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Covid-19 A Comprehensive Review of Signs, Symptoms, Diagnosis, and Treatment Strategies

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Abstract: *The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly impacted global health. This review aims to provide a comprehensive overview of the signs, symptoms, diagnosis, and treatment modalities of COVID-19. The clinical presentation of COVID-19 varies widely, ranging from asymptomatic or mild symptoms to severe respiratory distress and multiorgan failure. Common symptoms include fever, cough, fatigue, and dyspnea, with less frequent symptoms such as anosmia, ageusia, and gastrointestinal symptoms. Diagnosis primarily relies on reverse transcription-polymerase chain reaction (RT-PCR) testing of respiratory specimens. However, imaging modalities such as chest X-ray and Antibody Test Antigen test in diagnosis, especially in cases with atypical presentations. Treatment strategies include supportive care, antiviral therapy, and, in severe cases, and other intensive care measures. The development and distribution of vaccines have been pivotal in controlling the spread of the virus. Despite significant progress in understanding and managing COVID-19, ongoing research is crucial to refine diagnostic strategies, develop effective therapies, and improve patient outcomes. Antiviral drugs, such as remdesivir, poxolovid, molonupiravir, have been widely used to inhibit viral replication and reduce the severity and duration of symptoms. Immunomodulators, including tocilizumab have been used to target specific pathways involved in the hyperinflammatory response seen in severe COVID-19. Monoclonal antibodies, such as casirivimab/imdevimab and sotrovimab, have been employed for passive immunization to neutralize the virus and reduce the risk of severe disease progression*

Keywords: Covid-19, Sign& Symptoms, Diagnosis, Treatment

I. INTRODUCTION

History of Covid-19

In 1965, scientists discovered the first human coronavirus, called B814, in a person with a common cold. They found another virus, 229E, around the same time. These viruses were named coronaviruses because of their crown-like appearance. Over the years, researchers mainly studied two strains, OC43 and 229E, due to their ease of study. These viruses caused seasonal outbreaks, mostly in winter and spring, contributing to about 35% of respiratory viral infections during epidemics. Despite the focus on OC43 and 229E, other strains existed. Coronaviruses usually caused mild respiratory illnesses, with occasional pneumonia in young individuals. They could also worsen asthma in children and lead to chronic bronchitis in adults and the elderly.

Research on coronaviruses continued for decades, mainly focusing on strains OC43 and 229E because they were easier to study. These viruses caused seasonal outbreaks, primarily in winter and spring, contributing to around 35% of respiratory viral infections during epidemics. Despite the attention given to OC43 and 229E, other strains also existed. Coronaviruses typically caused mild respiratory illnesses, occasionally leading to pneumonia in young individuals. They could also exacerbate asthma in children and cause chronic bronchitis in adults and the elderly. However, their overall pathogenicity was considered low. (21)

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1. Early Outbreak in Wuhan, China (December 2019 - January 2020): The first cases of a mysterious pneumonia-like illness were reported in Wuhan, Hubei Province, China, in December 2019. The virus was later identified as a novel coronavirus, named SARS-CoV-2, and the disease it caused was termed COVID-19.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7153464/)
2. Identification and Global Spread (January - February 2020): The virus quickly spread to other parts of China and beyond, aided by global travel. On January 30, 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC). By February, cases had been reported in multiple countries, leading to concerns about a global pandemic. https://www.pnas.org/doi/10.1073/pnas.2009637117)
3. Pandemic Declaration and Lockdowns (March - May 2020): On March 11, 2020, the WHO declared COVID-19 a pandemic, highlighting its global reach and impact. Countries around the world implemented various measures, including lockdowns, travel restrictions, and social distancing, to slow the spread of the virus and prevent healthcare systems from becoming overwhelmed. https://www.pnas.org/doi/10.1073/pnas.2009637117)
4. Healthcare Challenges and Research Efforts (June - December 2020): The pandemic posed significant challenges to healthcare systems, with shortages of personal protective equipment (PPE), ventilators, and hospital beds reported in many places. Meanwhile, researchers raced to understand the virus, develop diagnostic tests, and explore potential treatments and vaccines. .https://www.niti.gov.in/sites/default/files/202302/InvestmentOpportunities_HealthcareSector.pdf)
5. Vaccine Development and Rollout (2020 - 2021): Several vaccines against COVID-19 were developed at an unprecedented pace, thanks to advances in vaccine technology and global collaboration. Emergency use authorizations were granted, and mass vaccination campaigns began in late 2020 and early 2021, offering hope for controlling the pandemic. https://www.ajmc.com/view/a-timeline-of-covid-19-vaccine-developments-in-2021)
6. Variants and Ongoing Challenges (2021 - 2022): The emergence of new variants of the virus raised concerns about their impact on vaccine effectiveness and transmissibility. Governments and health authorities continued to navigate the challenges of vaccination distribution, public health messaging, and balancing economic recovery with public health measures. https://www.annualreviews.org/doi/10.1146/annurev-med-042921-020956)
7Endemic Transition (2022 - Present): As of 2022, COVID-19 has transitioned to an endemic phase, meaning it continues to circulate in populations, but at lower levels compared to the peak of the pandemic. Efforts are focused on maintaining vaccination rates, monitoring for new variants, and managing outbreaks as they occur. https://humgenomics.biomedcentral.com/articles/10.1186/s40246-022-00392-1)

Information:

The emergence of the COVID-19 pandemic in December 2019 marked a pivotal moment in global health history. Originating in Wuhan, China, the virus quickly spread, alarming health authorities worldwide. The initial cases were linked to the Huanan wholesale seafood market, suggesting zoonotic transmission from animals to humans. China promptly activated its surveillance system, reminiscent of measures implemented during the SARS outbreak, and notified the World Health Organization (WHO) on December 31st, 2019.

By January 7th, 2020, the novel coronavirus was identified, sharing genetic similarities with bat coronaviruses and SARS-CoV. The closure of the Huanan seafood market followed on January 1st, but the virus had already begun its rapid dissemination. Human-to-human transmission was confirmed, with cases escalating exponentially, fueled by the Lunar New Year migration.

As the virus spread beyond China's borders, cases were reported in Thailand, Japan, South Korea, and subsequently in other countries. The first fatality occurred on January 11th, 2020, and healthcare workers became increasingly vulnerable to infection, highlighting the urgent need for protective measures.

Wuhan, with its 11 million inhabitants, was placed under lockdown on January 23rd, 2020, followed by stringent measures in other cities of Hubei province. The global response intensified, with airports worldwide implementing screening protocols for travelers from affected regions.

The evolving understanding of COVID-19 included the realization that asymptomatic individuals could transmit the virus, amplifying the challenges of containment. Countries like India, evacuating citizens from Wuhan and monitoring

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returning travelers, instituted strict isolation and testing protocols, recognizing the importance of early detection and prevention.

As the pandemic unfolded, collaborative efforts in research, public health interventions, and vaccine development became paramount. The COVID-19 crisis underscored the interconnectedness of nations and the critical role of international cooperation in addressing global health emergencies.

