BIOSENSORS & NANOTHERANOSTICS REVIEW

Biomaterials for 3D Printing of Patient-Specific Organ Models

Hilal Ahmad Rather [1], Jigar Vya [2], Sudarshan Singh [3]

Abstract

Organ bioprinting represents a transformative approach in regenerative medicine aimed at fabricating functional tissues and organs for transplantation and disease modeling. This review provides an overview of the current state, challenges, and future prospects of organ bioprinting technology. We discuss the principles, techniques, and biomaterials utilized in organ bioprinting, emphasizing the importance of achieving biocompatibility, structural integrity, and functionality in printed constructs. Key advancements, such as multi-material bioprinting, vascularization strategies, and integration with biomanufacturing technologies, are highlighted. Additionally, we explore the role of artificial intelligence and computational modeling in optimizing bioprinting processes and designing patient-specific constructs. Regulatory and ethical considerations, along with case studies of successful organ printing, are examined to contextualize the clinical translation of bioprinted organs. Finally, future perspectives and emerging trends in organ bioprinting, including organ-on-a-chip platforms and AI-driven computational modeling, are discussed. Overall, this review underscores the transformative potential of organ bioprinting in advancing regenerative medicine and personalized healthcare.

Significance | This study determined no significant link between serum Vitamin D levels and COVID-19 mortality, except with LDH.

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1. Introduction

3D printing, also known as additive manufacturing, is a transformative technology with diverse applications across various industries, including healthcare. Through layer-by-layer fabrication of three-dimensional objects from digital designs, 3D printing allows for the rapid conversion of information from digital models into physical objects (Shahrubudin, N., et al., 2019). The exact beginnings of 3D printing in medicine are debated, with some tracing the concept back to early ideas of replicating models from photographs (Liaw, C. Y., & Guvendiren, M. 2017). However, the wide acceptance of 3D printing in healthcare is generally attributed to the early 2000s (Ventola CL. 2014). Today, 3D printing in medicine holds immense promise. Researchers are exploring bioprinting of tissues and organs, while surgeons utilize 3D-printed guides for complex procedures (Eshkalak, S. K. et al., 2020).

In the pharmaceutical sector, 3D printing offers the capability to produce small batches of medicines with tailored dosages, shapes, and sizes, catering to individual patient needs. Furthermore, in medicine, this technology facilitates the creation of patient-specific anatomical models, surgical guides, prosthetics, implants, and drug delivery systems (Liaw, C. Y., & Guvendiren, M. 2017). Its advantages include customization, cost-effectiveness, and enhanced patient outcomes, while challenges such as regulatory considerations and material limitations must be addressed (Eshkalak, S. K. et al., 2020).

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Recent advancements in 3D printing technology have led to its widespread adoption across various biomedical applications. Various 3D printing technologies are commonly used in medical applications, such as Fused Deposition Modeling (FDM), Stereolithography (SLA), and Selective Laser Sintering (SLS) (Chia, H.N. and Wu, B.M. P2015). With techniques ranging from Fused Deposition Modeling (FDM) to bioprinting, 3D printing has revolutionized surgical procedures, pharmaceutical manufacturing, and personalized healthcare solutions (Bozkurt, Y., & Karayel, E. 2021).

Bioprinting, a specialized form of 3D printing, enables the fabrication of living tissues and organs by precisely layering bioinks containing patient-specific cells. This breakthrough technology holds immense promise for regenerative medicine, disease modeling, and drug testing, paving the way for groundbreaking advancements in healthcare (Agarwal, S. et al., 2020).

Moreover, the development of novel biomaterials optimized for 3D printing has expanded the capabilities of this technology (Bozkurt, Y., & Karayel, E. 2021). These materials, including bioinks and biocompatible polymers, offer enhanced biocompatibility, mechanical properties, and degradation profiles, facilitating the fabrication of complex structures with precise geometries (Griffith, L. G., & Swartz, M. A. 2006).

As 3D printing technology continues to advance, its integration into medical practice holds the potential to revolutionize patient care, personalized medicine, and biomedical research. Understanding the latest developments in 3D printing is essential for healthcare professionals, researchers, and industry stakeholders to harness its full potential in improving human health and well-being (Tappa, K., & Jammalamadaka, U. 2018).

This article will serve as an overview of the integration of 3D printing into the medical field, highlighting its potential to revolutionize patient care and treatment modalities. In addition, the readers will gain insight into the transformative potential of 3D printing technology in improving patient care and advancing medical practices.

2. Patient-Specific Organ Models and 3D Printing Technology.

Patient-specific organ models are detailed three-dimensional representations of individual patients' anatomical structures, created using advanced medical imaging techniques such as CT scans, MRI scans, or ultrasound. These models are tailored to a specific patient's anatomy and pathology, providing healthcare professionals with invaluable tools for various applications. They serve crucial roles in surgical planning, medical education, training, and patient communication (Liaw, C. Y., & Guvendiren, M. 2017).

2.1. Role of Patient-specific Organ Models in 3D Printing Technology

Patient-specific organ models play a crucial role in leveraging 3D printing technology for various medical applications:

Surgical Planning: These models allow surgeons to visualize and study a patient's unique anatomy before performing complex procedures. By analyzing the 3D-printed organ models, surgeons can develop personalized surgical plans, anticipate challenges, and optimize surgical outcomes (Sun Z. 2020).

