REVIEW ARTICLE

AL-ANBAR MEDICAL JOURNAL
Anb. Med. J. 21(4): 214–222, 2025

Pathogenesis of Acute Respiratory Distress in SARS-CoV-2 Infection: Molecular and Clinical Investigation

Abolfazl Jafari-Sales,[1,2,3] Elham Nozohour-Leilabadi,[2,3] Maryam Farahnaki-Sadabadi,[2,4] Maryam Safari,[2,3] and Mehrdad Pashazadeh[2,5,*]

[1] *Department of Microbiology, Kaz.C., Islamic Azad University, Kazerun, Iran.*
[2] *Infectious Diseases Research Center, TaMS.C., Islamic Azad University, Tabriz, Iran.*
[3] *Department of Microbiology, Ta.C., Islamic Azad University, Tabriz, Iran.*
[4] *Department of Cellular and Molecular Biology, Ta.C., Islamic Azad University, Tabriz, Iran.*
[5] *Department of Laboratory Sciences and Microbiology, TaMS.C., Islamic Azad University, Tabriz, Iran.*

(Received : 28 May 2025; Accepted : 22 August 2025; First published online: 1 October 2025)

ABSTRACT

Acute respiratory distress syndrome (ARDS) is a life-threatening condition with high mortality, often triggered by severe lung infections such as those caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By disrupting immune regulation and inducing excessive cytokine release, SARS-CoV-2 plays a key role in the onset and progression of ARDS. Approximately 10.4% of intensive care unit (ICU) admissions are due to ARDS, with mortality rates ranging from 30% to 50% depending on severity. Viral entry occurs when the spike (S) protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor and is primed by transmembrane protease serine 2 (TMPRSS2), enabling penetration into respiratory epithelial cells. Subsequent viral replication and immune hyperactivation trigger a "cytokine storm," leading to alveolar and capillary membrane damage, increased pulmonary permeability, and alveolar edema, hallmark features of ARDS. This study reviews the SARS-CoV-2 life cycle, structural and functional characteristics, ARDS pathophysiology, diagnostic approaches including real-time polymerase chain reaction (RT-PCR) and inflammatory biomarkers, and emerging therapeutic strategies. Understanding the molecular pathways underlying viral invasion, immune dysregulation, and lung injury may facilitate the development of targeted therapies for affected patients.

Keywords: Acute respiratory distress syndrome; SARS-CoV-2; Spike protein; Angiotensin-converting enzyme 2; Transmembrane protease serine 2.

DOI: 10.33091/amj.2025.160850.2269

INTRODUCTION

Acute respiratory distress syndrome (ARDS), a non-cardiogenic pulmonary edema, has a high death rate. The worldwide coronavirus disease 2019 (COVID-19) epidemic and the quick development of critical care medical technology in recent years have given the medical community new knowledge on how to diagnose and treat ARDS [1]. In acute cases, SARS-CoV-2 infection triggers a massive release of cytokines, leading to the appearance of pro-inflammatory cytokines. This cytokine storm can result in ARDS and acute cardiac failure, both of which are highly dangerous and may predispose patients to secondary bacterial infections [2]. Approximately 10.4% of all intensive care unit (ICU) admissions worldwide are of patients with ARDS, and the fatality rates for mild, moderate, and severe ARDS are 34.9%, 40.3%, and 46.1%, respectively. Despite the fact that ARDS is a prevalent syndrome in ICUs, there is still a lack of knowledge among physicians, and around 40% of ARDS patients go undetected, suggesting that the real frequency of the condition is likely underestimated [3]. The mortality rate of ARDS ranges between 30% and 50%, depending on multiple factors, including patient risk factors, ARDS severity, and its etiology [4].

* Corresponding author:E-mail:mehrdadpashazadeh85@gmail.com

One of the main causes of high mortality in pneumonia patients, particularly those linked to SARS-CoV-2, is acute lung injury (ALI), which quickly develops into ARDS [2]. Within the order Nidovirales, coronaviruses (CoVs) belong to the subfamily Coronavirinae, which, along with Torovirinae, form the family Coronaviridae. CoVs are enclosed viruses that may be spherical or pleomorphic [5]. The viral surface spike protein of SARS-CoV-2 penetrates host cells by its receptor-binding domain (RBD), attaches itself to the human angiotensin-converting enzyme 2 (hACE2) receptor, and is activated by human proteases through proteolysis [6]. Primarily affecting the lungs and respiratory system, SARS-CoV-2 disrupts immune system regulation, causing a severe cytokine imbalance. However, to date, no standardized treatment has been established for this disease [7].

The goal of this review paper was to thoroughly investigate SARS-CoV-2's entry tactics and the connections between them and the pathogenicity, transcription, and replication of the virus. It delves further into the pathogenic mechanisms of SARS-CoV-2 in the development and aggravation of ARDS. This work aims to clarify the molecular connection between SARS-CoV-2 infection and the pathogenesis of ARDS, given the high incidence of ARDS in COVID-19 patients and the substantial mortality linked to it. Furthermore, a thorough review of the several ways that SARS-CoV-2 spreads, as well as the most recent focused diagnostic and treatment strategies for SARS-CoV-2-induced ARDS, is given. By identifying novel therapeutic targets, this review aims to contribute to reducing complications and improving clinical outcomes.

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is caused by various intrapulmonary factors, such as pneumonia and aspiration, or extrapulmonary factors, including sepsis, acute pancreatitis, and trauma. The primary pathological feature of this syndrome is increased permeability of the pulmonary endothelium, which leads to leakage of fluids and proteins into the interstitial space [8]. Severe hypoxemia, reduced lung compliance, increased venous and arterial shunting, and an increase in physiological dead space are the outcomes of this disease [1]. The most frequent cause of ARDS is pneumonia, which is followed by trauma, aspiration, and extrapulmonary infection. Notably, SARS-CoV, Influenza A virus subtype H1N1, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and especially SARS-CoV-2, which caused the COVID-19 pandemic, are among the viruses that cause pneumonia that have a higher propensity to produce ARDS. The risk of ARDS is increased by smoking and long-term excessive alcohol use. Moreover, ARDS risk factors have been shown to include the usage of electronic cigarettes or vaping-associated lung injury (EVALI) and blood product infusions. Another known modifiable environmental risk factor for ARDS is prolonged exposure to air pollution, particularly ozone [9].