The number of COVID-19 cases has been rapidly increasing, especially outside of China. China even changed its definition of confirmed cases, causing a huge spike in reported cases. By March 5, 2020, there were 96,000 cases worldwide, with China having the most. Other countries like South Korea, Italy, and Iran have seen a sharp rise in cases too. About 20% of those infected are in critical condition, while 25% have recovered. Sadly, 3,310 people have died. India, which initially had few cases, has also seen a rise, with 29 cases reported by March 5. Many of these cases are linked to travelers or their contacts. Efforts like quarantine are being used to control the spread.

The situation with COVID-19 is serious. Cases are increasing rapidly, especially outside China. Even though China changed how it counts cases, the number worldwide keeps going up. Countries like SouthKorea, Italy, and Iran are struggling too. About 20% of people with the virus are in critical condition, and sadly, many have died. India, which didn't have many cases at first, now has more, mostly linked to travelers. Efforts like quarantines are being used to try to stop the virus from spreading further.(27)

Virology:

SARS-CoV-2 is a member of the Coronaviridae family, which also includes the viruses responsible for SARS and Middle East Respiratory Syndrome (MERS). It is an enveloped, single-stranded RNA virus with a genome size of approximately 30 kilobases. The virus primarily targets cells in the respiratory tract, using its spike (S) protein to bind to the angiotensin-converting enzyme 2 (ACE2) receptor, which facilitates viral entry into host cells.

Epidemiology:

COVID-19 spread rapidly across the globe, with the World Health Organization (WHO) declaring it a pandemic on March 11, 2020. The virus is primarily transmitted through respiratory droplets produced when an infected person coughs, sneezes, or talks. It can also spread by touching surfaces contaminated with the virus and then touching the face.

Clinical Manifestations:

COVID-19 can cause a wide range of symptoms, ranging from mild to severe, and can lead to pneumonia, acute respiratory distress syndrome (ARDS), and death, particularly in older adults and those with underlying health conditions. Common symptoms include fever, cough, shortness of breath, fatigue, muscle aches, and loss of taste or smell. Some individuals may remain asymptomatic but can still spread the virus to others.

Type of covid-19

1. Alpha (B.1.1.7): This variant was first identified in the United Kingdom and has since spread to many other countries. It is associated with increased transmissibility.
2. Beta (B.1.351): First identified in South Africa, this variant has mutations that may affect the efficacy of some vaccines.
3. Gamma (P.1): This variant was first identified in Brazil and has been associated with reinfections.
4. Delta (B.1.617.2): First identified in India, the Delta variant is highly transmissible and has become the dominant variant in many countries.
5. Omicron (B.1.1.529): This variant was first identified in Botswana and has a large number of mutations, raising concerns about its transmissibility and the potential for immune evasi.(8)

Mutation

1. Alpha (B.1.1.7): The Alpha variant (B.1.1.7) of the coronavirus, originally identified in the UK, has several mutations, including N501Y, P681H, and several others in the spike protein. These mutations are associated with

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increased transmissibility, but current vaccines remain effective against it, especially in preventing severe illness and death.

Beta (B.1.351):The Beta variant (B.1.351) of the coronavirus, first identified in South Africa, has mutations including E484K and N501Y in the spike protein. These mutations are concerning because they may impact the effectiveness of certain antibodies, including those generated by previous infection or vaccination. However, vaccines still provide a significant level of protection against severe disease caused by this variant. Ongoing research and surveillance are essential to understand the implications of these mutations on the effectiveness of vaccines and treatments

Gamma (P.1): The Gamma variant (P.1) of the coronavirus, initially identified in Brazil, has several mutations, including E484K, N501Y, and K417T, in the spike protein. These mutations are associated with increased transmissibility and potential immune escape, which means they could potentially reduce the effectiveness of vaccines and treatments. However, current vaccines are still largely effective against severe disease caused by this variant. Monitoring and research continue to be important to understand the impact of these mutations on the virus's behavior and the effectiveness of countermeasures.

Delta (B.1.617.2): The Delta variant (B.1.617.2) of the coronavirus has several mutations, including L452R and P681R, in the spike protein. It is known for its increased transmissibility compared to earlier variants and has become dominant in many countries. Vaccines have shown to be effective against severe disease caused by the Delta variant, although breakthrough infections can still occur. Ongoing research and surveillance are essential to understand the full impact of this variant and to inform public health responses.

Omicron (B.1.1.529): The Omicron variant (B.1.1.529) of the coronavirus has a large number of mutations, particularly in the spike protein. Some key mutations include N501Y, E484A, and K417N, among others. This variant has raised concerns due to its potential for increased transmissibility and immune evasion, which could affect the effectiveness of vaccines and treatments. However, more research is needed to fully understand the impact of these mutations on the virus's behavior and the effectiveness of countermeasures.(1)

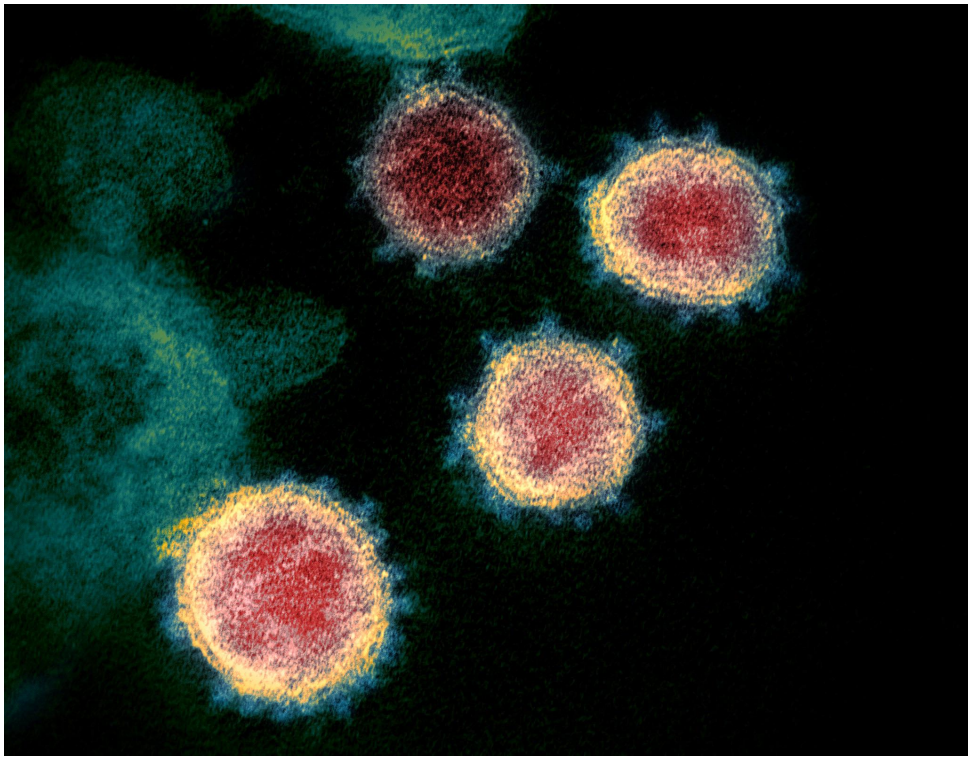

Fig Of Covid-19

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Transmission electron microscope image shows SARS-CoV-2, the virus that causes COVID-19, isolated from a patient in the U.S. Virus particles are emerging from the surface of cells cultured in the lab. The spikes on the outer edge of the virus particles give coronaviruses their name,

