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Review Article

A Comprehensive Review on COVID-19: Virology, Molecular Diagnosis and Exploration of Mesenchymal Stem Cells (MSCs) for Its Treatment

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Abstract

Background: COVID-19, instigated by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) appeared in 2019 and has since caused a universal health crisis. The virus's pathogenicity is primarily due to its unique structure, mode of transmission and capacity to evade the host immune response. While traditional treatment and diagnostic strategies have evolved, the elevated morbidity and mortality linked with severe infections necessitate advanced approaches. Among these, Mesenchymal Stem Cells (MSCs) have gained attention as a potential therapeutic strategy owing to their regenerative and immunomodulatory capabilities.

Methods and Findings This review explores SARS-CoV-2 virology, transmission mechanisms, immune response and the viral life cycle. It summarizes current molecular diagnostic methods-RT-PCR, RT-LAMP, CRISPR, ELISA, gene sequencing, biosensors and imaging techniques-and discusses their relative advantages and limitations. For treatment, various antivirals, monoclonal antibodies and glucocorticoids are examined. The paper extensively discusses MSCs sourced from bone marrow, adipose tissue and umbilical cord, which have shown promising results in managing severe COVID-19 symptoms. MSCs mitigate cytokine storms, promote lung repair and reduce inflammatory markers. Clinical trials have reported improved oxygen saturation, reduced ICU stays and lower mortality in critically ill patients receiving MSCs therapy.

Conclusion: Mesenchymal Stem Cells (MSCs) offer promise in COVID-19 treatment due to their immune modulation and tissue repair abilities and their resistance to SARS-CoV-2. However, issues like protocol variability, high cost and unknown long-term safety remain. Future work should refine dosage, delivery and explore synergies with gene editing and extracellular vesicles. Large trials and AI-driven frameworks are vital for mainstream clinical use.

Keywords: SARS-CoV-2; COVID-19; Acute Respiratory Distress Syndrome; Angiotensin-Converting Enzyme 2; Mesenchymal Stem Cells

Introduction

COVID-19, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is the fifth major global pandemic since 1918. SARS-CoV-2 is a positive-sense, single-stranded RNA virus with an envelope, comprising 14 open reading frames that encode 27 proteins, including the Spike (S) protein enabling ACE2 receptor-mediated host cell entry [1]. The virus spreads via respiratory droplets, aerosols and contaminated surfaces. The host immune response involves T cells, B cells, macrophages and dendritic cells. CD8+ T cells recognize viral antigens via MHC I and B cells produce IgM and IgG antibodies [2]. In severe cases, cytokine storms lead to systemic inflammation and multi-organ damage [3].

Molecular diagnostic techniques-including RT-PCR, CRISPR and RT-LAMP remain essential for detecting SARS-CoV-2 RNA from patient samples [4]. Imaging techniques like CT and antigen/antibody testing serve as supplemental tools [5]. While antivirals, monoclonal antibodies and glucocorticoids are standard COVID-19 treatments, their effects are often temporary [6]. Vaccination remains the most effective long-term preventive strategy.

Mesenchymal Stem Cells (MSCs) have shown promise as a therapeutic option owing to their immunomodulatory effects, regenerative capacity and resistance to SARS-CoV-2 infection. MSCs sourced from bone marrow, adipose tissue and umbilical cord blood can regulate immune responses and support tissue [7,8]. Clinical studies show that MSC therapy reduces inflammation (IL-6, CRP), improves lung function, resolves lesions and lowers ICU stays and mortality in severe cases. Despite these advantages, challenges remain: inconsistent protocols, high costs, limited availability and immunological risks [9-11]. Future research should focus on optimizing delivery, combining MSCs with microRNAs or extracellular vesicles and leveraging AI-driven precision treatment. With continued clinical validation, MSCs could become a cornerstone in regenerative COVID-19 therapy.

