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An All-Inclusive Overview Of COVID-19 (SARS-COV-2): Emphasising Immuno-Pathogenesis, Correlation With Comorbidities, Neurological Consequences, and Therapeutic Objectives

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It has been five years since the first COVID-19 cases emerged in China. The infection spread extensively around the world, impacting millions and presenting a significant risk to public health, leading to the breakdown of healthcare systems in various countries. The COVID-19 is caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and is a recent emergent virus that belongs to the beta (ß)-coronaviruses. The presence of comorbidities significantly influenced the mortality rate among patients infected with COVID-19. For a while, it was believed that the transmission of SARS-CoV-2 was limited to respiratory tract invasion; however, more research indicated that the infection may also affect the central and peripheral neurological systems, among many other organs and systems. Encephalopathy, encephalitis, meningitis, ischemic and hemorrhagic stroke, and cerebral venous sinus thrombosis are among the neurological side effects linked to the SARS-CoV-2 infection. Since the pandemic began, COVID-19 treatment has advanced swiftly, mostly emphasizing antiviral and immunomodulatory medications. Remdesivir and nirmatrelvir-ritonavir are examples of antivirals that have been observed to be most effective when used initially in an illness (for instance, as outpatient treatment) and in instances of milder disease. When treating serious disease or critical illness, immunomodulatory treatments like dexamethasone, Janus kinase inhibitors, or interleukin-6 are most beneficial. Mass vaccination campaigns as a preventative measure are the most effective means of preventing this pandemic. In order to mitigate or lower the rates of COVID-19 infections, hospitalizations, and fatalities, several vaccine platforms, such as vaccines based on nucleic acids (DNA and mRNA vaccines), adenovirus-vectored vaccines, inactivated vaccines, and protein-based subunit vaccines, have been created and developed. This article mainly emphasizes the taxonomy and structural virology with the probable viral immuno-pathogenesis mechanism of SARS CoV-2. It also outlines the correlation between comorbidities and neurological complications, and lastly, it mentions the prophylaxis and vaccines used for treating COVID-19 patients.

Keywords: Coronavirus; Comorbidities; COVID-19; Neurological complications; SARS CoV-2.

Contextual Background

Coronaviruses (CoVs) are associated with the extended family of positive, encased, extensively diverse, and single-stranded RNA viruses. [1,2] Coronaviruses were first perceived in the mid-1930s, and the first human coronavirus was notified in 1960, causing common cold-like symptoms. [3–5] In 2003, a beta (β) - coronavirus

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emerged from bats and disseminated through the palm civet (mediator host). It was transmitted to humans in China's Guangdong territory, where it was designated as the SARS (Severe Acute Respiratory Syndrome) virus, affecting approximately 8422 people, 916 of whom died. [4,6] In the middle of 2012, the initial instance of MERS (Middle East Respiratory Syndrome) was identified in Jeddah, Saudi Arabia. It emerged from bats, but the mediator host was a camel, and it affected 2994 individuals, 858 of whom died. [4,7] Wuhan, China was the initial location to identify instances of the COVID-19 obtained from patients with pneumonia. Later, it spread globally to almost every country, creating a nationwide lockdown. [4,8,9]

The WHO (World Health Organization) designated the outbreak as COVID-19 (Novel Coronavirus Disease 2019), which is caused by the SARS CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), on February 11, 2020. The assumed method of spreading COVID-19 is from one person to another through droplets expelled by infected individuals when they cough or sneeze nearby. [1,10,11] The primary signs of COVID-19 include are pyrexia (fever), tussis (cough), emesis (vomiting), and diarrhea. [1,12] The major health issues caused by SARS CoV-2 include and multiple organ failure, sepsis, ARDS (acute respiratory distress syndrome), septic shock, which are associated with co-morbidities (cancer, immunodeficiency, immunosuppressive disorders, cardiovascular diseases, diabetes, and asthma) (Table 1). [13–16] The geriatric section and patients with co-morbidities or chronic diseases are specifically vulnerable populations. [1,17] Nearly five years have passed since the first COVID-19 cases were reported in Wuhan, China. Over the past few challenging years, we've explored a variety of treatment approaches, implemented preventative measures, embraced social distancing, and fueled groundbreaking vaccine research. Unfortunately, in spite of these initiatives, especially concerning pharmacotherapy and patient management, over 775 million people worldwide have contracted SARS-CoV-2, and more than 7 million of those cases have resulted in death from COVID-19 infection. Furthermore, based on epidemiological mortality rate assessment research, the death rate has surpassed 18.2 million so far, and this deadly epidemic will claim many lives. [18]

MATERIALS AND METHODS

A comprehensive review was conducted to evaluate the progression of the SARS-CoV-2 virus (COVID-19), its impact on public health, associated neurological complications, and the available treatments and vaccination approaches. The review was based on an extensive search of peer-reviewed literature published on the COVID-19. The following methods were employed:

Literature Search Strategy

A systematic search was performed across multiple electronic databases including PubMed, ResearchGate, Scopus, Semantic Scholar, and Google Scholar. The search strategy incorporated a broad set of keywords related to COVID-19, such as: "COVID-19"; "SARS-COV-2"; "Coronavirus"; "SARS-COV-2 Variants"; "SARS-COV-2 Taxonomy"; "COVID-19 Pathology"; "COVID-19 Diagnosis"; "COVID-19 Comorbidities"; "COVID-19 Cardio-Vascular Disorder"; "COVID-19 Hypertension"; "COVID-19 Diabetes"; "COVID-19 Neurological Disorders"; "COVID-19 Encephalopathy"; "COVID-19 Guillain-Barré Syndrome"; "COVID-19 Stroke"; "COVID-19 Treatments"; "COVID-19 Immunomodulatory Treatment"; "COVID-19 Antiviral Drugs"; and "COVID-19 Vaccines". Studies were selected based on relevance, quality, and inclusion of information on the virology, pathology, comorbidities, neurological impact, and vaccine development significantly centred on the topic "COVID-19".

Selection Criteria

This review article included original research articles, reviews and studies that provided information on the structure and taxonomy, as well as the immuno-pathophysiology of SARS-CoV-2. Additionally, it incorporated studies exploring the relationship between comorbidities and COVID-19, investigations into the neurological effects of COVID-19, and articles highlighting COVID-19 management as well as examining the development, efficacy, and safety of COVID-19 vaccines.

RESULTS

Eligible studies, including full-text reviews and original research articles focused specifically

on COVID-19, were critically reviewed to extract data on viral taxonomy, structural virology, immuno-pathogenesis, neurological complications, treatments, and vaccine development. The extracted data was then categorized into the following areas:

• Taxonomy and Structural Virology: Information on the classification of SARS-CoV-2 within the coronavirus family and its structural composition and units.

• Immuno-Pathophysiology of SARS-CoV-2: Insights into the mechanisms of SARS-CoV-2 viral entry and developing a disease severity.

• Neurological Complications: Information on the incidence and types of neurological complications associated with COVID-19

• Rapid Detection of COVID-19: Methods and technologies for the swift identification of COVID-19, including rRT-PCR tests, lateral flow immunoassay, and emerging diagnostic tools for early detection.

• Impact of Comorbidities on COVID-19 Severity: Insights into how underlying conditions like diabetes, hypertension, and cardiovascular disease exacerbate the severity of COVID-19.

• Treatment Strategies: An overview of antiviral agents, immunomodulatory treatments, neutralizing antibodies, convalescent plasma therapy, and antithrombotic therapy, along with their application in managing mild to severe COVID-19 cases.

• Comprehensive List of COVID-19 Vaccines: An overview of available COVID-19 vaccines, highlighting their adverse effects, effectiveness, and efficacy against various SARS-CoV-2 variants.

By following this systematic approach, this review article offers a comprehensive summary of viral taxonomy, structural virology, immuno-pathogenesis, neurological complications, treatment strategies, and vaccine development , all focused specifically on COVID-19.

DISCUSSION

Taxonomy, Structural Virology and Circulating Sars-Cov-2 Variants

The International Committee on Taxonomy of Viruses (ICTV) classified coronaviruses under the order *Nidovirales* and the family *Coronaviridae* and subfamily *Orthocoronavirinae* (Figure 1A). [21] The 'Coronavirus' is named since the outer surface of the virus contains crown-like spike projections. [2] Based on serological evidence, the subfamily *Orthocoronavirinae* is divided into four genera: α-CoVs (alpha-coronavirus), β-CoVs (beta-coronavirus), γ-CoVs (gamma-coronavirus), and δ-CoVs (delta-coronavirus) (Figure 1A). [4,22,23] Coronaviruses are generally nurtured in mammals (bats, camels, cattle, cats, etc.) and birds. Alpha and beta-coronaviruses infect mostly mammals, whereas gamma-coronaviruses primarily infect birds and a few mammals. However, delta-coronaviruses infect both. Animal coronaviruses largely infect domestic birds and animals, affecting productivity along with economic loss. [22,23] These animal coronaviruses include Porcine Epidemic Diarrhoea Virus (PEDV), Avian Infectious Bronchitis Virus (IBV), Transmissible Gastroenteritis Virus (TGEV), and Swine Acute Diarrhoea Syndrome Coronavirus (SADS CoV). Coronaviruses are unusually potent human infectors and could spread through from one person to another. The initial coronaviruses identified were IBV, which caused respiratory illness in chickens, and Human Coronavirus 229E and OC43 (HCoV OC43 and HCoV 229E), which caused common cold-like symptoms in humans. Several other human coronaviruses were identified, such as in 2002 [Severe Acute Respiratory Syndrome Coronavirus (SARS CoV)], in 2004 [Human Coronavirus (HCoV)-NL63], in 2005 [Human Coronavirus (HCoV)- HKU1], in 2012 [Middle East Respiratory Syndrome-Coronavirus (MERS CoV)], and the recent global pandemic [Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2)]. [9,22,24–27]

Coronaviruses are observed under an electron microscope as minute, spherical, enveloped particles 60 to 140 nm in diameter, made up of single-stranded RNA (26 to 32 kbs in length). [2,4,28] The coronavirus mRNA encodes the four structural proteins: Spike (S) protein, Nucleocapsid (N) protein, Membrane (M) protein, and Envelope (E) protein (Figure 1B). The spike glycoprotein (S-protein) projections are a vital characteristic feature of coronaviruses. [4] It forms the bulky glycosylated peplomers embedded in the lipid bilayer, mediates attachment to the Angiotensin-Converting Enzyme 2 (ACE2) receptor, and facilitates membrane fusion to initiate viral pathogenicity in the host cell. The embedded hemagglutinin-esterase (HE) dimer

Table 1. Symptoms, Disease Pathogenesis and Clinical Manifestations Observed in Different Stages of COVID-19.