Table:Sign and Symptom

The Prevalence Of different symptom among COVID-19 patients according to age group

Symptom	Number Of Studies	Sample size	Pooled Estimated			I2 (%)	P	T2
			<40 Years Of old	>40 Years Of old	Total			
Chest tightness	14	1,967	8.1 (3.7-12.6)	20.1 (9.6-30.6)	17 (13.1-25.4)	96.8	< 0.001	0.01
cough	54	6,380	53.5 (44.3-62.7)	61.2 (56.3-66.1)	58.5 (54.2-62.8)	91.7	< 0.001	0.02
Diarrhea	36	4,995	3.5 (2.1-4.9)	8.6 (6.5-10.6)	7.6 (5.9-9.2)	83.9	< 0.001	0.001
Dyspnea	27	3,388	8.8 (2.6-15)	31.4 (24-38.7)	26.1 (20.04-31.8)	97.4	< 0.001	0.02
Fatigue	22	3,803	30.5 (21.9-39.1)	38.6 (29.9-47.2)	38.5 (30.6-45.3)	95.5	< 0.001	0.02
Fever	53	5,298	78.1 (73.3-82.8)	83 (79.1-86.9)	81.2 (77.9-84.4)	92.6	< 0.001	0.01
Hemoptysis	9	1,998	1.9 (0-4.6)	1.8 (0.008-2.9)	1.7 (0.008-2.6)	46.9	< 0.001	0.05
Headache	34	5,129	9.2 (5.4-13.1)	9.5 (7.1-12.0)	9.5 (7.5-11.6)	88.7	< 0.001	0.002
Myalgia	37	4,676	19 (14-23.9)	19.4 (14.9-24.0)	20.1 (16.5-23.7)	91.5	< 0.001	0.009
Shortness Of breath	13	1,828	17.3 (3.6-30.1)	19.3 (11.2-27.5)	18.5 (12-24.9)	93.3	< 0.001	0.01
Sore thorat	29	3,906	15 (9.6-20.4)	14.5 (10.9-18.2)	15 (12.1-18.0)	86	< 0.001	0.004
Sputum production	28	3,677	21 (15.4-26.7)	28 (22-34.1)	25.8 (21.1-30.4)	91	< 0.001	0.01

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Diagnosis Test

1) PCR Test (Polymerase Chain Reaction)

The RT-PCR test is commonly used to detect viruses like SARS-CoV-2, but it sometimes gives incorrect results. This can happen because the test isn't always very good at being specific or sensitive. For example, it might miss detecting the virus, especially if the patient doesn't have a lot of it in their body or if the sample isn't taken correctly.To make the test better, scientists are proposing a method called multiplex PCR. This method targets multiple parts of the virus's genetic material at once, increasing the chance of detecting it, especially in patients with low levels of the virus. They also add a human gene to make sure the sample was collected properly.The SARS-CoV-2 virus has different parts in its genetic material, like spike protein, envelope protein, matrix protein, and nucleocapsid protein. Some parts of the virus help it infect cells.RT-PCR tests focus on specific parts of the virus's genetic material, like the RdRP gene, which is found a lot in the virus. Tests targeting the RdRP gene are usually the most sensitive.To improve accuracy, scientists also include a human gene called RNase P as a control in the test. This helps ensure the test is working properly.It's important to compare different tests to see which ones work best and to make sure they're reliable and sensitive enough. This involves careful design of the test and choosing the right genes to target.The new multiplex RT-PCR test can detect SARS-CoV-2, including its latest variants, and has been tested using samples from patients known to have the virus. This test targets specific genes of the virus and uses optimized conditions for accurate results. It can simultaneously detect viral N, RdRP, and human RP genes in the same reaction, improving efficiency

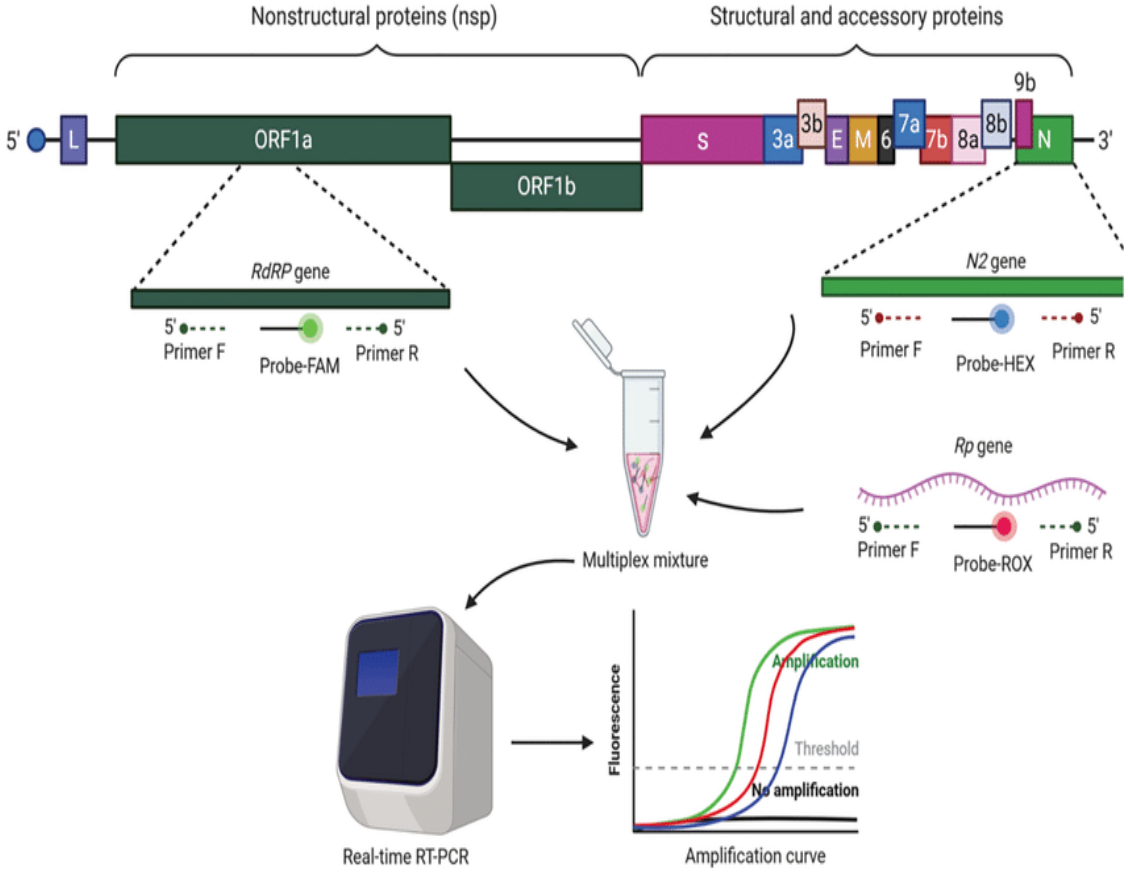

Figure 1. Genome structure of SARS-CoV-2 and the targeted genes in multiplex rRT-PCR assay

Diagnostic Performance.