Transmission of SARS-CoV-2

The main way that SARS-CoV-2 spreads is by respiratory droplets from breathing, sneezing or coughing. Although human-to-human transmission is the primary method, the virus can also spread indirectly through contaminated surfaces (fomite transmission). The virus can survive on surfaces like stainless steel and glass for up to several days, but the danger is regarded as minimal. Furthermore, infected persons' feces have been discovered to contain live virus, indicating the possibility of fecal-oral transmission [12].

Life Cycle of SARS-CoV-2

SARS-CoV-2 begins infection through its Spike (S) protein binding to the Angiotensin-Converting Enzyme 2 (ACE2) receptor, primarily on respiratory epithelial cells [13]. The S1 subunit attaches to ACE2, while the S2 subunit mediates membrane fusion, a step promoted by the host protease TMPRSS2 [14]. Notably, Mesenchymal Stem Cells (MSCs) lack ACE2 and TMPRSS2 expression, making them resistant to SARS-CoV-2 infection [15]. This innate resistance allows MSCs to retain function in inflamed environments, supporting their use as a therapeutic option in severe COVID-19 (Fig. 1).

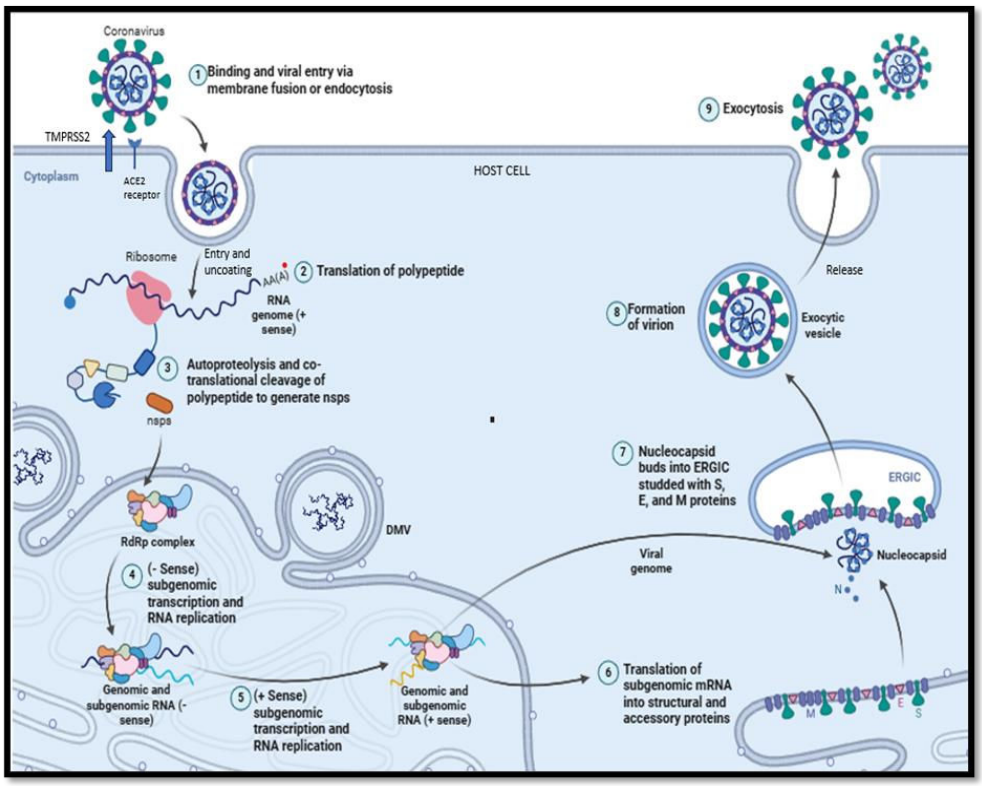

Figure 1: Life cycle of corona virus showing entry, replication inside host cell and release of virus from host cell.