Stage / severity	Symptoms	Disease Pathogenesis			Hospitalization Required or not
Asymptomatic / Pre-symptomatic	SARS-CoV-2 test resulted in a positive outcome, yet there are no symptoms present.[19,20]	Viral replication [19,20]			Hospitalization is not required [19,20]
Mild Illness	Mild signs (include fever, cough, changes in taste or smell, or their complete loss); sore throat; general discomfort; headache; muscle pain; nausea; vomiting; and diarrhea.[19,20] No SOB (shortness of breath) or imaging findings. [19,20]				
Moderate Illness	Clinical assessment and imaging results indicate the presence of a lower respiratory tract infection. [19,20] SOB (shortness of breath) or Affirmative imaging results. [19,20] O_2 saturation $\geq$ 94%. [19,20]	Viral replication [19,20]	Inflammation [19,20]		
Severe Illness	Lower respiratory tract disease. [19,20] Lung infiltrates > 50%. [19,20] O_2 saturation < 94%. [19,20] Respiratory rate 30/min. [19,20]	Viral replication [19,20]	Inflammation [19,20]	Hypercoagulability [19,20]	Hospitalization required [19,20]
Critical Illness	Multiple organ dysfunction/failure; septic shock; respiratory failure. [19,20] Intubated or ICU (intensive care unit) admission. [19,20]	Inflammation [19,20]	Hypercoagulability [19,20]		

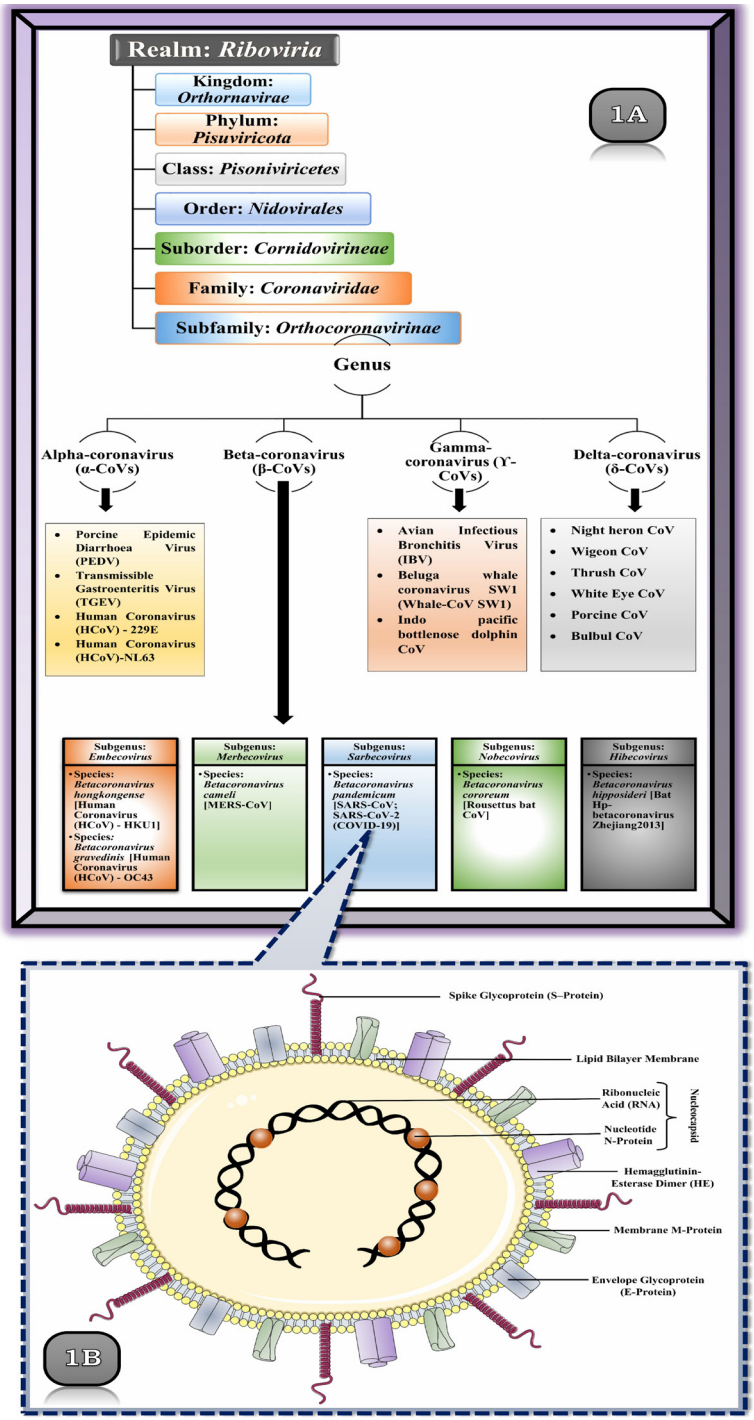


Fig. 1. Illustrating the taxonomical and schematic structure of SARS CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2).

1A) Schematically representing the taxonomical classification of coronaviruses.
Constructed using the following references: [2,4,9,21–27,32]
1B) Schematic structure of SARS CoV-2.
Constructed using the following references:[2,4,22,28,29] and this figure was partially made using Servier Medical Art [33]

designs the minute spikes on the viral outer surface. The positive-sense viral RNA is integrated with the viral nucleotide N-protein to form the nucleocapsid, which plays an important role in viral replication and transcription. The hydrophobic trans-membrane protein (M-protein) is the most prominent viral surface glycoprotein and is assumed to be the central organiser for assembling the coronaviruses. The trans-membrane envelope glycoprotein (E-protein) is the minor component

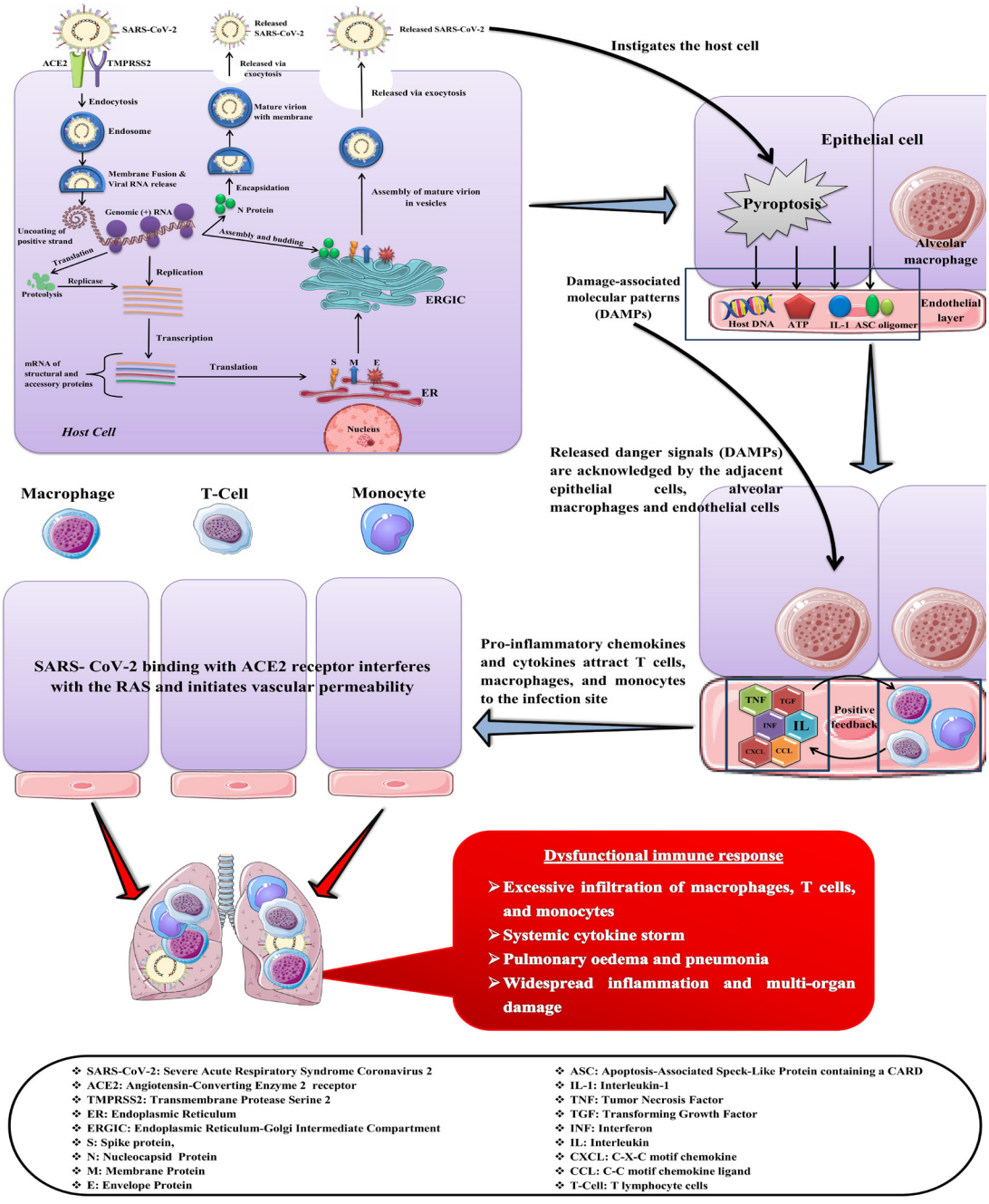


Fig. 2. The plausible immunopathogenesis mechanism of SARS-CoV-2. Constructed using the following references: [1,13,28,37–40,42–54,56–60] and this figure was partially made using Servier Medical Art[33]

of the coronaviruses and plays a prominent role in virus assembly, host cell membrane permeability, and also virus-host cell interaction. [2,4,22,28,29]

Eventually, researchers discovered a worldwide dominant variant, D614G, which was associated with increased transmissibility but not the potential to cause severe illness. [30] Several SARS-CoV-2 variations have been reported since then, some of which are regarded as variants of concern (VOCs) because they may result in