To check how well the new test (mCoV-2) works, we compared it to two other tests using samples from COVID-19 patients. We used the same RNA samples from 28 patients for all tests. The tests we used are called GeneFinder

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COVID-19 Plus RealAmp Kit and RealStar SARS-CoV-2 RT-PCR Kit 1.0. This helps us see if our new test is as good as or better than the ones already available

Data analysis. scientists looked at graphs called amplification curves for both viral and human genes to check the results. They used software called ABI 7500 (version 2.3) to help with this. After the software automatically adjusted a line called the cycle threshold (Ct or Cq) line, scientists determined a representative Ct value for each gene. They set a cutoff value for positivity at a Ct number of 37 or lower, where the curve showed a specific pattern called sigmoidal. If a patient's results met this criteria, meaning their Ct value was 37 or lower and their curve looked a certain way, they were considered positive for the virus.

Ethical Approval "The study got permission from the Institutional Review Board (IRB) at Imam Abdulrahman bin Faisal University (IAU) with the number IRB-2020-13-406. We followed all the rules and guidelines. We used leftover samples from tests that were made anonymous, so we didn't need to ask for permission from people."

II. RESULTS

Standardization of the multiplex rRT PCR. Researchers developed a test to detect COVID-19 using a method called multiplex rRT-PCR. This test looks for specific parts of the virus and a human gene to make sure it's working correctly. They tested it on samples from people known to have COVID-19 and those who don't.When the test was used on COVID-19 positive samples, it showed clear signals for the virus and the human gene. But in COVID-19 negative samples, only the human gene showed up.They also tested the accuracy of the test by diluting the virus samples several times and running the test again. Even when the virus was diluted a lot, the test still worked well.

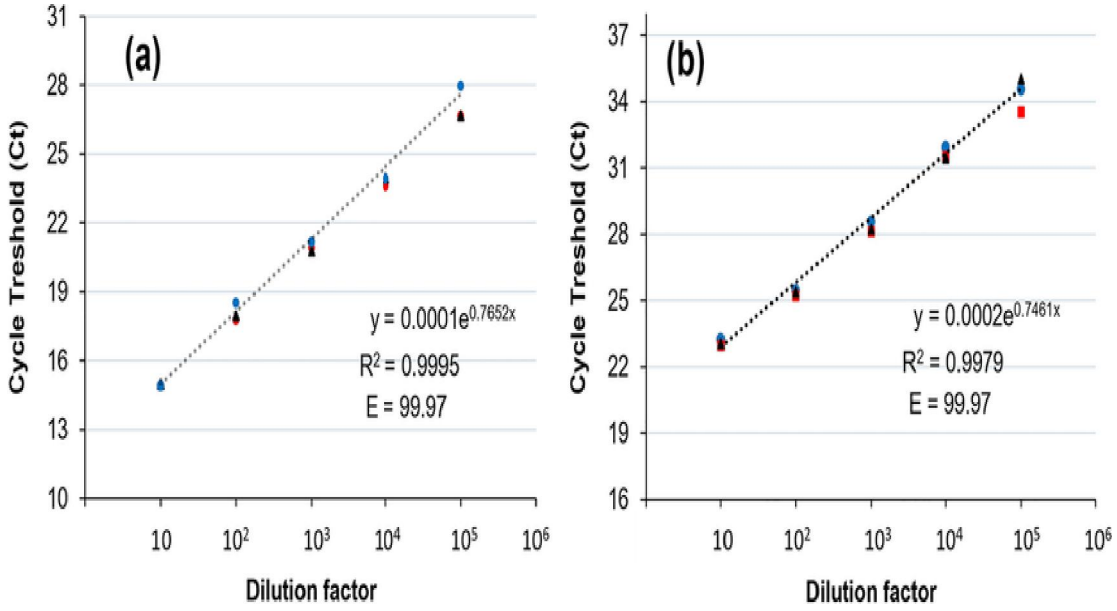

Figure 2. Standard curve analysis for multiplex rRT-PCR of (a) RdRP and (b) N primers. Te template RNA was serially diluted with a range of 105 to 101 . Te reactions were carried out in triplicate. Te amplification efficiencies (E) were shown on each graph. Te error bars represent the standard deviation between the replicates. Te error bars represent the standard deviation between the replicates. Te amplification plots are shown in Supplementary Fig. S2.

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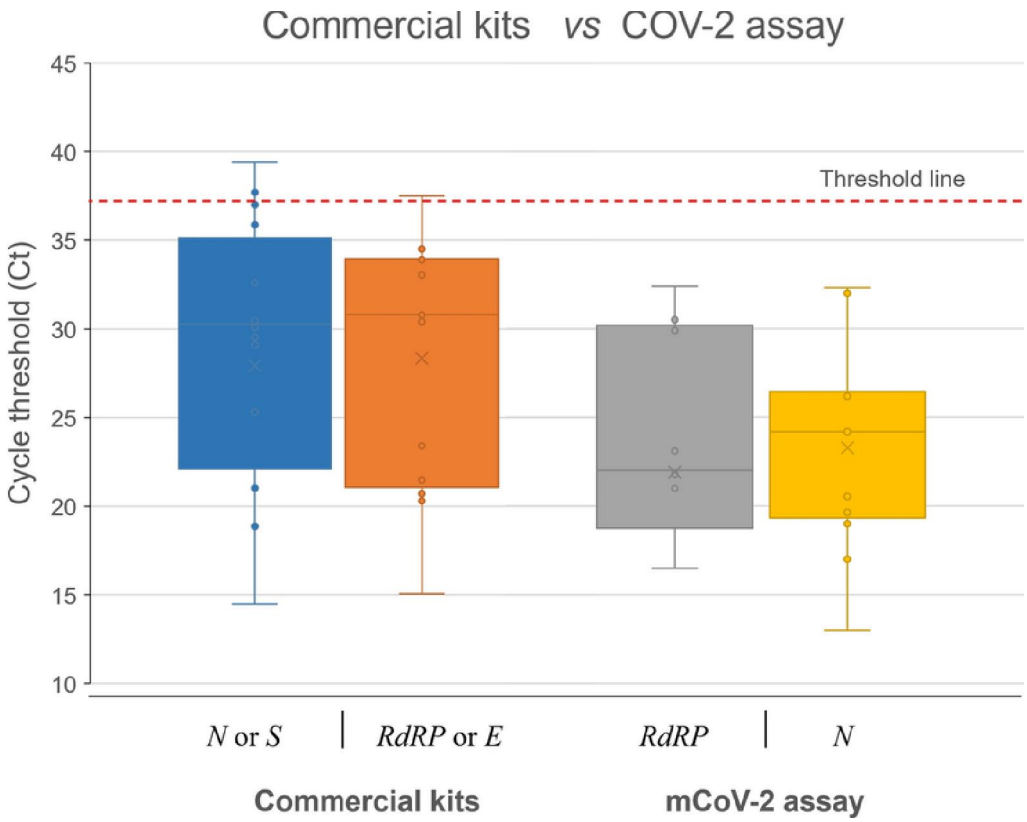