Medical Education: Patient-specific organ models serve as invaluable educational tools for healthcare professionals at all levels of training. They provide hands-on learning experiences, enabling medical students, residents, and practicing physicians to better understand complex anatomical structures, medical conditions, and surgical techniques (Nikitichev, D. I., et al., 2018).

Training and Simulation: Healthcare providers can use these models to practice procedures and surgical techniques in a risk-free environment. By simulating surgical scenarios on patient-specific organ models, medical professionals can enhance their skills, proficiency, and confidence, leading to improved patient care (Meyer-Szary J et al., 2022).

Improved Patient Communication: Patient-specific organ models facilitate clearer communication between healthcare providers and patients. By visualizing their own anatomy and understanding the proposed treatment plans, patients can make more informed decisions about their healthcare journey (Sun Z. 2020).

Research and Development: Researchers can use patient-specific organ models to study diseases, test new medical devices, and develop innovative treatment strategies. These models provide realistic representations of human anatomy, enabling researchers to conduct experiments and simulations that were previously impossible (Jin, Z., et al., 2021).

2.2. Various Patient-specific Organ Models Used in 3D Printing Technology

Patient-specific organ models produced through 3D printing technology have revolutionized medical practice in several ways:

Anatomical Models: These models accurately replicate a patient's anatomy, allowing clinicians to visualize complex structures and plan surgeries with precision. They help in preoperative planning, allowing surgeons to anticipate challenges and choose the most suitable approach (Figure 1) (Sun Z. 2020).

Pathological Models: Pathological models simulate specific diseases or conditions within an organ. They aid in understanding disease progression, evaluating treatment options, and training healthcare professionals in disease management (Jin, Z., et al., 2021).

Implant and Prosthetic Models: Patient-specific implant and prosthetic models are customized to fit a patient's unique anatomy. They help in designing and fabricating implants and prostheses tailored to individual patients, resulting in better functional

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outcomes and reduced risk of complications (Nikitichev, D. I., et al., 2018).

Educational Models: These models are invaluable for medical education and training. They provide hands-on learning experiences for students and healthcare professionals, allowing them to study anatomy, practice procedures, and improve surgical skills in a risk-free environment (Nikitichev, D. I., et al., 2018).

Disease Simulation Models: Disease simulation models replicate pathological conditions within organs, enabling researchers to study disease mechanisms, test new treatments, and develop innovative therapies. These models accelerate the pace of medical research and contribute to the development of personalized medicine (Jin, Z., et al., 2021).

Patient Communication Models: Patient-specific organ models enhance patient-provider communication by providing visual aids to explain medical conditions, treatment options, and surgical procedures. Patients can better understand their diagnosis and treatment plan, leading to improved patient satisfaction and adherence (Table 1) (Sun Z. 2020).

3. Biomaterials Used in 3D Printing

The efficacy of implantable medical devices is critically dependent on the biomaterial chosen for their fabrication (Figure 2). The ideal biomaterial profile encompasses biocompatibility (eliciting no adverse tissue response), inertity (chemical stability within the body), mechanical robustness to withstand physiological loads, and printability for precise anatomical customization. A diverse array of biomaterials, encompassing metals, ceramics, polymers, and composites, are currently utilized in medical 3D printing applications. Driven by continuous research advancements in biomaterial science, 3D printing has witnessed a rapid expansion in its applications, including the development of customized implants, prosthetics, drug delivery systems, and 3D scaffolds for tissue engineering and regenerative medicine. These materials must possess specific properties to ensure biocompatibility, structural integrity, and functionality in the printed objects (Figure 2) (Tappa, K., & Jammalamadaka, U. 2018).

3.1. Specific Properties of Biomaterials for 3D Printing

Biocompatibility: Biomaterials used in 3D printing must be biocompatible to ensure compatibility with biological systems without causing adverse reactions. This property is crucial for medical applications to avoid immune responses or tissue rejection.

Mechanical Strength: Structural integrity is vital to ensure that printed objects possess sufficient mechanical strength to withstand physiological forces or external loads. Biomaterials should exhibit adequate toughness, stiffness, and resilience to maintain their structural integrity under various conditions.

Degradation Rate: For implantable devices or scaffolds, biomaterials should degrade at a controlled rate compatible with tissue regeneration processes. Balancing degradation kinetics ensures proper integration with the surrounding tissues while providing temporary structural support.

Surface Properties: Biomaterials' surface characteristics, such as roughness, topography, and chemical composition, influence cell adhesion, proliferation, and differentiation. Optimal surface properties promote tissue ingrowth, vascularization, and overall biointegration.

Functionality: Depending on the application, biomaterials may require specific functionalities, such as bioactivity, antimicrobial properties, or stimuli-responsiveness. Functional biomaterials enhance the performance of printed objects by facilitating desired biological interactions or responses.

Printability: Biomaterials should exhibit suitable rheological and thermal properties for 3D printing processes. Factors like viscosity, flow behavior, and curing kinetics influence printability, ensuring accurate deposition and layer-by-layer fabrication of complex structures.