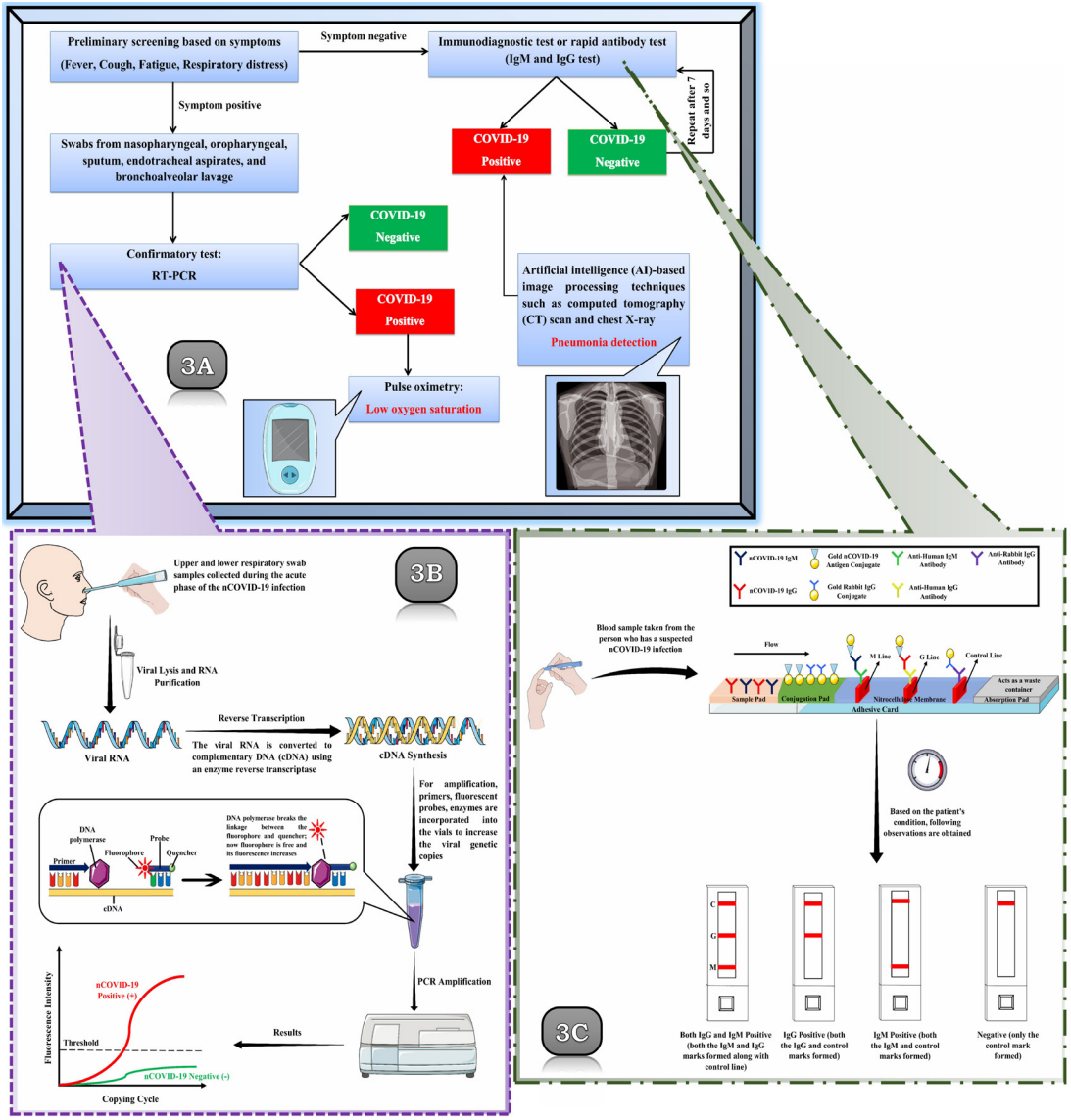


Fig. 3. Quick methods for identifying or diagnosing COVID-19.
3A) Rapid detection or diagnostic methods for detecting COVID-19.
Constructed using the following references: [4,61,62,74] and this figure was partially made using Servier Medical Art [33]
3B) The classic rRT-PCR (real-time reverse transcription-polymerase chain reaction) procedure is demonstrated, in which viral RNA is isolated and transformed into cDNA. By using rRT-PCR, specific regions of cDNA (target genes) are amplified and identified.
Constructed using the following references: [63–66] and this figure was partially made using Servier Medical Art [33]
3C) Steps representing LFIA (lateral flow immunoassay)-based COVID-19 diagnosis.
Constructed using the following references: [67–72,74] and this figure was partially made using Servier Medical Art [33]

Table 2. System of Classification for Differentiating the Emerging SARS-CoV-2 Variants

Variant Type	Variant Name	Lineage	First Detected	Spike Mutations	Important Points
Variants of Interest (VOIs)	XBB.1.5	Omicron	The USA, or United States of America[18,34-36]	N460K, S486P, and F490S[18,34-36]	• Identical to the baseline in terms of transmissibility, immunity, and disease severity. [18,34-36] • Poses no additional harm to public health and has a shallow risk of illness intensity and proliferation rate along with an average probability of antibody evasion.[18,34-36] • Decreased the neutralising power of the currently accessible mRNA vaccines.[18,34-36]
	XBB.1.16		_	_	• The genetic makeup is comparable to that of the XBB.1.5 lineage.[18,34-36] • No additional harm to public health.[18,34-36] • Slow growth rate and a moderate chance of antibody evasion.[18,34-36] • Has a shallow risk of illness intensity.[18,34-36]
	EG.5		_	F456L, N460K, S486P, and F490S[18,34-36]	• The most common variant of SARS-CoV-2 globally.[18,34-36] • Similarity in transmissibility to the initial sub-lineages of Omicron.[18,34-36] • A low pace of growth and a moderate chance of antibody evasion.[18,34-36] • Greater potential for antibody evasion, growth pace, and prevalence than others.[18,34-36]
	BA.2.86		Israel along with Denmark[18,34-36]	Has enormous mutations in the spike protein[18,34-36]	• Propensity to cause a sharp rise in COVID-19 instances, but there would be no increase in the disease's severity. [18,34-36] • XBB-infected individuals' convalescent plasma had sufficient neutralising activity against BA.2.86, indicating that XBB.1.5 monovalent COVID-19 vaccines could be effective against the BA.2.86 lineage.[18,34-36]
	JN.1	Sub-lineage of BA.2.86	First detected on August 2023[18,34-36]	_	• The most common sub-lineage of SARS-CoV-2 worldwide.[18,34-36] • Minimal risk to the public's health and no shifts in the severity of diseases or hospitalisation rates.[18,34-36] • Despite instances of immunological escape, the monovalent XBB.1.5 booster immunisation is still advantageous.[18,34-36]

Variants Under Monitoring (VUMs)	XBB, XBB.1.9.1, and XBB.2.3	Omicron	_	E180V, G446S, T478R, I332V, F486P, K444T, 483del, D339H, N450D, R403K, L452R, V445H, N481K, L452W, and E484K[18,34-36]	• Information about the immunological escape, growth rate, and transmissibility is limited.[18,34-36]
De-escalated SARS-CoV-2 variants	B.1.1.7	Alpha	In the United Kingdom in September 2020[18,34-36]	N501Y, Y144 P681H, and H69/V70[18,34-36]	• Demonstrated a 30% rise in viral contagiousness and transmissibility.[18,34-36] • Capable of causing a serious COVID-19 infection.[18,34-36] • Compared to SARS-CoV-2 wild type, the efficacy of vaccinations and monoclonal antibodies against this variation was decreased because of these mutations.[18,34-36] • A ten-fold increase in ACE2 binding potential.[18,34-36]
	B.1.351	Beta	In South Africa in October 2020[18,34-36]	K417N, L18F, N501Y, E484K, D80A, A701V, and D215G[18,34-36]	• Demonstrated a 50% rise in viral contagiousness and transmissibility.[18,34-36] • Capable of causing a severe COVID-19 infection.[18,34-36] • Comparing these alterations to the SARS-CoV-2 wild type, vaccinations and monoclonal antibodies were less effective against this variation. [18,34-36] • A two-fold increase in ACE2 binding potential.[18,34-36]
	P.1	Gamma	In Brazil and Japan in November 2020[18,34-36]	K417T, E484K, AND N501Y[18,34-36]	• Accompanied by 30-40% rise in viral contagiousness and transmissibility.[18,34-36] • Causing a serious case of COVID-19. [18,34-36] • When compared to the wild type of SARS-CoV-2, these alterations reduced the effectiveness of monoclonal antibodies and vaccines against this variant.[18,34-36] • A five-fold increase in ACE2 binding potential.[18,34-36]
	B.1.617	Delta	In India, in December 2020[18,34-36]	L452R, R158G, P681R, T478K, D950N, and D614G[18,34-36]	• Viral infectivity and transmissibility increased by more than 90%.[18,34-36] • Caused a serious COVID-19 illness. [18,34-36] • While comparing the infected individuals to the preceding variations, the viral RNA load was significantly higher. [18,34-36] • These mutations decreased the potency of the vaccination, yet it was still 80% effective against hospitalisation and serious COVID-19 illness. [18,34-36] • Hospitalisation and mortality rates from the Delta variant disease were found to be reduced when monoclonal antibodies, such as imdevimab, sorovimab, and casirivimab, were administered.[18,34-36] • A two-fold increase in ACE2 binding potential. [18,34-36]

Table 3. An Overview of the Primary Antiviral Medications and Immunomodulatory Therapy Used to Treat COVID-19.