Figure 3. Te cycle threshold (Ct) scores of the same clinical samples tested either the current mCoV-2 assay or commercial kits. Each bar represents different genes, which are RdRP (gray) and N (yellow) for mCoV-2 assay; and N or S (blue) and RdRP or E (orange) for commercial kits. Dashed line shows the positivity cut-of level equals to Ct 37.

Validation of the assay. The confirmation of the results has been performed by using two different Commercially available accoutrements (Gene Finder COVID- 19 Plus Real Amp Kit(Gene Finder, Korea) and Real Star SARS CoV- 2 RT- PCR tackle1.0(Altona, Germany)) that are targeting different genes similar as RdRP, N, S, and E. Among 28 clinically ‘ confirmed ’ SARS- CoV- 2 positive samples, the current assay set up 25 cons and three negatives (Supplementary Table S1). Consequently, the Ct value equals and lower than 37 is accepted as positive. either, in both assays, the Ct score of those negative samples was advanced than 37, which is out of the CDC and WHO recommendations 38,39. Therefore, the samples having a Ct score of ≥37.01 are accepted as SARS- CoV- 2 negative. In this case, the assay displayed 100 positive percent agreement with those marketable assays. Te distribution of Ct value attained from both marketable styles and this mCoV- 2 assay are displayed inFig. 3. Since these accoutrements target different genes, the Ct scores of those genes were combined. Consequently, it's egregious that the average Ct value of the current assay is lower than those of the genes targeted in the relative marketable accoutrements . Tis affect demonstrates the high perceptivity of the current assay.(19)

2) Antigen test

Test performance-: The performance of an Ag- RDT is determined by the perceptivity and particularity of the test to descry a SARS CoV- 2 infection compared with a reference standard, NAAT(generally rRT- PCR). perceptivity is the chance of cases positive by a NAAT reference standard that are detected as positive by the Ag- RDT under evaluation. particularity is the chance of cases negative by a NAAT reference standard that are detected as negative by the Ag- RDT under evaluation. The frequence of complaint in the community being tested explosively affects the prophetic value of a positive or negative result(see Addition 1). therefore, the clinical value of a positive or negative test result will depend on what action is taken on the base of the test result when interpreted in the environment of original

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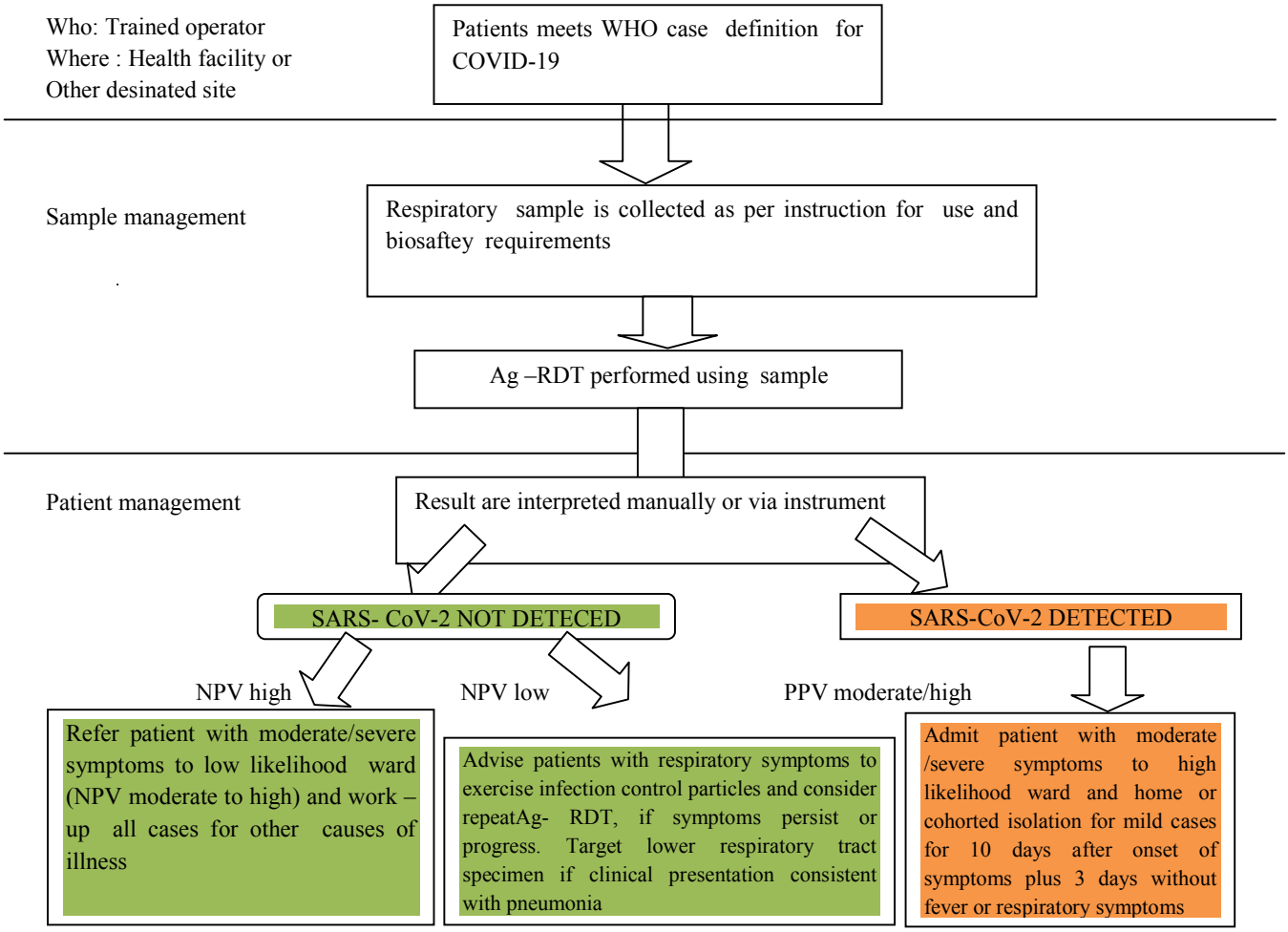
frequence. In general, the advanced the frequence of SARS- COv- 2 infection in the tested population, the more likely a person who tests positive is to have COVID- 19. The lower the frequence in the community, the more likely a test-negative patient is not to have the disease, see Annex 1. For example, when the prevalence of active SARS-CoV-2 infection in a community is 1%, even a test that is 99% specific would have a poor positive predictive value, since one-half of all positive results would be false positive