These specific properties ensure that biomaterials used in 3D printing technology meet the requirements of biocompatibility, structural integrity, and functionality, making them suitable for diverse biomedical applications.

3.2. Overview Biomaterials Used in 3D Printing:

Polymers: Polymers are versatile biomaterials widely used in 3D printing due to their biocompatibility, ease of processing, and availability in various forms. Examples include polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), polyethylene glycol (PEG), and polycaprolactone (PCL). Each polymer offers unique mechanical and degradation properties suitable for different applications (Table 2.).

Metals: Metals such as titanium, stainless steel, cobalt-chromium alloys, and nickel-titanium alloys are utilized in 3D printing for applications requiring high strength, durability, and biocompatibility (Table 3). Metal 3D printing techniques like selective laser melting (SLM) and electron beam melting (EBM) enable the fabrication of patient-specific implants and medical devices.

Ceramics: Ceramics like hydroxyapatite (HA) and bioactive glass are used in 3D printing for bone tissue engineering and dental applications due to their excellent biocompatibility and osteoconductivity. Ceramic 3D printing techniques include powder bed fusion and stereolithography (SLA) (Vanaei, S. et al., 2021).

3D printing ceramics is a relatively new technology that uses different feedstock forms to create ceramic components with complex shapes. The most common types of ceramics used in 3D printing are aluminum oxide (alumina), zirconium oxide (zirconia), aluminum nitride, silicon carbide, and silicon nitride. Ceramics are ideal for parts that need to be resistant to corrosion and mechanical wear and tear, even at high temperatures. They also

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have good thermal and chemical stability, and viable thermal, optical, electrical, and magnetic performance (Chen, Z. et al., 2019). 3D printing ceramics is more sustainable than traditional subtractive methods because it produces less waste and consumes less energy. The precision of 3D printing combined with the unique properties of ceramics results in parts that perform better under extreme conditions. This is particularly important in aerospace applications where components need to withstand high temperatures and pressures (Abdelkader, et al., 2024).

3D printing of ceramics involves technologies that use different feedstock forms, including: Slurry-based, Stereolithography (SL), Digital light processing (DLP), and Two-photon polymerisation (TPP). 3D printing enables ceramic geometries that could not be fabricated through traditional injection molding techniques. The turnaround time on printed ceramic parts is also much shorter (Bhatti, S. S., & Singh, J. 2023).

Hydrogels: Hydrogels are a promising material for 3D printing because of their high water content, tunable mechanical properties, and biocompatibility. Hydrogels are three-dimensional (3D) network polymers that can swell and store a large amount of water. They are made up of natural or synthetic polymers that have a high molecular weight backbone or side chain with many hydrophilic groups. They are used in bioprinting applications for fabricating tissue-engineered constructs and drug delivery systems. Common hydrogel materials include alginate, gelatin, hyaluronic acid, and agarose (Figure 3) (Bhatti, S. S., & Singh, J. 2023).

Hydrogels are commonly used as bioink material in scaffold-based bioprinting because of their various attractive features (Fang W et al., 2023):

Biocompatibility: Hydrogels are biocompatible

Cell-binding sites: Hydrogels have cell-binding sites for cell attachment, growth, or differentiation.

Protect cells: Hydrogels can protect cells from shear stress-induced cell membrane damage during 3D printing.

Improve cell viability: Hydrogels can improve cell viability in printed structures.

Maintain shape: Hydrogels' mechanical properties, such as their stiffness and toughness, determine the ability of the printed tissue constructs to maintain their shape and withstand mechanical forces during and after the printing process.

Good resolution: Hydrogels can yield a good resolution during printing.

e. Composite Materials: Composite materials are made of at least two components and have special properties that make them well-suited for various industries that use 3D printing to achieve desired mechanical, structural, and biological properties. For example, polymer-ceramic composites enhance mechanical strength and bioactivity, making them suitable for load-bearing implants and tissue scaffolds. Some composite materials that are frequently used in 3D printing are: Metal, Plastic, Resin, and PETG filament (Wasti, S., & Adhikari, S. 2020).

4. Synthetic Polymers for Organ Printing.

Synthetic polymers are used in 3D organ printing to support cellular and biomolecular activities before, during, and after the process. Synthetic polymers offer diverse properties and functionalities that make them valuable materials for organ printing, contributing to advancements in tissue engineering and regenerative medicine (Table 4.). Some commonly used biodegradable synthetic polymers are discussed here (Liu F, Wang X. 2020):

4.1. Poly(3-hexylthiophene): This synthetic polymer has been explored for organ printing due to its electrical conductivity and biocompatibility. It holds promise for applications in tissue engineering, particularly for electrically conductive scaffolds.

4.2. Poly(N-vinylcarbazole): Another synthetic polymer investigated for organ printing, poly(N-vinylcarbazole) exhibits favorable properties such as high thermal stability and film-forming ability. It has potential applications in optoelectronic devices and bioelectronics

***4.3. Polycaprolactone** (PCL):* Widely used in 3D printing, PCL is a biodegradable synthetic polymer with excellent mechanical properties. It is suitable for fabricating scaffolds for tissue engineering, providing structural support during tissue regeneration

4.4. Pluronic: Pluronic, also known as poloxamer, is a synthetic triblock copolymer with thermoresponsive properties. It has been investigated for its ability to form hydrogels at physiological temperatures, making it suitable for encapsulating cells in 3D Bioprinting.

