Trends in the development of COVID-19 and associated combating immunological strategies

AUTHORS DETAIL

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Abstract

The SARS-CoV-2 -caused COVID-19 pandemic has caused significant challenges for people worldwide with its severe complications and rapid spread, particularly for vulnerable populations like the elderly and those with underlying medical conditions. This review looks at the virological characteristics, clinical profile, pathobiology and preventative strategies associated with COVID-19. Similar to SARS-CoV, SARS-CoV-2 has strong antigenic cross-reactivity and uses ACE2 as its entry receptor. Direct contact and respiratory droplets are the main ways that it is spread, and asymptomatic carriers also play a role. In order to detect the disease, diagnostic techniques like rRT-PCR and CT imaging are essential, and treatment strategies focus on experimental vaccines that target the spike glycoprotein, passive immunization, and repurposed antivirals. To reduce the spread of viruses, preventive measures such as vaccination and SOP adherence are still crucial. This is thorough. Asymptomatic carriers aid in its spread, and respiratory droplets and direct contact are the main routes of transmission. While treatment efforts focus on repurposed antivirals, passive immunization, and experimental vaccines that target the spike glycoprotein, diagnostic techniques like rRT-PCR and CT imaging are essential for disease detection. To slow the spread of the virus, preventive measures like vaccination and SOP observance are still critical.

Keywords: COVID-19, Immunological potentials, Severity, Complications, Combating strategies

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the COVID-19 pandemic, which has caused a significant worldwide burden of infections and deaths since it was first identified in December 2019 (Feng et al., 2020). The beta coronavirus genus includes SARS-CoV-2, which is genetically similar to SARS-CoV. The spike protein and angiotensin-converting enzyme 2 (ACE2) interact to allow the virus to enter host cells (Malik, 2020). The host serine protease transmembrane protease serine 2 (TMPRSS2) facilitates this process by cleaving the spike protein and allowing for fusion with the cell membrane (Thunders & Delahunt, 2020). Furin, a host protease, also converts the spike precursor into S1 and S2

subunits. Potentially increasing viral infectivity, the S1 subunit binds directly to neuropilin-1 on the cell surface (Frolova et al., 2022). Other host molecules implicated in viral invasion include CD147, cyclophilins, and ACE2 and TMPRSS2, which are primarily expressed in the epithelial tissues of the skin and lung (Radzikowska et al., 2020). The widespread administration of COVID-19 vaccines has significantly reduced infection rates, disease severity, and mortality worldwide (Mohammed et al., 2022). However, the emergence of novel *SARS-CoV-2* variants of concern (VOCs) poses a threat to this progress, as these variants can partially evade immunity acquired through natural infection or vaccination, potentially leading to breakthrough infections (Caniels et al., 2021).
SARS-CoV-2 is the causative agent of Coronavirus disease (COVID-19). Infected individuals developed mild to moderate respiratory illness but these infected patients recovered after some time period without any specific treatment (Pal et al., 2020). There is an increased risk of developing serious illness in certain underlying medical conditions, such as diabetes, cardiovascular issues, chronic respiratory diseases, and cancer (Lisy et al., 2018). All these kinds of patients who suffer from COVID-19 develop severe illness or sometimes die. The effective way to get rid of and prevent virus transmission is to follow standard Operating procedures (SOPs) like maintaining a distance of 1 meter between persons, wearing masks, wearing gloves and frequently washing hands and followed by the Vaccines (Berlin et al., 2021). The spreading of the virus occurs via liquid particles that are released by the infected persons whenever they sneeze, cough, speak and breathe. The viral particles present in these droplets enter the encountered persons and start replicating in their alveoli and develop this contagious disease (Stadnytskyi et al., 2021). The transmission of COVID-19 is represented in Fig 1.