Role for antigen detecting RDTs for case operation and surveillance for COVID- 19-: Use of Ag- RDTs can be considered in countries or areas that are passing wide community transmission, where the health system may be over burdened and where it may not be possible to test all or any suspect cases by NAAT. As with all individual tests, but especially those with sub-optimal perceptivity and/ or particularity, to rightly interpret and act on the results of the RDT, the frequence of complaint(according to the reference standard) must be estimated grounded on surveillance, since this determines the positive and negative prophetic values(PPV and NPV, independently) of the RDTs(Addition 1). The proposed process for exercising an Ag- RDT for COVID- 19 case operation when there's wide community transmission is shown in Figure 1. In such a setting, the pre-test probability of COVID- 19 complaint(the liability that the case has COVID- 19 before their results are known, grounded on epidemiologic and clinical factors) is fairly high, and positive test results have a high prophetic value. Likewise, in a setting of community transmission, the prophetic value of a negative RDT result may be low, indeed when there are strong epidemiologic or clinical pointers of COVID-19 exposure or complaint.



NPV- negative predictive value; PPV – positive predictive value

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Factors Influcing test performance-: As mentioned over, numerous factors may affect the performance of Antigen-Detecting RDTs. Accordingly, findings in clinical settings may be variable. The following should be taken into account • patient factors similar as the time from illness onset and vulnerable status • sample type(upper or lower respiratory tract), quality and processing, including storehouse conditions and dilution in viral transport medium • viral factors including the attention and duration of viral antigen slipping and structural variation in the target antigen, cross reactivity with other contagions • specific protein target, as some antigens are produced in advanced attention than others, e.g. nucleocapsid versus shaft proteins • product design or quality issues including - inadequate antibody volume or affinity for the target antigens) -poor packaging and exposure to heat and moisture during indecorous transport and/ or storehouse, which can degrade antibodies in the rest unclear or incorrect instructions that can affect test performance inadequate training or competency of the test operator, which may lead to error in preparing the antigen-detecting RDT, performing the test or interpreting the result, with erroneous conclusions. (9)

3) Antibodies Test

Of the 98 COVID- 19 cases, 92 were positive for total antibodies and the rest were negative; of the 3022non-COVID-19 cases, 18 were positive for total antibodies and the rest were negative.Excluding those with negative total antibodies(n = 3010), the COI of the total antibodies in the COVID- 19 cases was advanced than that in thenon-COVID-19 cases(62.01(IQR,19.88 –150.4)vs.3.09(IQR,11.17 –4.95), p = 0.000)(Figure 1A). Using an ROC wind analysis, the area under the wind(AUC) for total antibodies was0.98(95 CI –0.99)(Figure 1B). The perceptivity, particularity, positive prophetic value, and negative prophetic value of the total antibodies in the opinion of COVID-19 was93.88(95 CI,87.28 –97.16),99.40(95 CI,99.06 –99.62),83.64(95 CI,75.61 –89.39), and99.80 95 CI,99.57 –99.91), independently. The kappa value between total antibodies and clinical diagnosis was0.88(95 CI,0.83 –0.93), indicating perfect Consistency (Table 2)

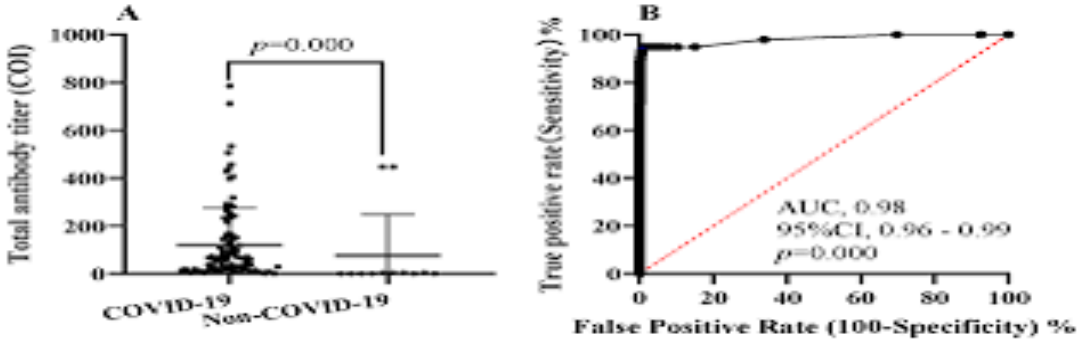

Figure 1. Diagnostic performance of the total antibody test for COVID-19. (A) Comparison of the titer of total antibodies in COVID-19 and non-COVID-19 patients; (B) ROC showing sensitivity as a function of specificity for the use of total antibodies for COVID-19 diagnosis. COI, the cutoff index

Total Antibody	Clinical Diagnosis (Gold Standard)		Sensitivity (%) (95% CI)	specificity(%) (95% CI)	Positive Predictive Value (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Accuracy (%) (95% CI)	Kappa (95% CI)
	COVID-19	Non-COVID-19						
Positive Negative	92 6	18 3004	93.88 87.28–97.16	99.40 99.06–99.62	83.64 75.61–89.39	99.80 99.57–99.91	99.23 98.92–99.54	0.88 (0.83 0.93)

Table 2. Diagnostic performance of the first total antibody for COVID-19 based on clinical diagnosis

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4)Chest X-ray Test

Detecting COVID- 19 Based on the Dataset of ChestX-ray Images-: This subsection describes the proposed methods to detect COVID- 19 based on symptoms. First, chestX-ray images are described. Second, the data preparation procedure involving data addition and image resizing is presented. Third, thepre-trained mod- els ResNet152V2, DenseNet201, VGG16, MobileNetV2, andinception_v3i are presented. Finally, we discuss how thepre-trained models were combined using stacking ensemble learning ways. Figure 5 shows the proposed methodology's overall workflow in detail. COVID- 19 ChestX-ray Images Description COVID- 19- chest-X-ray-1 Kaggle provided 317 chestX-ray images(51) in three classes 137 images with COVID- 19, 90 images with normal imaging, and 90 images with viral pneumonia. A total of 251 images are available for training and 66 images are available for testing. • COVID-19-chest-X-ray-2 A total of 2060 CHX- Ray images were downloaded from Kaggle(52). Of these, 696 images were selected for testing and 2060 for training. .

