the

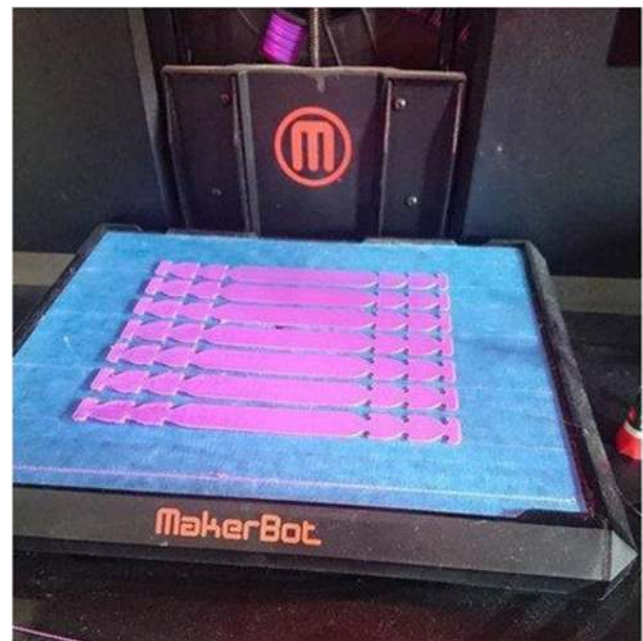
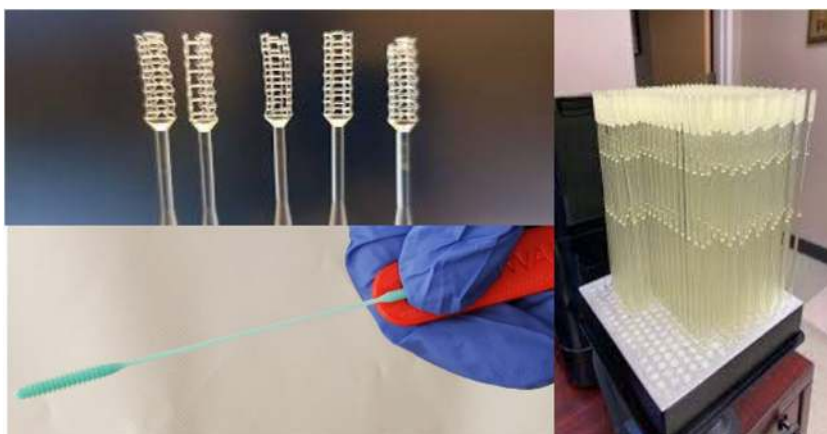


Fig. 5 Mask extender with 3D printing [64]

Fig. 6 3D-printed swabs



required quantities and specifications with the help of a 3D printer (Table 3).

It is concluded by researchers that with 3D printing, swabs can be easily and quickly produced in the hospital and laboratory environment in the appropriate quantity and format. Likewise, several swabs have been designed that can be easily produced by 3D printing. Williams et al. compared 3D-printed swabs to standard swabs using selective laser sintering technology. In the study, the feasibility and acceptability of 3D-printed swabs for collecting samples for the SARS-CoV-2 test were reported [69]. Starosolski et al., however, designed more flexible paediatric nasopharyngeal swabs, stating that the standard or 3D care swabs used are not applicable for paediatric use. Maxillofacial CT scans of 1–3-year-olds were used during the designing stage [67]. COX and KOEPESELL, on the other hand, printed a 15-cm-long swap consisting of 0.5-mm-thick discs with 1-mm spacing on a filament-based printer that they designed. In a clinical study with commercial swabs, 2 patients were positively identified with 3D-printed swabs and 2 patients with standard swabs, which is an example of how 3D-printed swabs can be used instead of normal swabs [68]. In a joint study conducted by teams from the USF Health

Radiology and Northwell Health System, swabs proper for 3D printing were designed. Moreover, 324–380 swabs could be printed in 10–11 h using form 2D and form 3D printers. Clinical studies have found that these swabs have a 94% similarity to standard swabs [70]. Gallup et al. made an open-source design that includes swabs produced with a short handle with SLA printers. The swab holder is manufactured with FFF-type 3D printers. Mechanical verification test results have shown that these swabs can withstand greater forces in clinical use. In addition, this design and printing process as a result of significant time and cost savings can be achieved [71]. A team from the University of Wolverhampton has designed a 3D-printed nasal swab that can reduce the pain patients experience when removing a swab from their nose. This swab has a design that will better fit the patient’s nasal cavity by adjusting itself. The 3D-printed stick inserted into the nose will shrink as it travels through the nasal cavity, causing less stress in the tissues [72].