4.5. Polyvinylpyrrolidone (PVP): PVP is a synthetic polymer commonly used as a binder or viscosity modifier in 3D printing. Its versatility and biocompatibility make it suitable for various applications, including drug delivery systems and tissue engineering.

4.6. Polyethylene Glycol (PEG): PEG is a synthetic polymer widely used in biomedical applications due to its hydrophilicity and biocompatibility. It has been employed in organ printing for its ability to form hydrogels and support cell growth.

5. Natural Biomaterials for 3D Printing and Their Applications

Natural biomaterials offer unique advantages such as biocompatibility, biodegradability, and mimicry of native tissue properties, making them valuable for various applications in 3D printing and tissue engineering. Natural biomaterials are used in tissue engineering and other fields. For example, scaffolds for bone tissue engineering need to have similar mechanical properties to human bone, such as compressive strength and histological properties. Polymers and other biomaterials can be added to these scaffolds to mimic the ECM found in osseous tissue and improve cells (Tappa, K., & Jammalamadaka, U. 2018). Naturally derived sources are often proposed as substitutes for synthetic materials, which may not have the necessary biological complexity (**Table 5**). Natural biomaterials for 3D printing include polymers, proteins, and polysaccharides. Some examples of natural biomaterials include:

5.1. Hydrogels

Made from natural polymers like gelatin, collagen, hyaluronic acid, and alginate, or synthetic polymers like polyurethane, polyacrylamide, or poly-(ethylene glycol) (PEG) (Song, D. et al., 2021).

Collagen: As the main structural protein in the body, collagen is widely used in 3D printing for its biocompatibility and ability to mimic the extracellular matrix. It finds applications in tissue engineering, wound healing, and regenerative medicine.

Gelatin: Derived from collagen, gelatin is a natural biomaterial commonly used in 3D printing due to its biocompatibility, low antigenicity, and ease of processing. It is employed in various biomedical applications, including drug delivery systems, tissue scaffolds, and wound dressings.

Alginate: Alginate, extracted from brown seaweed, is a natural polysaccharide used in 3D bioprinting for its ability to form hydrogels in the presence of divalent cations. It is utilized in tissue engineering, cell encapsulation, and drug delivery systems.

Chitosan: Derived from chitin, a natural polymer found in crustacean shells, chitosan exhibits antimicrobial properties and biodegradability. In 3D printing, chitosan is utilized for tissue engineering, wound healing, and drug delivery applications.

Hyaluronic Acid: Hyaluronic acid is a natural polysaccharide present in the extracellular matrix, known for its viscoelastic properties and role in tissue hydration. It is employed in 3D printing for applications such as cartilage regeneration, wound healing, and drug delivery.

Silk Fibroin: Derived from silk, silk fibroin is a biocompatible protein with excellent mechanical properties. It is utilized in 3D printing for tissue engineering, wound healing, and drug delivery due to its biodegradability and ability to support cell growth.

5.2. Proteins

Spider silk, gelatin methacrylamide (GelMA), fibrin, and extracellular matrix (ECM) derived-proteins like Matrigel are innovative biomaterials with diverse applications in 3D printing These biomaterials offer unique properties that enable the fabrication of complex structures with tailored functionalities, advancing the field of 3D printing in biomedical research and regenerative medicine (Liu, F., & Wang, X. 2020):

Spider Silk: Known for its exceptional strength and biocompatibility, spider silk is utilized in 3D printing for tissue engineering, wound healing, and drug delivery. Its unique properties make it suitable for creating scaffolds that mimic the natural extracellular matrix, promoting cell adhesion and tissue regeneration.

Gelatin Methacrylamide (GelMA): GelMA is a versatile biomaterial derived from gelatin, modified with methacrylamide groups to enhance its photocrosslinking properties. In 3D printing, GelMA hydrogels are widely employed for fabricating tissue scaffolds, organ-on-a-chip systems, and drug delivery platforms due to their biocompatibility, tunable mechanical properties, and support for cell proliferation.

Fibrin: Fibrin is a natural protein involved in blood clot formation and wound healing. In 3D printing, fibrin-based hydrogels are utilized for biofabrication of vascularized tissues, skin substitutes, and organoids. Fibrin's ability to support angiogenesis and cell migration makes it suitable for regenerative medicine applications.

ECM-Derived Proteins (Matrigel): Matrigel is a complex mixture of ECM proteins derived from Engelbreth-Holm-Swarm (EHS) mouse sarcoma cells. It serves as a bioactive scaffold in 3D printing for culturing cells, studying cell behavior, and modeling tissue microenvironments. Matrigel supports cell attachment, proliferation, and differentiation, making it valuable for tissue engineering and drug screening applications.