Molecular Diagnostic Methods

Molecular techniques are critical in detecting SARS-CoV-2 by targeting viral RNA or DNA (Fig. 2) [16]. The gold-standard RT-PCR offers high sensitivity and specificity by converting viral RNA to cDNA and amplifying target sequences, but it requires advanced labs and has limitations like long turnaround times, cost and risk of false negatives due to mutations (Fig. 3) [17-20]. CRISPR-based diagnostics provide an alternative with high specificity. Platforms like SHERLOCK (Cas13), STOP and DETECTR (Cas12) enhance sensitivity by integrating isothermal amplification (Fig. 4) [21-23]. Despite their promise, they are limited by complexity and target range [24].

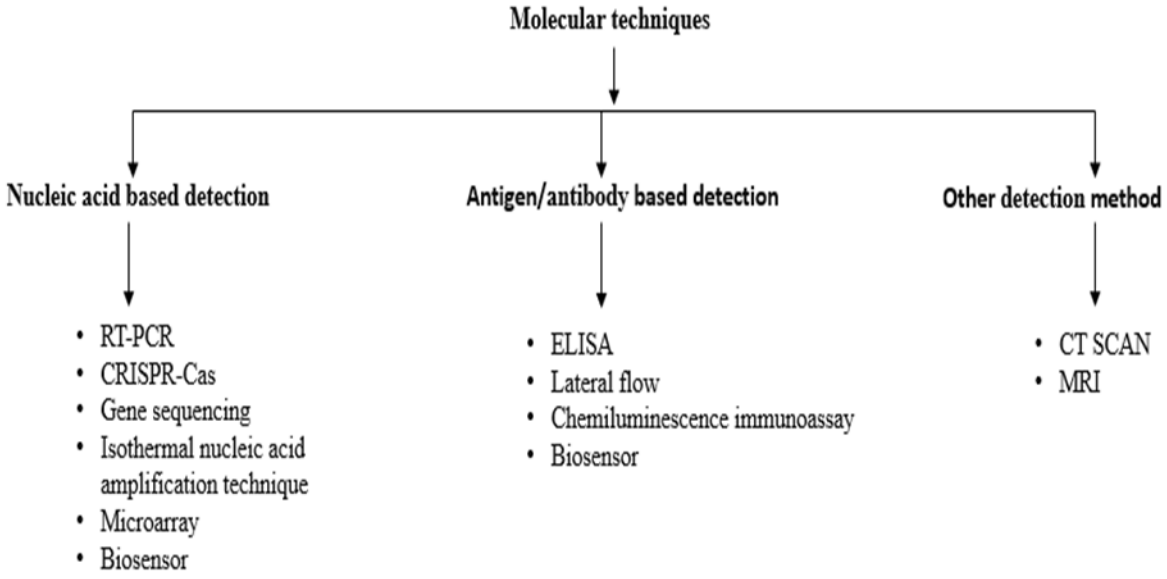

Figure 2: Schematic representation showing various molecular techniques used for detection of COVID-19.

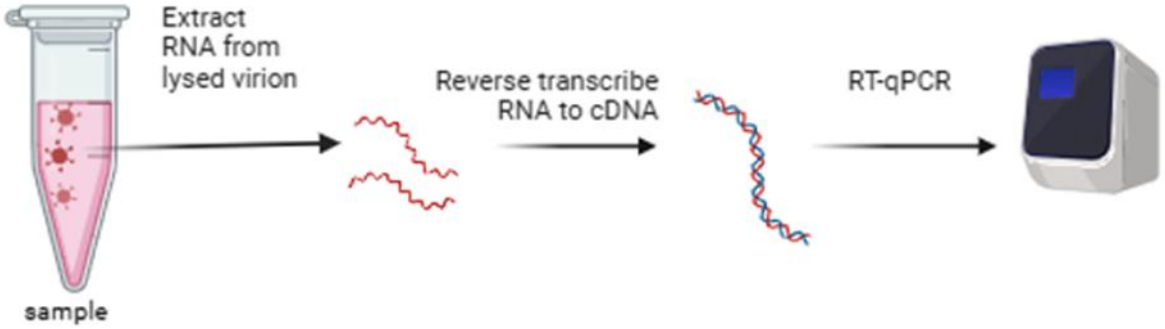

Figure 3: Illustration of COVID-19 detection by using RT-PCR technique.