Agent Type	Drug Name	Type (Delivery Route)	Eligible Patients	Information about the Drug	Significant Trials	An Overview of Data	NIH (National Institutes of Health) COVID-19 Treatment Guidelines Suggestions
Antiviral Medications	Remdesivir	Small molecule (intravenous injection) [152]	Outpatient s[b] ≤ 7 days of symptom onset, or inpatients[152] [b = Non-hospitalized individuals with mild-to-adequate COVID-19 are highly likely to escalate to critical COVID-19, potentially leading to hospitalization or even death.]	One of the first medications to show efficacy in a randomized controlled trial (RCT) during the early phases of the global outbreak was Remdesivir, a drug that inhibits viral RNA-dependent RNA polymerase.[19]	ACTT-1 [153]	Included 1,062 hospitalized, unvaccinated patients who needed supplemental oxygen. [153] The results of the trial indicated that the remdesivir group recovered more quickly than the placebo group [153]-10 days compared to 15 days-and that the group that needed traditional oxygen supplementation and those who started experiencing symptoms within 10 days of each other benefitted most from remdesivir. [153]	First-line treatment for hospitalized COVID-19 patients (in combination with immunomodulators if oxygen is required by the patient) and second-line treatment (subsequent nirmatrelvir-ritonavir) for vulnerable outpatients. [19,133,154]
					CATCO[155]	In Canada, an open-label randomized controlled trial (RCT) revealed a lower risk of transition to mechanical ventilation but no decrease in death when compared to standard treatment.[155]	
					SOLIDARITY[156]	A multinational study consortium found that patients who were mechanically ventilated at enrolment did not have a lower death rate; however, patients who needed	

					supplementary oxygen but were not mechanically ventilated did demonstrate a minor mortality advantage (14.6% versus 16.3%, ρ = 0.03). [156]	
				PINETREE[157]	Recruited unvaccinated outpatients were possessed at an elevated risk of advancement because of their age or comorbidities and who were within seven days of the onset of symptoms. The trial's findings showed that, in comparison to a placebo, a three-day course of remdesivir considerably reduced hospitalization and mortality from all causes (0.7% vs 5.3%, ρ = 0.008). [157]	
Nirmatrelvir -Ritonavir	Small molecule (oral) [152]	Outpatient s[b] ≤5 days of symptom onset[152] [b = Non-hospitalized individuals with mild-to-adequate COVID-19 are highly likely to escalate to critical COVID-19, potentially leading to hospitalisation or even death.]	Ritonavir, a pharmacologic enhancer, is used in conjunction with nimatrelvir, a medication used orally which inhibits the protease of SARS-CoV-2.[19,138]	EPIC-HR[138]	Recruited high-risk, unvaccinated outpatients and, in comparison to a placebo, showed an 89% decrease in the likelihood of being hospitalized or mortality.[138]	For high-risk, outpatient patients, oral nirmatrelvir-ritonavir is recommended as the initial course of treatment.[19,133,154]
				EPIC-SR[158]	The study assessed the medication's effectiveness in patients with standard risk (those who were at risk but had received vaccinations or did not have any factors that increased their chance of risk advancement). Hospitalization rates were low for patients in both arms of this trial, and there was no benefit of the medicine on long-term symptom relief.[158]	
				Retrospective Cohort Study [159]	Research conducted on highly -risk, vaccinated outpatients revealed that the nirmatrelvir -ritonavir group had a 45% proportional threat decrease in the cumulative outcome	

						of a visit to the hospital emergency department, hospitalization, or death in comparison to the placebo category (7.87% versus 14.4%, $\rho < 0.005$), indicating its continued relevance for clinical practice. [159]	
	Molnupiravir	Small molecule (oral) [152]	Outpatient s[b]≥18 years old and ≤ 5 days of symptom onset[152] [b = Non-hospitalized individuals with mild-to-adequate COVID-19 are highly likely to escalate to critical COVID-19, potentially leading to hospitalisation or even death.]	A prodrug of the minuscule molecule N-hydroxycytidine, which causes mutations to build up and depletes the viral viability of SARS-CoV-2.[19,139]	MOVe-OUT[139]	Assessed 1,433 vulnerable, unvaccinated outpatients. A 31% comparative risk decrease was observed in the 30-day hospitalization or mortality rate from all causes in the group receiving molnupiravir compared to the group receiving a placebo (7.3% versus 14.1%, $\rho = 0.001$). [139]	Molnupiravir is only recommended when remdesivir and nirmatrelvir-ritonavir are not capable of being administered.[19,133,154]
					PANORAMIC[160]	Molnupiravir did not reduce the rate of hospitalization or mortality among vulnerable outpatients, the majority of them had received vaccinations. This finding is less conclusive; due to the open-label nature of the trial, which may have influenced the research participants reported symptoms, the drug-treated group's self-reported recovery time was significantly reduced.[160]	
Immuno-modulatory Therapy	Corticos-teroids	Small molecule (intravenous injection)[152]	Hospitalized patients needing non- invasive or mechanical ventilation, high-flow oxygen, or conventional oxygen. [19,152]	Corticosteroids were the first drugs to be shown to improve survivability during the management of COVID-19.[135]	RECOVERY [144]	An open-label study involving 6,425 hospitalized unvaccinated treatment alone with a ten day regimen of dexame-thasone. Results showed that those receiving supplemental oxygen (23.3% against 26.2%) and those necessitating mechanical ventilation	For hospitalized patients needing non-invasive or mechanical ventilation, high-flow oxygen, or conventional oxygen, dexamethasone is still the fundamental component of

					(29.3% against 41.4%) had significantly lower 28-day death rates when compared to standard therapy in solitude.[144] There was no alteration seen for people who did not require additional oxygen, and in this group, dexamethasone was trending towards harm.[144] The normal amount of dexamethasone employed in the RECOVERY trial was 6 mg/day; however, there was considerable debate as to whether higher doses may be even more beneficial. But compared to the standard dosage of 20 mg of dexamethasone, those receiving a high dose had a higher death rate among patients needing conventional oxygen assistance. [161] Although large dosage of dexamethasone trials are presently being conducted in critically suffering patients, the data currently indicate that conventional dosage of dexamethasone is appropriate to be used in healthcare settings. [19,133]	COVID-19 therapy and is advised as first-line treatment.[19,133,154]
Interleukin-6 (IL-6) Inhibitors	Anti-IL-6R mAb (monoclonal antibody) [intravenous injection] [152]	Inpatients receiving systemic corticosteroids, requiring oxygen support, invasive or non-invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). [19,152]	The Food and Drug Administration (FDA) in the United States has formerly authorized monoclonal antibodies (mAbs) that block the proinflammatory cytokine interleukin-6 (IL-6) for the relief of autoimmune diseases such as cytokine release syndrome and rheumatoid arthritis associated with CAR-T (chimeric	RECOVERY[162]	In a UK trial, hospitalized patients with elevated CRP above 75 mg/L and hypoxaemia were randomized to receive tocilizumab rather than conventional regular medical treatment. When compared to the usual course of treatment, the tocilizumab group's mortality was significantly lower (31% versus 35%, $\rho = 0.0028$). [162]	Proposed that patients needing mechanical ventilation, high-flow nasal cannulas, non-invasive ventilation, ECMO (extracorporeal membrane oxygenation), or patients on traditional oxygen who have drastic elevating oxygen requirements and signs of systemic inflammation (such as raised CRP) are prescribed tocilizumab in

			antigen receptor T cell) treatment. A recombinant, humanized anti-IL-6 receptor monoclonal antibody called tocilizumab inhibits the IL-6 cytokine signaling cascade downstream. Early in the pandemic, there was inquisitiveness in its possible application because many individuals with severe COVID-19 were found to have elevated acute phase reactant levels, including ferritin and C-reactive protein (CRP). [19,162]			conjunction with dexamethasone. If tocilizumab is not accessible, sarilumab is advised as a backup. [19,133,154]
Janus kinase (JAK) inhibitor	Small molecule (oral)[152]	Individuals admitted to the hospital in need of extra oxygen, invasive or noninvasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[19,152]	Baricitinib is a Janus kinase (JAK) blocker that prevents the synthesis of cytokines, such as IL-6, by inhibiting the stimulation of the STAT (signal transducers and activating agents of transcription) pathway. The FDA has approved baricitinib for the treatment of rheumatologic conditions, including rheumatoid arthritis.[19,164]	COV-BARRIER [164]	The death rate was lower for hospitalized individuals randomly assigned to receive baricitinib along with to their normal medication (that included dexamethasone) than for those who received a placebo. [164]	It is recommended to combine baricitinib with dexamethasone for the patients requiring ECMO, noninvasive ventilation, mechanical ventilation, high-flow nasal cannulas, or patients receiving traditional oxygen who have evidence of systemic inflammation (such as elevated CRP) along with substantially increasing oxygen demand. [19,133,154]
				RECOVERY[165]	Patients hospitalized with COVID-19 who received baricitinib instead of conventional therapy alone experienced a decrease in 28-day all-cause death rates (12% vs 14%, $\rho = 0.028$) in an open-label platform study.[165]	

Table 4. The Comprehensive List of Vaccines for COVID-19 are presented with their Adverse Effects, Effectiveness, and Efficacy against several SARS-Cov-2 variants.

Type of vaccine	Vaccine Candidate	Vaccine Developer/ Manufacturer	Brand Name	Dosage	Route of Administration	Interval	Storage	About the Vaccine	Vaccine Effectiveness, And Efficacy Against an Array of SARS-Cov-2 Variants	Negative Effects
mRNA vaccine	BNT162b2	Pfizer-BioN Tech	COMIR-NATY®	0.3 mL (30 µg nucleosid-modified mRNA) (2 Shots) [167,170]	Intramuscular [167,170]	21 days[167]	-70 °C [167]	The mRNA-based vaccine BNT162b2 encodes for the spike glyco-protein of the SARS-CoV-2 virus and is encased in lipid nanoparticles (LNPs). The genetic information necessary to cause the recipient's cells to produce the antigen is contained in gene-based vaccinations, such as DNA and mRNA vaccines. The target antigen for COVID-19 is the surface spike protein that the virus employs to bind to and merge	• Two vaccination doses result in 95% vaccine effectiveness against wild-type SARS-CoV-2.[18,172-179] • The efficacy of the vaccine against the Alpha variant is 89%.[18,172-179] • The efficacy of the vaccine against the Beta variant is 87%.[18,172-179] • Vaccine efficacy in combating the Gamma variant is 88%.[18,172-179] • Opposing the Delta variant vaccine effectiveness is 84 - 88%.[18,172-179] • Compared with the wild-type virus, serum neutralising antibody titers with respect to the Epsilon variant were decreased by 2.9-13.4	Allergic reactions (such as paroxysmal ventricular arrhythmia, syncope, and anaphylaxis); redness; pain; headache; swelling; diarrhoea; exhaustion; muscle soreness; fever; joint pain; chills; right axillary lymphadeno-pathy; shoulder injury; lymphadeno-pathy; and right leg paraesthesia.[18,172-179]