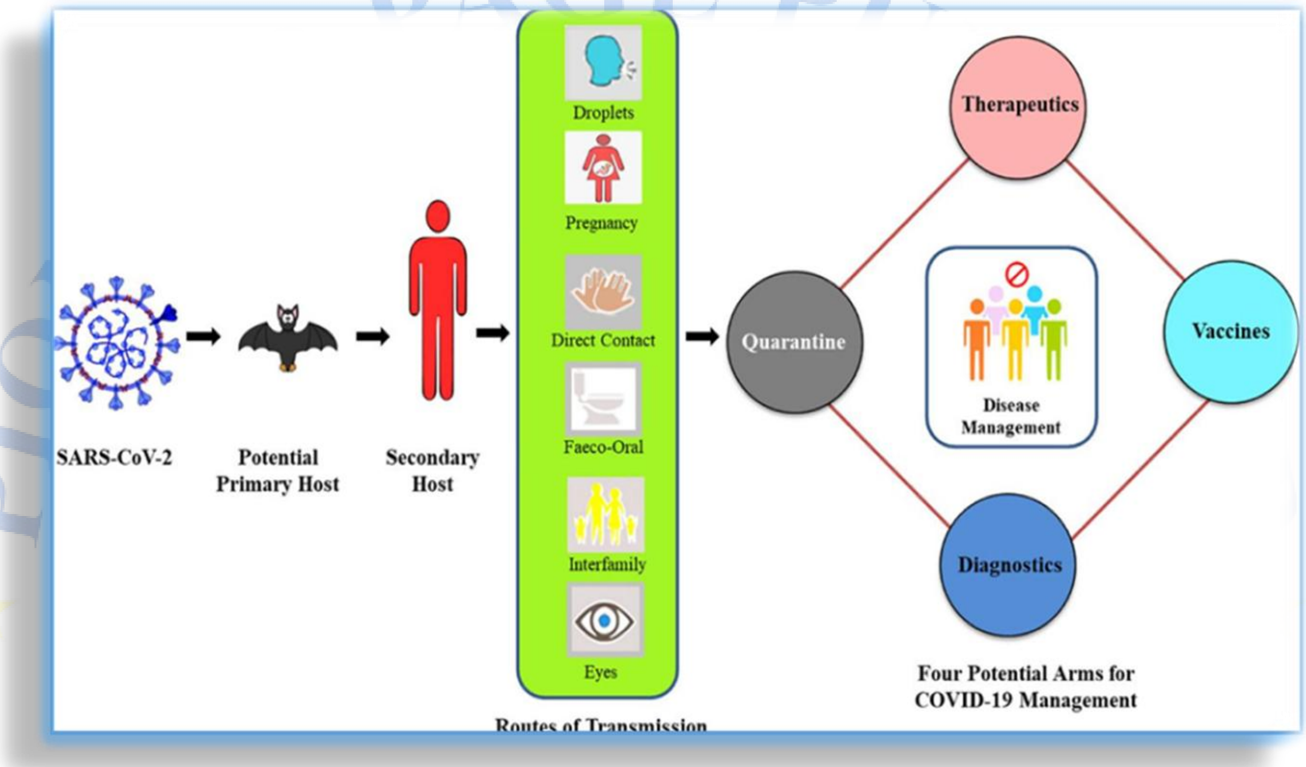

Fig. 1. Transmission of COVID-19

Classification

Kingdom: Orthornavirae
Phylum: Pisuviricota
Class: Pisoniviricetes
Order: Nidovirales
Family: *Coronaviridae*
Genera: *Alphacoronavirus*

Species: Coronavirinae

Morphology

A phylogenetic analysis of the Sarbeco-virus subfamily (genus Beta coronavirus) shows the links between SARS-CoV-2 and SARS-CoV are close (about 80 percent similar) (Al-ajmi et al., 2023). It is most likely bat-derived despite the lack of an intermediate host, as it shares a high level of genetic similarity (>95 percent) with Chinese bat coronaviruses (Fan et al., 2019). The spike (S) glycoprotein's receptor-binding domain (RBD) in pangolins differs from known bat viruses more than it does from SARS-2-CoV-2, even though somewhat similar coronaviruses have been found in these animals (Wu et al., 2012).

Genome

The genes most frequently shared by SARS-CoV-2 and SARS-CoV are the protein S glycoprotein, the RNA-dependent RNA polymerase (Nsp12), and two proteases called papain-like protease (PLpro) and 3C-like protease (3CLpro) (Gorkhali et al., 2021). A high level of antigenic cross-reactivity between SARS-CoV-2 and SARS-CoV is present. Like SARS-CoV, SARS-CoV-2 enters the body through the human respiratory tract epithelium, which expresses the angiotensin-converting enzyme 2 (ACE2) (Reche, 2020). Lab mice that express human ACE2 exclusively have been shown to develop pneumonia. According to Letko and Munster (2020), this is most likely mediated by the RBD of the S glycoprotein (Guo et al., 2023). Although there have been reports of cross-neutralization and similarities between SARS-CoV and SARS-CoV-2, especially in the S glycoprotein, significant biological differences have been identified (Pinto et al., 2020).

Replication and Life cycle

The life cycle of the virus and its replication is illustrated in Fig. 2.