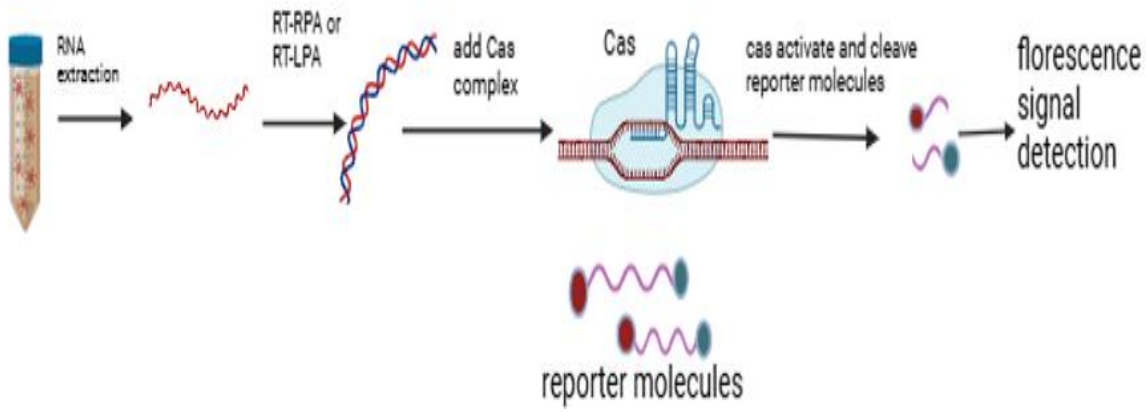

Figure 4: Illustration of COVID-19 detection by using CRISPR based technique.

Imaging techniques like CT are valuable for identifying lung lesions, especially when RT-PCR yields false negatives. CT findings include ground-glass opacities and consolidations [5,25]. MRI is less commonly used due to logistical constraints but can aid in soft-tissue assessment [26,27]. Overall, RT-PCR remains dominant despite its drawbacks. Antigen tests, biosensors and imaging methods serve as rapid adjuncts but lack consistent sensitivity [28]. Emerging approaches include AI-assisted diagnostics, wastewater surveillance and big data monitoring for early detection [4].

Treatment for SARS-CoV-2

More than 5,000 clinical trials are now being conducted worldwide to treat and prevent SARS-CoV-2. These investigations focus on antiviral small compounds, glucocorticoids and monoclonal antibodies. Uncertainty surrounds the precise mechanisms of SARS-CoV-2 entrance and infection, underscoring the need of applying previous coronavirus studies to future epidemics. Targeting the viral glycoprotein, neutralizing monoclonal antibodies are useful for mild cases and early in infection, but they provide little protection, highlighting the necessity of vaccinations. Treating COVID-19 requires the use of small molecule medications that target different phases of the viral lifecycle (Table 1) [6].

Agent	Therapy Method	Therapy Effect	Reference
Remdesivir	Intravenous	Reduced the duration of hospital stays, ease symptoms and lowered the risk of death.	[29]
Paxlovid (Nirmatrelvir plus ritonavir)	Orally administered, it can be paired with Molnupiravir to improve effectiveness	Reduced viral reproduction and transmission by inhibiting SARS-CoV-2's protease activity. This helped in control the course and symptoms of COVID-19.	[30]
Molunpiravir	Orally	It quickly dropped viral loads, minimized symptoms and reduced hospital stay and death rates.	[31]
Baricitinib	Orally	Reduced the inflammatory response in severe COVID-19 sufferers, stopped the cytokines generation and reduced hospital stays as well as death rates.	[32]
Dexamethasone	Intravenous	Reduced mortality rate	[33]
Lopinavir/Ritonavir	Orally	Shown antiviral property against COVID-19	[34]
Camostat mesylate	Orally	Japan-approved TMPRSS2 inhibitor, blocked virion infection in cells of lungs and currently in clinical trial for COVID-19 treatment.	[35]

Table 1: List of agents that are used for COVID-19 treatment, their mode of therapy method and effects.