5.3. Polysaccharides

Alginate, chitosan, gellan gum, agarose, and κ-carrageenan are polysaccharides extensively employed in 3D printing for various applications due to their biocompatibility, biodegradability, and tunable physical properties. In addition, these polysaccharides offer a wide range of properties that can be tailored to specific applications, making them valuable biomaterials in 3D printing technology (Table 5) (Song, D. et al., 2021):

a. Alginate: Alginate, derived from seaweed, forms hydrogels upon crosslinking with divalent cations like calcium ions. In 3D printing, alginate-based bioinks are used for constructing cell-laden scaffolds, tissue engineering, and drug delivery systems. Alginate's mild gelation conditions and ability to encapsulate cells make it suitable for bioprinting applications.

b. Chitosan: Chitosan, derived from chitin, possesses antimicrobial properties and promotes cell adhesion and proliferation. In 3D printing, chitosan-based materials are utilized for wound dressings, cartilage regeneration, and bone tissue engineering. Chitosan's biocompatibility and ability to support cell growth make it a promising biomaterial for bioprinting applications

c. Gellan Gum: Gellan gum is a polysaccharide derived from bacteria, capable of forming thermally reversible gels. In 3D printing, gellan gum hydrogels are used for creating tissue constructs, drug delivery vehicles, and food products. Gellan gum's shear-thinning behavior and excellent printability enable the fabrication of complex structures with high fidelity.

d. Agarose: Agarose, extracted from seaweed, forms thermally reversible gels upon cooling. In 3D printing, agarose-based bioinks are utilized for tissue engineering, drug screening, and organ-on-a-chip applications. Agarose's biocompatibility, tunable mechanical properties, and ability to mimic native tissue environments make it suitable for bioprinting.

e. κ-Carrageenan: κ-Carrageenan, extracted from red seaweed, forms thermoreversible gels with potassium ions. In 3D printing, κ-carrageenan hydrogels are employed for drug delivery, wound healing, and tissue engineering applications. κ-Carrageenan's biocompatibility, shear-thinning behavior, and tunable gelation kinetics make it suitable for bioprinting complex structures.

6. Bioprinting Techniques and Technologies

Bioprinting encompasses various techniques and technologies used to deposit biomaterials, cells, and growth factors layer by layer to create complex three-dimensional structures (Figure 4). Here are some key bioprinting techniques and technologies (Pugliese, R. et al., 2021):

6.1. Inkjet Bioprinting: Inkjet bioprinting is a type of 3D printing that uses living cells and biomaterials to create tissues and organs. It works in a similar way to traditional inkjet printing, but instead of ink, it deposits droplets of bioink, a mixture of living cells and a supporting material. It deposits droplets of bioink onto a substrate, allowing precise control over cell placement. Inkjet bioprinting is suitable for high-throughput applications and creating intricate patterns The bioink is ejected from a printhead onto a platform layer by layer, building up a 3D structure. The biomaterials in the bioink provide a scaffold for the cells to grow on, while the cells themselves form the building blocks of the tissue or organ. Inkjet bioprinting has the potential to revolutionize regenerative medicine by creating tissues and organs for transplantation. It could also be used to create new models for drug testing and disease research (Dababneh, A., & Özbolat, İ. T. 2014).

Some of the advantages of inkjet bioprinting are (Li, X. et al., 2020):

A. **High precision**: Inkjet bioprinting can create structures with very high precision, which is important for creating complex tissues and organs.

B. **Biocompatibility**: The biomaterials used in inkjet bioprinting can be designed to be compatible with living cells.

C. **Customization**: Inkjet bioprinting can be used to create tissues and organs that are customized for individual patients.

6.2. Extrusion-Based Bioprinting: Extrusion-based bioprinting (EBB) is a 3D printing technique that uses mechanical force to extrude bioinks, which are mixtures of cells, signaling molecules, and other materials, into a predetermined design in layers (Gillispie G et al., 2020). EBB is the most common and economical bioprinting method, and is a leading manufacturing technique for tissue engineering and regenerative medicine. EBB can be used to fabricate bioprinted organs, which could reduce the need for organ donation and provide an alternative to animal testing. EBB can also print various biologics, including cells, tissues, tissue constructs, organ modules, and microfluidic devices (Rasheed, A. et al., 2020). EBB printers have a pressure- and temperature-controlled reservoir and a dispensing mechanism that can move in the x, y, and z axes. As extrusion pressure increases, the flow rate of ink through the nozzle increases, and the print speed must increase as well. If the print speed is higher than the velocity of ink exiting the nozzle, the extruded filament may be elongated and may result in discontinuities or inferior mechanical properties (Tian, S., Zhao, H., & Lewinski, N. A. 2021).

6.3. Stereolithography (SLA): Stereolithography (SLA) is a 3D printing technology that uses a liquid, photosensitive resin and UV light to cure the resin layer by layer until the final object is complete. SLA is also known as vat photopolymerization and is the most common resin 3D printing process. It offers high resolution and the ability to print complex geometries, making it suitable for producing detailed tissue constructs and scaffolds. SLA is known for its precision and accuracy, with tolerances typically less than 0.05 mm. It also offers the smoothest surface finish of any additive manufacturing process. SLA 3D printing is popular for its ability to produce: High-accuracy parts, Isotropic parts, Watertight parts, Smooth surface finishes, and Fine features (Figure 5) (Subramanian, B. et al., 2023).