Callahan et al. have done extensive preclinical work on 3D-printed swabs. Twenty-four companies, laboratories and individuals received 160 swab designs and 48 materials as a result of their 4-step examinations on the high-speed production that

Table 3 Diagnostic tools generated by 3D printing

Diagnostic tools				
Producer	Materials	Purposes	Method	References
Swabs				
William et al.	Nylon 12	To collect samples for PCR testing	SLS	[65]
Starosolski et al.	N/A	Swab production for children	N/A	[66]
Cox and Koepsell	PETG	To remedy the swab deficiency with 3D printing	FDM	[43]
Gallup et al	Phenolic epoxy resin (head) PLA/PETG/ABS (Handle)	Producing easily manufactured and cost-effective swabs that will eliminate swab deficiency	SLA and FDM	[67]
Wolverhampton University	N/A	To reduce the stress created in the nose while taking a swab	N/A	[68]

can be done to eliminate swab shortages and produced swabs that show similar characteristics to test swabs [43].

Swabs designed and produced by 3D printing can be used in emergency and swab-scarce areas. On the other hand, many of these designs have not received FDA approval. Besides, there are some limitations to the use of design swabs. In particular, issues such as RT-PCR compatibility of swabs for SARS-CoV-2, their effects on the patient and the biocompatibility of the materials used need to be examined. Further, designs made by intellectual property rights should be prevented from being produced for commercial purposes. Despite these limitations, given the need for swabs, we believe that these swabs produced by 3D printing in hospitals and laboratories can be used to diagnose diseased people.

## 5.4 Ventilator devices

Ventilators are imperative devices for severe patients suffering from COVID-19 [73, 74]. COVID-19 leads to fibrosis in the lungs of patients and this situation causes patients to have difficulty breathing [73]. In patients who have difficulty breathing, the sufficient amount of oxygen cannot be conveyed in the blood and carbon dioxide cannot be removed as required [74]. Ventilator devices are required to regulate the breathing processes of patients [74]. As a result of the sudden increase in the number of patients at hospitals and in intensive care units, the demand for ventilators worldwide has increased at a time, and almost all hospitals have inadequate number of ventilators [73–75]. To overcome this situation and provide the required amount of ventilator devices to patients and hospitals, the researchers and the engineers have been trying various methods to produce ventilator devices. One of the solutions proposed in this regard is to produce new ventilators by 3D printing (Table 4).

### 5.4.1 Ventilators

Faryami et al. designed and manufactured a ventilation device that used a 3D vascularized and easily accessible component to eliminate the ventilator deficit (Fig. 7) [76]. This device is an open-source and a positive pressure ventilation device. Some parts of this device are quickly manufactured by 3D printing. There has been a decrease in the amount of the need for the number of ventilator devices, and a more effective care has been provided to patients [76].

Another study was done by Leitat engineer Magi Galindo who designed an apparatus for breathing devices, and this design was printed with 3D printers [72]. The device produced was originally described as a ventilator unit. It was later stated to be an emergency unit ventilator. In addition, this 3D-printed ventilator device is approved by the Agencia Española del

Medicamento (Spanish Department of Medicines and Medical Devices).

In another study, a team of engineers and doctors at the University of California developed a quickly-manufacturable, simple and ready-to-use ventilator [77]. The manual design normally featured a mask worn on the patient's face and a hand-wrung bag that allowed air to be delivered to the patient's lungs. Instead of this manual ventilator, they aimed to use 3D-printed parts that could be attached to the engine to compress the bag of the manual ventilator. In this way, the speed and volume of compressions can be controlled, and this automatic system ventilator will provide a more effective application than the manual device.

Another solution offered by researchers to address the need for a ventilator is the conversion of BiPAP used to regenerate the breathing in conditions such as sleep apnoea and congestive heart failure to a positive pressure ventilator. For this purpose, Northwell Health has developed a T-part adapter printed with 3D printers that allows the Philips Respironics V60 BiPAP machine to be turned into a pressure-controlled ventilator, and they can print 150 adapters within 24 h according to their needs [78, 79]. As a result of the converted BiPAPs, the need for a ventilator will be reduced.