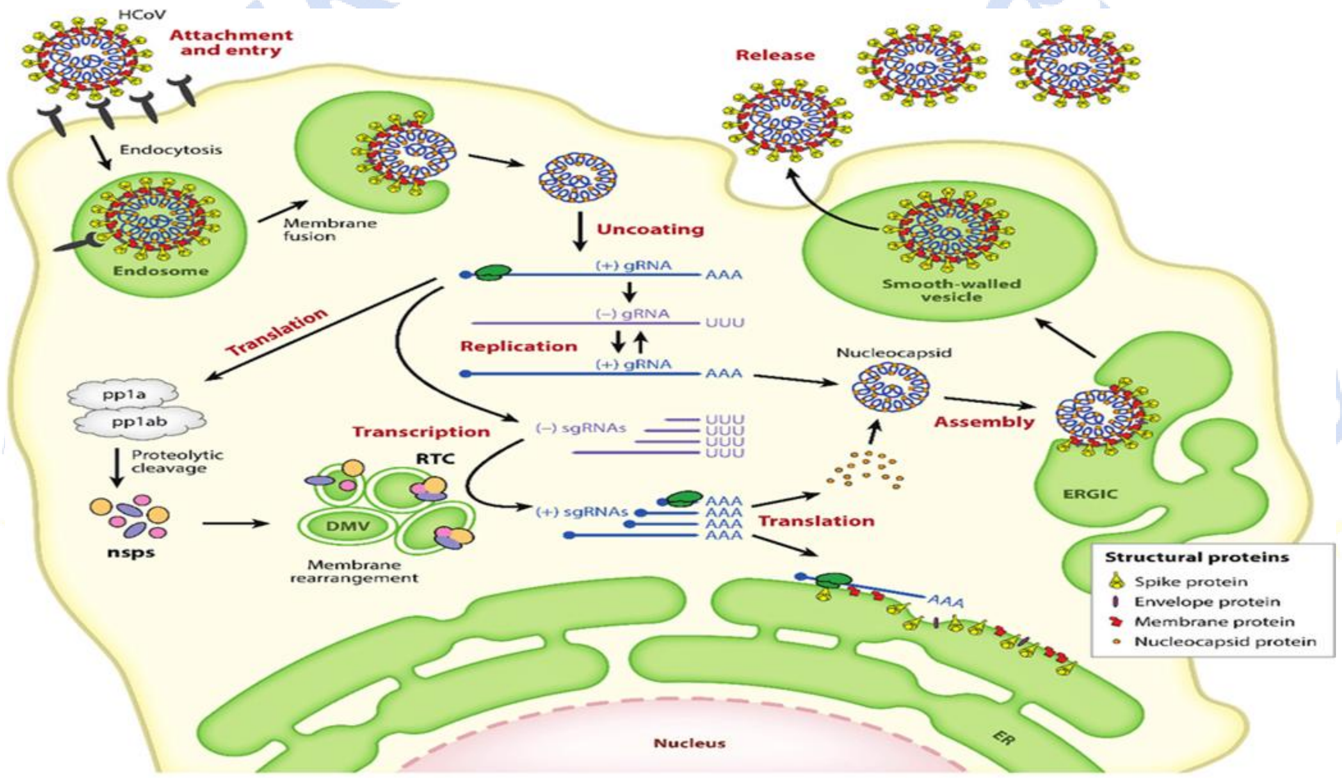

Fig. 2: Life cycle of COVID-19

Geographical distribution

The travel industry was devastated by the virus, with passenger numbers and flights falling by over 50% (Folinas and Metaxas, 2020). Most countries have imposed significant restrictions, with almost all countries requiring some form of quarantine for new arrivals. Arrival models vary from no quarantine and an instruction to isolate at home if a person feels unwell, to compulsory isolation at home (or at a hotel or temporary home), through to mandatory quarantine with arrivals taken to a designated hotel or facility (Table 1) (Khan et al., 2020).

Table. 1: Clinical Profile and Epidemiology

Aspect	Details
Clinical Presentation	Most patients (81%) have influenza-like illness (ILI) or mild pneumonia
	19% experience severe or critical pneumonia
	Common symptoms: fever, cough, fatigue and myalgia
	No specific symptom indicates COVID-19 without known exposure
Epidemiological Link	Majority of cases had a history of exposure to Wuhan epidemic area
	Symptoms in exposed patients: fever and cough
Source of Infection	Caused by *SARS-CoV-2* with both symptomatic and asymptomatic infections
Clinical Severity	80% of patients have mild disease
	20% require hospital admission
	5% need intensive care admission
Key Difference from Influenza	Potential for severe disease even in young adults without comorbidities

Pathobiology

Mortality rates are higher for those over 60 and those who have coexisting conditions, such as cardiovascular disease, diabetes, and hypertension (Davis et al., 2011).