6.4. Selective Laser Sintering (SLS): Selective Laser Sintering (SLS) offers versatility in material selection and can produce complex structures with high mechanical strength. It utilizes a laser to construct a part layer by layer from a fine powder bed. The fine powders undergo recrystallization (sintering) upon exposure to a high-power laser beam. The scanning laser beam is guided by a deflection system to build each layer, following a cross-section calculated from a pre-designed CAD model. Subsequently, the next layer is formed by depositing and spreading powder over the previously processed layer, continuing until the entire 3D part is manufactured. During the SLS process, the stack of layers is bonded together to achieve the desired shape outlined by the CAD model Figure 6. (Munir, K., Li, Y., & Wen, C. 2017,).

Table 1. The frequency and percentage of characteristic variables in 906 patients with COVID-19

Variable		Frequency	Percentage
Gender	Male	497	54.9
	Female	409	45.1
Oxygen therapy	Reservoir bag	702	77.5
	Non-invasive ventilation (NIV)	122	13.5
	Intubation	62	6.9
	Mask	13	1.4
	Canal	7	.8
Fate	Alive	739	81.6
	Death	167	18.4
BMI (kg/m²)	Less than 20	30	3.5
	20 ≤ and < 30	580	67.2
	30 ≤ and < 40	229	26.5
	More than 40	24	2.8
Underlying disease	None	725	80.0
	CVA	34	3.8
	CHF	22	2.4
	Heart disease	20	2.2
	COPD	5	.6
	Kidney disease	1	.1
	Other	99	10.9
CRP	-	284	31.3
	1	297	32.8
	2	260	28.7
	3	7	.8
	None	58	6.4
PCR	Positive	399	44.0
	Negative	353	39.0
	None	154	17.0
Vitamin D (ng/mL)	Less than 20	5	1.2
	20 ≤ and < 30	93	21.5
	More than 30	335	77.4
LDH (U/L)	Less than 500	180	31.1
	500 ≤ and < 1000	344	59.5
	More than 1000	54	9.3
Lymphocyte	More than 10 %	615	68.3
	Less than 10 %	285	31.7

Table 2. The descriptive statistics of Vitamin D Levels and inflammatory markers in 906 patients with COVID-19

		Vitamin3	LDH	Lymphocyte	WBC	BMI	age
N	Valid	433	578	900	894	863	900
	Missing	473	328	6	12	43	6
Mean		40.10	696.38	17.17	9058.46	28.09	64
Standard Deviation		37.06	610.195	11.42	6309.80	5.32	16
Variance		1373.63	372337.45	130.60	39813693.91	28.317	…
Minimum		4.0	151	0	100	.00	…
Maximum		551.0	8900	116	107000	58.59	…

According to Munir, K., Li, Y., and Wen, C. (2017), powder deposition in SLS typically involves a roller or scraper, facilitating the deposition of successive powder layers ranging in thickness from 20 to 150 µm. To prevent environmental contamination and powder oxidation during sintering, the deposition is often conducted under an inert atmosphere (e.g., argon or nitrogen). SLS printers can accommodate various lasers, including CO2, lamp, diode-pumped Nd:YAG, disk, or fiber lasers.

One notable advantage of SLS is its efficient powder utilization, with the remaining unmelted powder being recyclable. However, challenges such as poor surface finish and dimensional inaccuracies necessitate costly post-processing treatments like machining, heat treatments, and polishing. Control over the microstructures of porous structures and scaffolds can be achieved by optimizing critical processing parameters such as laser power, powder bed temperature, and laser scan speed (Munir, K., Li, Y., & Wen, C. 2017).

6.5. Electrospinning: Electrospinning and 3D printing are advanced manufacturing techniques that can be used together to create composite scaffolds with improved properties for biomedical applications. Electrospinning is a high-resolution technique that uses electrostatic forces to generate nano-microfibers from a liquid polymeric solution or melt. The fibers are formed by evaporation of the solvent or freezing of the melt (Ejiohuo, O. 2023). It is used to create nanofiber scaffolds with high surface area and porosity, suitable for applications in tissue engineering, drug delivery, and wound healing (Figure 7).

Electrospinning is particularly beneficial to the biomedical sector for the development of advanced systems that are relevant to tissue engineering and drug delivery. For example, aligned fibers have been demonstrated to promote osteogenic differentiation, axon guidance, neurite outgrowth, and more (Smith, J., & Mele, E. 2021). Electrospinning machines have three main components (Hernández-Vargas, J. et al., 2014):

- Spinneret: A metallic needle that creates a droplet of polymer solution at the tip
- High-voltage power supply: Generates the electric force
- Collector: A grounded collector that collects the charged fibers

The process of electrospinning involves (Xue J et al., 2019):

- High voltage: Applied to a liquid polymer, causing a jet strand to be directed toward a grounded collector
- Stretching: The jet is stretched and elongated to generate fibers
- Solidification: The solvent evaporates, solidifying the fibers

6.6. Magnetic Bioprinting: Magnetic bioprinting is a technique that uses biocompatible magnetic nanoparticles to print cells into 3D structures or 3D cell culture (Figure 8). These bioprinting techniques and technologies play a crucial role in advancing tissue engineering, regenerative medicine, and drug discovery by providing precise control over cell placement and scaffold architecture (Li J et al., 2016).

Magnetic Bioprinting, how does it work (Li J et al., 2016, Souza GR et al., 2010):

- Cells are tagged with magnetic nanoparticles to make them magnetic.
- A magnetic field is used to assemble layers of cells or magnetic nanoparticles onto a substrate.
- The magnetic field guides the cells or nanoparticles into a specific pattern to create a 3D structure.