Treatment By Stem Cells

Stem cells are primitive cells with the unique ability to both self-renew and differentiate into various specialized cell types. They are classified based on their differentiation potential into five main types: totipotent, pluripotent, multipotent, oligopotent and unipotent. Totipotent stem cells have the capacity to develop into an entire organism, including all embryonic and extraembryonic tissues. In contrast, multipotent stem cells such as Hematopoietic Stem Cells (HSCs) can differentiate into multiple cell types within a specific lineage. Oligopotent stem cells are more limited, producing only a few closely related cell types. Unipotent stem cells possess the most restricted differentiation potential but retain a strong capacity for self-renewal, making them valuable in regenerative medicine [36]. Pluripotent Stem Cells (PSCs), including Embryonic Stem Cells (ESCs) and induced Pluripotent Stem Cells (iPSCs), can form any cell type derived from the three germ layers but lack the ability to generate extraembryonic tissues like the placenta [37].

Source of Stem Cells

Stem cells originate from several sources, for instance human umbilical cord blood, bone marrow, adipose tissue, amniotic fluid and induced pluripotent stem cells. Umbilical cord blood provides both hematopoietic and mesenchymal stem cells, which can distinguish into red blood cells and immune cells. Bone marrow is rich in Mesenchymal Stem Cells (MSCs) and hematopoietic

stem cells, both essential for generating blood cells. Adipose tissue-derived stem cells have self-renewal and multipotency properties, making them useful for reconstructive surgery and tissue engineering. Amniotic fluid, which surrounds the foetus, is another important source of embryonic stem cells (blastocysts), which are pluripotent and may develop into many cell types. iPSCs, derived from somatic cells by genetic reprogramming, provide a new way for creating pluripotent stem cells with potential applications in regenerative medicine (Fig. 5) [8].

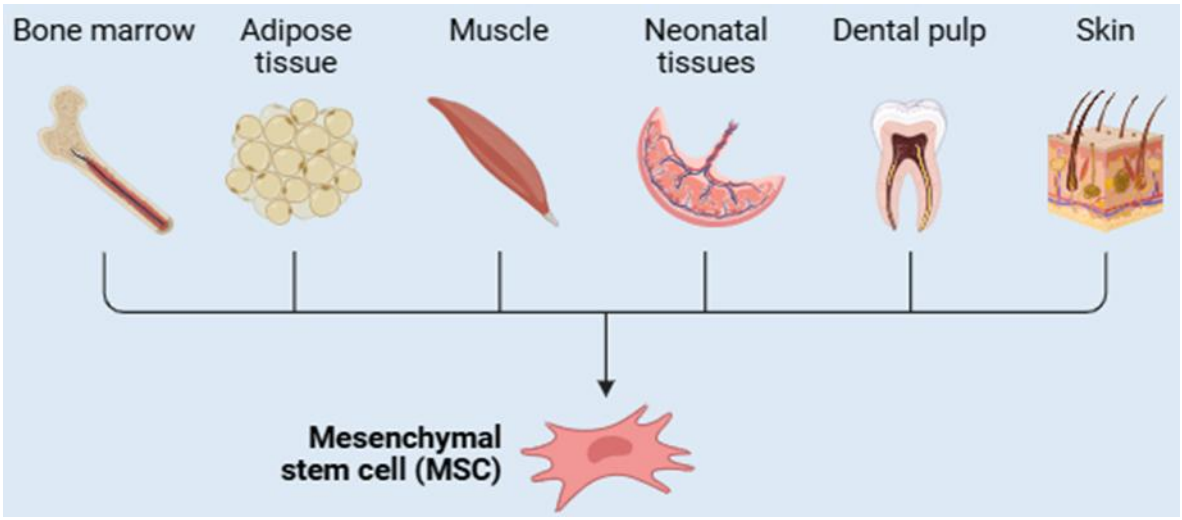

Figure 5: Illustration of various sources of MSCs extraction.