There are three primary phases that ARDS goes through. Exudative interstitial edema with a high protein content, which quickly fills the alveoli and is followed by bleeding and the production of hyaline membranes, is the hallmark of the first stage. Moreover, early ARDS cases without diffuse alveolar damage (DAD), which is marked by an inflammatory infiltrate, should not be classified as pneumonia. While, the development of fibrotic septa defines the third stage. The second stage, referred to as the proliferative phase, entails the organisation of the alveolar fluid (exudative). The proliferative and fibrotic stages of ARDS might be characterized by repeated exudative events, which can provide a mixed radiological picture [10].

SARS-COV-2 VIROLOGY

The Coronaviridae family includes coronaviruses that are common in humans and animals. Four endemic human CoVs usually cause common cold symptoms: Human CoV Dutch 63 (HCoV-NL63), Human CoV Hong Kong University 1 (HCoV-HKU1), Human CoV OC43 (HCoV-OC43), and Human CoV 229E (HCoV-229E). On the other hand, within the last 20 years, three zoonotic viruses—SARS-CoV, MERS-CoV, and SARS-CoV-2, have spread from animals to people [11]. A single-stranded, positive-sense ribonucleic acid (RNA) virus, SARS-CoV-2 is a member of the Beta CoV genus. It has a positive-sense RNA genome and is enclosed [12]. SARS-CoV-2 was first recognized as a sister virus to SARS-CoV because of genome sequencing similarities [13]. The linked condition was dubbed COVID-19 when the first reports of SARS-CoV-2 infections in people were made in late 2019 [14].

CoVs are members of the order Nidovirales, subfamily Orthocoronavirinae, and family Coronaviridae. They have a spherical form, measure around 125 nanometers in diameter, and are covered with projections that resemble spikes, giving them the appearance of a crown (corona) [15]. Alpha CoV (α-CoV), Beta CoV (β-CoV), Gamma CoV (γ-CoV), and Delta CoV (δ-CoV) are the four genera into which CoVs are divided according to genetic and antigenic criteria [16] (Table 1). MERS-CoV uses the host receptor dipeptidyl peptidase 4 (DPP4), whereas SARS-CoV-2 and SARS-CoV bind to the host's ACE2 receptor via the spike (S) protein [17]. The single-stranded RNA molecule that makes up the SARS-CoV-2 genome has a length of 26–32 kilobases. Similar to other CoVs, it encodes the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, which are structural proteins that help the virus enter host cells [13, 18]. The term SARS-CoV-2 comes from the spike S glycoprotein. This surface glycoprotein resembles a crown and is visible under an electron microscope on the lipid bilayer that envelops the virus particles. However, the Spike S glycoprotein, sometimes referred to as the S protein, is a particular antigen for neutralizing antibodies and providing protection, and it is responsible for the virus's attachment to host cells through the fusion of specific receptors [19]. The spike protein of the mature virion is made up of two subunits, S1 and S2, that are not covalently connected. While the S1 subunit attaches to the ACE2 receptor on the surface of the host cell, the S2 subunit secures the spike protein to the viral membrane [11] (Figure 1).

The spike (S) glycoprotein of MERS-CoV, like that of other coronaviruses, enables membrane fusion and receptor recognition and serves as the primary focus of the humoral immune response during infection [20]. The interaction between the viral spike protein (S) and ACE2 and TMPRSS2 is what defines SARS-CoV-2 entrance into host cells [21]. SARS-CoV-2's spike protein can interact with various host receptors to bind endothelial cells, resulting in multiple cases of endothelial damage [22].

SARS-COV-2 TRANSCRIPTION AND REPLICATION

CoVs express and replicate their genomic RNA to create new copies during their intracellular life cycle. CoVs have long RNA genomes with endogenous RNA secondary structures

Table 1. Coronavirus species, genera, and host receptors*.

Genus	Species	Receptor	Reference
Alpha CoV	Human CoV 229E	APN	[23]
	Human CoV NL63	ACE2	[24]
	PERV	APN	[25]
	FCoV serotype 2	APN	[5]
	CCoV serotype 2	APN	[26]
	TGEV	APN	[27]
	Rhinolophus bat CoV HKU2 Scotophilus bat CoV 512/05 Miniopterus bat CoV1 Miniopterus bat CoV HKU8		[5]
Beta CoV	MHV	CEACAM	[28, 29]
	Rat CoV Puffinosis virus		[5]
	BCoV	neu 5,9 Ac2	[30]
	HCoV-OC43 ECoV HECoV PHEV CrCoV Human CoV HKU9 Rousettus bat CoV HKU4 Tylonycteris bat CoV HKU5	neu 5,9 Ac2	[5]
	SARS-CoV	ACE2	[31]
	MERS-CoV	DPP-4	[32]
Gamma CoV	Avian CoV comprising Beluga Whale CoV SW1		[5]
Delta CoV	Bulbul CoV HKU11 Thrush CoV HKU12 Munia CoV HKU13		

* CoV: Coronavirus, APN: Aminopeptidase N, ACE2: angiotensin-converting enzyme 2, PEDV: Porcine Epidemic Diarrhea CoV, FCoV: Feline CoV, CCoV: Canine CoV, TGEV: Transmissible gastroenteritis virus, MHV: Existing species of mouse hepatitis virus, CEACAM: Carcinoembryonic antigen-related cell adhesion molecule, BCoV: Bovine CoV, neu 5,9 Ac2: 5-N-acetyl-9-O-acetylated neuraminic acid, HCoVOC43: Human CoV OC43, ECoV: Equine CoV, HECoV: Human enteric CoV, PHEV: Porcine haemagglutinating encephalomyelitis virus, CrCoV: Canine respiratory CoV, DPP-4: Dipeptidyl peptidase 4.

necessary for RNA synthesis bordered by 5' and 3' untranslated sequences. Two sizable open reading frames (ORFs), ORF1a and ORF1b, are located at the 5' end of the genomic RNA [33]. The positive-sense SARS-CoV-2 genome, the biggest RNA genome of any RNA virus, instantly translates two polyproteins from ORF1a and ORF1b in the cytoplasm when it enters a vulnerable cell. Since ORF1a and ORF1b significantly overlap, with ORF1b positioned in the –1 reading frame relative to ORF1a, the mechanism behind the need for a planned –1 ribosomal frameshift (–1 PRF) for