Prevalence/Incidence

Pakistan reported a total of 1,581,936 confirmed cases and 30,664 deaths in recent times. The pandemic has progressed through multiple waves, each varying in intensity and geographic distribution (Zia and Naeem, 2024). The first wave began in late May 2020, peaking in mid-June, followed by a second wave in early November 2020 and a third wave in mid-March 2021(Kharel, 2021). Each wave affected different regions, with the third wave notably impacting Punjab and Khyber Pakhtunkhwa (Ali et al., 2022). By December 12, 2022, it was estimated that 99% of Pakistan's population had been infected at least once. The distribution of cases has been uneven across the country. Karachi, for example, recorded about 189,000 confirmed cases as of May 7, 2021 accounting for approximately 22% of all cases in Pakistan (Rehman et al., 2023). Lahore the second-largest city, had about 170,000 cases as of September 5, 2020, representing around 19% of the national total. It's important to note that these records may not fully capture the true extent of the pandemic due to underreporting and variations in testing and reporting practices. For the most current and detailed information, consulting official health department updates and reputable sources is recommended (Oxman et al., 2007).

Transmission

As of right now, direct contact and respiratory droplets have been determined to be the primary routes of transmission. Transmission by aerosol and the digestive tract is still unknown. The disease typically takes 3–7 days to incubate, but no more than 14 days (Randall et al., 2021).

Laboratory diagnosis

Imaging is crucial to the diagnosis and assessment of the illness. According to a study, (rRT-PCR) positive results for coronavirus are required for the final diagnosis. Because COVID-19 is so contagious, it is imperative to use rapid and accurate diagnostic methods in order to quickly locate, segregate, and care for patients (Long et al., 2020). The risk of mortality rates and public contamination may be decreased as a result. In contrast, rRT-PCR results can be obtained much more quickly than CT test results, which typically take five to six hours. Uncertainty surrounds whether rRT PCR is the gold standard and whether false-positive or false-negative results are common. Based on metagenomic sequencing and targeted real-time polymerase chain reaction (qRT-PCR) assays, the first patient cluster in Wuhan supplied bronchoalveolar lavage fluid that contained a novel human CoVID-19 (SARS-CoV-2) (Houghton, 2023).

Treatment

Antivirals that are approved to treat SARS-CoV-2 are not yet available. There are several antivirals that have the potential to combat MERS-CoV or SARS-CoV in vitro and in vivo for COVID-19 that are presently undergoing clinical trials (Nascimento et al., 2020). The antiretroviral protease is, however, inhibited by lopinavir/ritonavir (LPV/r), showing mixed results in treating SARS. The first clinical trial utilizing LPV/r was just released. within 2020. A novel nucleotide analogue that inhibits nsp12 polymerase, remdesivir, is another intriguing medication. Effectiveness against several RNA viruses, such as SARS and MERS-CoV, has been demonstrated in vitro, outperforming LPV/r-IFNb in a mouse model for antiviral activity against MERS-CoV (Maciorowski et al., 2020).

Entry of CoV into Host Cells

CoVs utilize a characteristic spike (S) glycoprotein to gain infiltration of host cells. Human cells' angiotensin-converting enzyme 2 (ACE2) receptor is the target of the S protein's receptor-binding domain in both SARS-CoV-2 and SARS-CoV (Bourgonje et al., 2020). Upon binding, the virus is internalized. Recent studies highlight the role of host cell enzyme Furin, which cleaves and activates the SARS-CoV-2 spike protein, a feature absent in SARS-CoV. Because furin is widely expressed in tissues such as the lungs, intestines, and liver, SARS-CoV-2 infection can be particularly aggressive and potentially multi-organ. This furin-mediated activation may also influence viral transmissibility and stability (Braun and Sauter, 2019).