Another design that can replace a ventilator is a 3D-printed connector designed by Materialise Corporation to distribute oxygen and create high positive pressure without using a ventilator [80]. This non-invasive connector converts standard equipment in use at hospitals into a positive end expiratory pressure (PEEP) mask (nip) that can connect to an oxygen source. This system enables the mechanical ventilators to be used for patients with more critical conditions.

### 5.4.2 Splitter

It was also thought that another way to overcome ventilator distress could be to design and produce separator inserts that allow the use of a single ventilator for more than one patient (Fig. 8). For this purpose, Ayyıldız et al. have designed 3D-printed dividers that allow a single ventilator to be used for multiple patients [73]. In this study, 2-port or 4-port splitters were printed. Nevertheless, it has been noted that it is unlikely to reach the same percentage in ventilation, since the healing process of patients with multiple use will be different.

In another study, Clarke produced a splitter that can be used instead of a T-tube by 3D printing method [81]. Desktop tests have shown that they can be used in short-term emergency ventilation, though in both studies, it was noted that these separator parts designed and experimented with had some restrictions.

Unlike this study, Prisma Health produced a device called a VESper with 3D printing, which allows ventilation to be applied to two patients from a single ventilator [82]. This device has been granted an emergency use permit by the FDA and

**Table 4** Ventilator devices and parts produced by 3D printing

Ventilator devices				
Producer	Materials	Purposes	Method	References
<b>Ventilators</b>				
Faryami et al.	PLA	To create a device that can be produced quickly and easily to meet the need for ventilation devices	FDM	[73]
Leitat	N/A	To produce an emergency ventilator	FDM	[68]
California University	N/A	To produce a ventilator device that provides an eating setup for patients who need a ventilator	FDM	[74]
Northwell Health	N/A	To convert the V60 BiPAP machine to a ventilator	FDM	[75, 76]
Materialise	N/A	To provide patients with high positive pressure outside of ventilator devices	FDM	[77]
<b>Splitter</b>				
Ayyildiz et al.	Acrylic resin	To create an intensive care ventilator to serve multiple patients in the emergency departments	PolyJet	[70]
Clarke	N/A	To create an intensive care ventilator to serve multiple patients in the emergency departments	FDM	[78]
Prisma Health, Johnson & Johnson	N/A	To create an intensive care ventilator to serve multiple patients in the emergency departments	FDM	[79]
<b>Valves</b>				
Fraccasi et al.	N/A	To produce the required valves by the 3D printing method	FDM	[80]
Photocentric	Photoresin (RG35)	To produce large quantities of valves quickly	SLA	[81]
CRP Technology	Wildform P1	To produce Charlotte valves that are fast, cheap and in abundant to create ventilators	HSS	[82, 83]
Ferrari/Mares	Nylon 12	To produce large quantities of valves quickly	FDM	[84]

**Fig. 7** 3D-printed ventilators. **a** System designed by Faryami et al. [76] and **b** LEITAT 1 ventilator system [72])





**Fig. 8** Splitters manufactured in a 3D printer [73, 81]

allows more patients to be given ventilation during the pandemic.

#### 5.4.3 Valves

Valves are parts that are connected to the patient's mask in order to ensure that oxygen is delivered from ventilators to patients at constant concentration (Fig. 9). These parts have to be patient-specific and replaced in devices after each use. As a result of the increase in the number of patients and the constant arrival of new patients, there are not enough valves in hospitals. In order to overcome this problem, research and studies have been carried out on the production of valves by 3D printing method [75]. In a study conducted for this purpose, Fracassi et al. eliminated the need for valves used in breathing apparatus of a hospital in Italy by producing 3D-printed valves [83]. They managed to meet the needs of the hospital in Brescia by printing 100 valves ready for use in 24 h on 3D printers. Different companies also made productions on this subject. For example, the company Photocentric also reported that they can produce more than 40,000 3D-printed valves for use in ventilators at 1 week [84]. CRP Technology also produced functional prototypes of emergency valves [85, 86]. In addition to these valves, they also manufactured valves called "Charlotte valves", that are the emergency ventilator mask connection component, by 3D printing method. Other 3D-printed valves designed to fit scuba masks are manufactured by Ferrari [87]. This production was made in conjunction with Mares, a manufacturer of diving equipment.

## 5.5 Other auxiliary equipment

In addition to masks, face spears, swabs, ventilators and valves, many different equipment have been made by 3D printing in order to make people's life easier and eliminate deficiencies in the fight against COVID-19 (Table 5). These various equipment produced are described in Table 5.