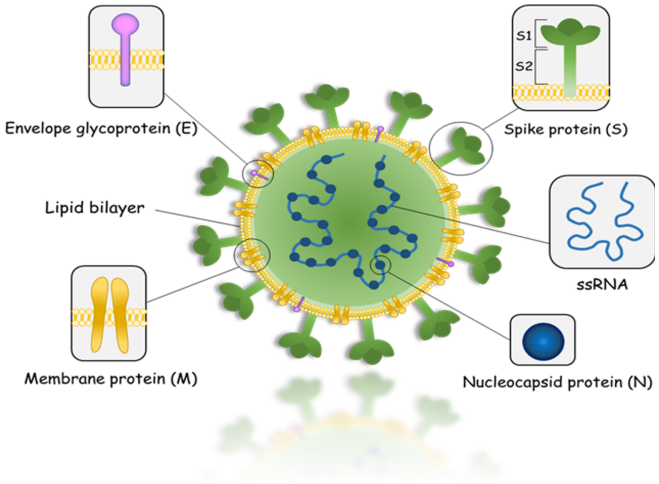

Figure 1. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus's ribonucleic acid (RNA) genome and four main structural proteins, the spike (S), envelope (E), membrane (M), and nucleocapsid (N), are shown graphically. S: spike, E: envelope, M: membrane, N: nucleocapsid, ssRNA: single-stranded ribonucleic acid.

ORF1b expression is yet unknown [34]. CoVs use an RNA-dependent RNA polymerase (RdRp) complex to transcribe their genes and duplicate their genomes [35].

All viruses in the Nidovirales order employ the same coding strategy as SARS-CoV viruses: two-thirds of the viral RNA is translated into two giant polyproteins, while the balance of the viral genome is transformed into a nested series of subgenomic mRNAs [36]. The two polyproteins, pp1a and pp1ab, encode the 16 non-structural proteins (nsp1–nsp16) that make up the viral replicase-transcriptase complex. Two viral proteases cleave these polyproteins. To facilitate viral transcription and replication, nsps transform the rough endoplasmic reticulum (RER) membrane into double-membrane vesicles [37, 38].

The SARS-CoV-2 genome encodes four structural proteins, six accessory proteins, and sixteen non-structural proteins. Non-structural proteins involved in transcription, RNA replication, and immune evasion are encoded by around 70% of the 5' end of the genome. The ORF1a and ORF1b polyproteins are cleaved to yield these proteins. The structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as auxiliary proteins 3a, 6, 7a, 7b, 8, and 9b, are encoded by the remaining 30% of the genome, which is found at the 3' end [39]. ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8b, ORF9b, and ORF14 are a collection of auxiliary genes that encode accessory proteins and are found among the structural genes. Except for the structural proteins, accessory proteins such as ORF3a and ORF7a may not be incorporated into the virion but play essential roles in regulating viral infection [40].

LIFE CYCLE AND MECHANISM OF ARDS IN CONNECTION WITH SARS-COV-2

The N (nucleocapsid) protein, which binds to the viral genomic RNA, is compacted within the virion of SARS-CoV-2, whilst the structural proteins S (spike), E (envelope), and M

http://doi.org/10.33091/amj.2025.160850.2269

(membrane) are incorporated into the virion membrane [41]. When the S protein attaches to its particular receptor, ACE2, the life cycle of SARS-CoV-2 starts [42]. Through fusion and adhesion to the cell membrane, the homotrimerized S protein facilitates viral entrance into the host cell. Enzymes like furin break down the S protein in some CoVs into two subunits, S1 and S2, within infected cells. While the S2 subunit includes the fusion peptide required for entrance into the new cell and adheres the viral membrane to the host cell membrane, the S1 subunit attaches itself to ACE2 [6, 43]. Moreover, the SARS-CoV spike protein has to be proteolytically activated at the S1/S2 border for membrane fusion to take place, causing S1 to separate and S2 to undergo substantial conformational changes. Proteases that trigger SARS-CoV entry include lysosomal proteases such as cathepsins and the cell surface protease TMPRSS2 [5, 44]. TMPRSS2 on the cell surface and cathepsins within endosomes must cleave the S2' site, which is situated just downstream of the S1–S2 barrier, to correctly start the fusion process. Although its primary physiological function and substrate specificity are yet unclear, TMPRSS2 is a type II transmembrane protein with serine protease activity [45, 46].

To promote virus assembly and budding, the E and M proteins interact with other viral proteins. When virus-containing vesicles fuse with the plasma membrane, viral particles are discharged into the extracellular space. The secretory route carries viruses to the plasma membrane when they first sprout into the lumen of the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [41] (Figure 2). Infected cells generate a lot of specific inflammatory mediators once SARS-CoV-2 enters the body, which triggers macrophages to release cytokines such as tumor necrosis factor-α (TNF-α) and interleukins interleukin-1 (IL-1) and interleukin-6 (IL-6). These cytokines cause endothelial contraction brought on by TNF-α, IL-1, and IL-6, which compromises the integrity of the alveolar-capillary membrane, causes vasodilation, and increases vascular permeability [13]. CoVs may harm the pulmonary endothelium directly or indirectly, which raises vascular permeability and causes alveolar edema, both of which contribute to hypoxia [47].

An essential component of coronavirus replication is the multimeric protein complex known as the RNA-dependent RNA polymerase (RdRp) complex [48]. RNA processing and genome replication depend on some other viral nsps. Copying the viral RNA is how the replication–transcription complex (RTC) works [48]. Some co-factors involved in RNA proofreading and 5' capping of viral RNAs, as well as nonstructural protein 12 (nsp12), which is directly responsible for RNA synthesis, make up the RNA production machinery of SARS-CoV-2, which makes it a prime target for drugs [49]. In addition to being an exoribonuclease with its essential cofactor nsp10, SARS-CoV-2 nsp14 is also an S-adenosyl methionine-dependent (guanine-N7) methyltransferase (MTase) [50]. SARS-CoV-2 in viral replication, nsp13 is crucial for helicase (nucleoside triphosphate enzymes, or NTPs). Nsp13 is an RNA 5'-triphosphatase, and its 5'-3' directionality RNA or DNA duplex unwinding activity is powered by the hydrolysis of NTPs [50].