							into host cells. The SARS-CoV-2 spike protein is encoded by the BNT162b2 mRNA, which also acknowled the mutations that balance the spike protein.[166,172]	fold.[18,172-179] • Serum neutralising antibody titers towards the Kappa viral variant were eight fold lower than those against the wild-type virus. [18,172-179] • Compared with the wild-type virus, serum neutralising antibody titers with respect to the Lambda variant were decreased by 2.5-4 fold.[18,172-179] • The titers of serum neutralising antibodies regarding the Mu variant were 3.1-fold lower than those against the wild-type virus. [18,172-179]	
mRNA-1273	Moderna	SPIKE VAX®	0.5 mL (100 µg mRNA) (2 Shots) [167,170]	Intramuscular[167,170]	28 days[167]	-20 °C[167]	The spike glycoprotein-coding mRNA of the SARS-CoV-2 virus is encased in lipid nanoparticles (LNPs), which allow it to cross cell membranes and enter the cytosol, where it produces a spike protein that will be	• The vaccine's effectiveness opposing wild-type SARS-CoV-2 is 94.1% after two doses.[18,167,173, 177-179,181-183] • The efficacy of the vaccine against the Alpha variant is 92%. [18,167,173, 177-179,181-183] • The efficacy of the vaccine against the Beta variant is 89%. [18,167,173, 177-179,181-183]	The symptoms may include urticaria, arthralgia, myalgia, vomiting, headache fever, chills, pain, oedema, and redness at the injection site. Bell's palsy , facial swelling, anaphylaxis, and other allergic reactions were

	presented as an antigen later on and trigger the immune system.[166,180]	• Vaccine efficacy in combating the Gamma variant is 89%. [18,167,173,177-179,181-183] • Opposing the Delta variant vaccine effectiveness is 84 - 95%. [18,167,173,177-179,181-183] • In comparison to the wild-type virus, serum neutralising antibody titers in response to the Epsilon variant were decreased by 2.8 fold. [18,167,173,177-179,181-183] • Serum neutralising antibody titers toward the Kappa viral variant were eight fold lower than those against the wild-type virus.[18,167,173,177-179,181-183] • Compared with the wild-type virus, serum neutralising antibody titers with respect to the Lambda variant were decreased by 2.5 -4 fold.[18,167,173,177-179,181-183] • The titers of serum neutralizing antibodies regarding the Mu variant	among the clinical symptoms (which ranged from light to adequate symptoms following the initial vaccination dosage and moderate to severe symptoms following the second dosage).[18,167,173,177-179,181-183]

									were 3.1-fold lower than those against the wild-type virus. [18,167,173,177-179,181-183]	
Adeno virus-vectored vaccines (Recomb-inant)	ChAdOx1-S	Oxford/ Astra Zeneca	COVI-SHIELD™	0.5 mL (5 × 1010 viral particles) (2 Shots) [167,170]	Intramuscular [167,170]	4-12 weeks[167]	2-8 °C [167]	An illustration of a vector-centric COVID-19 vaccine involves the application of vectors, like AZD1222 (AstraZeneca vaccine) or the ChAdOx1 nCoV-19, which has been designed by AstraZeneca (pharmaceutical company) and the Oxford University. The spike glycoproteins are encoded by the viral structural interface glycoprotein antigen gene, which is present in the non-replicating viral vector AZD1222. AZD1222 induces immunity on both a humoral	• The vaccine's effectiveness towards wild-type SARS-CoV-2 is 79% after two doses. [18,174,176,178,187] • The efficacy of the vaccine regarding the Alpha variant is 91%. [18,174,176,178,187] • The efficacy of the vaccine opposing the Delta variant ranges from 64 to 67%. [18,174,176,178,187]	Fever, headache, malaise, chills, erythema, nausea, vomiting, diarrhoea, myalgia, arthralgia, pruritus, soreness at the site of injection, pain, warmth, bruises , swelling, and as well as exhaustion, and venous throm-boembolis. [18,174,176,178,187]

								and cellular level.[166,184-186]		
	Janssen, Ad26. COV2.S	Johnson & Johnson	Jcovden	0.5 mL (5 × 1010 viral particles) (1 Shot) [167,170]	Intramuscular [167,170]	-	2-8 °C [167]	Ad26.COV2.S is basically a human adenovirus variety 26, a single-dose, non-replicating recombinant virus. The complete, settled SARS-CoV-2 spike protein, which is encoded by Ad26.COV2.S, triggers the SARS-CoV-2 infection to initiate an immunological reaction.[166,188]	• The vaccine's effectiveness towards wild-type SARS-CoV-2 is 66.9% following a single dose. [18,177,182,188-190] • The efficacy of the vaccine in opposition to the Alpha variant is 70.2%.[18,177,182,188-190] • The efficacy of the vaccine concerning the Beta variant ranges from 51.9 to 64.7%. [18,177,182,188-190] • The efficacy of the vaccine regarding the Gamma variant is 36.5%. [18,177,182,188-190] • The efficacy of the vaccine directed at the Delta variant ranges from 84 to 60%. [18,177,182, 188-190] • Serum neutralising antibody titers against the Lambda variant are reduced by 3.2 to 4.9 fold when compared to the wild-type virus. [18,177,182,188-190]	Fever, headache, malaise, chills, erythema, nausea, vomiting, diarrhoea, myalgia, arthralgia, pruritus, soreness at the site of injection, pain, warmth, bruises, swelling, and as well as exhaustion, and venous thromb-oembolis. [18,174,176,178,187]
Protein subunit	Nuvaxovid, NVX-	Novavax	NUVA-XOVID™	0.5 mL (5 µg SARS	Intramuscular [167,170]	21 days[167]	-20 °C [167]	The first recombinant	• After double vaccination	Fatigue, headache, and

vaccines	CoV2373	/ COVO-VAX™	-CoV-2 rS adjuvant /50 µg Matrix-M1 adjuvant) (2 Shots) [167,170]	protein-based vaccination to be approved by regulators to be administered in opposition to SARS-CoV-2 is NVX-CoV2373. The immuno-genic vaccine NVX-CoV2373 reply upon nanoparticles. Recombinant expression of the SARS-CoV-2 spike protein is employed in its development. The complete, trimeric spike glycoproteins of the SARS-CoV-2 are used in the formulation of this vaccine, which is formed into nanoparticles along with an adjuvant based on saponins called Matrix-M. The vaccination and adjuvant dosages are as follows: two doses of 50 µg Matrix-M1 and 5 µg SARS-	doses, the vaccine has 89.7% efficacy against wild-type SARS-CoV-2.[18,189,192,193] • Against the Alpha variant vaccine effectiveness is 86.3%. [18,189,192,193] • Against the Beta variant vaccine effectiveness is 51.1 - 60%. [18,189,192,193]	malaise. [18,189,192,193]

								CoV-2 rS adjuvant with an interval of 21 days.[166,191]		
Inacti-vated vaccines	Sinovac	CoronaVac	Corona Vac®	0.5 mL (3 µg in aluminum adjuvant) (2 Shots) [167,170]	Intramuscular [167,170]	28 days[167]	2-8 ° C [167]	One of the mostoften used vaccinations in the world is an inactivated viral vaccine. They are primarily used in low- and middle-income nations due to their less stringent cold chain preservation requirements, ease of delivery, and reduced cost as compared to mRNA vaccines. CoronaVac is an inactivated SARS-CoV-2 vaccine created by Sinovac Life Sciences of Beijing, China, which has been observed to elicit an immune response. Two doses of Corona Vac are administered, separated by two weeks. [166,194]	• The vaccine's effectiveness towards wild-type variants SARS-CoV-2 is 51% following two doses. [18,183,195] • Efficacy regarding the Delta variant vaccination ranges from 59 to 60%. [18,183,195]	Pain at the injection site, elevated blood pressure, dizziness, exhaustion, headache, and rash. [18,166,183,195,196]

	BBIBP-CorV	Sinopharm	Sino-pharm®	0.5 mL (4 µg in aluminum adjuvant) (2 Shots) [167,170]	Intramuscular [167,170]	21 to 28 days [167]	2-8 °C [167]	The Sinopharm COVID-19 vaccine, an inactivated vaccine against SARS-CoV-2, was created by the Beijing Bio-Institute of Biological Products (BBIBP) and is the very initial Chinese COVID -19 vaccine approved by the WHO for immediate use. Two 4 µg doses of the Sinopharm vaccine are administered, separated by 28 days.[166,197,198]	• After double doses of vaccine administration, the vaccine has 79% efficacy against wild-type SARS -CoV-2. [18,199] • Against the Gamma variant vaccine effectiveness is 46.8%.[18,199]	In addition to allergic dermatitis, the frequent symptoms included vomiting, nausea, and fever, headaches, exhaustion, and dizziness. Within 28 days following immunization, some minor to serious negative reactions have been documented; however, no significant events have occurred. [166,198]
	COVAXIN, BBV152	Bharat Biotech	CO-VAXIN®	0.5 mL (6 µg in Aluminum hydroxi-quim-II adjuvant) (2 Shots) [167,170]	Intramuscular[167]	28 days[167]	2-8 °C [167]	In collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV), Bharat Biotech developed and produced BBV152/ Covaxin, an inactivated COVID-19 vaccine. This is the first indigenous COVID-19 vaccine produced in India.[166,200]	• The vaccine's effectiveness regarding the wild-type strain SARS-CoV-2 is 79% following two doses of vaccination. [18,178,183] • The efficacy of the vaccine opposing the Delta variant is 65.2%. [18,178,183]	High temperature, exhaustion, pain at the injection site, nausea, and vomiting. [18,178,183]

increased transmissibility or pathogenicity. A categorization method for differentiating the new SARS-CoV-2 variations into variants of interest (VOIs) and variants of concern (VOCs) has been separately developed by the World Health Organisation (WHO) and the United States Centres for Disease Control and Prevention (CDC) (Table 2). [31] Fortunately, no SARSCoV-2 variant that satisfies the VOC requirements is currently in circulation. Certain Omicron lineages, such as EG.5, XBB.1.5, and XBB.1.16, are considered to be VOIs that are currently in circulation (Table 2). [18] A number of Omicron lineages have been identified as presently circulating variants under monitoring (VUMs), such as XBB, XBB.1.9.1, and XBB.2.3. Information about the immunological escape, growth rate, and transmissibility of these new Omicron lineages is limited. These lineages have been associated with the following primary spike mutations: I332V, D339H, R403K, V445H, G446S, K444T, L452R, N450D, L452W, E180V, T478R, F486P, N481K, 483del, and E484K. More research and observation are necessary because the epidemiological and phenotypic effects of these mutations and associated lineages are still uncertain. [18]

Immuno-Pathophysiology of SARS-COV-2

The genome of a coronavirus consists of about 30,000 nucleotides, and its structural proteins are encoded by its mRNA. [1,28] Earlier research shows that the main targets of SARS-CoV are the host's pulmonary system, especially the macrophages, alveolar epithelial cells, vascular endothelial cells, and airway epithelial cells, which have Angiotensin-Converting Enzyme 2 (ACE2) receptors. In a similar manner, SARS-CoV-2 utilizes the ACE2 receptor on the host cell to facilitate entry (Figure 2). When the virus attaches to the ACE2 receptor, it reduces its expression and causes the lung cells to down-regulate, which results in acute lung damage. [37–46]