### 5.5.1 3D printing lung model

Teams from Axial3D and the Belfast Health and Social Care Foundation printed a 3D lung model of a patient in the fourteenth day of catching up with the infection by using CT scanners [88, 92]. The effect of the virus on the lungs of the patient was visualized in this model. Moreover, the lung damage caused by the SARS-CoV-2 was better understood with this lung model (Fig. 10).

### 5.5.2 Endotracheal tube clamp

Aerosol emission due to the endotracheal tube (ETT) is the most severe way of exposure to the virus for health workers. In order to reduce this aerosol particle distribution, the ETT attached to the ventilator has to be compressed. Jacop et al. have proposed a 3D-printed disposable clamp design that allows the performance of several procedures such as tightening and opening during intubation/extubation (Fig. 11) [89]. The main purpose of this equipment is to compress ETT and prevent aerosol emission, protecting the health of health workers from the viruses.

### 5.5.3 Button pusher

Due to the high probability of the virus spreading from various common devices such as elevator buttons, ATM buttons, keyboard, mouse and phone, studies have been made to find a solution to this issue. Button pushers made by François et al. aim to minimize this risk [90]. It has a cylindrical shape and contains a tip. This tip can be taken out of the cylinder and retracted after use. This apparatus is also printed using a 3D printer (Fig. 12).

### 5.5.4 Door opener

The usage of door handles in public places or workplaces can increase the spread of SARS-CoV-2. For this reason, an auxiliary apparatus was designed to open the door. François et al. designed hand-free door openers suitable for the door handle for this purpose, and they have obtained these apparatuses with a 3D printing device. Hand-free door openers are attached to the door handles. Apparatuses are fixed to the door handle using clips on a straight handle or cable. The door is opened using an elbow or forearm. At the same time, the

**Fig. 9** 3D-printed valves with different designs



apparatus is quick to manufacture and easy to clean and fit. Thus, it is used in many hospitals in Paris. Materialise company has also developed narrow and wide hand-free door openers for home type and door types with above average weight for the same purpose [91]. Likewise, these openers come in different designs for cylindrical-, rectangular-, circular-, bar- and circular-type door handles. Thus, they aimed to minimize the spread of the virus from door

handles. The door should be opened with the help of door openers using handles and elbows, and the door openers should be disinfected regularly.

In addition to door openers, they also worked on door hooks using a 3D printer. While some door handles are not proper for a door opener design, a door hook has been developed using an easily retractable sheath [90] (Fig. 13).

**Table 5** Other auxiliary equipment produced by 3D printing

Other Auxiliary equipment					
Producer	Materials	Purposes	Method	References	
Lung model					
Axial3D/Belfast Health and Social Care Foundation	Resin	To observe the effect of COVID-19 disease on the lungs	SLA	[85, 86]	
Endotracheal tube clamp					
Jacob et al.	PLA	To reduce the possibility of endotracheal tube virus transmission	N/A	[87]	
Button pusher					
François et al.	ABS	To reduce contact with door handles	FDM	[88]	
Isolation ward					
Winsun	Urban Construction Waste	To meet the need for a clean room from COVID-19 in hospitals	N/A	[89]	
Water circulator					
Gonzales et al.	N/A	To create an incubation room for PCR tubes	N/A	[90]	
Bottle holder					
Moath Abuysa	N/A	To provide an easy handling of disinfectant bottles	N/A	[91]	

**Fig. 10** 3D-printed lung model belonging to COVID-19 patients [88]



### 5.5.5 Isolation ward

Due to the COVID-19 outbreak, the need for beds and clean rooms in hospitals has increased. China-based 3D printing company Winsun builds 3D-printed rooms using solid urban construction waste to address the lack of beds and clean rooms in hospitals (Fig. 14) [93]. For this purpose, fifteen 3D-printed quarantine rooms were first sent to Xianning Central Hospital.

### 5.5.6 Water circulator

Unlike other designs, Gonzalez and colleagues used a 3D-printed design for use in an experimental method [94]. The method proposes the combined use of a 3D-printed incubator for commercial Eppendorf PCR tubes and a colorimetric arrangement of a loop-mediated isothermal amplification (LAMP) reaction scheme for the detection of SARS-CoV-2. The combined LAMP system states that RT-qPCR may be a suitable method for COVID-19 testing when it is not possible or unavailable. They also note that the fact that this system is portable, easy to use and reproducible makes it a reliable alternative for deploying SARS-CoV-2 detection efforts during pandemics.