TRANSMISSION OF SARS-COV-2

Although aerosols, direct contact with infected surfaces, and fecal-oral transmission were all reported during the SARS pandemic, respiratory droplets are the main way that human CoVs are spread [51, 52]. Based on initial reports from patients with coughing, lung ground glass opacities, and symptoms of severe progressive pneumonia, SARS-CoV-2 may be transmissible through the respiratory tract [53, 54]. The human respiratory epithelium, which includes the throat and upper airways, is the primary site for host target receptors. Additionally, the gastrointestinal tract and conjunctiva suggests, which are susceptible to infection, may serve as entry points for disease spread [55].

The risk of infection increases significantly in enclosed spaces compared to open areas. Prolonged exposure to crowded, poorly ventilated indoor environments can still contribute to aerosol transmission (transmission can occur at distances greater than 2 meters) [56]. Aerosols that asymptomatic people emit into the air when they breathe and talk are responsible for a significant amount of the spread of COVID-19 illness. Universal mask use and extensive, regular testing to identify and isolate asymptomatic carriers are two essential steps that should be taken to minimize aerosol transmission [57].

IMMUNE RESPONSE AND CYTOKINE STORM IN SARS-COV-2 INFECTION

During the COVID-19 pandemic, some recovered patients showed elevated antibody levels, although neutralizing antibodies and memory T cells against MERS-CoV decreased in previous years. This most likely happened as a result of cross-reactive immunity brought on by SARS-CoV-2 infections or vaccinations. Antibody responses to different CoVs show a strong association, suggesting that they share immunogenic epitopes [58]. So far, the majority of the global population has either been infected with SARS-CoV-2 or vaccinated against it. Since SARS-CoV-2 and other human coronaviruses (HCoVs) share common epitopes, exposure to SARS-CoV-2 is expected to enhance cross-reactive antibody responses against other HCoVs [59].

Macrophages in the alveolus and epithelial cells in the lungs are two examples of SARS-CoV-2-infected cells that produce cytokines and chemokines in the plasma. Cytokines, including ILs, IFNs, and chemokines, are the leading cause of cytokine storm (CS) and cytokine release syndrome (CRS). The high inflammatory response and the production of many proinflammatory cytokines that set off the CS are the results of these cytokines' subsequent activation of macrophages, dendritic cells (DCs), and other immune cells [60]. Large volumes of inflammatory cytokines and chemokines are secreted when infected with the SARS-CoV-2 virus. Serum samples from patients with severe COVID-19 showed elevated levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), TNF, CXC-chemokine ligand 10 (CXCL10), monocyte chemoattractant protein-1 (MCP1), and macrophage inflammatory protein 1 alpha (MIP1α) [61].

SARS-COV-2 DIAGNOSIS LINKED TO ARDS

The incubation period for CoV -induced ARDS averages approximately five days, with 95% of patients developing symptoms within 13 days post-exposure [36]. While gastrointestinal symptoms, including diarrhea, vomiting, and nausea, are less common, the first clinical signs usually include fever, chills, cough, lethargy, headache, and myalgia. Early and accurate diagnosis of ARDS is critical for the timely initiation of both pharmacological and non-pharmacological interventions, with precise etiological determination being essential

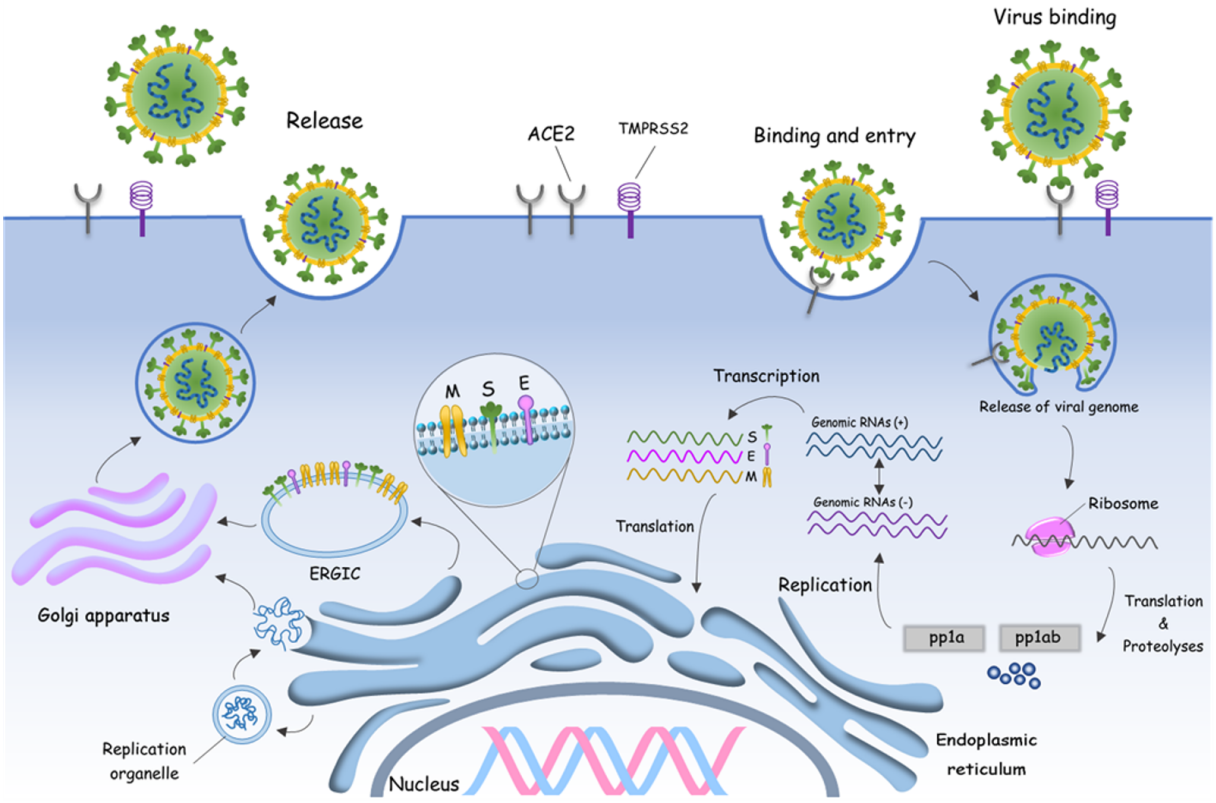

Figure 2. When the spike (S) protein binds to the angiotensin converting enzyme 2 (ACE2) receptor, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) life cycle begins. Viral entry into host cells occurs through two distinct pathways: (1) Cleavage at the S1/S2 site by the TMPRSS2 (transmembrane protease serine 2), facilitating direct membrane fusion, or (2) Endocytosis followed by cathepsin L-mediated cleavage in endosomes. After the virus successfully enters the body, its genomic ribonucleic acid (RNA) is translated into the polyproteins pp1a and pp1ab, which are then broken down into smaller functional components by proteolysis. Negative-sense RNA templates are subsequently synthesized to enable genomic replication and subgenomic mRNA transcription. Within the cytoplasm, newly synthesized genomic RNA associates with nucleocapsid (N) proteins to form complete nucleocapsids. These viral components are then packaged into vesicles derived from the endoplasmic-reticulum–Golgi intermediate compartment (ERGIC) and ultimately released from the infected cell through the secretory pathway, completing the infectious cycle. E: envelope, M: membrane.

for appropriate therapeutic management [62].