The two subunits that make up the spike (S) glycoprotein are S1 and S2. An ATD (Amino-Terminal Domain) and a RBD (Receptor-Binding Domain) make up the subunit S1. [43,47–49] The RBD starts the viral infection phase by attaching itself to the host cellular target ACE2. RBD connects to the cellular receptor ACE2, which triggers the endocytosis of SARS CoV-2 virion and exposes it to the host endosomal proteases furin and trypsin. HR1 and HR2, the Heptad Repeat Regions, and the FP (Fusion Peptide) region make up subunit S2. After the subunit S1 is broken down within the endosome, FP emerges and enters the host membrane. The viral payload is subsequently released into the host cell's cytoplasm when the subunit S2 coincides on itself to connect the two heptad repeat sections in proximity, triggering the membrane fusion (Figure 2). [43,50–52] Biophysical tests and computer modelling show that the RBD of SARS CoV-2 attaches to ACE2 with greater proximity than that of SARS-CoV. Like MERS-CoV and HC-OC43, the spike glycoprotein of SARS-CoV-2 forms a furin-like cleavage site, increasing the pathogenicity in comparison to SARS-CoV. TMPRSS2 (Transmembrane Protease Serine 2) is necessary for the recognition of the SARS CoV-2 spike glycoprotein and for facilitating the viral entrance into the host cell. [43,53,54] After the virus enters the host cell's cytoplasm by endocytosis, the SARS CoV-2 RNA gets released and processed into two polyproteins and structural proteins that eventually replicate the virus's genome. [1,28] The replicating viral component mediates viral genome replication and is composed of an exonuclease N, a helicase, an RdRp (RNA-dependent RNA polymerase), and other related proteins. [55] The mechanism by which N protein encapsidates duplicated genomes in the cytoplasm results in nucleocapsids, which then consolidate within the membrane to self-assemble into new virions. The ER (Endoplasmic Reticulum) and Golgi Apparatus membranes both include the recently synthesised structural glycoproteins in the cytoplasm, which are then transferred to the ERGIC (Endoplasmic Reticulum-Golgi Intermediate Compartment). [1,28,56] Finally, the novel virions are fused with the plasma membrane via exocytosis, and the virus is released (Figure 2). [1,28]

The released virus instigates the host cell to initiate pyroptosis and release ATP, ASC oligomers, Interleukin-1 (IL-1), and nucleic acids, which constitute the Damage-Associated Molecular Patterns (DAMPs). Adjacent epithelial cells, alveolar macrophages, and endothelial cells recognise the released danger signals (DAMPs), which trigger pro-inflammatory cytokines (such as TNF–α [Tumor Necrosis Factor-alpha]; TGF–β [Transforming Growth Factor-beta]; IFN–α [Interferon-alpha]; IFN–γ [Interferon-

gamma]; Interleukin [IL]–1β, 6, 12, 18, 33, 281) and chemokines (such as CCL [C C motif chemokine ligand]–2, 3, 5, and CXCL [C-X-C motif chemokine]–8, 9, 10). [1,13,43,57–59] T cells, macrophages, and monocytes are drawn to the infection site by pro-inflammatory chemokines and cytokines, which also promote further inflammation through the production of interferon-gamma (IFN-γ) by T cells and a pro-inflammatory feedback looping mechanism. When the spike glycoprotein of SARS CoV-2 binds to the ACE2 receptor, it affects the RAS and causes vascular permeability. This can result in a faulty immunological response where immune system cells build up in the lungs, producing excessive pro-inflammatory cytokines and adversely impacting the lung (Figure 2). [1,28,37–39,43,56] The subsequent cytokine storm spreads to neighboring organs, leading to malfunction or failure of several organs. Moreover, through Antibody-Dependent Enhancement (ADE), non-neutralizing antibodies produced by B lymphocyte cells (B cells) increase the SARS CoV-2 disease and exacerbate organ dysfunction or injury. In favorable immune responses, virus-specific CD^{4+} and CD^{8+} T cells draw in and destroy the virus at the onset of inflammation, preventing it from spreading. The alveolar macrophages recognizes the viral cells and neutralized them. They phagocytose the apoptotic cells to eliminate the virus and maintain minimal lung damage with resultant recovery. [1,13,43,57–59]

Rapid Detection of COVID-19

Rapid diagnosis or detection is a predominant health care function since it imparts details about the health issues of a patient and provides consecutive decisions. [61] The vital advantages of rapid diagnostic techniques are the prospect of rapid intervention and a focused solution to potential problems. Similarly, COVID-19 can be detected using rapid diagnostic techniques like RT-PCR (real-time polymerase chain reaction), primary screening through an immunodiagnostic test (rapid antibody test), and finally by Artificial Intelligence (AI)-based image processing techniques such as chest X-ray and CT (Computed Tomography) scan (Figure 3A). [4,61,62]

The most recent technique for qualitatively and quantitatively identifying the SARS-CoV-2 nucleic acid in both upper and lower respiratory swab samples in the intense period of illness is real-time reverse transcription-polymerase chain reaction, or rRT-PCR. [4,61,62] One of the best and most efficient scientific techniques for tracking, treating, and analyzing the COVID-19 is rRT-PCR. By using particular primers for the COVID-19 viral genes, cDNA is produced using this technique from the COVID-19 virus's retrieved RNA. Specific areas of cDNA (target genes) are amplified and identified using various fluorescent dyes (Figure 3B). The use of rRT-PCR assays has several important advantages, but the main one is that the amplification and analysis would take place in a contained system, reducing the likelihood of false-positive findings. [63–66]

After contracting SARS-CoV-2, the patient produces IgM or IgG antibodies which are specific for the viral antigens to the receptor binding domain (RBD), the spike glycoprotein (S1, S2 subunits), or the nucleocapsid (N) protein. [67,68] IgM first appears after infection and remains detectable for a couple of days and then IgG follows. All current quick SARS-CoV-2 antibody assessments rely on the ability of the N, S1, S2, or RBD domain of the SARS-CoV-2 spike protein to associate with IgM or IgG antibodies in the patient's blood. [68–70] Time-dependent detection of IgM or IgG isotypes only reaches high sensitivity around three weeks after symptoms start. [68,71] Lateral flow detection [Lateral Flow Immunoassay (LFIA)] is used in rapid SARS-CoV-2 antibody testing (Figure 3C). [68,72] The blood sample taken from the person who has a suspected COVID-19 infection is used for LFIA. In lateral flow testing, an absorbent pad attached to the leading edge of the strip allows an antigen or antigen-antibody complex to flow across it. The polymeric strip's different zones are travelled by a liquid sample that contains the analyte. As a sponge, the sample pad allows fluid to go to the next conjugate pad after it has been moistened. A chemical reaction between an antigen and an antibody can be carried out using the chemicals included on the conjugate pad. The antigen passes through the pad, leaving a mark behind. The antigen continues to flow via the test and control lines. Following its passage through these lines, the fluid enters a porous material that serves as a disposal storage. [72] Observations are made based on the state of the patient and can be classified into the following categories: negative (just the control sign formed), IgM positive (both the IgM mark and control markings formed), IgG

positive (both the IgG mark and control markings formed), or just both IgG and IgM positive (both the IgM and IgG markings developed along with the control line) (Figure 3C). [72,73]

Comorbidities of Cardiovascular Disease, Diabetes, and Hypertension in the Context of COVID-19

Patients with COVID-19 are more likely to have acute cases and greater fatality rates if they have underlying comorbidities and are older than 70. The prominent comorbidities that are associated with COVID-19 are cardiovascular diseases, diabetes mellitus, and hypertension. [16,75–78] This can be suggested by a study conducted by *Li et al.,* [17] among 1527 COVID-19 patients admitted; 17.1% had hypertension, 16.4% had cardiovascular disease, and 9.7% had diabetes mellitus. [17] The survey by *Huang et al.,* [13] comprised 41 hospitalized patients with a confirmed COVID-19 infection; 32% of these patients had concomitant conditions such as cardiovascular illnesses (15%), diabetes (20%), and hypertension (15%). [13] Similarly, the study of *Wang et al.,* [79] suggests the prevalence of one or more comorbidities (likely 31% of patients with hypertension, 14.5% with cardiovascular diseases, and diabetes 10.0%) in 64 individuals from 138 hospitalized COVID-19 patients. [79] In general, COVID-19 infects both sexes; however, men have a 3.6% case fatality rate compared to women's 1.6%. [80] Patients with cardiovascular diseases who contracted COVID-19 were three times more likely to experience an acute illness or require admission to the intensive care unit (ICU) than those with diabetes mellitus or hypertension. [17,76,80] According to a Chinese Centre for Disease Control and Prevention [81] study, 44,672 patients out of 72,314 distinct records had COVID-19 confirmed in them; 1,023 of these patients died, resulting in a crude case fatality rate of 2.3% (number of confirmed mortality divided by the overall number of confirmed infections). Additionally, a greater fatality frequency was noted for individuals with underlying comorbidities: 10.5% of patients having cardiovascular disorders, 7.3% of patients with diabetes, and 6.0% of patients with hypertension. [81]

A survey by *Chen et al.,* [82] involving 99 patients confirmed with COVID-19 revealed that 51% of the admitted patients were detected with chronic medical illness (40% with cerebrovascular or cardiovascular disease). [82] A retrospective multi-centre study by *Ruan et al.,* [83] included 150 patients with confirmed COVID-19 and found that people with cardiovascular diseases have a much higher risk of dying from SARS-CoV-2 infection. [83] Secondary infections were seen in 1% (1/82) and 16% (11/68) of the patients in the discharge group and death groups, respectively. According to laboratory results, white blood cell counts, platelets, absolute values of lymphocytes, total bilirubin, albumin, blood creatinine, blood urea nitrogen, cardiac troponin, CRP (C-reactive protein), IL-6 (interleukin-6), myoglobin, and all were significantly different between the two groups. [83] According to reports, SARS-CoV-2 is thought to infect the myocardium and cause myocarditis because of the myocardial infiltration by the interstitial mononuclear inflammatory cells that were found there during the post-mortem biopsy. [45,80] In some instances, acute myocarditis with reduced systolic function is observed post-COVID-19. [80,84,85] Research on cardiac biomarkers suggested that hospitalized COVID-19 patients had a significant probability of cardiac injury. [45,80,86,87] Myocardial injury is probably accompanied by myocarditis and/or ischemia and is a vital predictive aspect of COVID-19. [80] A single-centre observational study by *Shi et al.,* [87] revealed the significance of cardiac injury in 416 admitted COVID-19 patients, of whom 82 (19.7%) died of cardiac injury. Admitted older patients with more underlying comorbidities and high levels of leukocytes are reported to have cardiac injury due to greater hs-cTnI (high sensitive cardiac troponin I). [87] A retrospective single-centre case series by *Guo et al.,* [86] where 187 patients with confirmed COVID-19 were admitted to the hospital; 66 (35.3%) of these patients had preexisting cardiovascular conditions (cardiomyopathy, hypertension, and coronary heart disease), and 52 (27.8%) had myocardial damage, which suggests elevated cTnT (cardiac troponin T) readings. [86]