Antigen Presentation in SARS-CoV-2 Infection

Viruses attached to major histocompatibility complex (MHC) class I or II molecules are displayed by antigen-presenting cells (APCs) in order to stimulate CD8 cytotoxic T cells and CD4 helper T cells (Kedzierska and Koutsakos, 2020). Innate and adaptive immunity are crucially linked by dendritic cells (DCs), which are widely distributed in the respiratory system. Parallels between SARS-CoV and MERS-CoV research can be made, even though antigen presentation in SARS-CoV-2 is still poorly understood. Antiviral cytokines like IFN-α, IFN-β, and IFN-γ are expressed at low levels, TNF-α and IL-6 are moderately elevated, and chemokines like IP-10 and MIP-1 are significantly upregulated during SARS-CoV infection. While the expression of Toll-like receptors is mainly unchanged, there is a notable upregulation of chemokine receptors CCR5, CCR3, and CCR1. With higher levels of IFN-γ and associated cytokines, MERS-CoV exhibits a more robust antigen presentation response in DCs than SARS-CoV. In *SARS-CoV*, MHC-I is the primary antigen presentation mechanism (Arshad et al., 2023).

Humoral Immune Response

Plasma cell-produced antibodies are essential for the humoral immune response because neutralizing antibodies prevent viruses from entering cells. Both B and T cell epitopes of structural proteins (S, N, M, and E) in SARS-CoV have undergone extensive characterization (Slamanig and Nolte, 2021). The receptor-binding domain of the spike protein is a crucial B cell epitope that neutralizes SARS-CoV-2. Helper T cells promote isotype switching from IgM to IgG, with IgM disappearing by week 12 post-infection, while IgG persists longer and may offer prolonged protection. Evidence from SARS-CoV and MERS-CoV suggests a predominant Th1-type response is essential for effective viral control (Prompetchara et al., 2020).

Cellular Immune Response

T lymphocytes are involved in cellular immunity, where they target and eliminate infected cells (Moss, 2022). The lack of T cells hinders the removal of the virus, as demonstrated by experimental models of SARS-CoV and MERS-CoV. $CD4^+$ and $CD8^+$ memory T cells can proliferate, produce IFN-γ, and mount delayed-type hypersensitivity responses in SARS-CoV, and they can remain active for years. Animal models that are infected with MERS-CoV exhibit comparable $CD8^+$ responses. However, patients with SARS-CoV-2 frequently have lower $CD4^+$ and $CD8^+$ counts, which may affect their long-term immune memory (Dan et al., 2021).

SARS-CoV-2 Infection:

Cytokine Storm Syndrome Cytokine storm is a condition in which proinflammatory cytokines are released uncontrollably due to excessive immune activation (Jarczak and Nierhaus, 2022). This phenomenon has been closely associated with acute respiratory distress syndrome (ARDS) and the severity of COVID-19. TNF-α, IL-6, IL-12, IL-18, and IL-1β are among the cytokines that are elevated in SARS-CoVs along with chemokines such as CCL2, CCL3, and CXCL10. MERS-CoV similarly triggers IFN-α, IL-6, and CXCL10 elevation. ARDS from cytokine storms leads to multi-organ failure, a pattern seen in both prior CoV outbreaks and COVID-19. Therapies targeting IL-6 and other cytokines have shown promise, with IL-6 blockers yielding encouraging outcomes in some COVID-19 patients (Jones and Hunter, 2021).

Immune Responses and Pathogenesis of COVID-19

Numerous immunological mechanisms underlie COVID-19, some of which may be related to SARS-CoV-2 's virulence and an imbalance between innate and adaptive immune responses (Gusev et al., 2022). Other elements that could affect the immune response to the virus include autoimmune reactions, superantigen activity, and pre-existing immunity. It is the SARS-CoV-2 spike protein that the adaptive immune system mainly targets. Toll-like receptors (TLR-3/7/8) find viral RNA, and a cytoplasmic RNA sensor called RIG-I can stop the spread of viruses in lung cells (Luqman et al., 2024). But RIG-I activation also causes epithelial cells to release signals that cause inflammation, which in turn causes macrophages to release cytokines and intensify immune activation, especially in inflammatory environments. Replication of SARS-CoV-2 inhibits the MDA5 pathway-controlled type I interferon (IFN) response in lung cells. Furthermore, the activation of the NLRP3 inflammasome plays a role in the progression and severity of COVID-19 with successful viral cleavage. IgM and IgA antibodies are present in the early stages of infection, while IgG is present later. Higher IgG titers are associated with better outcomes, and hospitalized or severely infected COVID-19 patients have elevated anti-RBD IgA and IgG levels (Lo Sasso et al., 2021). A worse prognosis, particularly in children, is linked to weak or delayed IgM/IgG responses. Cross-reactivity with infections other than SARS-CoV-2 has been noted (e.g. chicken aerosol and infectious bronchitis virus) vaccinations, especially in veterinarians who are regularly exposed to them (Ardicli et al., 2022). However, these antibodies are very different from those specific to SARS-CoV-2 in that they do not have neutralizing activity and mainly target non-RBD regions. The development of SARS-CoV-2 -specific memory B and T cell responses in mild COVID-19 cases may provide long-term protection. It can take up to six months after infection for memory B cell activity to mature. Diverse autoantibody responses have been found in COVID-19 patients and have been linked to the illness (Wang et al., 2021).