Optimal diagnostic sampling for SARS-CoV-2 detection in outpatient settings is achieved through combined nasopharyngeal and oropharyngeal swabs, which demonstrate superior diagnostic performance compared to single-site sampling techniques [63]. Real-time PCR (RT-PCR) is still the gold standard for SARS-CoV-2 identification in suspected COVID-19 patients with ARDS [64]. Current RT-PCR assays exhibit diagnostic sensitivity ranging from 45–60%, often necessitating repeat testing during early infection stages to confirm diagnosis [65]. Serological testing serves as a complementary diagnostic approach, primarily identifying previous infection through the detection of viral-specific antibodies. Enzyme-linked immunosorbent assay (ELISA) provides qualitative measurement of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies directed against the viral spike (S) protein, with applications in contact tracing, assessment of immune protection, and epidemiological investigations [66].

In SARS-CoV-2-associated ARDS patients, systemic cytokine levels have emerged as potential biomarkers of disease severity [67]. The degree of hypoxemia, which is an essential predictor of decreased survival, is used to measure the severity of ARDS. This is calculated as the ratio of partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) [68]. Molecular-based and antibody-detection assays collectively constitute the reference standard diagnostic modalities for SARS-CoV-2 confirmation, providing comprehensive diagnostic information when used in combination [69]. Several sampling tools and techniques for SARS-CoV-2 detection employ various strategies for distance, floor height, flow rates, and sampled air volumes. Solid impactors outperform liquid impactors or filters in terms of each mechanism's effectiveness, and a mix of several approaches may be suggested. Liquid impactors were the second most used mechanism, followed by other/different ways, while solid impactors were the least utilized mechanism. The majority of the research included in this evaluation used various filtration systems to gather air samples for SARS-CoV-2 detection [70].

PREVENTION AND TREATMENT STRATEGIES

The rapid global dissemination of SARS-CoV-2 and the substantial proportion of asymptomatic carriers necessitate

http://doi.org/10.33091/amj.2025.160850.2269

Table 2. Therapeutic strategies and their estimated efficacy in SARS-CoV-2 infection and ARDS*.

Treatment Strategy	Estimated Efficacy	Reference
Corticosteroids (e.g., Dexamethasone)	∼ 30–34% reduction in mortality in patients requiring oxygen or mechanical ventilation	[71]
Tocilizumab (IL-6 receptor blocker)	∼4% reduction in 28-day mortality in hospitalized patients	[72]
Baricitinib + Remdesivir	∼31% lower progression to death or ventilation by day 29	[73]
Convalescent Plasma	∼14% mortality reduction in early treatment in ventilated patients	[74]
Prone Positioning	Improved oxygenation; mortality reduction in moderate–severe ARDS	[75]
Mesenchymal stem cell therapy	Early-phase trials show reduced inflammation; promising but limited data	[71]

* Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ARDS: Acute respiratory distress syndrome, IL-6: Interleukin-6.

the urgent development of effective therapeutic interventions [76]. Despite extensive therapeutic efforts and the clinical application of remdesivir (RDV), the current lack of potent antiviral agents continues to hinder treatment optimization. Notably, nitric oxide (NO) has emerged as a promising therapeutic candidate due to its broad-spectrum antimicrobial properties [77]. Among antiviral pharmacotherapies, nucleotide/nucleoside analogs represent a critical class of agents that function through polymerase inhibition. RdRp inhibitors such as favipiravir and RDV have demonstrated clinical utility in SARS-CoV-2 management [78] (Table 2).

According to centers for disease control and prevention (CDC) guidelines, high-risk populations requiring particular vigilance include individuals with chronic pulmonary conditions, severe cardiovascular disease, chronic kidney impairment, type 2 diabetes mellitus, obesity, and pregnant women [79]. Systemic cytokine profiling serves as a valuable biomarker for disease severity assessment and may guide glucocorticoid (GC) therapy administration [67]. Emerging evidence suggests that circulating ACE2 expression patterns may confer protective effects against SARS-CoV-2 infection by competitively binding viral particles and preventing cellular entry [80]. Therapeutic administration of channel inhibitors has shown efficacy in reducing viral load and attenuating inflammatory cytokine secretion in the lungs of hACE2-expressing individuals infected with SARS-CoV-2 [81]. Mesenchymal stem cells (MSCs) exhibit significant therapeutic potential through juxtacrine and paracrine mechanisms that modulate immune cell activity and mitigate pulmonary inflammation in ARDS [82]. The pathophysiological cascade initiated by SARS-CoV-2 involves damage-associated molecular patterns (DAMPs) release and neutrophil recruitment, with neutrophil extracellular traps (NETs) exacerbating alveolar inflammation and lung injury [83].

Vaccination remains a cornerstone of prevention, effectively reducing transmission rates and preventing severe disease progression [84]. One of the most essential methods for avoiding SARS-CoV-2 infection or lessening the severity of the disease is vaccination. Inducing antibodies that stop the SARS-CoV-2 receptor binding domain (RBD) from interacting with ACE2 was a key vaccine strategy [85]. Patients with COVID-19 who received the vaccine had a lower relative risk (RR) of ARDS. Thus, hospitalized individuals who were not immunized had a 2.5-fold increased risk of ARDS. In multivariate analysis, this risk reduction remained after controlling for several confounding variables [86].