Diabetes is one of the vital co-factors of morbidity and fatality throughout the world and is accompanied by various microvascular and macrovascular problems that eventually affect the overall patient's survival. [76] The prevalence of diabetes was found to be 35% (mean age, 79.5 years) in an analysis of a randomly chosen

sample of fatal SARS-CoV-2 patients in Italy. [88,89] A comprehensive retrospective study of 1591 SARS-CoV-2 patients admitted in ICUs in Lombardy, Italy, over the course of four weeks revealed an occurrence of T2DM (Type 2 Diabetes Mellitus) of 17%. [88,90] In T2DM, apart from the pro-inflammatory storm of cytokines, a disproportion between coagulation and fibrinolysis occurs, with an inflated proportion of clotting factors and relative fibrinolytic system inhibition. [76] Both T2DM and insulin resistance are accompanied by endothelial malfunction and inflated platelet accumulation and activation, which instigate the progression of a hypercoagulable pro-thrombotic state. [76,91] Older people with COVID-19 are noted to have impaired T-cell and B-cell functions and an inflammatory cytokine storm. Consequently, T2DM by itself or in conjunction with advanced age and other comorbidities may encourage unchecked SARS CoV-2 proliferation, increasing the disease's lethality. [76,92] Since the elderly population is most impacted by COVID-19 and hypertension is particularly widespread in older people, the prevalence of hypertension in these patients is not wholly uncommon. [77,93] Recent studies indicate that a high death rate was detected in COVID-19 individuals who had underlying comorbidities, most notably diabetes, hypertension, and cardiovascular disorders. [76,77,93,94]

COVID-19 and Pathophysiological Aspects of Neurological Complications

Neurological problems are prevalent in COVID-19 patients, especially in hospitalized patients, who exhibit greater rates than in patients with less severe disease. [95,96] Smell and taste problems, intracranial haemorrhage, ischemic stroke, encephalopathy, encephalomyelitis, and neuromuscular illnesses are among the most frequent neurological consequences. [97,98] A variety of factors, such as SARS-CoV-2 neurotropism, endothelial dysfunction, hypercoagulability, hypoxia, systemic illness, and response, may cause the development of neurological manifestation signs. [97]

Neurological problems can result from the SARS-CoV-2 virus's ability to enter the central neuronal system and affect both neurons and glial cells. Various patho-mechanisms give rise to neurological diseases. Findings indicate that the initial mechanism by which SARS-CoV-2 enters host cells is the ACE2 (angiotensin-converting enzyme type 2), which is found on the cell periphery of many tissues. [97,99–104] By adhering to ACE2 in a variety of organs, including as the neurological system, skeletal muscle, and vascular endothelium, SARS-CoV-2 can enter the central neuronal system and impair blood vessels. [97,103,104] Massive intracerebral haemorrhage can emerge from ruptured blood vessels triggered by disruption to the cerebral endothelium and a rise in cerebral blood pressure. [97,103] However, concomitant COVID-19 infection, hypercoagulability, and thromboembolic circumstances may result in an ischemic stroke. [97,105] The brainstem—which comprises the paraventricular nuclei and the nucleus of the solitary tract—is where ACE2 is mostly expressed in the brain and is responsible for cardiac and vascular function. [97,101,102] Additionally, it has been demonstrated that an infection can spread via synaptic connections from peripheral neuronal to the central neuronal system. [106,107] The dissemination of SARS-CoV-2 through the olfactory nerve may be an example of how disease proceeds along a neural route because of the peculiar structure of the olfactory nerve including associated olfactory fibres inside the nasal canal. Through the olfactory nerve and bulb routes, coronaviruses can colonize the nasal passages before entering the brain and cerebrospinal fluid, resulting in an inflammatory and demyelinating reaction. [100,101] Another source of negative consequences is the development of an extremely wide systemic inflammatory response (SIRS), which results in an excess of interleukin (IL-6,12,15) and TNF-α (tumour necrosis factor-alpha). This inflammation triggers glial cell activation and a strong proinflammatory phase in the central nervous system, which in turn causes severe hypoxia, leading to cerebral oedema, cerebral vasodilation, and ischemia. [97,106,107]

The most prevalent neurological side effects are problems related to taste and smell. Anosmia and taste abnormalities were identified as preliminary markers of COVID-19 in one study, affecting more than 80% of patients. [108] Smell dysfunction impacted 48% of patients, according to a meta-analysis of 83 research involving over 27,000 participants (95% CI 41.2–54.5). [109] Anosmia is reported by younger patients more frequently than by older ones. Additionally, women

experience it more frequently than men do. [110] The majority of patients have either significant improvement or overall regression in 2-3 weeks, indicating a typically good prognosis for smell and taste impairments linked to COVID-19. As a result, the prognosis is probably more favorable than it would be for other aetiologies of smell disorders. However, in 10% to 20% of cases, severe and persistent deficiencies persist. [98] Fortunately, most COVID-19 patients experience a natural recovery of their taste and smell problems, indicating that no special management is needed. However, smell training approaches could be helpful as a treatment if smell abnormalities last longer than four weeks. [97,111]

In most cases, patients in critical condition acquire encephalopathy. Delirium associated with encephalopathy is extremely uncommon and may manifest early or even without symptoms. In a cohort investigation involving 2088 COVID-19 individuals admitted to intensive care units, 55% of patients experienced delirium. [112] *Shah et al.,* [113] found that out of 12,601 hospitalized patients, 1092 (8.7%) had acute encephalopathy. [113] In an alternate study, 509 hospitalized COVID-19 patients were found to have encephalopathy in 31.8% of them. [95] It usually has a multifaceted etiology. Older male patients who have previous instances such as neurological ailments, cancer, cerebral vasculitis, diabetes, renal diseases, dyslipidemia, cardiovascular disease, hypertension, or smoking are primarily affected. [95,97] Indications of encephalopathy and encephalitis include neuropsychological issues, agitation, delirium, motor impairments linked to extrapyramidal manifestations, abnormal coordination, seizures, diminished consciousness, and specific neurological impairments. [97,98]

In COVID-19, stroke appears to be slightly less prevalent. [114–117] Among hospitalized patients, the proportions of intracranial haemorrhage were 0.2–0.9%, and the rates of ischemic stroke associated with COVID-19 were 0.4–2.7%. [118,119] Additionally, there are reported cases of cerebral venous thrombosis (CVT) in COVID-19 individuals. [120,121] In a retrospective analysis involving more than 13,000 patients, twelve people with CVT were found within three months, indicating 8.8 cases per 10,000 patients. [122] A comprehensive evaluation of 34,331 hospitalized patients infected with SARS-CoV-2 estimated the prevalence of CVT to be 0.08% (95% CI 0.01–0.5). [123] The majority of the time, a stroke occurs one to three weeks after COVID-19 symptoms initially manifest. [122,124–126]

In both the moderate and severe COVID-19 variations, myalgia is frequently experienced. [97] It has been reported in 22–63% of patients, [98] and in more extreme instances (19 vs. 5%), it is accompanied by elevated creatinine kinase (CK) levels; myopathy, or muscle injury, is also suspected. [110] A rare and infrequent repercussion of COVID-19 is severe rhabdomyolysis. [127] In 0.2% of patients, it was noticed, and in 13.7% of cases, elevated CK levels were found. Within five to seven days of the SARS-CoV-2 infection-induced fever, three Italian patients experienced prevalent myasthenia including positive acetylcholine receptor antibodies. [128] While it is hypothesized that myasthenia may be caused by the immune system's reaction to SARS-CoV-2, another possibility is that the infection just catalysis the onset of symptoms in individuals who already have myasthenia. Amyotrophic lateral sclerosis (ALS) cases have also been shown to involve an exacerbation of a pre-existing neuromuscular condition. It indicates that people with neuromuscular disorders do not have a significantly higher risk of contracting SARS-CoV-2 disease. [98] Peripheral nerve abnormalities, inflammatory/autoimmune muscle disorders, and neuromuscular junction issues should all be managed according to the current guidelines. Immunoglobulin therapy and plasmapheresis are advised. It is recommended to postpone the use of rituximab or long-term oral immunosuppressive medicine in accordance with the patient's clinical status and medical background. [97,98]

About 0.4% of COVID-19 patients experience Guillain-Barré syndrome (GBS), which usually appears five to ten days after the viral infection. [129] It implies that GBS is a parainfectious condition based on the appearance of the initial COVID-19 manifestations. [130] It has been observed in specific studies that the symptoms are more intense and might manifest prematurely than those reported in conventional GBS. [131] In one study, mechanical ventilation was necessary for three out of five patients. [131] In a span of one month, three hospitals in Italy's northern region admitted almost

1200 individuals with COVID-19, but only five cases of GBS were found. [129] Within one to four days, the majority of COVID-19 and GBS patients manifest progressive limb weakness. [132] For GBS management in COVID-19, lacks particular recommendations. Patients should receive the same treatment as other individuals with GBS. [97]