Future perspectives

Human activities, climate change, and global mobility create ideal conditions for new zoonotic disease outbreaks (Esposito et al., 2023). The COVID-19 pandemic has highlighted the pressing need for novel approaches to anticipate, stop, and manage new infections. improved monitoring of SARS-CoV-2 variations. It is essential to monitor vaccine breakthrough rates and transmissibility to inform international policy. Additionally, close monitoring of COVID-19's evolution is necessary to understand waning immunity, viral mutations, and potential spillback from animal reservoirs (Kilpatrick, 2023). Updated vaccines that target circulating variants and routine booster shots are two examples of vaccination strategies that must change as the virus continues to evolve. Experts in immunology and allergies must (Wolff et al., 2023). It conducts additional research to determine the long-term impacts of COVID-19 on allergic sensitization and allergic diseases. In contrast to diseases that have been eradicated, like smallpox, COVID-19 is probably here to stay. In order to manage the illness going forward, especially for high-risk groups, and avoid complications like multisystem inflammation, new strategies are required (Cacciatore et al., 2025).

Conclusion

The COVID-19 pandemic has had a significant impact on world health, highlighting the urgent need for ongoing innovation and care in the fight against infectious diseases. SARS-CoV-2 's complicated virological traits, pathobiology and clinical profile were highlighted in this review, along with developments in diagnostic, treatment, and prevention techniques. Rapid diagnostic tools and experimental antiviral treatments have shown promise, but the need for continuous research and development is highlighted by the lack of universally approved antivirals and the dependence on preventive measures like vaccinations and SOP adherence.

References

1. Al-ajmi, A., Bazighifan, A. S., Alamery, S., & Zargar, S. (2023). Covid-19 origin, transmission, immune response and treatment: A review. International Archives of Integrated Medicine, 10(1).
2. Ali, M. A., Hassan, M., Mehmood, M., Kazmi, D. H., Chishtie, F. A., & Shahid, I. (2022). The potential impact of climate extremes on cotton and wheat crops in Southern Punjab, Pakistan. Sustainability, 14(3), 1609.
3. Ardicli, O., Carli, K. T., Satitsuksanoa, P., Dreher, A., Cusini, A., Hutter, S., ... & van de Veen, W. (2022). Exposure to avian coronavirus vaccines is associated with increased levels of SARS-CoV-2-cross-reactive antibodies. Allergy, 77(12), 3648-3662.
4. Arshad, N., Laurent-Rolle, M., Ahmed, W. S., Hsu, J. C. C., Mitchell, S. M., Pawlak, J., ... & Cresswell, P. (2023). *SARS-CoV-2* accessory proteins ORF7a and ORF3a use distinct mechanisms to down-regulate MHC-I surface expression. Proceedings of the National Academy of Sciences, 120(1), e2208525120.
5. Berlin, D. A., Gulick, R. M., & Martinez, F. J. (2020). Severe covid-19. New England Journal of Medicine, 383(25), 2451-2460.