This review has several limitations, including the reliance on rapidly evolving and sometimes conflicting evidence on SARS-CoV-2 pathogenesis, potential selection bias due to the inclusion of predominantly observational and preclinical studies, and the heterogeneity of clinical definitions and molecular methodologies across studies, which may impact the consistency and generalizability of our conclusions. Additionally, the dynamic nature of the pandemic means that newer variants and emerging therapeutic approaches may not be fully captured in this synthesis.

CONCLUSION

ARDS is a severe complication of SARS-CoV-2 infection with high mortality and significant challenges in intensive care. It is characterized by endothelial barrier disruption, impaired gas exchange, and excessive immune activation, causing pulmonary dysfunction. SARS-CoV-2 enters cells via spike protein binding to ACE2 receptors, triggering inflammatory cascades and alveolar edema. Early diagnosis using RT-PCR and cytokine profiling, as well as vaccination, is essential, while preventive measures like mask-wearing, ventilation, and carrier detection help limit transmission. Current treatments include antivirals, glucocorticoids, NO, and mesenchymal stem cell therapy, with vaccination playing a key role in reducing disease severity. The complex interaction between virus and host immune response necessitates further research to develop targeted therapies addressing both viral replication and immune dysregulation to reduce ARDS mortality.

ETHICAL DECLARATIONS

Acknowledgment

None.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

Not applicable.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

No funding.

Authors' Contributions

Idea: A.J.S, M.P; Data Collection or Processing: A.J.S; Writing-Review and Editing E.N.L, M.F.S, M.S; Figure design: E.N.L; Table design: E.N.L; Supervision: A.J.S, M.P. All authors reviewed the results and approved the final version of the manuscript.

REFERENCES

[1] T. Sun. Guidelines for diagnosis of adult acute respiratory distress syndrome (ards) and non-mechanical ventilation treatment in china (2023). *Intensive Care Research*, 5(1):1–18, 2025.

[2] A. Kosyreva, D. Dzhalilova, A. Lokhonina, P. Vishnyakova, and T. Fatkhudinov. The role of macrophages in the pathogenesis of sars-cov-2-associated acute respiratory distress syndrome. *Frontiers in Immunology*, 12:682871, 2021.

[3] G. Bellani *et al.* Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *Jama*, 315(8):788–800, 2016.

[4] J. Lee, K. Corl, and M. M. Levy. Fluid therapy and acute respiratory distress syndrome. *Crit Care Clin*, 37(4):867–875, 2021.

[5] S. Belouzard, J. K. Millet, B. N. Licitra, and G. R. Whittaker. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses*, 4(6):1011–1033, 2012.

[6] J. Shang *et al.* Cell entry mechanisms of sars-cov-2. *Proceedings of the National Academy of Sciences*, 117(21):11727–11734, 2020.

[7] S. Mahendiratta *et al.* Stem cell therapy in covid-19: Pooled evidence from sars-cov-2, sars-cov, mers-cov and ards: A systematic review. *Biomedicine & pharmacotherapy*, 137:111300, 2021.

[8] I. Sbaraini Zernini, D. Nocera, R. D'Albo, and T. Tonetti. Acute respiratory distress syndrome and fluid management: Finding the perfect balance. *Journal of Clinical Medicine*, 14(6):2067, 2025.

[9] W. Ma *et al.* Advances in acute respiratory distress syndrome: focusing on heterogeneity, pathophysiology, and therapeutic strategies. *Signal Transduction and Targeted Therapy*, 10(1):75, 2025.

[10] G. P. Ramadori. Sars-cov-2-infection (covid-19): clinical course, viral acute respiratory distress syndrome (ards) and cause (s) of death. *Medical Sciences*, 10(4):58, 2022.

[11] M. M. Lamers and B. L. Haagmans. Sars-cov-2 pathogenesis. *Nature reviews microbiology*, 20(5):270–284, 2022.

[12] R. Lu *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The lancet*, 395(10224):565–574, 2020.

[13] R. Badraoui, M. M. Alrashedi, M. V. El-May, and F. Bardakci. Acute respiratory distress syndrome: a life threatening associated complication of sars-cov-2 infection inducing covid-19. *Journal of Biomolecular Structure and Dynamics*, 39(17):6842–6851, 2021.

[14] B. Salzberger *et al.* Epidemiology of sars-cov-2. *Infection*, 49:233–239, 2021.

[15] Y. A. Malik. Properties of coronavirus and sars-cov-2. *The Malaysian journal of pathology*, 42(1):3–11, 2020.

[16] P. C. Woo. Discovery of seven novel mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. *Journal of virology*, 86(7):3995–4008, 2012.

[17] R. Noor. A comparative review of pathogenesis and host innate immunity evasion strategies among the severe acute respiratory syndrome coronavirus 2 (sars-cov-2), severe acute respiratory syndrome coronavirus (sars-cov) and the middle east respiratory syndrome coronavirus (mers-cov). *Archives of microbiology*, 203(5):1943–1951, 2021.

[18] D. Singh and S. V. Yi. On the origin and evolution of sars-cov-2. *Experimental & molecular medicine*, 53(4):537–547, 2021.

[19] M. A. Khalil. Origin, causative and new approach of vaccine design of covid-19. *Al-Anbar Medical Journal*, 16(2):25–27, 2020.

[20] J. Pallesen *et al.* Immunogenicity and structures of a rationally designed prefusion mers-cov spike antigen. *Proceedings of the National Academy of Sciences*, 114(35):E7348–E7357, 2017.

[21] G. Sberna *et al.* In vitro evaluation of antiviral efficacy of a standardized hydroalcoholic extract of poplar type propolis against sars-cov-2. *Frontiers in Microbiology*, 13:799546, 2022.

[22] L. Perico, A. Benigni, and G. Remuzzi. Sars-cov-2 and the spike protein in endotheliopathy. *Trends in microbiology*, 32(1):53–67, 2024.

[23] C. L. Yeager *et al.* Human aminopeptidase n is a receptor for human coronavirus 229e. *Nature*, 357(6377):420–422, 1992.

[24] H. Hofmann, K. Pyrc, L. Van Der Hoek, M. Geier, B. Berkhout, and S. Pöhlmann. Human coronavirus nl63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proceedings of the National Academy of Sciences*, 102(22):7988–7993, 2005.

[25] B. Li, J. Ge, and Y. Li. Porcine aminopeptidase n is a functional receptor for the pedv coronavirus. *Virology*, 365(1):166–172, 2007.