### 5.5.7 Bottle holder

Another design that seems plain but is crucial is a 3D-printed wrist buckle made by Moath Abuysa to hold a disinfectant bottle. Disinfection of hands with this wrist buckle is achieved without polluting the bottle with antiseptic gel inside the bottle [95] (Fig. 15).

### 5.5.8 3D-printed drone

In China, drones or unmanned aerial vehicles (UAVs), some parts of which are manufactured in a 3D printer, are used for disease control purposes [95].

## 5.6 Drug delivery

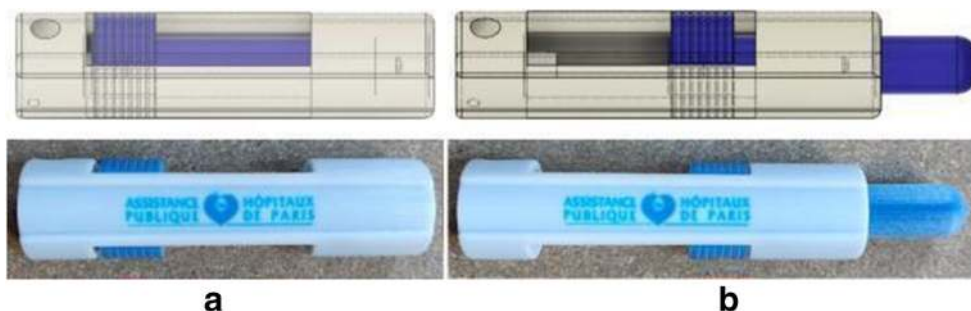
Drug delivery system is a technology that enables the therapeutic agent to be delivered directly to the target cell, tissue or organ. Studies with 3D printers can provide a system in which personal doses can be prepared to meet the drug needs of patients. How to obtain tablets that can release the desired dose or release systems using 3D printers is among the current research topics. In 2015, the first 3D printing drug was approved by the US Food and Drug Administration. Thus, stud-

**Fig. 11** Endotracheal tube clamp [89]





**Fig. 12** Button pusher: **a** close and **b** open [90]



ies on 3D printing drugs have increased. Studies are conducted on drugs with immediate or continuous release properties. 3D printing systems contain a large number of drug components and have a polymer matrix. Besides this technology, it is thought that the mandatory drug delivery can be provided for the recovery of COVID-19 patients. In addition, systems that can deliver different amounts of drugs by calculating according to the genetic and physical characteristics of the person can also be used in the treatment of COVID-19 patients. Although there are not many studies in this area, drug transport systems that can be done with a 3D printer can be designed in COVID-19 patients [61, 96].

### 6 How can damaged organs be treated in COVID-19 patients with 3D printing?

In this section, studies on the treatment of damage caused by SARS-CoV-2 on different organs and systems using a 3D printing method are mentioned.

#### 6.1 Respiratory system

Overexpression of cytokines is a common symptom for COVID-19. The overexpression of cytokines causes oedema, acute respiratory distress syndrome (ARDS) and lung tissue damage. As a result of its regenerative properties and anti-inflammatory capacity, MSCs can provide repair of damaged

lung tissue caused by COVID-19. Additionally, MSCs have been noted to stabilize endothelial fluid leakage and reduce alveolar-capillary barrier function, thereby reducing the development of interstitial lung oedema [97]. Nichols et al. stated that from natural rat lungs, acellular tracheal lung scaffolds can be produced and protect important components of the extracellular matrix and can be used to produce lung tissue by re-cellularization using embryonic stem cells [98]. The obtained results are encouraging and suggest that repopulation of the lung matrix is an appropriate strategy for lung regeneration [99]. Macchiarini et al. have developed a new method for airway replacement in a human by tissue engineering [100]. Cells and MHC antigens were removed from the donor trachea; then, it is cultured with the mesenchymal stem cells and epithelial cells, which are from the recipient. The graft was then implanted into the patient to replace the left main bronchus of the recipient. Based on the results, the graft provided the recipient with a functional airway quickly, further improving the quality of life and resulting in a normal appearance and mechanical properties in about 4 months. In this way, damage to the respiratory tract after COVID-19 can be corrected with an implantable airway that has the same mechanical properties as the natural airway. In addition, the risk of immune rejection is eliminated with this method. Takabe et al. have studied liver production using human-derived pluripotent stem cells. Vascularized and functional human liver production was performed using liver buds and induced pluripotent stem cells created in vitro. Human transplantation has