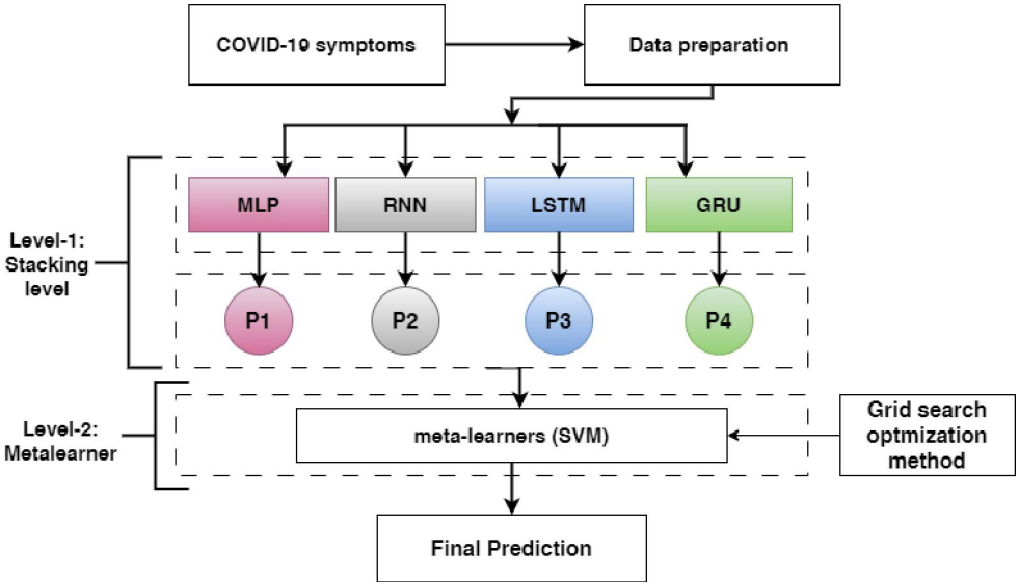

Figure . The proposed method for detecting COVID-19 based on symptoms (P1, P2, P3, and P4 referto the probability outputs of each model).

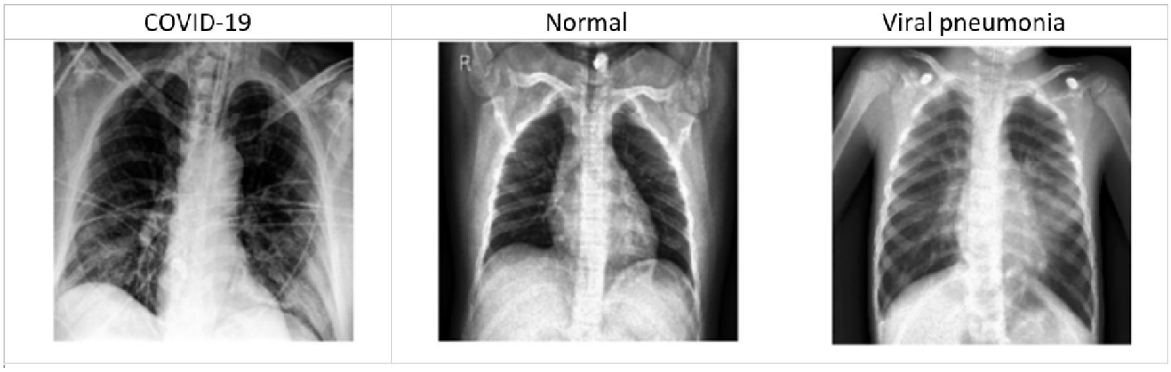

Figure. Example of chest X-ray images.

Data Augmentation

Preprocessing the firstX-ray chest images is required to enhance image features and improve image data quality. First, RGB is modified for the image channel sequence. Second, these images are resized to 224 × 224 × 3. Third, image addition is per- formed, which is a system of producing fresh dataset points from being data by developing changed

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copies of adataset. A variety of augmentation strategies are applied rescale1./ 255,zoom_range0.1,rotation_range20,width_shift_range0.1, height_shift_range0.1, andhorizontal_flipTrue.

III. EXPERIMENTS RESULTS

This section describes the results of testing DL models and the proposed models using two COVID- 19 symptom datasets and two chestX-ray image datasets to detect COVID- 19. .

Experiment Setup The experiments were conducted with Python using Google Colab. The Scikit- learn package was used for ML, while the Keras library was used for DL. .

Evaluation The evaluation metrics were applied to assess the learning algorithms. The following four metrics were used to assess classification performance accuracy(A), precision(P), recall(R), and F1- score(F1).

Accuracy is a popular evaluation parameter for classification problems. It's the proportion of correct forecasts relative to total predictions.

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+TN+EN}$$

Precision is a measure for determining categorization accuracy. The equation rep- resents the proportion of correct positive classifications relative to total anticipated positive classifications.

$$\text{Precision} = \frac{TP}{TP+FP}$$

Recall is the number of accurately detected positive cases out of the total number of positive cases. Returning to the fraud issue, the recall value will be quite precious in fraud scenarios. A high recall value indicates that a significant number of fraud cases are recognized in comparison to the total number of frauds.

$$\text{Recall} = \frac{TP}{TP+FN}$$

The F1- score measures the mean of the model's precision and recall.

$$\text{F1- score} = \frac{2 \cdot \text{precision} \cdot \text{recall}}{\text{precision recall}}$$

True positive(TP), true negative(TN), false positive(FP), and false negative(FN) values were recorded. A TP indicates the set of correctly formed positive values, a FP indicates the number of negative values generated incorrectly, a TN indicates the number of negative values generated correctly, and a FN indicates the number of positively predicted values that were correctly created.(3)

Treatment

Table Current approved/authorized COVID-19 drugs: mechanisms of action in COVID-19, other uses, adverse effects, and precautions

Drug I. Antiviral Drugs	Indications in Covid 19	Mechanism of action in COVID-19	Other uses	Adverse Effect	REFERENCE
Remdesivir	FDA-approved for the treatment of adults and pediatric patients with mild-to-moderate COVID-19 at high risk of disease progression Recommendedby NIH, IDSA, and NICE guidelines	Adenosine analog inhibiting viral RNA-dependent RNA polymerase → inhibition of viral replication Effective against the Omicron variant	Ebola virus SARS-CoV-1	↑ Liver transaminases PT, Nausea Hypersensitivity Not recommended for patients with eGFR < 30 mL/min	(30)