6. Bourgonje, A. R., Abdulle, A. E., Timens, W., Hillebrands, J. L., Navis, G. J., Gordijn, S. J., ... & van Goor, H. (2020). Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). The Journal of pathology, 251(3), 228-248.
7. Braun, E., & Sauter, D. (2019). Furin-mediated protein processing in infectious diseases and cancer. Clinical & translational immunology, 8(8), e1073.
8. Cacciatore, S., Andaloro, S., Bernardi, M., Oterino Manzanas, A., Spadafora, L., Figliozzi, S., ... & Sabouret, P. (2025). Chronic inflammatory diseases and cardiovascular risk: current insights and future strategies for optimal management. International Journal of Molecular Sciences, 26(7), 3071.
9. Caniels, T. G., Bontjer, I., van der Straten, K., Poniman, M., Burger, J. A., Appelman, B., ... & Sanders, R. W. (2021). Emerging *SARS-CoV-2* variants of concern evade humoral immune responses from infection and vaccination. Science Advances, 7(36), eabj5365.
10. Dan, J. M., Mateus, J., Kato, Y., Hastie, K. M., Yu, E. D., Faliti, C. E., ... & Crotty, S. (2021). Immunological memory to *SARS-CoV-2* assessed for up to 8 months after infection. Science, 371(6529), eabf4063.
11. Davis, J. W., Chung, R., & Juarez, D. T. (2011). Prevalence of comorbid conditions with aging among patients with diabetes and cardiovascular disease. Hawaii medical journal, 70(10), 209.
12. Esposito, M. M., Turku, S., Lehrfield, L., & Shoman, A. (2023). The impact of human activities on zoonotic infection transmissions. Animals, 13(10), 1646.
13. Fan, Y., Zhao, K., Shi, Z. L., & Zhou, P. (2019). Bat coronaviruses in China. Viruses, 11(3), 210.
14. Feng, W., Zong, W., Wang, F., & Ju, S. (2020). Severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*): a review. Molecular cancer, 19(1), 100.
15. Folinas, S., & Metaxas, T. (2020). Tourism: The great patient of coronavirus COVID-2019.
16. Frolova, E. I., Palchevska, O., Lukash, T., Dominguez, F., Britt, W., & Frolov, I. (2022). Acquisition of furin cleavage site and further *SARS-CoV-2* evolution change the mechanisms of viral entry, infection spread, and cell signaling. Journal of Virology, 96(15), e00753-22.
17. Gorkhali, R., Koirala, P., Rijal, S., Mainali, A., Baral, A., & Bhattarai, H. K. (2021). Structure and function of major *SARS-CoV-2* and *SARS-CoV* proteins. Bioinformatics and biology insights, 15, 11779322211025876.
18. Guo, H., Li, A., Dong, T. Y., Si, H. R., Hu, B., Li, B., ... & Letko, M. (2023). Isolation of ACE2-dependent and-independent sarbecoviruses from Chinese horseshoe bats. Journal of Virology, 97(9), e00395-23.
19. Gusev, E., Sarapultsev, A., Solomatina, L., & Chereshnev, V. (2022). *SARS-CoV-2* -specific immune response and the pathogenesis of COVID-19. International journal of molecular sciences, 23(3), 1716.
20. Houghton, R. L. (2023). Acute undifferentiated febrile illness in the UK and investigating the diagnostic utility of metagenomic next generation sequencing (Doctoral dissertation, University of Southampton).
21. Jarczak, D., & Nierhaus, A. (2022). Cytokine storm—definition, causes, and implications. International journal of molecular sciences, 23(19), 11740.
22. Jones, S. A., & Hunter, C. A. (2021). Is IL-6 a key cytokine target for therapy in COVID-19?. Nature Reviews Immunology, 21(6), 337-339.
23. Kedzierska, K., & Koutsakos, M. (2020). The ABC of major histocompatibility complexes and T cell receptors in health and disease. Viral Immunology.
24. Khan, S., Siddique, R., Ali, A., Xue, M., & Nabi, G. (2020). Novel coronavirus, poor quarantine, and the risk of pandemic. Journal of Hospital Infection, 104(4), 449-450.
25. Kharel, P. (2021). Nepal's fight against the second wave of COVID-19 pandemic.
26. Kilpatrick, A. M. (2023). Ecological and Evolutionary Insights About Emerging Infectious Diseases from the COVID-19 Pandemic. Annual Review of Ecology, Evolution, and Systematics, 54(1), 171-193.
27. Lisy, K., Campbell, J. M., Tufanaru, C., Moola, S., & Lockwood, C. (2018). The prevalence of disability among people with cancer, cardiovascular disease, chronic respiratory disease and/or diabetes: a systematic review. JBI Evidence Implementation, 16(3), 154-166.
28. Lo Sasso, B., Giglio, R. V., Vidali, M., Scazzone, C., Bivona, G., Gambino, C. M., ... & Ciaccio, M. (2021). Evaluation of anti-*SARS-CoV-2* S-RBD IgG antibodies after COVID-19 mRNA BNT162b2 vaccine. Diagnostics, 11(7), 1135.
29. Long, C., Xu, H., Shen, Q., Zhang, X., Fan, B., Wang, C., ... & Li, H. (2020). Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT?. European journal of radiology, 126, 108961.
30. Luqman, M., Ali, S. N., Khalid, Z., Anwar, I., Goyal, S. M., & Mahmood, M. S. (2024). Toll-Like Receptors and Emerging Viral Infections. In Thirty Years since the Discovery of Toll-Like Receptors. IntechOpen.
31. Maciorowski, D., Idrissi, S. Z. E., Gupta, Y., Medernach, B. J., Burns, M. B., Becker, D. P., ... & Kempaiah, P. (2020). A review of the preclinical and clinical efficacy of remdesivir, hydroxychloroquine, and lopinavir-ritonavir treatments against COVID-19. SLAS DISCOVERY: Advancing the Science of Drug Discovery, 25(10), 1108-1122.
32. Malik, Y. A. (2020). Properties of coronavirus and *SARS-CoV-2* . The Malaysian journal of pathology, 42(1), 3-11.