7. Challenges and Limitations in Organ Printing.

Organ printing, a groundbreaking technology with immense potential, also faces several challenges and limitations that need to be addressed for its widespread implementation and success which have been discussed by researchers from time to time as follows (Özbolat, İ. T., & Hospodiuk, M. 2016, Yan, Q et al., 2016, Li, J. et al., 2016):

7.1. Biocompatibility: Ensuring that the printed organs are biocompatible with the recipient's body is crucial to prevent rejection and ensure long-term functionality. Challenges lie in selecting suitable biomaterials and bioinks that mimic the natural extracellular matrix and cellular environment.

7.2. Vascularization: Adequate vascularization is essential for supplying nutrients and oxygen to the printed tissues and organs. Challenges include integrating vascular networks within the printed structures to support cell survival and function.

7.3. Cell Viability: Maintaining cell viability throughout the printing process and post-printing is critical for the organ's functionality.

Challenges include optimizing printing parameters to minimize cell damage and providing a conducive environment for cell proliferation and differentiation.

7.4. Structural Integrity: Achieving the desired structural integrity of the printed organs, including mechanical strength and stability, poses challenges. Optimizing printing techniques and biomaterial formulations to withstand physiological forces and mimic natural tissue properties is essential.

7.5. Scalability: Scaling up organ printing to produce complex organs with intricate architectures remains a significant challenge. Overcoming limitations related to printing speed, resolution, and reproducibility is necessary to meet the growing demand for transplantable organs.

7.6. Regulatory Hurdles: Navigating regulatory frameworks and obtaining approvals for clinical use present obstacles to the widespread adoption of organ printing technologies. Addressing safety, efficacy, and ethical concerns is essential for gaining regulatory approval.

7.7. Cost: The high cost associated with organ printing, including materials, equipment, and labor, poses a barrier to accessibility. Developing cost-effective printing techniques and biomaterials without compromising quality is crucial for making organ printing more affordable and accessible.

7.8. Ethical Considerations: Ethical concerns surrounding the use of human cells, organ donation, and patient consent need to be carefully addressed. Ensuring transparency, equity, and respect for human dignity are paramount in the development and application of organ printing technologies.

8. Regulatory and Ethical Considerations.

Regulatory and ethical considerations play a pivotal role in the development, implementation, and utilization of organ printing technologies. Here we delve into the complex landscape of regulations and ethical frameworks that govern organ printing, addressing key issues and challenges.

8.1. Regulatory Frameworks: Organ printing technologies are subject to stringent regulatory oversight to ensure safety, efficacy, and quality. Regulatory agencies, such as the FDA (Food and Drug Administration) in the United States, impose regulations on the development, testing, and approval of printed organs and bioinks. Compliance with Good Manufacturing Practices (GMP) and other quality standards is essential for obtaining regulatory approval for clinical use (Vermeulen, N et al., 2017).

8.2. Safety and Efficacy: Demonstrating the safety and efficacy of printed organs through rigorous preclinical and clinical studies is paramount. Regulatory agencies require comprehensive data on biocompatibility, immunogenicity, and long-term outcomes to assess the risks and benefits of organ printing technologies accurately (Goldring, C et al., 2011).

8.3. Ethical Considerations: Ethical considerations surrounding organ printing encompass a range of issues, including patient consent, equity in access to technology, and the use of human cells and tissues. Respecting patient autonomy, privacy, and confidentiality is essential throughout the organ printing process, from cell sourcing to transplantation (Rasheed, A et al., 2020).

8.4. Equity and Access: Ensuring equitable access to organ printing technologies is essential to prevent disparities in healthcare. Addressing socioeconomic barriers, including cost and geographical accessibility, is crucial for promoting equitable distribution and utilization of organ printing services (Li, P. 2014).

8.5. Intellectual Property Rights: Protecting intellectual property rights, including patents and copyrights, is important for fostering innovation and investment in organ printing technologies. Balancing the need for intellectual property protection with the promotion of open access and collaboration is key to advancing the field ethically and responsibly (McGill, M. L. 2013).

8.6. Social and Cultural Considerations: Organ printing raises complex social and cultural considerations, including attitudes towards biotechnology, organ donation, and the definition of life and death. Engaging stakeholders, including patients, healthcare providers, policymakers, and ethicists, in discussions about these issues is essential for developing ethical guidelines and policies (Vijayavenkataraman, S. et al., 2016).

9. Case Studies of Successful Organ Printing.

Successful organ printing represents a groundbreaking advancement in regenerative medicine, offering hope for patients with organ failure. Several remarkable case studies demonstrate the feasibility and potential of this innovative technology:

9.1. Bladder Reconstruction: In one pioneering case, researchers at Wake Forest Institute for Regenerative Medicine successfully implanted bioengineered bladders into patients with bladder disease. These bladders were constructed using the patients' own cells and a biodegradable scaffold, resulting in functional organs capable of storing and expelling urine (El-Taji OM et al., 2015).

9.2. Tracheal Transplantation: A landmark case involved the transplantation of a bioengineered trachea into a patient with tracheal cancer. The trachea was constructed using the patient's own stem cells seeded onto a synthetic scaffold and was subsequently implanted, providing a life-saving treatment option for the patient (Genden EM et al., 2023).