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Ritonavir/ Nirmatrelvir (Paxlovid)	FDA-approved (May 2023) for the treatment of adults with mildto-moderate COVID-19 at high risk of disease progression Recommended by NIH, IDSA, and NICE guidelines	A protease inhibitor		Diarrhea, impaired taste, hypertension, and myalgia	(31)
Molnupiravir	FDA-authorized (December 2021) for the treatment of certain adults with mild-to-moderate COVID-19 at high risk of disease progression as an alternative to Paxlovid and rem desivir Recommended by NIH, IDSA, and NICE guidelines	Incorporates into viral RNA strands → 'error catastrophe' during viral replication Effective against the Omicron variant		Not recommended in patients with severe renal orhepatic impairment Used cautiously in patients with liver Diseases May induce HIV-1 drug resistance Diarrhea, nausea, and dizziness Not recommended in pregnancy and lactation Not authorized for patients ≤ 18 years with COVID-19 due to bone and cartilage growth affection	(6)
II. Anti-SARS-CoV2 antibody agents Sotrovimab "Anti-SARS-CoV-2 monoclonalantibodies	Sotrovimab is recommendedby the NICE for the treatmentof COVID-19 as an alternative to Paxlovid in patients with increased riskfordisease progression only if theydo not need supplemental O2	Single mAb that binds to and blocks S-protein of SARS-CoV-2 Hypersensitivity, anaphylaxis (infusionrelated reactions)Effective against Omicron variant (B.1) but not against subvariants B.2		Hypersensitivity, anaphylaxis (infusionrelated reactions)	(10)
COVID-19 Convalescence Plasma (CCP)	FDA-authorized (August 2020) for the treatment of COVID-19in patients with immunosuppressive disease or receiving	Antiviral effects of neutralizing antibodies (NAbs) IgM and IgG against S-protein	CCP is widely used in outbreaks and epidemics until reaching a definitive	Mild allergic reaction, nausea, skin erythema, and fever	(24)

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	immunosuppressive treatment Suggested by the IDSA in ambulatory patients with mild-to-moderate COVID-19 at high risk of disease progression who have no other treatment options	NAbs → ↓autoantibodies, cytokine storm, Th1/Th17 ratio, complement Transmission of infection as HIV, HBV, or HCV NAbs → ↑ IL-10 Regulate coagulation and ↓Clotting	treatment	Transmission of infection as HIV, HBV, or HCV	
III. Anti-inflammatory and immunomodulatory drugs Corticosteroids	Life-saving—recommended by the WHO for patients with severe or critical COVID-19 Recommended by NIH, IDSA, and NICE guideline	To suppress both acute respiratory distress syndrome (ARDS) and systemic inflammation	Wide range of uses including autoimmune diseases, inflammatory diseases, and organ transplantation	Hyperglycemia, neuropsychiatric symptoms,secondary infections with ↑risk of opportunistic fungal infections (e.g.,mucormycosis, aspergillosis), and reactivation of latent infections (e.g., HBV, herpesvirus infections, and TB)	(23)
Interleukin-6 inhibitors Tocilizumab Sarilumab	Tocilizumab is FDA-approved (December 2022) for the treatment of hospitalized adults with COVID-19 who are receiving systemiccorticosteroids and require supplemental O2,mechanical ventilation, or ECMO Recommended by NIH, IDSA,and NICE guidelines	↓ Cytokine storm	Rheumatoid arthritis and giant cell arteritis	Runny nose, sore throat, sinus infection, headache	(25)
Interleukin-1 inhibitors Anakinra	Anakinra is FDA-authorized (November 2022) for the treatment	↓ Cytokine storm	Rheumatoid Arthritis Cryopyrin-associated	High blood pressure Injection site reactions GIT perforations	(26) (16)

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Canakinumab	of hospitalized adults with COVID-19 with pneumonia requiring supplemental O2who are at risk of diseaseprogression and likely to have an elevated plasma soluble urokinase plasminogen activator receptor		periodic syndromes (CAPS)	Headache, nausea, vomiting, and liver enzyme elevations	
JAK Inhibitors Baricitinib Tofacitinib	Baricitinib is FDA-approved (May 2022) for the treatment of hospitalized adults with COVID-19 requiringsupplemental O2, mechanical ventilation,or ECMO Recommendedby NIH, IDSA, and NICE guidelines	Inhibits JAK1/JAK2 → inhibitionof the inflammatory cascade Inhibits IL-6-induced STAT3 phosphorylation Inhibition of viral entry into the host cell	Rheumatoid arthritis Psoriatic arthritis Ulcerative colitis	Hypersensitivity reactions Infections: respiratory and urinary tract infections, reactivation of herps Myelosuppression, thrombosis, elevation of liver enzymes Cardiac-related events (MI and stroke) Baricitinib needs dose adjustment in renal patients Pneumonia, sepsis	(11) (5)
Vilobelimab	FDA-authorized (April 2023) for the treatment of hospitalized adults with COVID-19 when initiated within 48 h of receiving invasive mechanical ventilation or ECMO	A monoclonal antibody that binds to the soluble form of the complement component “C5a” → inhibits the inflammatory response → ↓ Cytokine storm		Infections: herpes simplex, enterococcal infection, bronchopulmonary aspergillosis Delirium Pulmonary embolism, DVT Hypertension Elevated liver enzymes Thrombocytopenia Rash	(29)

Table -: Vaccine list and efficacy (as of August 2022)

Manufacturer	Vaccine	Platform	No. of Countries in Use	Efficacy* (Infection	Efficacy* (Severe	REFERENCE
1) Moderna	Spikevac (mRNA-1273	RNA	87	93.2%	98.2%	(20)

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2)Pfizer/BioNTech	Comirnaty (BNT162b2)	RNA	146	91.3%	96.7%	(28)
3) Janssen (Johnson & Johnson	Ad26.COV2.S	Non Replicating ViralVector	111	52.4%	74.6%	(7)
4) Oxford/AstraZeneca	Vaxzevria (ChAdOx1 nCoV-19, AZD1222)	Non Replicating ViralVector	141	74.0%	100%	(15)
5) Serum Institute of India	Covishield (Oxford/ AstraZeneca formulation)	Non Replicating ViralVector	49			(12)
6) Bharat Biotech	Covaxin (BBV152	Inactivated	14	77.8% (symptomatic), 63.6%(asymp)	93.4%	(2)
7) Beijing Institute of Biological Products/ Sinopharm	Covilo (BBIBP-CorV)	Inactivated	91	78.1%	100%	(22) (13)
8) Sinovac Biotech	CoronaVac (PiCoVacc)	Inactivated	56	50.7% (Brazil) 65.3% (Indonesia) 83.5%(Turkey)	100% (Brazil)	(18) (14)
9) Novavax	Nuvaxovid (NVXCoV2373	Protein subunit	38	89.7 (UK) 90.4% (US&Mexico)	100%	(18)
10) Serum Institute of India	COVOVAX (Novavax formulation	Protein subunit	5			
11) CanSino Biologics	Convidecia (AD5-nCoV	Non Replicating Viral Vector	10	57.5%	91.7%	(17)

IV. CONCLUSION

Here's a sample conclusion for a review article on the signs, symptoms, diagnosis, and treatment of coronavirus:"In conclusion, this review has highlighted the diverse array of signs and symptoms associated with coronavirus infection, ranging from mild respiratory symptoms to severe pneumonia and multi-organ failure. The rapid and accurate diagnosis of coronavirus is crucial for effective disease management and prevention of transmission. Current diagnostic methods, including PCR-based tests and serological assays, play a pivotal role in identifying infected individuals. However, there is a need for continued research to develop more sensitive and specific diagnostic tools. Treatment options for coronavirus infection remain limited, with supportive care being the mainstay of therapy. Antiviral agents and immunomodulatory drugs have shown some promise, but further clinical trials are warranted to establish their efficacy and safety.

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