Therapeutic Options for the Treatment of COVID-19

Since the pandemic outbreak, COVID-19 treatment has shifted rapidly, and it currently consists mainly of antiviral and immunomodulatory medications. Remdesivir and nirmatrelvir-ritonavir are two varieties of antivirals that have been reported to be most effective when used early in an illness (like outpatient treatment) and in cases of less acute illness. Janus kinase inhibitors Interleukin-6, and Dexamethasone, are examples of immunomodulatory therapies that work best when used in cases of extreme illness or critical condition. Due to the appearance of viral variations that are not expected to respond to these treatments, the significance of anti-SARS-CoV-2 monoclonal antibodies has decreased, and opinions regarding the use of convalescent plasma are still divided. The following sections cover the wide spectrum of available treatments, categorized by the classification of agent: antiviral medications, immunomodulators, neutralizing antibodies and convalescent plasma, and antithrombotic treatment. Patients undergoing various treatments have been explored with varying degrees of disease severity: mild to adequate COVID-19 in non-hospitalized patients; serious COVID-19 in hospitalized patients who need additional oxygen; and severe conditions in patients who need non-invasive or mechanical ventilation. [19] The discussion mostly centres on randomized trials, which have contributed significantly to the current treatment paradigms. Every therapeutic section ends with a reference to the National Institutes of Health (NIH) COVID-19 Treatment Guidelines, which offer insight into the recommended usage of each therapy (Table 3). [19,133]

Primary Antiviral Agents utilized in the Management of COVID-19

Individuals with mild COVID-19 disease typically exhibit indications including myalgia, a high temperature, cough, and sore throat; on the other hand, patients with moderate disease show signs of lower respiratory tract involvement on radiographic or clinical examinations while still maintaining an oxygen saturation level of at least 94%. [134,135] The majority of these individuals can be safely treated in outpatient settings, such as emergency rooms, clinics, and telemedicine consultations. [136,137] One of the first medications to show efficacy in a randomized controlled trial (RCT) during the early phases of the global outbreak was Remdesivir, a drug that inhibits viral RNA-dependent RNA polymerase. [19] The effectiveness of two oral anti-SARS-CoV-2 antiviral medications, molnupiravir and nirmatrelvir-ritonavir, provided to outpatients was assessed in two seminal phase 3 randomised trials, the EPIC-HR and MOVe-OUT trials. Molnupiravir and nirmatrelvir-ritonavir decreased hospitalization or mortality by 30 and 89%, respectively, when administered to unvaccinated people with COVID-19 disease (mild to adequate) within five days of apparition of symptoms and who were at risk of disease development. [138,139] Hospitalization for symptomatic COVID-19 disease or non-COVID-related reasons may also be necessary for patients with mild-to- adequate illness. Compared to patients treated as outpatients, these patients had a higher chance of developing a severe clinical manifestation and a faster rate of disease development. [135] The clinical efficacy of molnupiravir and nirmatrelvir-ritonavir in patients hospitalized having mild-to-moderate COVID-19 disease was evaluate in three real-world studies conducted in Hong Kong and Japan. The majority of the patients involved in the research were older than sixty years, and their recommended immunization rates ranged from 10 to 80%. [140–142] In comparison to controls that were matched, molnupiravir and nirmatrelvir-ritonavir were consistently linked to a 40–55% decreased risk of clinical deterioration. Additionally, it was found that nirmatrelvir-ritonavir and molnupiravir were linked to 66–90% and 52–69% decreased risk of death, respectively. [140–142] An overview of the primary antiviral medications used to treat COVID-19 is discussed in (Table 3).

Primary Immunomodulatory Agents utilized in the Management of COVID-19

Severe and serious COVID-19 disease is treated with immunomodulatory substances, which include Janus kinase inhibitors (like baricitinib), interleukin-6 inhibitors (like tocilizumab), and

corticosteroids. [135,143] Corticosteroids were the first medications to improve survival in the treatment of COVID-19. [144] It is advised to add interleukin-6 or Janus kinase inhibitors to corticosteroids in individuals whose condition progresses quickly and they show signs of systemic inflammation, such as increasing C-reaction protein. In summary, current research supports the application of remdesivir for the whole range of pulmonary assistance in hospitalized patients with serious and potentially fatal illnesses. Patients using low-flow supplemental oxygen should have their use of oral antivirals carefully assessed. In their clinical care, corticosteroids and other immunomodulatory therapies are indispensable. [135] The primary immunomodulatory medications used to treat COVID-19 are summarized in (Table 3).

Neutralizing Antibodies and Convalescent Plasma Therapy

During the early stages of the global outbreak, antibody therapy proved to be a powerful treatment and prevention strategy for COVID-19. Convalescent plasma (CP) from recovered COVID-19 sufferers and monoclonal antibodies (mAbs) that aimed the S1 region of the SARS-CoV-2 spike protein were the two types of antibody products used. Pre-exposure prophylactic for immunocompromised individuals with the anti-SARS-CoV-2 monoclonal antibodies tixagevimab and cilgavimab (Evusheld™) was authorized by the FDA. Many anti-SARS-CoV-2 treatments with monoclonal antibodies were approved, encompassing bamlanivimab plus etesevimab, bebtelovimab, sotrovimab, and casirivimab plus imdevimab. As the prevalence of various variants of concern (VOCs) increased, the pseudo-viral and in vitro viral neutralization activities of the monoclonal antibodies were utilized to forecast medical efficacy. In 2020, VOCs dominated the strains; however, numerous mAbs continued to have a neutralizing effect against B.1.1.7 (Alpha). [19] But only bebtelovimab and sotrovimab retained relevance after Omicron (B.1.1.529) was fixed at the end of 2021, and not any of the approved mAbs sustained cross-neutralizing activity after Omicron subvariants continued to evolve in 2022. [145] Consequently, the anti-SARS-CoV-2 monoclonal antibodies (mAbs) are not anymore used for pre-exposure prophylaxis, prophylaxis, or for the COVID-19 treatment. [19,133]

Antithrombotic Therapy

In the initial pandemic phase, hospitalized COVID-19 suffers experienced a higher prevalence of venous thromboembolism (VTE) episodes, which were most likely attributed to thromboinflammation. [146] It is difficult to establish the precise rate when compared to historical controls, although it has been estimated to be as high as three times the adult hospitalization baseline rate. [147] The effectiveness of empiric anticoagulation and VTE prophylaxis has been assessed in numerous trials in addressing the elevated load of VTE (venous thromboembolism). The OVID and ETHIC randomized controlled trials (RCTs) examined individuals who were not hospitalized and contrasted enoxaparin or the conventional treatment. None of the two trials demonstrated effectiveness in lowering hospitalization or mortality, and both terminated prematurely. [148,149] Unless there is a contraindication, prophylactic-dose heparin is advised for anticoagulation in hospitalized patients. Relying on the outcomes of randomized controlled trials assessing the application of anticoagulant therapy in non-critically condition and severely diseased hospitalized patients, the NIH (National Institutes of Health) COVID-19 Treatment Guidelines suggested therapeutic-dose heparin for adults who need traditional oxygen but not critical care, but only in cases where the D-dimer concentration is raised and there aren't any circumstances which boost the likelihood of blood loss. Moreover, prophylactic-dose heparin should be administered to individuals needing intensive care or high-flow oxygen rather than therapeutic-dose heparin (except when there are restrictions, such as confirmed thromboembolic disease). [19,133,150,151]

Vaccines Available for the Prevention of COVID-19

The development of treatment options and preventative vaccinations against SARS-CoV-2 has garnered international attention since the pandemic's onset and the disease's effects. Prophylactic vaccinations were intended to produce protective immunity in opposition to SARS-CoV-2, whereas the treatment goals were whereas the treatment goals were centred around measures that might reduce hospitalization time and improve the survival rate of infected patients. The development of effective preventive

vaccinations in opposition to SARS-CoV-2 was crucial because of the urgent global outbreak situation and its related repercussions, including limited hospital capacity and ventilators. [166–168] The process of developing vaccines is lengthy and intricate, and it might take years or even decades to generate a vaccine that proves effective. On the other hand, the COVID-19 vaccine development effort took a year and was an international triumph. [169,170] Developing a COVID-19 vaccine within the allotted 12-to 24-month timeframe posed an immense challenge for the researchers. [170,171] A number of factors contributed to the immediate development of the COVID-19 vaccine, including the timely release of the viral genome sequence, technological advancements and innovation, active participation from the international scientific community, a strong regulatory framework, sufficient government funding, and high market demand. Researchers from all around the world reported outstanding progress in the development of vaccines by the beginning of December 2020. On December 2, 2020, a vaccine developed by Pfizer in partnership with BioNTech, a German biotech company became the first completely tested vaccine to be authorized for use in an emergency. [170] Global vaccination campaigns have primarily employed five types of COVID-19 vaccines: protein subunit, replicating and non-replicating viral vector, nucleic acid (DNA and RNA), inactivated complete virus, and virus-like particles (VLPs) vaccines. In (Table 4), the most recent COVID-19 vaccines updates are presented with adverse effects as well as their efficacy and coverage versus various SARS-Cov-2 variants. [166,167,170]

CONCLUSION

Five years have passed since Wuhan, China, reported the initial COVID-19 occurrences. Worldwide, more than 775 million people have been infected with SARS-CoV-2, while more than 7 million of those cases have led to COVID-19 infection-related deaths. Every aspect of the socioeconomic framework has been significantly impacted by the COVID-19 outbreak, but it has especially highlighted inadequacies in the healthcare system. It demonstrated the futile struggle the world was in against the biggest threat of the twenty-first century. Infection with COVID-19 has been associated with complications in several organs, including cardiovascular, respiratory, the renal system, and gastrointestinal tract, haematological, cognitive, and dermatological issues. The comorbidities have a strong relationship with the mortality rate of COVID-19 patients. Acute instances and higher death rates are linked to COVID-19 individuals, and they are more common in people over 70 who also have underlying comorbidities. Individuals with cardiovascular illnesses had a threefold greater risk of developing an acute illness or requiring an intensive care unit (ICU) admission, compared to patients with hypertension or diabetes mellitus. Additionally, SARS-CoV-2 is recognized to have exceptional neurotropic potential. Numerous neurotoxins that cause neurological symptoms are released during the cytokine storm, which affects both the lungs and the central nervous system. In an effort to control COVID-19-related death rates and pathologies during these difficult years, a number of treatment alternatives and preventative measures, such as the COVID-19 vaccine, were considered. Since the pandemic began, there has been a tremendous evolution in the field of scientific study on COVID-19 disease treatment. Even those who have received the SARS-CoV-2 vaccination are susceptible of contracting a mild-to-moderate illness; nevertheless, effective antiviral therapy is currently available for early administration. The frequent emergence of variations resistant to existing products limits the usage of monoclonal antibodies. The management of severe and critical diseases requires the combination of immunomodulatory therapy and antiviral therapy. It is anticipated that future developments may benefit difficult-to-treat populations that are immunocompromised or have coexisting comorbidity conditions that limit the use of currently available choices. These patients may need individualized care in terms of the selection, combination, and duration of antiviral medications.

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