9.3. Skin Grafts: Organ printing technology has also been utilized for skin regeneration in patients with severe burns or wounds. Researchers have successfully printed skin grafts using a combination of patient-derived cells and biocompatible materials, facilitating wound healing and minimizing scarring (Prohaska J, Cook C. 2023).

9.4. Cartilage Repair: Patients suffering from cartilage defects or injuries have benefited from the development of bioengineered cartilage implants. These implants, created using 3D printing technology and patient-specific cells, have demonstrated promising outcomes in restoring joint function and alleviating pain (Liu Y et al., 2021).

9.5. Liver Tissue Engineering: Researchers have made significant strides in the development of bioengineered liver tissues for transplantation and drug testing purposes. By mimicking the complex architecture and functionality of the liver, these engineered tissues hold great promise for addressing liver diseases and advancing drug development (Heydari Z et al., 2020).

9.6. Heart Patch Implantation: In cases of myocardial infarction or heart failure, bioengineered heart patches have shown therapeutic potential. These patches, composed of patient-derived cells and supportive biomaterials, can be implanted onto damaged cardiac tissue to promote regeneration and improve cardiac function (Mei, L et al., 2021).

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10. Future Perspectives and Emerging Trends in Organ Bioprinting

The future of organ bioprinting holds immense promise, with numerous emerging trends and advancements poised to revolutionize the field. Here are some key perspectives and Trends as discussed by researchers (Matai, I et al., 2020):

10.1. Bioink Development: Advances in bioink formulation will continue to drive innovation in organ bioprinting. Researchers are exploring novel biomaterials, including hydrogels, decellularized extracellular matrix (dECM), and cell-laden bioinks, to enhance cell viability, functionality, and tissue-specific properties.

10.2. Multi-material Bioprinting: The development of multi-material bioprinting techniques enables the fabrication of complex, heterogeneous tissues and organs with precise spatial control. Integration of different cell types, growth factors, and biomaterials within a single construct facilitates the recreation of native tissue architecture and functionality.

10.3. Vascularization Strategies: Vascularization remains a critical challenge in organ bioprinting. Emerging strategies focus on incorporating pre-formed vascular networks, bioactive factors, and perfusion-based culture systems to promote angiogenesis and ensure adequate nutrient and oxygen supply within printed constructs.

10.4. Integration of Biomanufacturing Technologies: Integration of bioprinting with other biomanufacturing technologies, such as tissue engineering, organ-on-a-chip systems, and microfluidics, offers new opportunities for advanced organ model development, drug screening, disease modeling, and personalized medicine.

10.5. Organ-on-a-Chip Platforms: Organ-on-a-chip platforms mimic the physiological microenvironment of organs, enabling the study of organ-level functions, disease mechanisms, and drug responses in vitro. Combining bioprinting with organ-on-a-chip technology allows for the creation of more physiologically relevant models for drug testing and toxicity screening.

10.6. Artificial Intelligence (AI) and Computational Modeling: AI-driven computational modeling plays a crucial role in optimizing bioprinting processes, predicting cell behavior, and designing patient-specific constructs. Machine learning algorithms analyze large datasets to optimize bioink properties, printing parameters, and tissue maturation protocols.

10.7. Clinical Translation and Regulatory Considerations: The translation of organ bioprinting technologies from the laboratory to the clinic requires rigorous preclinical validation, regulatory approval, and clinical trials. Collaboration between academia, industry, and regulatory agencies is essential to navigate the regulatory pathway and ensure the safety and efficacy of bioprinted organs for clinical use.

Conclusion

In conclusion, organ bioprinting holds immense promise in revolutionizing regenerative medicine and addressing the critical need for organ transplantation. Throughout this review, we have explored the foundational principles, techniques, and biomaterials driving the advancement of organ bioprinting technology. From selective laser sintering to extrusion-based bioprinting, significant progress has been made in achieving biocompatibility, structural integrity, and functionality in printed constructs.

Despite the remarkable advancements, challenges and limitations persist, particularly concerning vascularization, immune response, and scalability. Regulatory and ethical considerations also pose significant hurdles to the widespread clinical translation of bioprinted organs. However, through collaborative efforts between researchers, clinicians, policymakers, and ethicists, these challenges can be addressed to facilitate the ethical and safe integration of bioprinted organs into clinical practice.

Case studies of successful organ printing demonstrate the feasibility and potential of this technology in creating functional tissues and organs for transplantation. Yet, further research is needed to optimize bioprinting processes, enhance cellular viability, and improve long-term functionality.

Looking ahead, future perspectives and emerging trends in organ bioprinting, including organ-on-a-chip platforms and AI-driven computational modeling, offer exciting opportunities for innovation and personalized healthcare. By harnessing these advancements and addressing existing challenges, organ bioprinting can fulfill its promise of transforming the landscape of regenerative medicine and improving patient outcomes.

Author contributions

All authors made equal contributions to the study design, statistical analysis, and drafting of the manuscript. The corresponding author, along with the co-authors, reviewed and approved the final version of the article prior to submission to this journal.

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The authors have no co Baktash nflict of interest.

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