[26] L. Benbacer, E. Kut, L. Besnardeau, H. Laude, and B. Delmas. Interspecies aminopeptidase-n chimeras reveal species-specific receptor recognition by canine coronavirus, feline infectious peritonitis virus, and transmissible gastroenteritis virus. *Journal of virology*, 71(1):734–737, 1997.

[27] B. Delmas *et al.* Aminopeptidase n is a major receptor for the enteropathogenic coronavirus tgev. *Nature*, 357(6377):417–420, 1992.

[28] P. Nedellec *et al.* Bgp2, a new member of the carcinoembryonic antigen-related gene family, encodes an alternative receptor for mouse hepatitis viruses. *Journal of virology*, 68(7):4525–4537, 1994.

[29] R. K. Williams, G.-S. Jiang, and K. V. Holmes. Receptor for mouse hepatitis virus is a member of the carcinoembryonic antigen family of glycoproteins. *Proceedings of the National Academy of Sciences*, 88(13):5533–5536,

http://doi.org/10.33091/amj.2025.160850.2269

1991.
[30] B. Schultze and G. Herrler. Bovine coronavirus uses n-acetyl-9-o-acetylneuraminic acid as a receptor determinant to initiate the infection of cultured cells. *Journal of general virology*, 73(4):901–906, 1992.
[31] W. Li *et al.* Angiotensin-converting enzyme 2 is a functional receptor for the sars coronavirus. *Nature*, 426(6965):450–454, 2003.
[32] V. S. Raj *et al.* Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-emc. *Nature*, 495(7440):251–254, 2013.
[33] P. V'kovski, A. Kratzel, S. Steiner, H. Stalder, and V. Thiel. Coronavirus biology and replication: implications for sars-cov-2. *Nature Reviews Microbiology*, 19(3):155–170, 2021.
[34] J. A. Kelly, M. T. Woodside, and J. D. Dinman. Programmed– 1 ribosomal frameshifting in coronaviruses: a therapeutic target. *Virology*, 554:75–82, 2021.
[35] H. S. Hillen, G. Kokic, L. Farnung, C. Dienemann, D. Tegunov, and P. Cramer. Structure of replicating sars-cov-2 polymerase. *Nature*, 584(7819):154–156, 2020.
[36] E. De Wit, N. Van Doremalen, D. Falzarano, and V. J. Munster. Sars and mers: recent insights into emerging coronaviruses. *Nature reviews microbiology*, 14(8):523–534, 2016.
[37] A. R. Fehr and S. Perlman. Coronaviruses: an overview of their replication and pathogenesis. *Coronaviruses: methods and protocols*, 1282:1–23, 2015.
[38] K. Knoops *et al.* Sars-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS biology*, 6(9):e226, 2008.
[39] A. C. Brant, W. Tian, V. Majerciak, W. Yang, and Z.-M. Zheng. Sars-cov-2: from its discovery to genome structure, transcription, and replication. *Cell & bioscience*, 11:1–17, 2021.
[40] H. Yang and Z. Rao. Structural biology of sars-cov-2 and implications for therapeutic development. *Nature Reviews Microbiology*, 19(11):685–700, 2021.
[41] C. B. Jackson, M. Farzan, B. Chen, and H. Choe. Mechanisms of sars-cov-2 entry into cells. *Nature reviews Molecular cell biology*, 23(1):3–20, 2022.
[42] A. G. Harrison, T. Lin, and P. Wang. Mechanisms of sars-cov-2 transmission and pathogenesis. *Trends in immunology*, 41(12):1100–1115, 2020.
[43] M. Hoffmann, H. Kleine-Weber, and S. Pöhlmann. A multibasic cleavage site in the spike protein of sars-cov-2 is essential for infection of human lung cells. *Molecular cell*, 78(4):779–784. e5, 2020.
[44] T. Heald-Sargent and T. Gallagher. Ready, set, fuse! the coronavirus spike protein and acquisition of fusion competence. *Viruses*, 4(4):557–580, 2012.
[45] H. Limburg *et al.* Tmprss2 is the major activating protease of influenza a virus in primary human airway cells and influenza b virus in human type ii pneumocytes. *Journal of virology*, 93(21):10.1128/jvi. 00649–19, 2019.
[46] K. Sakai *et al.* Tmprss2 independency for haemagglutinin cleavage in vivo differentiates influenza b virus from influenza a virus. *Scientific reports*, 6(1):29430, 2016.
[47] C. Quan, C. Li, H. Ma, Y. Li, and H. Zhang. Immunopathogenesis of coronavirus-induced acute respiratory distress syndrome (ards): potential infection-associated hemophagocytic lymphohistiocytosis. *Clinical Microbiology Reviews*, 34(1):10.1128/cmr. 00074–20, 2020.
[48] B. J. J. Subong and I. L. Forteza. Sars-cov-2 replication revisited: Molecular insights and current and emerging antiviral strategies. *COVID*, 5(6):85, 2025.
[49] A. P. Walker, H. Fan, J. R. Keown, M. L. Knight, J. M. Grimes, and E. Fodor. The sars-cov-2 rna polymerase is a viral rna capping enzyme. *Nucleic acids research*, 49(22):13019–13030, 2021.
[50] J. Chen *et al.* Au (i)-based compounds inhibit nsp14/nsp10 and nsp13 (helicase) to exert anti-sars-cov-2 properties. *JBIC Journal of Biological Inorganic Chemistry*, 30:425–441, 2025.
[51] I. T. Yu *et al.* Evidence of airborne transmission of the severe acute respiratory syndrome virus. *New England Journal of Medicine*, 350(17):1731–1739, 2004.
[52] Y. Li, X. Huang, I. T. Yu, T. W. Wong, and H. Qian. Role of air distribution in sars transmission during the largest nosocomial outbreak in hong kong. *Indoor air*, 15(2):83–95, 2005.
[53] P. Zhou *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *nature*, 579(7798):270–273, 2020.
[54] C. Huang *et al.* Clinical features of patients infected with 2019 novel coronavirus in wuhan, china. *The lancet*, 395(10223):497–506, 2020.
[55] K. P. Hui *et al.* Tropism, replication competence, and innate immune responses of the coronavirus sars-cov-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures. *The Lancet Respiratory Medicine*, 8(7):687–695, 2020.
[56] M. Cevik, K. Kuppalli, J. Kindrachuk, and M. Peiris. Virology, transmission, and pathogenesis of sars-cov-2. *bmj*, 371:1–6, 2020.
[57] K. A. Prather, C. C. Wang, and R. T. Schooley. Reducing transmission of sars-cov-2. *Science*, 368(6498):1422–1424, 2020.
[58] S.-H. Kim *et al.* Rise in broadly cross-reactive adaptive immunity against human β-coronaviruses in mers-recovered patients during the covid-19 pandemic. *Science Advances*, 10(9):eadk6425, 2024.
[59] R. S. Lee *et al.* Cross-reactive antibody responses to coronaviruses elicited by sars-cov-2 infection or vaccination. *Influenza and Other Respiratory Viruses*, 18(5):e13309, 2024.
[60] M. S. Qudus *et al.* The roles of critical pro-inflammatory cytokines in the drive of cytokine storm during sars-cov-2 infection. *Journal of medical virology*, 95(4):e28751, 2023.
[61] P. Niedźwiedzka-Rystwej *et al.* Immune signature of covid-19: In-depth reasons and consequences of the cytokine storm. *International Journal of Molecular Sciences*, 23(9):4545, 2022.
[62] F. Arrivé, R. Coudroy, and A. W. Thille. Early identification and diagnostic approach in acute respiratory distress syndrome (ards). *Diagnostics*, 11(12):2307, 2021.
[63] N. N. Y. Tsang, H. C. So, K. Y. Ng, B. J. Cowling, G. M. Leung, and D. K. M. Ip. Diagnostic performance of different sampling approaches for sars-cov-2 rt-pcr testing: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 21(9):1233–1245, 2021.
[64] L. Lanser *et al.* Evaluating the clinical utility and sensitivity of sars-cov-2 antigen testing in relation to rt-pcr ct values. *Infection*, 49:555–557, 2021.
[65] J. A. Al-Tawfiq and Z. A. Memish. Diagnosis of sars-cov-2 infection based on ct scan vs rt-pcr: reflecting on experience from mers-cov. *The Journal of hospital infec-*