**Fig. 13** Hand-free door opener [90]

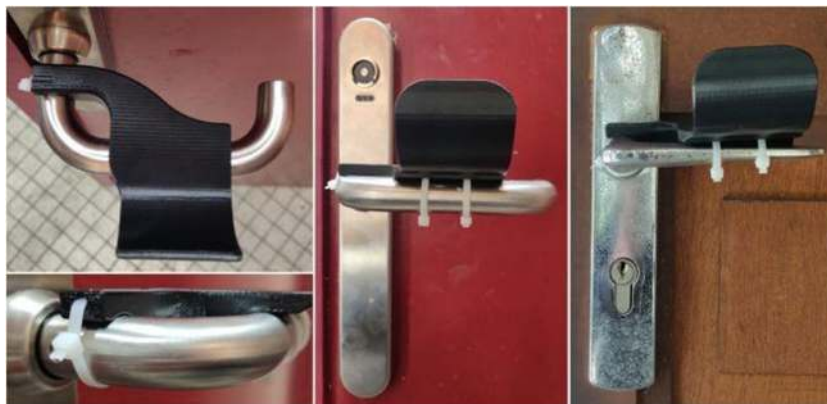




Fig. 14 3D-printed isolation ward [93]

not been performed, but the results have been reported to be promising [101]. This current study could be improved to prevent severe liver damage from COVID-19.

## 6.2 Cardiovascular system

Patients who have cardiovascular disease before the pandemic have worse consequences and increased risk of death with COVID-19. Additionally, COVID-19 is able to enhance myocardial injury, arrhythmias, acute coronary syndrome and thromboembolism. Besides, it has been defined that there can be a possible link between COVID-19 and Kawasaki disease-like syndrome in kids. Lastly, reduced physical activity because of the quarantine might also induce cardiovascular risk factors [102].

3D printing techniques might be useful for the treatment of cardiovascular diseases and complications. For instance, there is a study assessing the treatment of myocardial injury that contains 3D-printed stem cell-loaded micro-channelled hydrogel patch to better achieve the therapeutic potential of the



Fig. 15 Hand-free door opener [95]

cells and reduce the degradation of myocardial tissue postinfarction. As a result of this study, it can be seen that the microchannels sharply decreased the cells number needed to recover cardiac function (Fig. 16) [103].

## 6.3 Nervous system

The fact that SARS-CoV-2 infects cells with the ACE-2 receptor strengthens the possibility that the virus may affect the nervous system [13]. As a result of the studies, it was observed that SARS-COV-2 causes complications and diseases that damage the nervous system, such as viral encephalitis, infectious toxic encephalopathy and stroke [104]. In addition, some researchers believe that sensitivity to neurological syndromes may be increased by triggering systemic inflammation as a result of SARS-CoV-2 infection. In addition, SARS-CoV-2 is thought to be able to trigger neurodegenerative diseases [105]. Considering its negative effects on the nervous system, SARS-CoV-2 can cause nerve degeneration. For this reason, the importance of studies on nerve cell regeneration has increased even more.

3D printing is a promising method for the regeneration of the nervous system. There are many studies on the use of 3D printing for nervous system regeneration. 3D-printed scaffolds are often used as a model to understand the structure of the brain [106]. In a study conducted for this purpose, Lozano et al. produced 3D-printed brain-like structures with multiple cortical layers, encapsulated with gellan gum hydrogel modified with RGD [107]. In the study, it was observed that the neurons encapsulated in the structure showed 80% viability, and the encapsulated neurons were able to differentiate into glia (Lee et al.). Amine-functionalized multi-walled carbon nanotubes (MWCNTs) combined with PEGDA polymer produced scaffolding using 3D printing [108]. As a result of the study, it has been reported that the multi-walled carbon nanotube (MWCNT) scaffold promotes the growth of neutralite. In another study, gelatin methacrylate-dopamine (GelMA-DA) nerve scaffolds with hierarchical structures were manufactured in 3D using our specially designed stereolithography-based printer [109]. This study indicates that 3D-printed customizable GelMA-DA scaffolds have a positive role in promoting neural differentiation, promising for future nerve repair and regeneration. Although 3D-printed scaffolds offer positive results for the treatment of nerve damage, they are not yet sufficient for the final treatment of central nervous system damage. For this reason, more research should be done on 3D-printed scaffolds.