Mesenchymal Stem Cells (MSCs) Use in COVID-19 Treatment

The COVID-19 pandemic has resulted in widespread organ damage, particularly Acute Respiratory Distress Syndrome (ARDS). MSCs-sourced from bone marrow, adipose tissue and peripheral blood-have shown promise due to their immunomodulatory properties and regenerative capabilities [15]. They release growth factors such as Keratinocyte Growth Factor (KGF), Vascular Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF), which aid in lung tissue repair. KGF-modified MSCs improved lung permeability and regeneration in lipopolysaccharide-induced lung injury, while HGF-modified MSCs enhanced survival and reduced inflammation in ischemia/reperfusion injury (Fig. 6) [38,39].

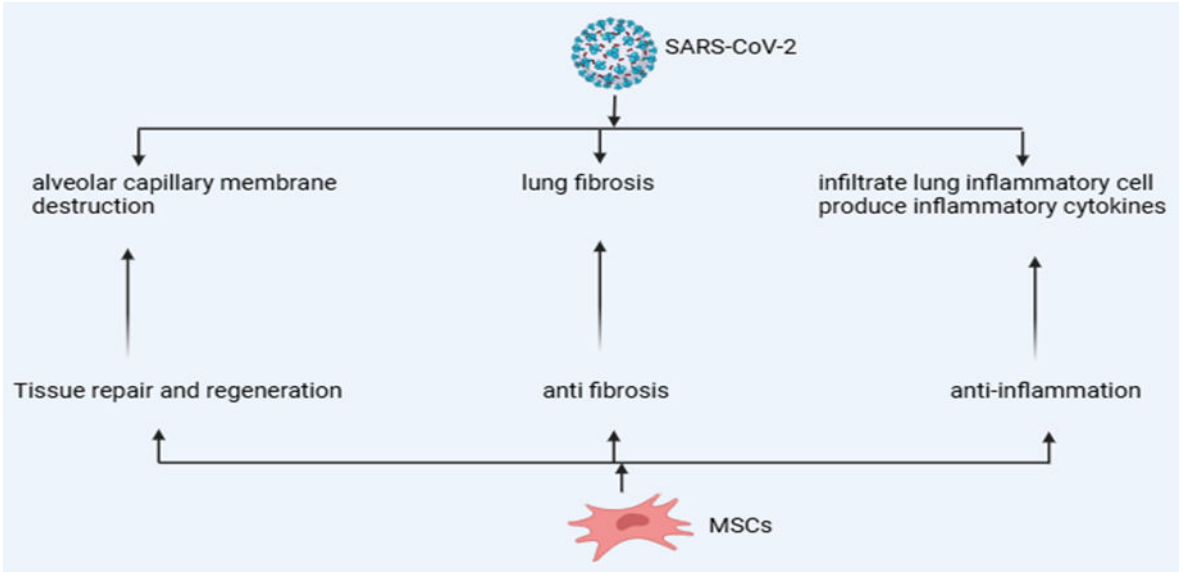

Figure 6: Effects of MSCs therapy in treatment of COVID-19 symptoms.

MSCs are recruited to inflamed tissue and modulate immune responses via interactions with NK cells, dendritic cells and T/B lymphocytes [15]. They release key immunoregulatory mediators including indoleamine 2,3-dioxygenase, TGF-β, HLA isoforms and prostaglandin E2 which help control the hyperinflammation seen in severe COVID-19 [15,40]. Importantly, MSCs lack ACE2

expression, rendering them resistant to SARS-CoV-2 infection and allowing them to function safely in inflamed tissues [41,42]. Another therapeutic advantage of MSCs is their ability to reduce Neutrophil Extracellular Trap (NET) formation, which contributes to immunothrombosis in ARDS. In a clinical study of 58 patients, treated groups showed a significant and sustained reduction in plasma NET-DNA levels, unlike the placebo group [15].