tion, 105(2):154, 2020.
[66] B. D. Kevadiya *et al.* Diagnostics for sars-cov-2 infections. *Nature materials*, 20(5):593–605, 2021.
[67] F. Salton. Cytokine profiles as potential prognostic and therapeutic markers in sars-cov-2-induced ards. *Journal of Clinical Medicine*, 11(11):2951, 2022.
[68] S. Kassirian, R. Taneja, and S. Mehta. Diagnosis and management of acute respiratory distress syndrome in a time of covid-19. *Diagnostics*, 10(12):1053, 2020.
[69] V. Bayat *et al.* A severe acute respiratory syndrome coronavirus 2 (sars-cov-2) prediction model from standard laboratory tests. *Clinical Infectious Diseases*, 73(9):e2901–e2907, 2020.
[70] J. T. Borges, L. Y. K. Nakada, M. G. Maniero, and J. R. Guimarães. Sars-cov-2: a systematic review of indoor air sampling for virus detection. *Environmental Science and Pollution Research*, 28(30):40460–40473, 2021.
[71] G. Zanirati *et al.* Stem cell-based therapy for covid-19 and ards: a systematic review. *NPJ Regenerative medicine*, 6(1):73, 2021.
[72] I. O. Rosas *et al.* Tocilizumab in hospitalized patients with severe covid-19 pneumonia. *New England Journal of Medicine*, 384(16):1503–1516, 2021.
[73] A. C. Kalil *et al.* Baricitinib plus remdesivir for hospitalized adults with covid-19. *New England Journal of Medicine*, 384(9):795–807, 2021.
[74] S. Abel *et al.* Associations between findings from myelin water imaging and cognitive performance among individuals with multiple sclerosis. *JAMA network open*, 3(9):e2014220–e2014220, 2020.
[75] C. Guérin *et al.* Prone positioning in severe acute respiratory distress syndrome. *New England journal of medicine*, 368(23):2159–2168, 2013.
[76] K. Nissen *et al.* Presymptomatic viral shedding and infective ability of severe acute respiratory syndrome coronavirus 2. v1:1–10, 2020.
[77] D. Akaberi *et al.* Mitigation of the replication of sars-cov-2 by nitric oxide in vitro. *Redox biology*, 37:101734, 2020.
[78] Q. Wang *et al.* Structural basis for rna replication by the sars-cov-2 polymerase. *Cell*, 182(2):417–428. e13, 2020.
[79] J.-W. Liu, X. Huang, M.-K. Wang, and J.-S. Yang. Diabetes and susceptibility to covid-19: Risk factors and preventive and therapeutic strategies. *World Journal of Diabetes*, 15(8):1663, 2024.
[80] F. A. Cadegiani, C. G. Wambier, and A. Goren. Spironolactone: an anti-androgenic and anti-hypertensive drug that may provide protection against the novel coronavirus (sars-cov-2) induced acute respiratory distress syndrome (ards) in covid-19. *Frontiers in Medicine*, 7:453, 2020.
[81] B. Xia *et al.* Sars-cov-2 envelope protein causes acute respiratory distress syndrome (ards)-like pathological damages and constitutes an antiviral target. *Cell research*, 31(8):847–860, 2021.
[82] C. R. Harrell, B. P. Jovicic, V. Djonov, and V. Volarevic. Therapeutic potential of mesenchymal stem cells and their secretome in the treatment of sars-cov-2-induced acute respiratory distress syndrome. *Analytical cellular pathology*, 2020(1):1939768, 2020.
[83] J. Desilles *et al.* Efficacy and safety of aerosolized intratracheal dornase alfa administration in patients with sars-cov-2-induced acute respiratory distress syndrome (ards): a structured summary of a study protocol for a randomised controlled trial. *Trials*, 21:1–3, 2020.
[84] B. T. Marine and D. T. Mengistie. An analysis of various factors underlying covid-19 prevention practice and strategy in jigjiga town, northeast ethiopia. *Infection and Drug Resistance*, 17:187–206, 2024.
[85] C.-X. Li *et al.* A critical analysis of sars-cov-2 (covid-19) complexities, emerging variants, and therapeutic interventions and vaccination strategies. *Biomedicine & Pharmacotherapy*, 146:112550, 2022.
[86] J. Madrid *et al.* Vaccination protects against acute respiratory distress syndrome (ards) in hospitalized patients with covid-19. *Clinical and Experimental Medicine*, 24(1):21, 2024.

http://doi.org/10.33091/amj.2025.160850.2269