## 6.4 Reproductive and excretory system

Results of tests performed on samples taken from the urine of COVID-19 patients indicated that these patients

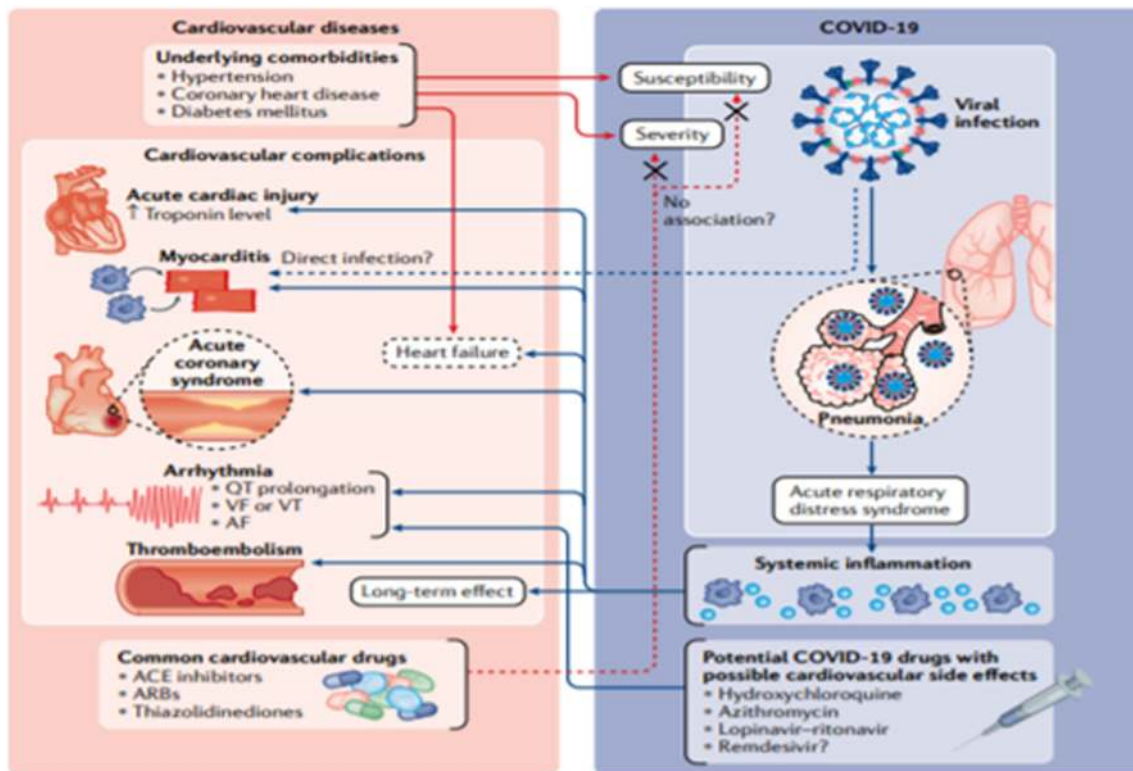


Fig. 16 Interactions among cardiovascular diseases and COVID-19 [103]

had high concentrations of protein, blood urea nitrogen and plasma creatinine [110]. Concurrently, this virus has been isolated from the urine of COVID-19-infected patients with recent studies. Thus, it was concluded that the virus harms the kidneys [111]. Although the exact mechanism by which the virus damages the kidneys is not known, there are many possible mechanisms. Dialysis is the most commonly used treatment for non-functioning kidneys. However, today, there are a lot of researches on 3D-printed kidneys [112]. Therefore, damages can be solved by 3D printing. For example, in a study by Kusaka et al., kidneys were obtained with a 3D printer designed with personal simulation for kidney transplantation [113]. It was concluded that using the personalized kidney graft and the pelvic cavity copy for simulating kidney transplant surgeries may be beneficial for doctors and their assistants. For this study, a 3D model was obtained by transferring the results obtained from medical imaging techniques to software programs. TangoPlus, VeroWhitePlus and VeroMagenta materials were used to obtain 3D models. It is concluded that these copies can be successful for preoperative simulation and navigation. Due to the complex structure of the kidney, kidney production with 3D technology is very difficult, but obtaining the kidney structure with this simulation has created a resource for artificial kidneys. However,

studies are conducted on the production of mini-tissue structures for the kidney. King et al. succeeded in constructing kidney tubules with 3D printing technique [114].