Clinical Studies on MSCs in COVID-19

Mesenchymal Stem Cells (MSCs), especially those resulting from the Umbilical Cord (UC-MSCs), have shown clinical benefit in treating severe COVID-19 and ARDS. Patients receiving therapy experienced improved oxygenation (SpO_2, PaO_2/FiO_2), reduced symptoms like dyspnea and fatigue and faster recovery within 2-4 days [43-45]. Long-term follow-up confirmed better physical function in recipients [6].

MSCs also improved inflammatory profiles, significantly lowering CRP and IL-6 levels, while normalizing lymphocyte counts more rapidly [46]. Additional trials reported decreases in LDH, D-dimer and ferritin and specific reductions in TNF-α, IL-8, ferritin and MCP1-CCL2 levels in ARDS patients [43,47-49].

CT imaging showed better lung lesion clearance within two weeks post-UC transfusion [50]. Beyond pulmonary improvement, MSCs helped mitigate cytokine storms and modulate immune overactivation associated with COVID-19-related Cytokine Release Syndrome (CRS), leading to reduced mortality (33% vs. 67%) and fewer ICU stays [49,51]. The therapy is well-tolerated and supports immune regulation through modulation of the microenvironment and inflammation suppression, though further studies are needed to optimize protocols and assess long-term effects [46].

Challenges of MSCs Treatment

The use of MSCs treatment for COVID-19 faces multiple challenges, such as the absence of standardized protocols, ambiguous mechanisms of action and the possibility of immune system rejection [52]. The effects of MSCs can vary based on the patient demographic, severity of the disease and existing health conditions. There are also concerns regarding the potential for tumour development. The long-term safety and effectiveness of this treatment remain undetermined, highlighting the need for prolonged follow-up studies [53]. Additionally, the high costs and limited availability of MSCs therapy restrict its widespread use [54]. The regulatory guidelines and reimbursement frameworks are still developing, leading to uncertainty for both healthcare providers and patients. Moreover, the potential interactions of MSCs therapy with other COVID-19 treatments need further exploration [55].

Future Prospects

Mesenchymal Stem Cells (MSCs) have shown promise in treating COVID-19-related problems, including ARDS, severe instances and bronchopulmonary dysplasia in newborns, by improving lung structure, lowering inflammation and increasing survival rates [52]. However, further study is needed to determine their impact on cardiovascular and renal disorders in COVID-19 individuals. The outlook for MSCs treatment in COVID-19 encompasses improving effectiveness, safety and accessibility, by emphasizing standardized protocols, optimized dosing and delivery methods combined therapies, gene editing like CRISPR/Cas9, which increase the cell's capacity for immunomodulation, anti-apoptosis and regeneration, while the use of extracellular vesicles are becoming a powerful, cell-free substitute with comparable therapeutic efficacy, improved safety profiles and simpler scaling for clinical use. microRNAs and regenerative medicine used for tissues and organs affected by COVID-19 and therapy protocols driven by artificial intelligence [51,56].

Conclusion

Mesenchymal Stem Cells (MSCs) have shown considerable promise in the treatment of severe COVID-19 and ARDS due to their immunomodulatory properties, ability to regenerate lung tissue and resistance to SARS-CoV-2 infection. Significant obstacles still exist despite of promising results, such as the lack of established clinical procedures, exorbitant expenses and worries regarding long-term safety and effectiveness. In addition to integrating gene editing, extracellular vesicle-based therapeutics and AI-driven customization, future developments should concentrate on well planned, extensive clinical trials. MSCs may be essential to future treatment approaches for COVID-19 and related viral diseases with more study and regulatory improvement.

Conflict of Interest
The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate
Not applicable.

Consent for Publication
All authors have consent for publication.

Availability of Data and Materials
Not applicable.

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