33. Mohammed, I., Nauman, A., Paul, P., Ganesan, S., Chen, K. H., Jalil, S. M. S., ... & Zakaria, D. (2022). The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. Human vaccines & immunotherapeutics, 18(1), 2027160.
34. Moss, P. (2022). The T cell immune response against *SARS-CoV-2* . Nature immunology, 23(2), 186-193.
35. Nascimento Junior, J. A. C., Santos, A. M., Quintans-Junior, L. J., Walker, C. I. B., Borges, L. P., & Serafini, M. R. (2020). SARS, MERS and *SARS-CoV-2* (COVID-19) treatment: a patent review. Expert opinion on therapeutic patents, 30(8), 567-579.
36. Oxman, A. D., Lavis, J. N., & Fretheim, A. (2007). Use of evidence in WHO recommendations. The Lancet, 369(9576), 1883-1889.
37. Pal, M., Berhanu, G., Desalegn, C., & Kandi, V. (2020). Severe acute respiratory syndrome coronavirus-2 (*SARS-CoV-2*): an update. Cureus, 12(3).
38. Pinto, D., Park, Y. J., Beltramello, M., Walls, A. C., Tortorici, M. A., Bianchi, S., ... & Corti, D. (2020). Cross-neutralization of *SARS-CoV-2* by a human monoclonal *SARS-CoV* antibody. Nature, 583(7815), 290-295.
39. Prompetchara, E., Ketloy, C., & Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pacific journal of allergy and immunology, 38(1), 1-9.
40. Radzikowska, U., Ding, M., Tan, G., Zhakparov, D., Peng, Y., Wawrzyniak, P., ... & Sokolowska, M. (2020). Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. Allergy, 75(11), 2829-2845.
41. Randall, K., Ewing, E. T., Marr, L. C., Jimenez, J. L., & Bourouiba, L. (2021). How did we get here: what are droplets and aerosols and how far do they go? A historical perspective on the transmission of respiratory infectious diseases. Interface Focus, 11(6), 20210049.
42. Reche, P. A. (2020). Potential cross-reactive immunity to *SARS-CoV-2* from common human pathogens and vaccines. Frontiers in immunology, 11, 586984.
43. Rehman, Z. U., Parveen, A., & Ali, A. (2023). Islamic Financial Engineering Role in Combating Covid-19 Epidemic Issues: A Case Study of Pakistan. Journal of Quranic and Social Studies, 3(2), 119-155.
44. Slamanig, S. A., & Nolte, M. A. (2021). The bone marrow as sanctuary for plasma cells and memory T-cells: implications for adaptive immunity and vaccinology. Cells, 10(6), 1508.
45. Stadnytskyi, V., Anfinrud, P., & Bax, A. (2021). Breathing, speaking, coughing or sneezing: What drives transmission of SARS-CoV-2?. Journal of Internal Medicine, 290(5), 1010-1027.
46. Thunders, M., & Delahunt, B. (2020). Gene of the month: TMPRSS2 (transmembrane serine protease 2). Journal of clinical pathology, 73(12), 773-776.
47. Wang, E. Y., Mao, T., Klein, J., Dai, Y., Huck, J. D., Jaycox, J. R., ... & Ring, A. M. (2021). Diverse functional autoantibodies in patients with COVID-19. Nature, 595(7866), 283-288.
48. Wolff, D., Drewitz, K. P., Ulrich, A., Siegels, D., Deckert, S., Sprenger, A. A., ... & Apfelbacher, C. (2023). Allergic diseases as risk factors for Long-COVID symptoms: Systematic review of prospective cohort studies. Clinical & Experimental Allergy, 53(11), 1162-1176.
49. Wu, Z., Ren, X., Yang, L., Hu, Y., Yang, J., He, G., ... & Jin, Q. (2012). Virome analysis for identification of novel mammalian viruses in bat species from Chinese provinces. Journal of virology, 86(20), 10999-11012.
50. Zia, A., & Naeem, Z. (2024). Re-Emergence of *SARS-CoV-2* : Frequent Mutations, Amplified Transmissibility and Immune Elusion. Journal of Islamabad Medical & Dental College, 13(1), 4-6.