By the isolation of the virus from the urine, the possibility has arisen that this virus could directly damage the bladder by binding to the receptors [115]. Although there is no definite information in this direction yet, this situation may cause acute or chronic diseases in the urinary system. Organ acquisition by 3D printing method started in 1999 and the first 3D printing bladder was implanted into the human body [116]. In 2004, as a result of studies carried out by Dr. Atala, a 3D bio-printed bladder was implanted in a child with a damaged bladder [117]. Dr. Atala acquired a scaffold with an inkjet printer and used the patient's cells to grow a bladder within 2 months. The implantation process has been successful.

Receptors to which SARS-CoV-2 binds are also expressed in the female and male reproductive systems [118, 119]. Thus, these systems become potential infection sites for the virus. Although it is not known exactly, it is thought that this virus may cause some acute or chronic functional losses on the reproductive system. In the reproductive system, there are studies of obtaining the desired tissue by printing the scaffold with polymers such as PLA using a 3D printer and then seeding it with its own cells [120, 121].

## 7 Benefits and challenges of 3D printing

There are numerous benefits and challenges of 3D printing. The presented ones in this part are the least, but not last. The list was kept short due to space limitation.

### 7.1 Benefits

There are undeniable benefits of 3D printing such as freedom of design, mass customization, waste minimization, the ability to manufacture complex structures and fast prototyping [23]. The selected and exemplified benefits of 3D printing are listed below:

- In terms of methods, fused deposition modelling (FDM) is one of the most common 3D printing technologies because of its low-cost, simplicity and high-speed processing.
- The benefits of metal additive manufacturing are reduced tooling costs, freedom of design and manufacturing of complex and lightweight structures and presence of multiple part consolidation, which can eliminate part assemblies [23].
- 3D printing of porous ceramics or lattices introduced numerous benefits by developing advanced lightweight materials that are tailored for different applications. Ceramic scaffolds used in tissue engineering have become more convenient and faster compared to traditional methods of casting and sintering [122].
- A significant benefit of bio-printing is that it prevents homogeneity issues that accompany post-fabrication cell seeding, as cell placement is included during fabrication. The advantages of homogeneously distributed cell-laden scaffolds have been demonstrated by faster integration with the host tissue, lower risk of rejection and uniform tissue growth in vivo [123].

### 7.2 Challenges

There are several challenges in the field of 3D printing that would require further research and technological development. These challenges include high costs, limited applications in large structures and mass production, inferior and anisotropic mechanical properties and limitation of materials and defects [23]. The selected and exemplified challenges are listed as follows:

- At present, there are no valid regulations concerning design, manufacturing process and quality testing considerations. To overcome this issue, there is a strong need to make some regulations for those particular groups of manufacturing methods [124].

- The limited materials available for 3D printing pose challenges in utilizing 3D technology in different industries. To handle this limitation, there is a need for developing suitable materials that can be used for 3D printing. Further, developments are also needed to enhance the mechanical properties of 3D-printed parts [23].
- Additive manufacturing has become an essential method for manufacturing of advanced ceramics for biomaterials and tissue engineering, e.g. scaffolds for bones and teeth. Despite the accuracy of printing, layer-by-layer appearance and a limited selection of materials are the main challenges for 3D printing of ceramics [125].
- The long processing time and higher cost of 3D printing are the main challenges that inhibit the mass production of any repetitive parts, which can easily be performed by other conventional methods at a fraction of the time and cost [23].

## 8 Conclusion and future perspective

In this study, 3D printing technology and its applications were reviewed to counter COVID-19 pandemic and diminish pandemic-related emerging causes. The main methods applied and the materials used in 3D technology were identified in addition to trending applications in this emerging sector. It has been obvious that there is an immense role of 3D printing for combatting against COVID-19 through layered manufacturing of face masks and face shields; auxiliary accessories, door opener and button pusher have been discovered as possibilities and opportunities. The main challenges and undeniable benefits of 3D printing were identified and listed in detail. Several future perspectives or trends for further research in 3D printing were summarized below:

- Future trends in 3D printing may concentrate on the gaps for further development and improvement. The development of automatic methods to combine CT scan results and design analyses with AM technologies can manufacture patient-specific implants quickly [23].
- Research and development may help to upscale bio-printed scaffolds and tissues for clinical applications and to improve the cost-effectiveness of AM for tissue engineering. Therefore, in situ repair of organs and tissues would become possible in the future [126].
- Inkjet bio-printing is of great interest as it exhibits high resolution and cell viability. With this process, an accurate position of multiple cell types is possible [127]. However, the limitations of vertical printing and restricted viscosities may mean that inkjet bio-printing needs to be combined with other printing techniques for future developments.

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